Prospective Study

Development of a Model for Predicting the Effectiveness of Low-Temperature Plasma on Zoster-Associated Pain

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Background: Zoster-associated pain (ZAP) is a condition characterized by severe, persistent pain caused by herpes zoster (HZ), which impacts the patient's daily activities, mental health, and quality of life significantly. Low-temperature plasma (LTP) technology, as an emerging therapeutic approach, has been applied widely in various biomedical fields. At our center, this technology has been utilized for the treatment of postherpetic neuralgia. Preliminary studies have demonstrated that LTP can effectively alleviate pain symptoms in patients with ZAP. However, a small subset of patients experiences suboptimal outcomes, with limited pain relief following LTP treatment.

Objectives: This study was conducted to investigate the efficacy of LTP for treating ZAP, analyze the risk factors for poor therapeutic response, and establish a predictive model to provide clinical decision-making support.

Study Design: A single-center prospective cohort study was conducted to analyze outcomes of using LTP to treat ZAP.

Setting: Patients treated at the Pain Department of Zhongda Hospital, Southeast University, between January 2018 and December 2023, were included.

Methods: Patients who received LTP treatment underwent a 6-month follow-up, during which their Visual Analog Scale (VAS) scores were recorded. A post-treatment VAS score ≥ 4 was defined as a poor therapeutic response. Risk factor analysis was performed on patients with poor therapeutic response, and a predictive model was developed. The model was evaluated using threefold cross-validation, with its performance assessed by the area under the receiver operating characteristic (ROC) curve (AUC). Calibration curves and decision curve analysis were used to assess the model's calibration and clinical applicability.

Results: A total of 120 patients who underwent LTP treatment were included in the study, with an overall response rate of 67.5%. Analysis of 43 variables revealed that age, coronary heart disease (CHD), disease duration, albumin-to-globulin ratio (AGR), white blood cell (WBC) count, neutrophil count, and scores on the VAS, Dermatology Life Quality Index (DLQI), Pittsburgh Sleep Quality Index (PSQI), Hamilton Anxiety Rating Scale (HAMA1), HAMA2, and Barthel Index were significantly different between the groups ($P < 0.05$). Stepwise bidirectional regression identified 4 independent factors significantly associated with outcomes: CHD, AGR, PSQI, and HAMA1. Using logistic regression, a predictive model was constructed and validated through 3 cross-validation methods. The mean AUC for the training set was 0.768 (95% CI: 0.690-0.942), with a sensitivity of 68.7% and a specificity of 83.7%. The mean AUC for the validation set was 0.762 (95% CI: 0.589-0.935), with a sensitivity of 58.5% and a specificity of 76.4%.

Limitations: The study was conducted at a single center with a small number of cases, which might have limited generalizability. Larger, multicenter prospective studies are needed to validate the findings.

Conclusion: For ZAP patients, CHD, AGR, and PSQI and HAMA1 scores are high-risk factors for the continuation of chronic pain after the administration of LTP treatment. The predictive model

demonstrated relatively high sensitivity and specificity. This finding suggests that combining these indicators can, to some extent, predict patients' therapeutic response to LTP.

Key words: Zoster-associated pain, varicella-zoster virus, low-temperature plasma radiofrequency ablation, postherpetic neuralgia, predictive model, Visual Analog Scale (VAS), risk factors, chronic pain, albumin-to-globulin ratio (AGR), Pittsburgh Sleep Quality Index (PSQI)

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Varicella-zoster virus (VZV) is a linear double-stranded DNA virus specific to humans, characterized by its neurotropism and dermatotropism (1). This virus establishes latency in nerve ganglia and causes 2 distinct diseases: varicella (commonly occurring in childhood) and HZ (typically occurring in adulthood). The pathogenicity of VZV is associated with high morbidity (2), multiple risk factors, and severe sequelae (3).

Zoster-associated pain (ZAP) is a hallmark clinical manifestation during the acute phase of HZ as well as the postherpetic stage. The treatment of acute HZ relies primarily on antiviral drugs, along with analgesics and neurotrophic agents. Most existing antiviral drugs are nucleoside analogs, which have low bioavailability and may cause mitochondrial toxicity and drug resistance with prolonged use (4). These substances can even lead to acute renal failure, which limits their application significantly for patients with renal dysfunction, organ transplantation, or histories of long-term immunosuppressant use. Although the early administration of sufficient doses and a full course of antiviral drugs has a positive impact on suppressing VZV replication (5), accelerating the healing of herpes lesions, and relieving pain, these medications cannot prevent acute HZ from progressing to postherpetic neuralgia (PHN) (6). Currently, the primary goal of PHN treatment is pain relief. However, it has been reported that fewer than 50% of PHN patients achieve 50% relief in pain through conservative pharmacological therapy (7,8). Methods such as nerve blocks, botulinum toxin injections, transcutaneous electrical stimulation, pulsed radiofrequency (PRF), and spinal cord stimulation have been employed (9), but their overall efficacy remains unsatisfactory. Therefore, exploring an effective treatment strategy for PHN is of significant clinical importance.

Plasma is the fourth state of matter, distinct from solid, liquid, and gas. Low-temperature plasma (LTP) can generate high reactivity at low gas temperatures (below 40°C), enabling safe and effective disease treatment. As a result, LTP has been applied widely in various biomedical fields, including otorhinolaryngology, dentistry, and oncology. Our center's preliminary research applied LTP technology to the treatment of ZAP (10,11) and found that this technology effectively alleviated patients' symptoms. However, a small subset of patients experiences suboptimal outcomes, with limited pain relief following LTP treatment. Therefore, this study was conducted to investigate the efficacy of LTP in treating ZAP, analyze the risk factors for poor therapeutic response, establish a predictive model, and offer validation to provide support for making clinical decisions.

Methods

Study Design and Patients

This was a single-center, prospective cohort study. The participants were recruited from hospitalized patients in the Pain Department of Zhongda Hospital, Southeast University. All patients signed informed consent forms for the procedure. The study was approved by the Ethics Committee of Zhongda Hospital, Southeast University. Participants included ZAP patients who underwent LTP treatment and met the inclusion criteria during the period spanning January 2018 to December 2023.

The inclusion criteria were as follows: age ≥ 50 years; disease duration ≥ one month; meeting the diagnostic criteria for HZ-related pain; moderate or severe pain (VAS ≥ 4/10); persistent chronic pain lasting more than half a day during the disease course; ability to cooperate with treatment and follow-up; having signed informed consent forms prior to treatment.

Exclusion criteria consisted of the following characteristics: systemic or surgical site infection; severe dysfunction of the heart, lungs, liver, or kidneys; concurrent chronic pain disorders; coagulopathy or bleeding disorders; mental disorders or inability to cooperate with the procedure; having undergone other surgical treatments within the past month.

Study Protocol and Procedure

Upon hospital admission, the patients underwent relevant blood tests, including hematological examinations, comprehensive biochemical panels, high-sensitivity C-reactive protein (hs-CRP) tests, and fibrinolytic function analyses. All patients received minimally invasive LTP surgical treatment.

The procedures for the head and facial regions (trigeminal ganglion/sensory nerve root) were as follows: The patient was positioned supine on the operating table with the head tilted back. The affected side of the head and face was disinfected, and a sterile drape was applied. A needle was inserted one cm outside the corner of the mouth and advanced to the external opening of the foramen ovale. Needle advancement was stopped upon reaching the foramen ovale, and aspiration was performed to confirm the absence of blood or cerebrospinal fluid. The stylet was then withdrawn, and a specialized plasma ablation probe was inserted through the cannula of the puncture needle. The plasma ablation probe was connected to the plasma generator, which was set to level 3. The position of the probe tip at the external opening of the foramen ovale was confirmed again, guided by CT imaging. Plasma ablation was performed at 60-degree intervals, with each treatment point ablated for 10 seconds followed by 10 seconds of electrocoagulation. After the ablation was completed, the needle was withdrawn.

Procedure for the Chest, Back, and Limbs (Dorsal Root Ganglion)

The patient was positioned prone or lateral on the operating table. Based on the extent of the skin lesions, the target point was determined as the nerve segment near the lower edge of the lesions. The skin entry point was marked, followed by local disinfection and placement of sterile drapes. Local infiltration anesthesia was performed using 1% lidocaine. A specialized puncture needle was inserted at an angle. Under CT guidance, the needle was confirmed to be near the dorsal root ganglion. After blood and cerebrospinal fluid were confirmed to be absent upon aspiration, the stylet of the puncture needle was removed, and a specialized plasma electrode was inserted. The electrode was connected to the plasma generator, which was set to level 3. The position of the electrode was confirmed again, guided by imaging. Plasma ablation was performed at 60-degree intervals, with each treatment point ablated for 10 seconds followed by 10 seconds of electrocoagulation. After the ablation was completed, the needle was withdrawn.

Data Collection

Each patient's gender, age, height, weight, disease duration, medical history (hypertension, diabetes, coronary heart disease, cerebral infarction, etc.), herpes location, and previous treatments were recorded.

Upon admission, the patients were evaluated on the Visual Analog Scale (VAS), Dermatology Life Quality Index (DLQI), Pittsburgh Sleep Quality Index (PSQI), Hamilton Anxiety Scale (HAMA1), HAMA2, and Barthel Index. To assess the long-term efficacy of the LTP procedure, 3-month and 6-month follow-ups were scheduled after the operation. The patoents returned to the hospital as scheduled, where their VAS scores were assessed by health care professionals.

Statistical Analysis

For continuous variables that met a normal distribution or approximated doing so, data were presented as mean ± SD, and an independent sample t-test was used for comparisons between the 2 groups. For variables with a skewed distribution, data were presented as the median (interquartile range), and the rank-sum test was applied for comparisons between the groups. Categorical data were expressed as N (%), and inter-group comparisons were conducted using the chi-square test or Fisher's exact test. For risk factor analysis, variables with significant differences were included in stepwise regression to identify independent influencing factors. Cross-validation was performed to select the dataset with a more reasonable fit for model training and validation. The performance of the model was evaluated using the ROC and AUC; and calibration and clinical applicability were assessed with a calibration curve and a decision curve, respectively.

Results

Basic Patient Information

A total of 120 patients were included in this study, consisting of 54 women and 66 men, with an average age of 72.98 ± 9.52 years and an average body mass index (BMI) of 23.93 ± 3.51. Among all patients who underwent LTP treatment, after a 6-month follow-up, 39 still exhibited signs of chronic pain (VAS $\geq$ 4), while 81 patients showed no significant symptoms, resulting in a response rate of 67.5%. A total of 43 variables were recorded. The basic statistical data are presented in Table 1.

Table 1. *General information about patients included in the analysis.*

Factors	Non-Chronic Pain (n = 81)	Chronic Pain (n = 39)	Overall (n = 120)	Statistics	*P*
Age	71.22 ± 9.67	76.62 ± 8.15	72.98 ± 9.52	-3.004	0.003
Gender				0.031	0.860
F	36 (44.4)	18 (46.2)	54 (45.0)		
M	4 (55.6)	21 (53.8)	66 (55.0)		
BMI	23.91 ± 3.31	23.95 ± 3.93	23.93 ± 3.51	-0.061	0.951
Allergy				1.563	0.211
No	74 (91.4)	38 (97.4)	112 (93.3)		
Yes	7 (8.6)	1 (2.6)	8 (6.7)		
DM				0.183	0.669
No	67 (82.7)	31 (79.5)	98 (81.7)		
Yes	14 (17.3)	8 (20.5)	22 (18.3)		
Hypertension				2.692	0.101
No	42 (51.9)	14 (11.7)	56 (46.7)		
Yes	39 (48.1)	25 (64.1)	64 (53.3)		
CHD				4.586	0.032
No	71 (87.7)	28 (71.8)	99 (82.5)		
Yes	10 (12.3)	11 (28.2)	21 (17.5)		
Tumor				0.266	0.606
No	70 (86.4)	35 (89.7)	105 (87.5)		
Yes	11 (13.6)	4 (10.3)	15 (12.5)		
DIS				0.570	0.450
No	67 (82.7)	30 (76.9)	97 (80.8)		
Yes	14 (17.3)	9 (23.1)	23 (19.2)		
IND				0.007	0.935
No	69 (85.2)	33 (84.6)	102 (85)		
Yes	12 (14.8)	6 (15.4)	18 (15)		
ISD				0.280	0.597
No	75 (92.6)	35 (89.7)	110 (91.7)		
Yes	6 (7.4)	4 (10.3)	10 (8.3)		
Course (Month)	2 (1, 8)	4 (2, 18)	2 (1, 9)	-2.674	0.007
Primary Site				1.576	0.455
1	14 (17.3)	4 (10.3)	18 (15)		
2	54 (66.7)	26 (66.7)	80 (66.7)		
3	13 (16)	9 (23.1)	22 (18.3)		
Pre-Treatment				3.610	0.057
1	33 (40.7)	9 (23.1)	42 (35.0)		
2	48 (59.3)	30 (76.9)	78 (65.0)		
Albumin 1 (g/L)	39 ± 4.07	38.42 ± 4.22	38.83 ± 4.1	0.754	0.452
Albumin 2 (mg/L)	197.8 (0.28, 222.7)	185.3 (0.29, 219.2)	187.3 (0.28, 222.3)	-0.670	0.503
AGR	1.76 ± 0.35	1.59 ± 0.34	1.7 ± 0.35	2.435	0.016
SAP (U/L)	77.01 ± 35.75	73.97 ± 23.14	76.03 ± 32.13	0.484	0.630

Intergroup Differences in Variables

As shown in Table 1, between the chronic pain group and the nonchronic pain group, significant differences were observed in age, CHD, course, AGR, WBC, neutrophil levels, and scores on the VAS, DLQI, PSQI, HAMA1, HAMA2, and Barthel Index ($P < 0.05$). The *P*-value for the difference in pre-treatment was close to the critical value ($P = 0.057$), suggesting a potential difference as well.

Risk Factor Analysis

The variables identified as having significant differences were included in a multivariate stepwise regression analysis. The bidirectional stepwise regression found that CHD, AGR, PSQI, and HAMA1 were independent risk factors for the development of postoperative chronic pain (Table 2).

Model Construction Based on Independent Risk Factors

Using 3 cross-validation methods, we constructed logistic regression-based predictive models incorporating the aforementioned independent risk factors. The ROC curve for the model was then generated. The results showed that the AUCs for the training set were 0.782 (95% CI: 0.670-0.985), 0.704 (95% CI: 0.699-0.908), and 0.817 (95% CI: 0.700-0.934), with sensitivities of 75.9%, 66.7%, and 63.6% and specificities of 76.5%, 84.9%, and 89.7%, respectively. For the validation set, the AUCs were 0.750 (95%

CI: 0.564-0.935), 0.771 (95% CI: 0.592-0.950), and 0.765 (95% CI: 0.609-0.920), with sensitivities of 50%, 66.7%, and 58.8% and specificities of 76.7%, 78.6%, and 73.9% (Table 3). The calibration curve demonstrated good calibration, while the decision curve showed an ideal range for decision probabilities (Figs. 1-5).

Table 1 cont. *General information about patients included in the analysis.*

Factors	Non-Chronic Pain (n = 81)	Chronic Pain (n = 39)	Overall (n = 120)	Statistics	*P*
UA (μmol/L)	298.12 ± 88.67	319.03 ± 90.28	304.92 ± 89.36	-1.202	0.232
Glucose (mmol/L)	5.53 ± 1.98	5.37 ± 1.23	5.48 ± 1.77	0.459	0.647
Cholesterol (mmol/L)	4.53 ± 1.1	4.51 ± 1.21	4.52 ± 1.13	0.058	0.954
Triglyceride (mmol/L)	1.67 ± 1.13	1.51 ± 0.79	1.62 ± 1.03	0.841	0.402
ApoA1 (g/L)	1.26 ± 0.27	1.23 ± 0.27	1.25 ± 0.27	0.572	0.284
ApoB (g/L)	0.87 ± 0.25	0.85 ± 0.26	0.86 ± 0.25	0.367	0.357
HDL (mmol/L)	1.26 ± 0.37	1.25 ± 0.34	1.26 ± 0.36	0.076	0.470
LDL (mmol/L)	2.55 ± 0.86	2.46 ± 0.87	2.52 ± 0.86	0.515	0.304
Lipoprotein (mg/L)	172 (98, 369.5)	284 (105, 402)	210.5 (100.5, 387.75)	-1.353	0.176
FIB (g/L)	3.25 ± 0.8	3.12 ± 0.75	3.2 ± 0.78	0.818	0.208
D2 (μg/L)	274 (170, 572)	387 (215, 726)	283 (196.25, 611.5)	-1.402	0.161
CRP (mg/L)	1.29 (0.47, 3.31)	1.58 (0.46, 3.4)	1.31 (0.46, 3.39)	-0.269	0.788
WBC (10^9/L)	5.69 ± 2.03	6.42 ± 2.07	5.93 ± 2.06	-1.818	0.036
Neutrophil (10^9/L)	3.58 ± 1.66	4.15 ± 1.89	3.77 ± 1.75	-1.678	0.048
Lymphocyte (10^9/L)	1.56 ± 0.6	1.64 ± 0.58	1.58 ± 0.59	-0.724	0.235
Monocyte (10^9/L)	0.41 ± 0.16	0.42 ± 0.18	0.41 ± 0.16	-0.107	0.457
Eosinophil (10^9/L)	0.11 (0.07, 0.17)	0.12 (0.06, 0.19)	0.11 (0.07, 0.18)	-0.508	0.612
TB (μmol/L)	10.9 (7.65, 14.95)	9.1 (7, 13.8)	10.7 (7.5, 14.7)	-0.989	0.323
VSA	7.07 ± 1.24	7.56 ± 1.1	7.23 ± 1.21	-2.100	0.019
DLQI	11 (9, 18)	17 (10, 20)	13 (10.18)	-2.271	0.023
PSQI	11.42 ± 3.7	13.72 ± 3.44	12.17 ± 3.77	-3.342	< 0.001
HAMA1	8 (5, 11)	12 (7, 16)	9 (5, 14)	-2.849	0.004
HAMA2	7 (4, 10.5)	10 (6, 16)	8 (4, 13)	-2.617	0.009
Barthel	87.04 ± 13.71	77.44 ± 18.63	83.92 ± 16.05	2.866	0.003

Discussion

Summary of Key Findings

This study conducted a 6-month follow-up of 120 patients with ZAP who received LTP treatment. The results showed that 81 of the patients achieved satisfactory outcomes, while 39 patients experienced a recurrence of pain after temporary relief. Effectively improving such patients' symptoms remains a significant challenge in the treatment of ZAP. To further explore the predictive factors for the efficacy of LTP treatment in patients with ZAP, we analyzed 43 variables and identified significant differences in age, CHD, course, AGR, WBC, neutrophil levels, and scores on the VAS, DLQI, PSQI, HAMA1, HAMA2, and Barthel Index ($P < 0.05$). Subsequently, with the use of bidirectional stepwise regression, 4 independent factors significantly associated with persistent post-treatment chronic pain were identified: CHD, AGR, and PSQI and HAMA1 scores. Based on these variables, we constructed a predictive model that demonstrated ideal sensitivity and specificity in cross-validation, providing valuable reference data for the personalized treatment of affected patients.

Table 2. *Independent risk factors for the development of chronic pain.*

Factors	B	OR	95% CI
CHD	1.237	3.445	1.123-10.574
AGR	-2.124	0.120	0.031-0.465
PSQI	0.185	1.203	1.045-1.385
HAMA1	0.112	1.119	1.030-1.215

Comparison with Other Studies

Treatment options for ZAP include pharmacological therapies, acupuncture, and minimally invasive interventions. Pharmacological treatment aims primarily to relieve pain. Opioids are the most common initial

Table 3. *Cross-validation*.

Cross-Validation	Training Set				Validation Set		
	Threshold	AUC (95% CI)	Sen	Spe	AUC (95% CI)	Sen	Spe
Fold 1	0.431	0.782 (0.670-0.985)	0.759	0.765	0.750 (0.564-0.935)	0.500	0.767
Fold 2	0.472	0.704 (0.699-0.908)	0.667	0.849	0.771 (0.592-0.950)	0.667	0.786
Fold 3	0.398	0.817 (0.700-0.934)	0.636	0.897	0.765 (0.609-0.920)	0.588	0.739
Mean	0.434	0.768	0.687	0.837	0.762	0.585	0.764

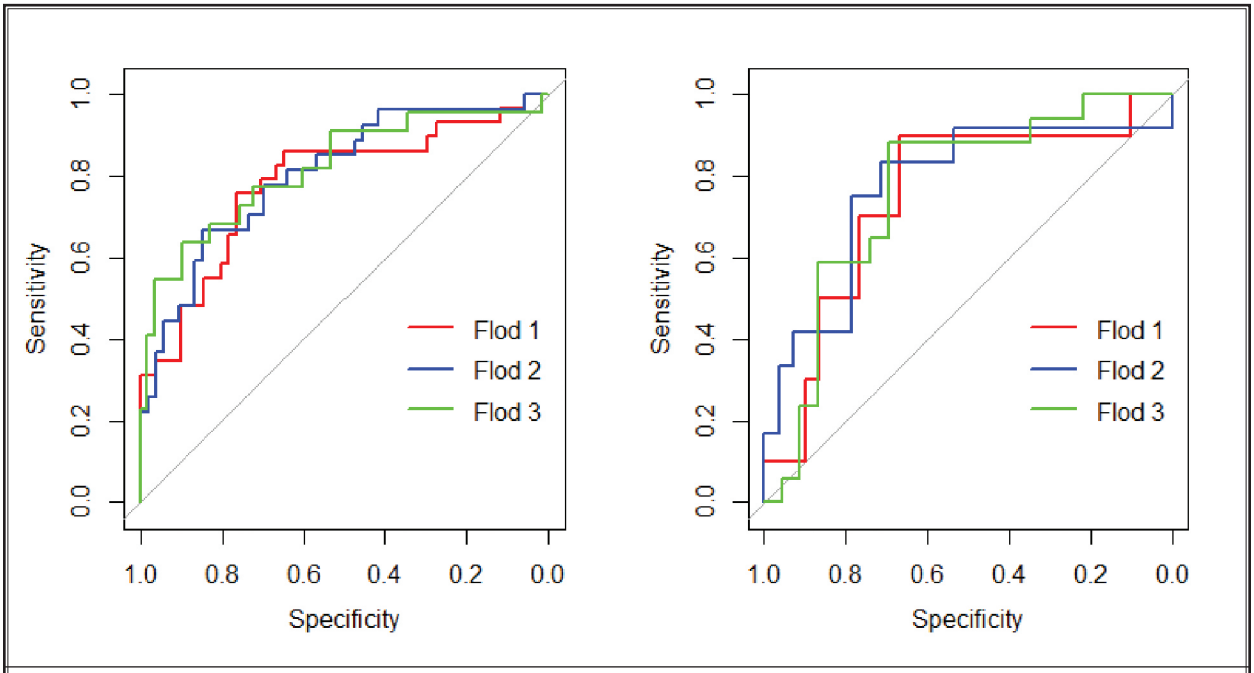

Fig. 1. *ROC curve of logistic regression in the training and validation models.*

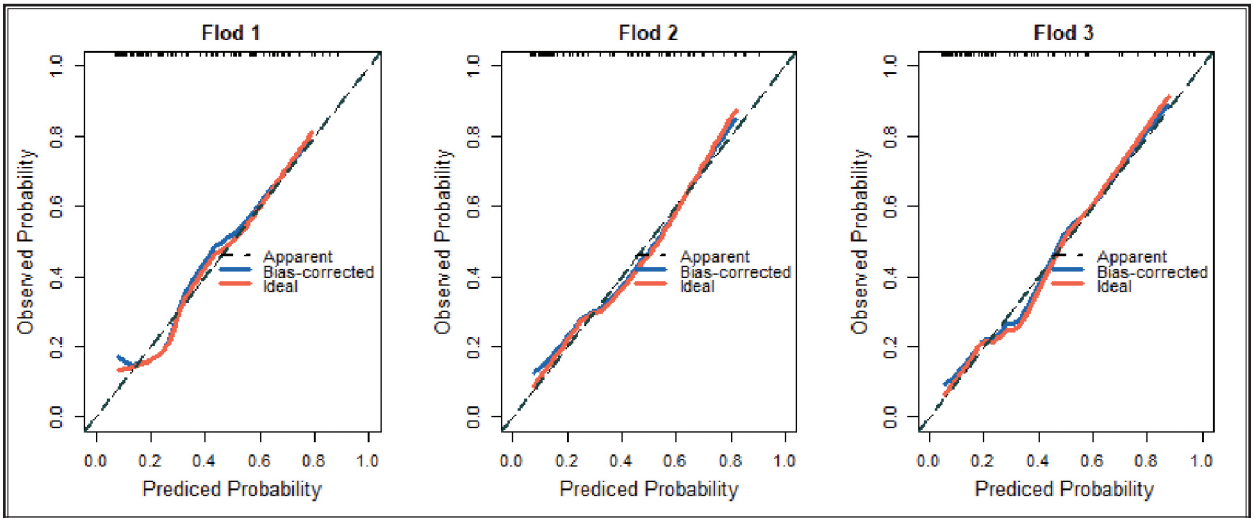

Fig. 2. *Calibration curves for the training models.*

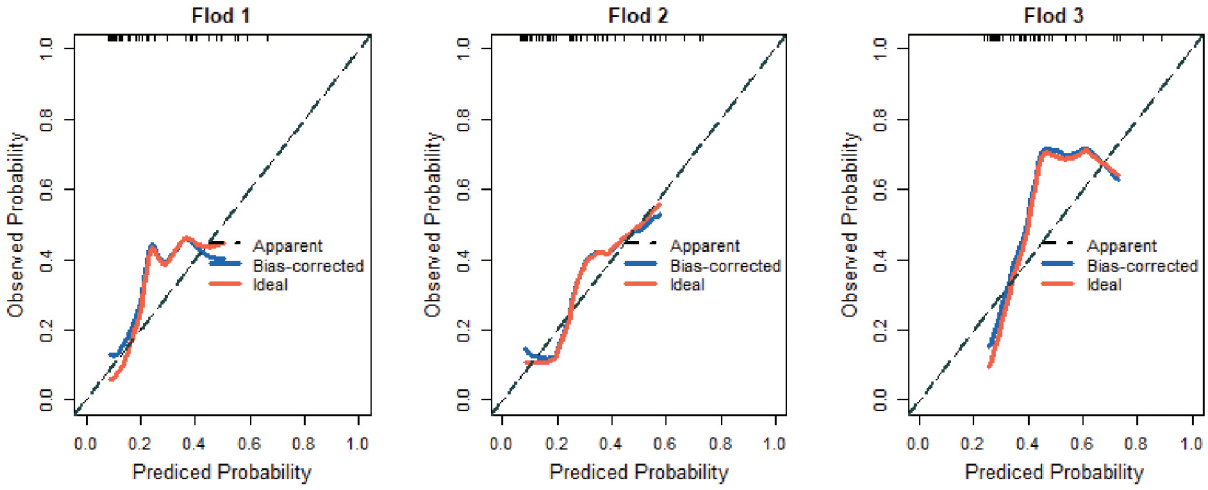

Fig. 3. *Calibration curves for the validation models.*

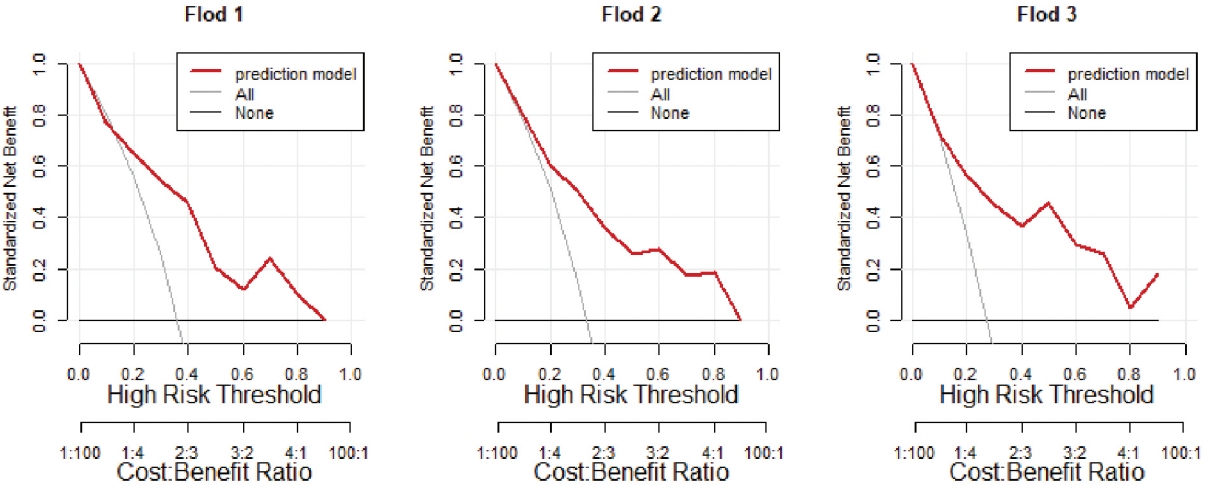

Fig. 4. *Decision curve analysis for the training models.*

prescription for PHN (12), but studies have shown insufficient evidence for their efficacy in treating neuropathic pain and PHN (13). Other medications, such as calcium channel modulators (pregabalin, gabapentin), tricyclic antidepressants (amitriptyline), and 5% lidocaine patches, have also been used, but the overall efficacy of conservative pharmacological treatments remains unsatisfactory (7,8).

Interventional treatments, the primary choice when conservative treatments are inadequate, include nerve blocks, botulinum toxin injections, PRF, and spinal cord stimulation. Nerve blocks have been shown to be effective (14), but the duration of symptom relief associated with them is often short. In one study, botulinum toxin type A injections demonstrated a 50% response rate at a 3-month follow-up; however, that study was limited by a small sample size (50 patients) and a lack of efficacy data and follow-up over the long term (15). PRF relieves pain by releasing energy in intermittent pulses, thereby raising the temperature of local tissues to modulate neuronal electrical activity and nerve signal transmission. For patients with chronic PHN, the response rate associated with PRF has been reported as 52% (16). In comparison, the LTP technology we employed demonstrated significant advantages. Its low-temperature nature results in less tissue damage, while

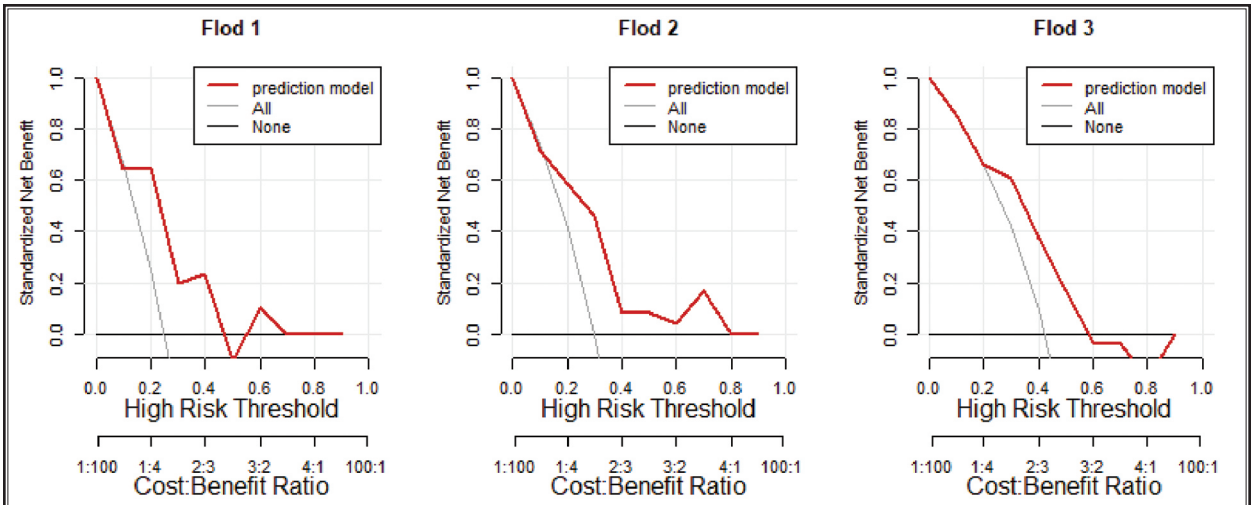

Fig. 5. *Decision curve analysis for the testing models.*

the array of active factors generated by plasma can exert physicochemical therapeutic effects more effectively. Additionally, patients treated with plasma technology do not typically experience side effects such as local tissue numbness or temporary sensory loss, which is a highlight of this approach. Spinal cord stimulation (SCS) is also applied in certain cases. A meta-analysis showed that 41.1% of PHN patients achieved effective pain relief, with pain relief exceeding 50% after SCS treatment (17). However, the high cost of SCS makes it inaccessible for many patients. Additionally, the procedure carries notable risks of postoperative complications, including infection, epidural hematoma formation, electrode migration, and fractures, all of which can cause considerable harm to the patient. Therefore, careful evaluation is required prior to the use of SCS in clinical practice.

In this research, efficacy was defined using the VAS score, with a score ≥ 4 indicating poor therapeutic response. This criterion was established primarily to facilitate quantification and ensure the consistency of the results. However, this criterion may seem more conservative when compared to the clinical remission standards that are typically employed. In clinical practice, the efficacy of minimally invasive surgery for postherpetic neuralgia is typically assessed by clinical remission rate, defined as significant pain reduction and improved quality of life, rather than relying solely on absolute VAS scores. In accordance with established literature (5,7), pain relief criteria were as follows: complete remission was defined as a VAS score of 0, indicating complete absence of pain; significant remission was defined as a ≥ 50% reduction in VAS score, with notable relief of symptoms; partial remission was defined as a 20%-50% reduction in VAS score, with symptom alleviation but incomplete control; and no response was defined as a minimal change in VAS score or a reduction of < 20%. Based on clinically relevant response criteria, the study yielded a complete remission rate of 11.7%, a marked remission rate of 62.5%, a partial remission rate of 21.6%, and a nonresponse rate of 3.3%. These results are considered favorable in clinical research.

Discussion of Risk Factors

CHD

Studies have shown a significant association between CHD and ZAP, with the former identified as one of the high-risk factors for the latter. The onset of HZ is linked to the reactivation of the VZV, which can spread not only through peripheral nerve fibers but also infect cerebral and coronary arteries, triggering inflammation and thereby leading to vascular lesions (18,19). A systematic review and meta-analysis revealed that chronic diseases, including cardiovascular diseases, increase the risk of HZ significantly (20). Specifically, the incidence of HZ is 1.14 times higher in patients with CHD than in those without CHD (21). This association may be related to factors commonly observed in CHD patients, such as chronic inflammation, immune dysfunction, and endothelial dysfunction, highlighting the critical role of inflammation and immune imbalance in the disease pathogenesis.

AGR

AGR is an important indicator reflecting the inflammatory status and immune balance of the body and is closely associated with the occurrence and prognosis of various diseases. Although no studies have linked AGR with ZAP directly, it is well known that chronic inflammation and immune dysfunction are key mechanisms in the pathogenesis of HZ. A low AGR, typically characterized by decreased albumin levels and/or elevated globulin levels, indicates an aggravated systemic inflammatory state and disrupted immune regulation (22). Cell-mediated immunity, particularly T-cell activity, plays a crucial role in controlling the latency and reactivation of VZV. Immune dysfunction, such as impaired T-cell function, increases the risk of HZ and ZAP significantly.

Several studies have demonstrated that low AGR is closely associated with poor prognoses in various inflammation-related diseases, including major cardiovascular events, cancer, and chronic kidney disease (23). While serum albumin, globulin levels, and lymphocyte counts can also reflect inflammation, these biomarkers are highly susceptible to confounders, which limits their accuracy (24). As a stable biomarker that reflects inflammation and immune status comprehensively, AGR provides a more accurate assessment of HZ risk than does the individual use of albumin or globulin. Therefore, AGR may serve as an important risk predictor for ZAP. Early monitoring and intervention targeting AGR could provide more precise prevention and management strategies for high-risk populations.

PSQI

PSQI is a simple, reliable, and multidimensional tool for evaluating sleep quality, which plays a significant role in studying the relationship between sleep and the onset and progression of diseases. Although studies linking PSQI directly to HZ are limited, existing evidence has suggested that the connection between PSQI and ZAP may primarily involve the impact of sleep quality on immune function and inflammation. A bidirectional relationship exists between sleep and the immune system (25). Sleep deprivation or poor sleep quality can impair adaptive and innate immune responses by disrupting the circadian rhythm of cytokines and T-cell function, while simultaneously increasing low-grade inflammation (25,26). These 2 factors are high-risk triggers for the onset of ZAP. A Mendelian randomization study investigating the association between 731 immune cells and insomnia identified significant causal relationships between insomnia risk and 14 immune cell traits (27). Furthermore, sleep disturbances or inadequate sleep (such as short sleep duration) can increase the likelihood of viral infections, which may also explain why patients with sleep problems are more prone to persistent ZAP.

HAMA1

Anxiety and chronic pain interact via shared neural mechanisms. Through mechanisms such as overlapping neural networks, synaptic plasticity changes, and enhanced descending modulation, anxiety amplifies pain perception and prolongs pain duration, making anxiety one of the significant risk factors for chronic pain (28). Anxiety not only transmits pain signals via neurotransmitters but also affects inflammatory cytokines and immunosuppression, contributing to the development of chronic pain under multiple factors (29).

Various studies have shown that in surgeries such as joint replacement, minimally invasive thoracic surgery (30), and breast cancer surgery (31), patients with preoperative anxiety and insomnia experienced more severe postoperative pain (32). A comprehensive meta-analysis encompassing 29 studies revealed that 16 studies (55%) established a direct correlation between preoperative anxiety and subsequent development of persistent postoperative chronic pain (33). This is consistent with our findings.

In summary, CHD, AGR, PSQI, and HAMA1 are closely associated with the development of chronic pain and exert a significant influence on the effectiveness of pain management. Based on our study, while these factors may influence the efficacy of LTP, they may not be the sole determinants of the outcome of the treatment. In alternative treatment approaches, such as seen in a study that used a combination of medication and nerve block therapy to treat ZAP (34), NRS scores, RBC counts, and cancer-related complications were identified as risk factors for poor prognosis. According to the predictive model Peng et al developed for identifying risk factors associated with inadequate postoperative pain relief experienced by ZAP patients who receive PRF treatment (35), gender, HZ stage, pregabalin dosage, SF-36 scores, lymphocyte count, low-density lipoprotein cholesterol (LDL-C), and complement C4 in peripheral blood are risk factors after PRF therapy. Consequently, future therapeutic strategies should emphasize personalized approaches that incorporate individual high-risk factors to optimize treatment regimens, thereby improving therapeutic efficacy and patients' quality of life.

Discussion of Models

Due to the refractory nature of ZAP, other related studies have also conducted independent risk factor analyses and established predictive models for the condition. Sun et al (36) analyzed the risk factors and predictive model for poor pain control in ZAP patients receiving combinations of drug therapy and nerve block treatment, using a multivariable logistic regression model. The model's AUC was 0.730, indicating a moderate predictive performance. Tang et al (34) investigated the relationship between electrophysiological indicators (CMAP and SNAP amplitudes) and the severity of upper-limb HZ as well as the prognosis of PHN. The AUCs for predicting outcomes using CMAP and SNAP individually were 0.657 and 0.773, respectively, while the combined prediction yielded an AUC of 0.785, demonstrating superior predictive performance over individual indicators. Peng et al (35) developed a model using LASSO regression to evaluate the efficacy of PRF treatment for ZAP. The model achieved an AUC of 0.701, with a sensitivity of 90% and an overall accuracy of 73%. In comparison to the studies mentioned above, the present study constructed a predictive model based on logistic regression with 3 types of cross-validation. Despite comparable AUC values ranging from 0.7 to 0.8, this model exhibited superior robustness and reliability through enhanced resistance to overfitting and improved model stability.

Thus, we conclude that the approach used in the present study exhibits a high degree of replicability. The model development in this study adhered to established statistical modeling procedures, encompassing variable selection, model selection, cross-validation, and performance evaluation (e.g., ROC curve analysis and AUC calculation). This modeling procedure can be implemented readily by other investigators to predict the treatment efficacy of various therapeutic modalities, including but not limited to radiofrequency ablation and spinal cord stimulation. Nevertheless, it is important to recognize that although our modeling framework demonstrates strong generalizability, the mechanisms underlying pain relief may differ across various therapeutic modalities. This variability could result in differences in the critical variables that affect treatment efficacy. Therefore, to apply the model to alternative therapeutic interventions, it is imperative that the model be updated and retrained based on data derived from the new treatment modality. This process necessitates the recollection of patient data specific to the new treatment protocols, reevaluation of feature selection, and subsequent model recalibration to optimize predictive accuracy in the novel therapeutic setting.

Therefore, future studies can build upon this foundation by employing the same modeling framework and incorporating data from alternative therapeutic interventions to retrain and validate the model. Doing so is expected to improve the model's generalizability and, importantly, to facilitate in-depth exploration of the shared characteristics and unique effects of various treatment modalities in pain management, thereby informing more individualized and evidence-based clinical decisions.

Limitations

The use of LTP technology to treat ZAP is a relatively novel therapeutic approach and remains in the exploratory stage. Further research is needed to investigate this technology's mechanisms and efficacy in greater depth. Secondly, although the predictive model in this study demonstrated relatively favorable sensitivity and stability, the limited number of cases imposes significant constraints on the discussion of the model. In future studies, we will expand the sample size further and, based on the independent risk factors identified in this study, incorporate inflammatory factors and immune-related indicators to deepen the research and exploration of LTP treatment for ZAP.

Conclusion

This study innovatively employed LTP technology to treat ZAP, analyzed the technique's risk factors, and constructed a predictive model. The results showed that 67.5% of patients achieved satisfactory therapeutic outcomes after treatment. CHD, AGR, and PSQI and HAMA1 scores were identified as independent risk factors for the development of chronic postoperative pain. The predictive model demonstrated favorable sensitivity and specificity, offering a solid objective basis for enhancing the therapeutic efficacy of ZAP treatment. The model also provides clinicians with innovative insights and strategies for designing personalized treatment plans.

Author Contributions

All authors contributed to the study conception and design. Zhao Gao contributed conceptualization, software use, and reviewing and editing of the writing. Chengxi Xi curated the data. Hao Zhou operated the

software and provided validation. Jinxia Yin supervised the study. Youwei Li operated the software. Yanjun Sun contributed to the methodology, supervision, and project administration. All authors commented on previous versions of the manuscript in addition to reading and approving its final form.

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