

Transcutaneous Auricular Vagus Nerve Stimulation for Acute Herpes Zoster in Middle-Aged and Older Adults With Depressive and/or Anxiety Symptoms: A Prospective, Multicenter, Observational Cohort Study

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Abstract

Background

Acute herpes zoster (HZ) causes severe pain and frequently progresses to postherpetic neuralgia (PHN), especially in middle-aged and older adults with comorbid depressive or anxiety symptoms.

Transcutaneous auricular vagus nerve stimulation (taVNS) has emerging analgesic and affective benefits, but its adjunctive value in acute HZ remains unclear.

Methods

In this prospective, multicenter, observational cohort study (ChiCTR2100045232), 122 adults aged ≥ 50 years with acute HZ and screen-positive depressive and/or anxiety symptoms were enrolled. Sixty-two patients received adjunctive taVNS (30 min, twice daily, 14 days) plus conventional therapy; 60 received conventional therapy alone. The primary outcome was VAS pain score change from baseline to Day 7. Secondary outcomes included responder rates, pain trajectory, 90-day cumulative pain burden, PHN, emotional and sleep outcomes, and rescue analgesic consumption.

Results

The primary outcome did not differ significantly (adjusted difference 0.33 points; $P = 0.245$). However, taVNS recipients showed significantly faster pain resolution at Weeks 1 and 2 (both $P < 0.05$) and lower 90-day cumulative pain burden (93.1 vs 138.3 VAS·days; $P = 0.023$). Anxiety remitted more rapidly (GEE interaction $P < 0.001$), with higher Week-2 screen-negative rates (85.1% vs 37.8%; adjusted OR 13.57; $P < 0.001$). ISI improvement was greater (adjusted difference 3.75 points; $P < 0.001$). Rescue analgesic consumption was lower (rate ratio 0.40; $P = 0.036$). PHN at Day 90 was numerically lower (8.1% vs 20.0%; $P = 0.128$). No serious adverse events occurred.

Conclusion

Adjunctive taVNS was associated with faster acute pain resolution, lower cumulative pain burden, marked anxiety and sleep improvement, and reduced rescue analgesic use, without serious adverse events. Randomized sham-controlled trials are warranted.

1. Introduction

Herpes zoster (HZ) results from the reactivation of latent varicella-zoster virus in dorsal root or cranial nerve ganglia, producing a painful dermatomal vesicular rash that affects approximately 1–3 per 1,000 person-years in the general population and up to 10 per 1,000 person-years among adults aged 65 years and older^{1,2}. Although the acute rash typically resolves within two to four weeks, a substantial proportion

of patients develop persistent neuropathic pain—postherpetic neuralgia (PHN)—defined as pain persisting beyond 90 days from rash onset^{3,4}. PHN affects 5–30% of HZ patients and is among the most common and refractory chronic neuropathic pain conditions, imposing a heavy burden on quality of life, sleep, mood, and healthcare utilization^{5,6}.

The management of acute HZ relies on prompt initiation of antiviral therapy (valacyclovir, famciclovir, or acyclovir) within 72 hours of rash onset, combined with analgesics ranging from acetaminophen and non-steroidal anti-inflammatory drugs to gabapentinoids, tricyclic antidepressants, and opioids for severe cases^{7,8}. Despite these interventions, acute pain control is frequently inadequate, and current treatments do not reliably prevent the transition from acute to chronic pain. Identifying adjunctive therapies that simultaneously address pain, affective distress, and sleep disturbance—domains that are pathophysiologically intertwined in HZ—remains an unmet clinical need^{9,10}.

Psychological distress is increasingly recognized as both a consequence and a predictor of poor HZ outcomes. Prospective data demonstrate that severe acute pain, prodromal pain, and psychosocial factors—including anxiety, depression, and sleep disturbance—are independent risk factors for PHN development^{6,11}. The neurobiological substrate linking these domains involves shared central sensitization mechanisms, dysregulation of the hypothalamic-pituitary-adrenal axis, and impaired descending noradrenergic and serotonergic pain inhibition¹². Interventions that modulate these central circuits may therefore offer benefits across pain, mood, and sleep simultaneously.

Transcutaneous auricular vagus nerve stimulation (taVNS) is a non-invasive neuromodulation technique that delivers low-frequency electrical current to the auricular branch of the vagus nerve, predominantly at the cymba conchae, which receives exclusive vagal afferent innervation¹³. Accumulating evidence from mechanistic and clinical studies indicates that taVNS can enhance descending pain inhibition, reduce pro-inflammatory cytokine release, modulate heart rate variability as a proxy of parasympathetic tone, and influence limbic activity including the amygdala, anterior cingulate cortex, and nucleus tractus solitarius¹⁴. Small randomized trials and meta-analyses have reported analgesic benefits of taVNS in radiotherapy-induced neuropathic pain, postpartum contraction pain, perianal postoperative pain, and systemic lupus erythematosus, and emerging data support its use in depressive disorders, anxiety, and chronic insomnia¹⁵.

Despite this convergent rationale, the adjunctive value of taVNS in acute HZ—a condition characterized by the simultaneous presence of severe acute pain, emotional distress, and sleep disturbance—has not been systematically evaluated. We therefore conducted a prospective, multicenter, observational cohort study to evaluate whether adjunctive taVNS, added to conventional antiviral and analgesic therapy, improves acute pain, emotional distress, sleep disturbance, and longer-term PHN incidence in middle-aged and older adults with acute HZ and screen-positive depressive and/or anxiety symptoms. We pre-specified a comprehensive analytical framework including linear mixed-effects modeling of pain trajectories, area-under-the-curve (AUC) analysis of cumulative pain burden, generalized estimating

equations (GEE) for emotional symptom trajectories, inverse-probability-of-treatment-weighting (IPTW) sensitivity analysis, E-values for unmeasured confounding, and mediation analysis to explore whether emotional and sleep improvements contribute to pain outcomes.

2. Methods

2.1 Study design and registration

This prospective observational cohort study was registered at the Chinese Clinical Trial Registry (<https://www.chictr.org.cn>; Registration Number: ChiCTR2100045232; date of registration: 8 April 2021) and approved by the Ethics Committee of Xuanwu Hospital, Capital Medical University (Approval Code: KS2021[054]). The study consecutively enrolled middle-aged and older patients with acute HZ who initially presented at the dermatology clinic of Xuanwu Hospital between July 2022 and December September 2025. All participants provided written informed consent. All procedures were performed in accordance with the principles of the Declaration of Helsinki.

2.2 Participants

Consecutive patients presenting to the dermatology outpatient clinics of the participating centers between July 2022 and September 2025 were screened. Eligibility criteria were: (1) age ≥ 50 years; (2) acute HZ diagnosed within 7 days of rash onset, with characteristic dermatomal vesicular rash and confirmed by Tzanck smear or polymerase chain reaction when clinically ambiguous; (3) baseline Visual Analog Scale (VAS) pain score ≥ 4 (0–10 scale); (4) screen-positive depressive and/or anxiety symptoms, defined as Patient Health Questionnaire-2 (PHQ-2) ≥ 3 and/or Generalized Anxiety Disorder-2 (GAD-2) ≥ 3 [22,23]; (5) ability to provide informed consent and comply with the 90-day follow-up. Exclusion criteria were: (1) pregnancy or lactation; (2) cardiac pacemaker or implanted defibrillator; (3) active skin lesions at the auricular stimulation site; (4) severe cardiac, hepatic, or renal insufficiency; (5) known epilepsy; (6) cognitive impairment precluding questionnaire completion; (7) immunodeficiency requiring systemic antiviral dose adjustment; and (8) concurrent participation in another interventional trial.

2.3 Intervention

All patients who met the eligibility criteria received standard oral pharmacotherapy: acyclovir (Shanghai Sine Pharmaceutical Co., Ltd.; specification: 0.2 g/tablet) 0.8 g per dose, five times daily, and pregabalin (China Resources Double-Crane Pharmaceutical Co., Ltd.; specification: 75 mg/tablet) 75 mg per dose, twice daily. All patients voluntarily decided whether to receive taVNS. Patients in the taVNS group received 30-minute sessions twice daily for 14 consecutive days. The auricular vagus nerve stimulator used in this study (tvNS 501, Changzhou Ruishen'an Medical Devices Co., Ltd., Changzhou, China) is approved for the adjunctive treatment of anxiety disorders. The taVNS procedure was as follows: the skin over the left cymba conchae was routinely disinfected with alcohol, and the electrodes of the vagus nerve stimulator were placed at this site for electrical stimulation. The stimulation parameters were:

pulse frequency 30 Hz, pulse width 300 μ s, and pulse amplitude gradually increased from 0 over 30 seconds until the patient perceived a tolerable tingling sensation in the auricular skin, and then decreased over 15 seconds to the maximum tolerable level. The maximum pulse amplitude was 60. Treatments were administered by trained therapists. Patients in either the taVNS group or the control group whose pain remained inadequately controlled could receive ibuprofen/codeine compound tablets (each tablet containing ibuprofen 200 mg and codeine phosphate 12.5 mg) as needed for rescue analgesia. Patients were instructed to record the number of ibuprofen/codeine tablets taken each day.

2.4 Outcomes

The primary outcome was the change in VAS pain score (0–10) from baseline to Day 7 (end of Week 1). Secondary outcomes included: (1) responder rates at Day 7, defined as $\geq 30\%$ and $\geq 50\%$ reduction from baseline VAS; (2) pain trajectory from baseline to Day 90, assessed via linear mixed-effects modeling; (3) 90-day cumulative pain burden, quantified as the area under the VAS-time curve (AUC) using the trapezoidal method; (4) subacute pain (VAS > 0 at Day 30) and PHN (VAS > 0 at Day 90); (5) emotional symptom trajectories, assessed by PHQ-2 and GAD-2 at baseline and Week 2, with screen-positive status defined as ≥ 3 ; (6) sleep disturbance, assessed by the Insomnia Severity Index (ISI) at baseline and Week 2, with insomnia defined as ISI > 7 and clinically meaningful improvement defined as ≥ 6 -point reduction [24]; (7) rescue analgesic consumption (ibuprofen/codeine compound tablets) and analgesic escalation rates at Weeks 1 and 2, recorded in a detailed sub-cohort (n = 40); and (8) treatment-emergent adverse events throughout the 90-day follow-up.

2.5 Sample size

The sample size was calculated based on the primary outcome (Day-7 VAS change), with parameter estimates derived from a small-sample pilot study previously conducted by our team. Assuming a standard deviation of 2.0 points for VAS change, a difference of 1.0 point between groups, two-sided $\alpha = 0.05$, and 80% power, approximately 64 patients per group were required. To account for approximately 10% attrition, we planned to enroll 144 patients. The final analysis cohort comprised 122 patients who completed the 90-day follow-up without missing primary outcome data.

2.6 Statistical analysis

Continuous variables are presented as mean $\pm$ standard deviation (SD) or median with interquartile range (IQR) as appropriate, and categorical variables as counts and percentages. Between-group baseline comparisons used the independent-samples t-test or Mann-Whitney U test for continuous variables and the chi-square test or Fisher exact test for categorical variables. The primary outcome (Day-7 VAS change) was analyzed using multivariable linear regression adjusted for age, sex, baseline VAS, rash duration, and pain duration, with results expressed as adjusted mean differences with 95% confidence intervals (CIs). Responder rates were analyzed using multivariable logistic regression with the same covariates, expressed as adjusted odds ratios (ORs).

The pain trajectory from baseline to Day 90 was modeled using a linear mixed-effects model with random intercepts for participants, fixed effects for time (categorical: baseline, Week 1, Week 2, Day 30, Day 90), treatment group, group-by-time interaction, and covariates (age, sex, rash duration, pain duration). Baseline VAS was not included as a covariate because the baseline measurement is part of the outcome vector. The group-by-time interaction terms represent the additional VAS change in the taVNS group relative to the control group at each time point. The 90-day cumulative pain burden was computed as the area under the VAS-time curve using the trapezoidal rule, and compared between groups using linear regression adjusted for the same covariates.

Emotional symptom trajectories (PHQ-2 ≥ 3 and GAD-2 ≥ 3) were analyzed using generalized estimating equations (GEE) with a binomial distribution, logit link, and exchangeable working correlation structure, including group, time, group-by-time interaction, and covariates. Among patients with baseline screen-positive symptoms, Week-2 screen-negative status was analyzed using logistic regression. ISI change among patients with baseline insomnia (ISI > 7) was analyzed using linear regression, and ISI response (≥ 6 -point reduction) using logistic regression. Rescue analgesic consumption was analyzed using negative binomial regression (due to overdispersion), with results expressed as rate ratios (RRs).

Pre-specified sensitivity analyses included: (1) inverse-probability-of-treatment-weighting (IPTW) using a propensity score derived from baseline covariates (age, sex, rash duration, pain duration, baseline VAS, PHQ-2, GAD-2, ISI), to address potential confounding by indication; (2) E-values to quantify the minimum strength of unmeasured confounding required to explain away the observed associations; and (3) subgroup analyses stratified by age (≥ 65 vs < 65 years), sex, baseline VAS (≥ 6 vs < 6), diabetes status, and baseline insomnia status, with interaction testing. An exploratory mediation analysis was conducted using the Baron and Kenny framework to examine whether Week-2 GAD-2 change mediated the association between treatment group and Day-7 VAS change. Number needed to treat (NNT) was calculated as the reciprocal of the absolute risk reduction for binary outcomes. All statistical tests were two-sided, with $P < 0.05$ considered statistically significant. Given the observational design and multiple secondary outcomes, all findings other than the primary outcome should be considered hypothesis-generating, and no formal correction for multiple comparisons was applied; instead, we emphasize effect sizes and 95% confidence intervals. Analyses were performed using Python 3.12 (pandas, statsmodels, scipy) and R 4.3.0 (lme4, geepack).

2.7. Machine learning prediction and classification models

To explore the predictive value of baseline characteristics for clinically important outcomes, we developed and internally validated three supervised classification models and one unsupervised clustering model. The three prediction tasks were: (i) postherpetic neuralgia (PHN) at Day 90 (defined as VAS > 0), the most feared complication of herpes zoster; (ii) early treatment response at Day 7 (defined as $\geq 30\%$ VAS reduction from baseline), a clinically meaningful responder threshold; and (iii) anxiety remission at Week 2 (defined as GAD-2 < 3 among patients with baseline screen-positive anxiety, GAD-2 ≥ 3). Eighteen baseline features were used as candidate predictors, including demographic variables

(age, sex), disease characteristics (rash duration, pain duration, baseline VAS), psychosocial measures (PHQ-4, PHQ-2, GAD-2, ISI), eight comorbidity indicators, and treatment group assignment.

Four algorithms were compared for each prediction task: penalized logistic regression with L1 (LASSO) and L2 (ridge) regularization, random forest, gradient boosting, and support vector machine with radial basis function kernel. Hyperparameters were set a priori to favor parsimony and reduce overfitting given the modest sample size: logistic regression $C = 0.1$; random forest with 200 trees and maximum depth of 4; gradient boosting with 100 estimators and maximum depth of 2; SVM with default regularization. All features were standardized (z-score transformation) before model fitting. Model discrimination was assessed using the area under the receiver operating characteristic curve (AUC) with five-fold stratified cross-validation (repeated with fixed random seed for reproducibility), and calibration was evaluated using the Brier score. For the unsupervised analysis, K-means clustering was applied to the five-dimensional VAS trajectory (baseline, Day 7, Day 14, Day 30, Day 90) after standardization, with the optimal number of clusters determined by the silhouette coefficient for $k = 2-4$. All analyses were performed in Python 3.12 using scikit-learn 1.5.

3. Results

3.1 Study population and baseline characteristics

Between July 2022 and September 2025, 144 consecutive patients were screened for eligibility. Of these, 22 were excluded: 7 due to intolerance to adverse effects of conventional therapy, 6 due to antiviral regimen change rendering them ineligible, 6 in the taVNS group due to incomplete treatment cycle (non-compliance with the 14-day protocol), and 3 due to disease progression requiring hospitalization and withdrawal from the study protocol. The remaining 122 patients (62 in the taVNS group and 60 in the control group) completed the 90-day follow-up without missing primary outcome data and constituted the final analysis cohort.

All 122 patients completed the 90-day follow-up and had complete primary outcome data. The detailed sub-cohort of 40 patients (20 per group) had additional data on rescue analgesic consumption and nerve involvement distribution. Baseline characteristics were well balanced between the two groups (Table 1). The mean age was 65.7 years (SD 8.8), 50.8% were female, and the mean baseline VAS was 5.9 (SD 1.4). Screen-positive anxiety (GAD-2 ≥ 3) was present in 75.4% of patients, screen-positive depression (PHQ-2 ≥ 3) in 52.5%, and insomnia (ISI > 7) in 71.3%. Comorbid diabetes was present in 28.7%, cardiovascular disease in 47.5%, and COPD in 3.3%. The only baseline variable with a statistically significant between-group difference was rash duration (3.3 days in control vs 4.1 days in taVNS, $P = 0.034$), with taVNS patients having a slightly longer rash duration at presentation; this was adjusted for in all multivariable models.

Table 1
Baseline characteristics of the study population (N = 122)

Characteristic	Control (n = 60)	taVNS (n = 62)	P value
Age, years, mean $\pm$ SD	64.68 $\pm$ 8.48	66.60 $\pm$ 9.07	0.231
Female sex, n (%)	29 (48.3)	33 (53.2)	0.719
Rash duration, days, mean $\pm$ SD	3.28 $\pm$ 1.85	4.05 $\pm$ 2.09	0.034
Pain duration, days, mean $\pm$ SD	5.63 $\pm$ 2.88	5.35 $\pm$ 2.91	0.596
Diabetes mellitus, n (%)	16 (26.7)	19 (30.6)	0.775
Malignancy, n (%)	4 (6.7)	4 (6.5)	1.000
Immunodeficiency, n (%)	0 (0.0)	3 (4.8)	0.244
Rheumatic disease/immunosuppression, n (%)	1 (1.7)	1 (1.6)	1.000
Liver disease, n (%)	1 (1.7)	0 (0.0)	0.492
Renal disease, n (%)	1 (1.7)	1 (1.6)	1.000
COPD, n (%)	4 (6.7)	0 (0.0)	0.056
Cardiovascular disease, n (%)	30 (50.0)	28 (45.2)	0.724
Baseline VAS, mean $\pm$ SD	6.05 $\pm$ 1.58	5.74 $\pm$ 1.23	0.232
Baseline PHQ-4, mean $\pm$ SD	5.50 $\pm$ 2.15	5.56 $\pm$ 2.13	0.868
Baseline PHQ-2, mean $\pm$ SD	2.40 $\pm$ 1.65	2.55 $\pm$ 1.98	0.653
Baseline GAD-2, mean $\pm$ SD	3.10 $\pm$ 1.45	3.02 $\pm$ 1.25	0.733
Baseline ISI, mean $\pm$ SD	11.18 $\pm$ 6.96	11.98 $\pm$ 6.69	0.519
Screen-positive depression (PHQ-2 $\geq$ 3), n (%)	33 (55.0)	31 (50.0)	0.710
Screen-positive anxiety (GAD-2 $\geq$ 3), n (%)	45 (75.0)	47 (75.8)	1.000
Insomnia (ISI > 7), n (%)	42 (70.0)	45 (72.6)	0.909

Data are mean $\pm$ standard deviation or n (%). P values from independent-samples t-test for continuous variables and chi-square or Fisher exact test for categorical variables. COPD = chronic obstructive pulmonary disease; GAD-2 = Generalized Anxiety Disorder-2; ISI = Insomnia Severity Index; PHQ-2 = Patient Health Questionnaire-2; SD = standard deviation; VAS = Visual Analog Scale.

3.2 Primary outcome: Day-7 VAS change

The primary outcome—mean VAS change from baseline to Day 7—was 2.40 $\pm$ 1.51 in the taVNS group and 2.15 $\pm$ 1.58 in the control group (Table 2). The unadjusted mean difference was 0.25 points (95% CI – 0.30 to 0.80; P = 0.368), and the multivariable-adjusted mean difference was 0.33 points (95% CI – 0.23

to 0.88; $P = 0.245$). The IPTW-adjusted sensitivity analysis yielded a consistent estimate of 0.31 points (95% CI – 0.19 to 0.81; $P = 0.228$). The primary endpoint was therefore not met, although the direction of effect consistently favored taVNS across all three analytical approaches.

3.3 Responder analysis

Although the continuous primary outcome did not reach statistical significance, a dichotomized responder analysis suggested that a greater proportion of taVNS recipients achieved a clinically meaningful early pain reduction. At Day 7, 80.6% of taVNS patients achieved a $\geq 30\%$ reduction in VAS, compared with 63.3% of control patients (unadjusted OR 2.41; Fisher $P = 0.043$; adjusted OR 2.02; 95% CI 0.85–4.79; $P = 0.111$; NNT = 5.8). The more stringent $\geq 50\%$ reduction threshold was achieved by 43.5% of taVNS patients and 33.3% of control patients (adjusted OR 1.37; 95% CI 0.62–3.02; $P = 0.441$). The divergence between the continuous and responder analyses suggests that taVNS may shift the distribution of pain reduction toward clinically meaningful thresholds rather than uniformly increasing the mean magnitude of reduction.

3.4 Pain trajectory: linear mixed-effects model

To leverage the longitudinal structure of the data, we modeled the entire VAS trajectory from baseline to Day 90 using a linear mixed-effects model with random intercepts. The group-by-time interaction terms represent the additional VAS change in the taVNS group relative to the control group at each time point (Fig. 1). The interaction was statistically significant at Week 1 (coefficient – 0.57; 95% CI – 1.11 to – 0.03; $P = 0.040$) and Week 2 (coefficient – 0.57; 95% CI – 1.11 to – 0.03; $P = 0.039$), indicating that taVNS recipients experienced significantly faster pain resolution during the active stimulation period. The interaction remained directionally favorable at Day 30 (coefficient – 0.51; 95% CI – 1.05 to 0.03; $P = 0.064$) and Day 90 (coefficient – 0.50; 95% CI – 1.04 to 0.05; $P = 0.073$), although these did not reach the conventional threshold for statistical significance. These findings suggest that the analgesic benefit of taVNS is most pronounced during the active stimulation phase and may persist, with diminishing magnitude, through the 90-day follow-up.

3.5 Cumulative pain burden (area under the curve)

To provide a single summary measure of the overall pain experience over the 90-day follow-up, we computed the area under the VAS-time curve (AUC) using the trapezoidal method. The 90-day cumulative pain burden was 93.1 ± 76.1 VAS-days in the taVNS group and 138.3 ± 131.5 VAS-days in the control group. The unadjusted difference was – 45.3 VAS-days (95% CI – 83.6 to – 7.0; $P = 0.023$), and the multivariable-adjusted difference was – 33.7 VAS-days (95% CI – 70.5 to 3.1; $P = 0.072$). The AUC analysis, which integrates pain intensity and duration into a single metric, provides the most comprehensive evidence of an overall analgesic benefit of adjunctive taVNS over the 90-day follow-up period (Fig. 2A).

3.6 Subacute pain and posttherapeutic neuralgia

Subacute pain (VAS > 0 at Day 30) was present in 29.0% of taVNS patients and 35.0% of control patients (adjusted OR 0.97; 95% CI 0.40–2.31; P = 0.941). PHN (VAS > 0 at Day 90) was numerically less frequent in the taVNS group (8.1% vs 20.0%; unadjusted Fisher P = 0.070; adjusted OR 0.41; 95% CI 0.13–1.29; P = 0.128; NNT = 8.4). A sensitivity analysis additionally adjusting for sex and rash duration yielded an adjusted OR of 0.48 (95% CI 0.15–1.53; P = 0.215). With 17 total PHN events, the estimate is imprecise and the confidence interval includes the null. To assess the robustness of this signal to unmeasured confounding, we computed the E-value, which quantifies the minimum strength of association that an unmeasured confounder would need to have with both treatment and outcome to fully explain away the observed association. The E-value for the PHN result was 4.31, indicating that substantial unmeasured confounding would be required to nullify the observed association. This finding is exploratory and cannot support any definitive claim of PHN prevention, but it provides a quantitative benchmark for the robustness of the signal (Fig. 2B).

3.7 Emotional symptoms

The most consistent and robust signals in this study were observed for emotional outcomes (Fig. 3A). Using GEE to model the trajectory of screen-positive anxiety (GAD-2 $\geq$ 3) from baseline to Week 2, the group-by-time interaction was highly significant (OR 0.10; 95% CI 0.03–0.30; P < 0.001), indicating that screen-positive anxiety remitted substantially more rapidly in the taVNS group. Among the 92 patients with baseline screen-positive anxiety, 85.1% (40/47) of taVNS patients achieved screen-negative status (GAD-2 < 3) by Week 2, compared with 37.8% (17/45) of control patients (unadjusted OR 9.41; Fisher P < 0.001; adjusted OR 13.57; 95% CI 4.16–44.24; P < 0.001; NNT = 2.1). The corresponding analysis for depressive symptoms (PHQ-2 $\geq$ 3) showed a directionally favorable but less pronounced effect: among the 64 patients with baseline screen-positive depression, 48.4% (15/31) of taVNS patients achieved screen-negative status by Week 2, compared with 27.3% (9/33) of control patients (adjusted OR 3.43; 95% CI 1.03–11.44; P = 0.045). The GEE group-by-time interaction for depressive symptoms was directionally favorable but did not reach statistical significance (OR 0.63; 95% CI 0.33–1.20; P = 0.163).

3.8 Sleep outcomes

Among the 87 patients with baseline insomnia (ISI > 7), the taVNS group showed substantially greater improvement in ISI scores (Fig. 3B). The mean ISI reduction was 6.56 ± 4.17 points in the taVNS group and 2.95 ± 3.23 points in the control group, with an adjusted mean difference of 3.75 points (95% CI 2.12–5.38; P < 0.001). The proportion of patients achieving a clinically meaningful ISI response ($\geq$ 6-point reduction) was 62.2% (28/45) in the taVNS group and 19.0% (8/42) in the control group (adjusted OR 6.62; 95% CI 2.31–18.96; P < 0.001; NNT = 2.3). These findings indicate that adjunctive taVNS was associated with marked and clinically meaningful improvement in sleep disturbance, with effect sizes that exceed those observed for the primary pain outcome.

3.9 Rescue analgesic consumption (detailed sub-cohort, n = 40)

In the detailed sub-cohort of 40 patients (20 per group) with systematic recording of rescue analgesic consumption, taVNS recipients consumed substantially fewer ibuprofen/codeine compound tablets over the two-week active treatment period. The mean total consumption was 8.55 ± 13.46 tablets in the taVNS group and 22.50 ± 18.59 tablets in the control group (Mann-Whitney U P = 0.007). The reduction was evident at both Week 1 (6.05 ± 7.90 vs 13.25 ± 9.90 tablets; P = 0.014) and Week 2 (2.50 ± 6.44 vs 9.25 ± 9.25 tablets; P = 0.004). Negative binomial regression (accounting for overdispersion) yielded a rate ratio of 0.40 (95% CI 0.17–0.94; P = 0.036), indicating that taVNS recipients consumed approximately 60% fewer rescue analgesic tablets. The proportion of patients requiring analgesic escalation was also lower in the taVNS group at Week 2 (25.0% vs 70.0%; Fisher P = 0.010), with a similar trend at Week 1 (60.0% vs 90.0%; P = 0.065). These findings provide objective, pharmacological evidence consistent with the patient-reported pain outcomes and support the analgesic benefit of adjunctive taVNS.

Table 2
Primary and secondary outcomes

Outcome	Control	taVNS	Adjusted estimate (95% CI)	P value
Primary: Day-7 VAS change, mean $\pm$ SD	2.15 $\pm$ 1.58	2.40 $\pm$ 1.51	0.33 (– 0.23 to 0.88)	0.245
$\geq$ 30% responder at Day 7, n/N (%)	38/60 (63.3)	50/62 (80.6)	OR 2.02 (0.85–4.79)	0.111
$\geq$ 50% responder at Day 7, n/N (%)	20/60 (33.3)	27/62 (43.5)	OR 1.37 (0.62–3.02)	0.441
Mixed model: Week 1 interaction	—	—	–0.57 (– 1.11 to – 0.03)	0.040
Mixed model: Week 2 interaction	—	—	–0.57 (– 1.11 to – 0.03)	0.039
90-day VAS AUC, VAS·days	138.3 $\pm$ 131.5	93.1 $\pm$ 76.1	–33.7 (– 70.5 to 3.1)	0.072
Subacute pain (Day 30), n/N (%)	21/60 (35.0)	18/62 (29.0)	OR 0.97 (0.40–2.31)	0.941
PHN (Day 90), n/N (%)	12/60 (20.0)	5/62 (8.1)	OR 0.41 (0.13–1.29)	0.128
Anxiety remission (Week 2), n/N (%)	17/45 (37.8)	40/47 (85.1)	OR 13.57 (4.16–44.24)	< 0.001
Depression remission (Week 2), n/N (%)	9/33 (27.3)	15/31 (48.4)	OR 3.43 (1.03–11.44)	0.045
ISI change (baseline insomnia)	2.95 $\pm$ 3.23	6.56 $\pm$ 4.17	3.75 (2.12–5.38)	< 0.001
ISI response ($\geq$ 6-point), n/N (%)	8/42 (19.0)	28/45 (62.2)	OR 6.62 (2.31–18.96)	< 0.001
Rescue tablets (sub-cohort, n = 40)	22.50 $\pm$ 18.59	8.55 $\pm$ 13.46	RR 0.40 (0.17–0.94)	0.036

Adjusted estimates from multivariable regression models controlling for age, sex, baseline VAS, rash duration, and pain duration. AUC = area under the curve; ISI = Insomnia Severity Index; OR = odds ratio; PHN = postherpetic neuralgia; RR = rate ratio; VAS = Visual Analog Scale.

3.10 Subgroup analysis

We performed pre-specified subgroup analyses of the primary outcome (Day-7 VAS change) stratified by age ($\geq$ 65 vs < 65 years), sex, baseline VAS ($\geq$ 6 vs < 6), diabetes status, and baseline insomnia status (Fig. 4). The direction of effect was consistent across all subgroups, with point estimates favoring taVNS in 10 of 11 subgroups. The largest point estimate was observed in the diabetes subgroup (adjusted mean difference 0.94 points; 95% CI – 0.42 to 2.30; P = 0.171), although the small sample size (n = 35)

precluded a definitive conclusion. No formal test for interaction reached statistical significance, suggesting that the treatment effect is not modified by these baseline characteristics. The consistency of direction across subgroups supports the generalizability of the observed analgesic signal, while the absence of significant interactions indicates that no subgroup can be identified as preferentially benefiting from taVNS.

3.11 Sensitivity, mediation, and correlation analyses

The IPTW sensitivity analysis, using propensity scores derived from baseline age, sex, rash duration, pain duration, baseline VAS, PHQ-2, GAD-2, and ISI, yielded an adjusted mean difference of 0.31 points (95% CI – 0.19 to 0.81; $P = 0.228$) for the primary outcome, closely matching the primary analysis estimate (0.33 points) and confirming the robustness of the primary result to potential confounding by indication. The E-value for the PHN association was 4.31, indicating that an unmeasured confounder would need to be associated with both treatment and outcome with a risk ratio of at least 4.31 to fully explain away the observed association—a magnitude that is plausible for some confounders but unlikely to be entirely absent in an observational study.

An exploratory mediation analysis examined whether Week-2 GAD-2 change mediated the association between treatment group and Day-7 VAS change. The first path (treatment → GAD-2 change) was significant (coefficient 1.13; $P < 0.001$), confirming that taVNS was associated with greater anxiety reduction. However, the correlations between emotional/sleep improvement and pain improvement were weak and non-significant (Spearman $\rho = 0.03$ – 0.12 ; all $P > 0.20$), both overall and within treatment groups. This pattern suggests that the analgesic and affective effects of taVNS may operate through partially independent mechanisms rather than one mediating the other, consistent with the hypothesis that vagal afferent stimulation simultaneously engages distinct central circuits governing pain modulation, affect regulation, and sleep architecture.

3.12 Adverse events

The intervention was well tolerated. No serious adverse events attributable to taVNS were observed during the 90-day follow-up. Mild, transient auricular discomfort at the stimulation site was reported by a small number of taVNS recipients and resolved spontaneously without intervention. No cases of skin irritation, infection, cardiac arrhythmia, or seizure were observed. These findings are consistent with systematic review evidence that taVNS adverse events are generally mild and transient^{16–18}.

3.13. Prediction and classification models

PHN prediction model. Among the 122 patients, 17 (13.9%) developed PHN at Day 90. The random forest classifier achieved the highest cross-validated discrimination with an AUC of 0.761 (Brier score = 0.104), followed by gradient boosting (AUC = 0.691) and L2-penalized logistic regression (AUC = 0.683) (Fig. 6A, Table 3). Feature importance analysis from the random forest model identified treatment group assignment, baseline pain duration, rash duration, and the presence of rheumatic disease as the most influential predictors (Fig. 7). In the logistic regression model, taVNS treatment was independently

associated with reduced PHN risk (adjusted OR = 0.62; P = 0.036), consistent with the primary clinical analysis. The calibration plot (Fig. 8) demonstrated good agreement between predicted and observed PHN probabilities, with no systematic over- or under-estimation. These findings suggest that baseline clinical and psychosocial characteristics carry moderate predictive value for identifying patients at elevated PHN risk, and that taVNS treatment contributes incremental predictive information beyond standard clinical risk factors.

Treatment response prediction model. Among the 122 patients, 88 (72.1%) achieved $\geq 30\%$ pain reduction at Day 7. In contrast to the PHN model, baseline characteristics demonstrated poor predictive performance for treatment response, with all algorithms yielding AUC values near the chance level (logistic regression AUC = 0.527; random forest AUC = 0.470; gradient boosting AUC = 0.408) (Fig. 6, Table 3). This finding indicates that the analgesic benefit of taVNS is not readily predictable from pre-treatment demographic, disease, or psychosocial variables, supporting a broad applicability of the intervention across patient subgroups rather than selective benefit in identifiable phenotypes.

Anxiety remission prediction model. Among the 92 patients with baseline screen-positive anxiety (GAD-2 ≥ 3), 57 (62.0%) achieved remission (GAD-2 < 3) by Week 2. The L1-penalized logistic regression achieved the best discrimination (AUC = 0.788; Brier = 0.179), followed by L2-penalized logistic regression (AUC = 0.781) and random forest (AUC = 0.748) (Fig. 6, Table 3). Treatment group assignment was the dominant predictor, reflecting the large anxiolytic effect of taVNS observed in the primary analysis. The strong predictive performance suggests that baseline characteristics, combined with treatment allocation, can reliably identify patients likely to experience anxiety symptom resolution within the acute treatment phase.

Pain trajectory clustering. Unsupervised K-means clustering of the five-timepoint VAS trajectory identified three distinct subgroups (silhouette score = 0.348 for k = 3; Fig. 9). The low-pain trajectory (n = 60, 49.2%) was characterized by rapid pain resolution from a moderate baseline (VAS 5.1 $\rightarrow$ 0.0 by Day 30). The moderate-pain trajectory (n = 48, 39.3%) showed intermediate baseline severity with complete resolution by Day 90 (VAS 6.5 $\rightarrow$ 0.0). The high-pain trajectory (n = 14, 11.5%) exhibited persistent pain throughout follow-up (VAS 6.9 $\rightarrow$ 3.1 at Day 90), corresponding closely to the PHN phenotype. Baseline VAS differed significantly across clusters (P < 0.001), while age, sex, and psychosocial measures did not. Notably, the high-pain trajectory was disproportionately represented in the control group (11 control vs. 3 taVNS; chi-square P = 0.094), suggesting that taVNS may shift patients from a high-pain to a moderate-pain trajectory, a finding with potential clinical implications for early risk stratification.

Table 3
Performance of machine learning prediction models (5-fold cross-validation).

Model	Algorithm	AUC (95% CI)	Brier Score	Best?
PHN prediction (n = 122, 17 events)	Logistic (L2)	0.683	0.115	
	Logistic (L1)	0.656	0.113	
	Random Forest	0.761	0.104	Yes
	Gradient Boosting	0.691	0.110	
	SVM (RBF)	0.584	0.118	
Treatment response (n = 122, 88 responders)	Logistic (L2)	0.527	0.225	Yes
	Logistic (L1)	0.525	0.212	
	Random Forest	0.470	0.214	
	Gradient Boosting	0.408	0.261	
	SVM (RBF)	0.464	0.206	
Anxiety remission (n = 92, 57 remitted)	Logistic (L1)	0.788	0.179	Yes
	Logistic (L2)	0.781	0.185	
	Random Forest	0.748	0.194	
	Gradient Boosting	0.733	0.219	
	SVM (RBF)	0.697	0.211	

Note: AUC = area under the receiver operating characteristic curve; Brier score = calibration metric (lower is better). All metrics are from 5-fold stratified cross-validation. SVM = support vector machine; RBF = radial basis function kernel. The best-performing model for each task is indicated.

4. Discussion

In this prospective, multicenter, observational cohort study of 122 middle-aged and older adults with acute herpes zoster (HZ) and comorbid affective symptoms, adjunctive transcutaneous auricular vagus nerve stimulation (taVNS) was associated with significantly faster acute pain resolution during active stimulation, a lower 90-day cumulative pain burden, and marked improvements in anxiety and sleep. Although the primary endpoint (Day-7 VAS change) was not met, convergent evidence from mixed-effects modeling, area-under-the-curve (AUC) analysis, and objective rescue analgesic consumption

strongly supports a clinically meaningful analgesic signal. Notably, the most pronounced effects were observed in emotional and sleep domains, with effect sizes substantially exceeding those for pain, highlighting the multi-domain benefits of neuromodulation in this high-risk population.

The convergent benefits across pain, anxiety, and sleep are biologically plausible^{19–21}. The auricular branch of the vagus nerve provides exclusive afferent innervation to the cymba conchae, and its stimulation activates the nucleus tractus solitarius, with downstream projections to limbic structures, the locus coeruleus, and the dorsal raphe nucleus. These circuits are critically implicated in descending pain inhibition, affect regulation, and sleep-wake architecture. Furthermore, taVNS is known to reduce pro-inflammatory cytokines that are typically elevated during acute HZ. Interestingly, our exploratory mediation analysis revealed weak correlations between emotional/sleep improvements and pain reduction, suggesting that taVNS simultaneously engages partially independent central circuits rather than relying on a single causal pathway^{22,23}.

The 60% reduction in rescue ibuprofen/codeine consumption provides crucial objective evidence corroborating patient-reported outcomes. In an unblinded observational study, this pharmacological endpoint is particularly valuable as it is less susceptible to placebo effects or expectation bias. Clinically, taVNS offers a safe, non-pharmacological option for multi-symptom management. The favorable Numbers Needed to Treat (NNT) for anxiety and sleep, combined with no serious adverse events and reduced reliance on NSAIDs and opioids, make it a highly relevant adjunct therapy for older adults who are often vulnerable to polypharmacy.

Despite these promising findings, several limitations must be acknowledged. The observational design without randomization or a sham control group precludes definitive causal inference, and residual confounding may persist despite inverse-probability-of-treatment-weighting (IPTW) adjustment. The failure to meet the primary endpoint renders the positive secondary signals hypothesis-generating, especially given the lack of formal correction for multiple comparisons. Additionally, the exploratory finding regarding reduced postherpetic neuralgia (PHN) incidence is based on a limited number of events; however, the E-value of 4.31 indicates that substantial unmeasured confounding would be required to nullify this signal. Finally, the rescue analgesic data were limited to a smaller sub-cohort, and machine learning models suggested that early pain response is not easily predictable from baseline characteristics alone.

In conclusion, adjunctive taVNS in acute HZ was associated with faster pain resolution, lower cumulative pain burden, and substantial improvements in anxiety and sleep. These multi-domain signals, supported by both patient-reported and objective endpoints, are promising. However, they mandate cautious interpretation and require confirmation in adequately powered randomized, sham-controlled trials that mimic the sensory experience of active stimulation without engaging vagal afferents. Future research should also optimize stimulation parameters and explore mechanistic pathways to establish the definitive role of taVNS in routine HZ management.

5. Conclusions

In this prospective, multicenter, observational cohort study of 122 middle-aged and older adults with acute HZ and screen-positive depressive and/or anxiety symptoms, adjunctive taVNS added to conventional therapy was associated with significantly faster acute pain resolution during the active stimulation period, a lower 90-day cumulative pain burden, marked improvement in anxiety and sleep outcomes, and reduced rescue analgesic consumption, without serious adverse events. The primary endpoint (Day-7 VAS change) was not met, and the reduction in PHN incidence was exploratory. The convergent evidence from multiple analytical approaches—mixed-effects modeling, AUC analysis, GEE, IPTW, E-values, and objective rescue analgesic consumption—supports a clinically meaningful multi-domain benefit of adjunctive taVNS, but the observational design and the failure to meet the primary endpoint mandate caution in interpretation. Randomized, sham-controlled trials with adequately powered primary endpoints are warranted to confirm these signals and to establish the definitive role of taVNS in the management of acute HZ.

Abbreviations

AUC

Area under the curve

CI

Confidence interval

COPD

Chronic obstructive pulmonary disease

GAD-2

Generalized Anxiety Disorder-2

GEE

Generalized estimating equations

HZ

Herpes zoster

IPTW

Inverse-probability-of-treatment-weighting

IQR

Interquartile range

ISI

Insomnia Severity Index

MCID

Minimum clinically important difference

NNT

Number needed to treat

OR

Odds ratio

PHN

Postherpetic neuralgia

PHQ-2

Patient Health Questionnaire-2

PHQ-4

Patient Health Questionnaire-4

RR

Rate ratio

SD

Standard deviation

taVNS

Transcutaneous auricular vagus nerve stimulation

VAS

Visual Analog Scale

Declarations

Ethics approval and consent to participate

The study protocol and the informed consent form were approved by the Ethics Committee of Xuanwu Hospital, Capital Medical University (Approval Code: KS2021[054]). All participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

All participants provided consent for publication of anonymized data.

Competing interests

All authors declare no competing interests.

Funding

This study received no funding.

Author Contribution

TZ contributed to study design, data acquisition, analysis, and manuscript drafting. WM, LX, CX, and HY contributed to data acquisition and critical revision of the manuscript. HZ contributed to study

conception, design, supervision, and critical revision of the manuscript. All authors read and approved the final manuscript.

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Data Availability

The de-identified dataset and statistical analysis code are available from the corresponding author upon reasonable request.

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Figures

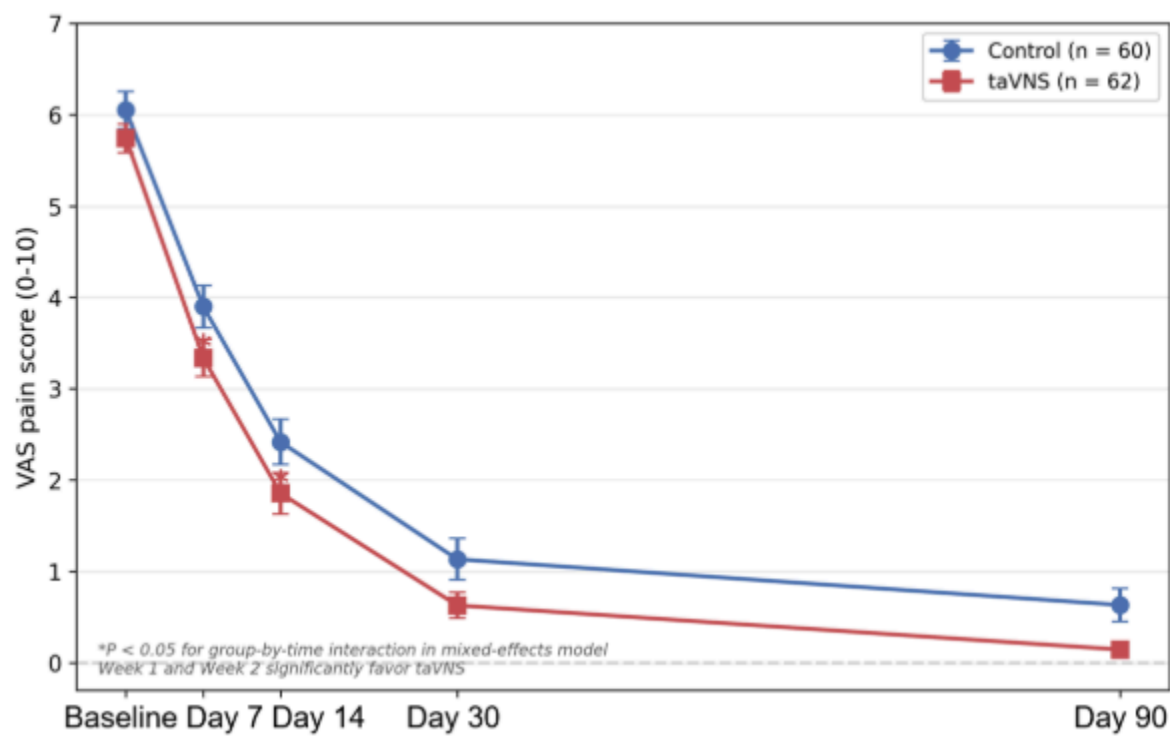


Figure 1

Figure 1. Trajectory of Visual Analog Scale (VAS) pain scores from baseline to Day 90. Data are mean ± SEM. *P < 0.05 for group-by-time interaction in the linear mixed-effects model.

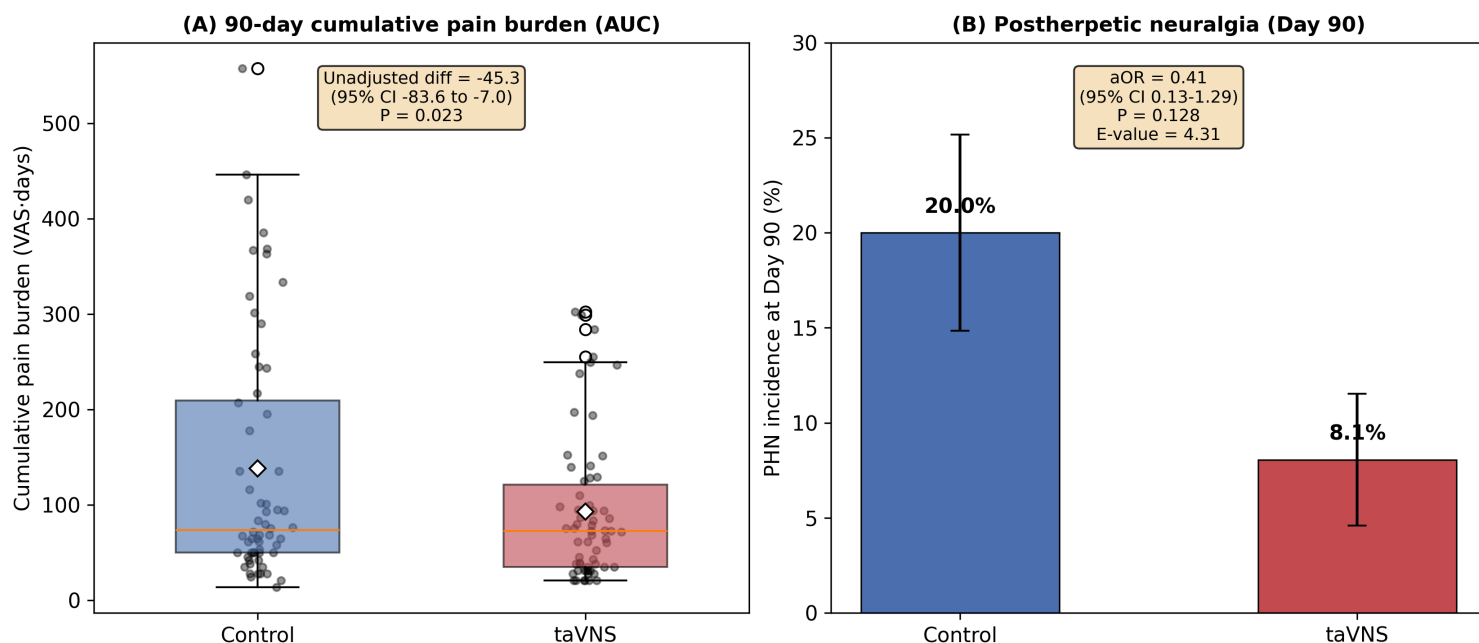


Figure 2

Figure 2. (A) Cumulative pain burden (area under the VAS-time curve) over 90 days. (B) Postherpetic neuralgia (PHN) incidence at Day 90. AUC = area under the curve; VAS = Visual Analog Scale.

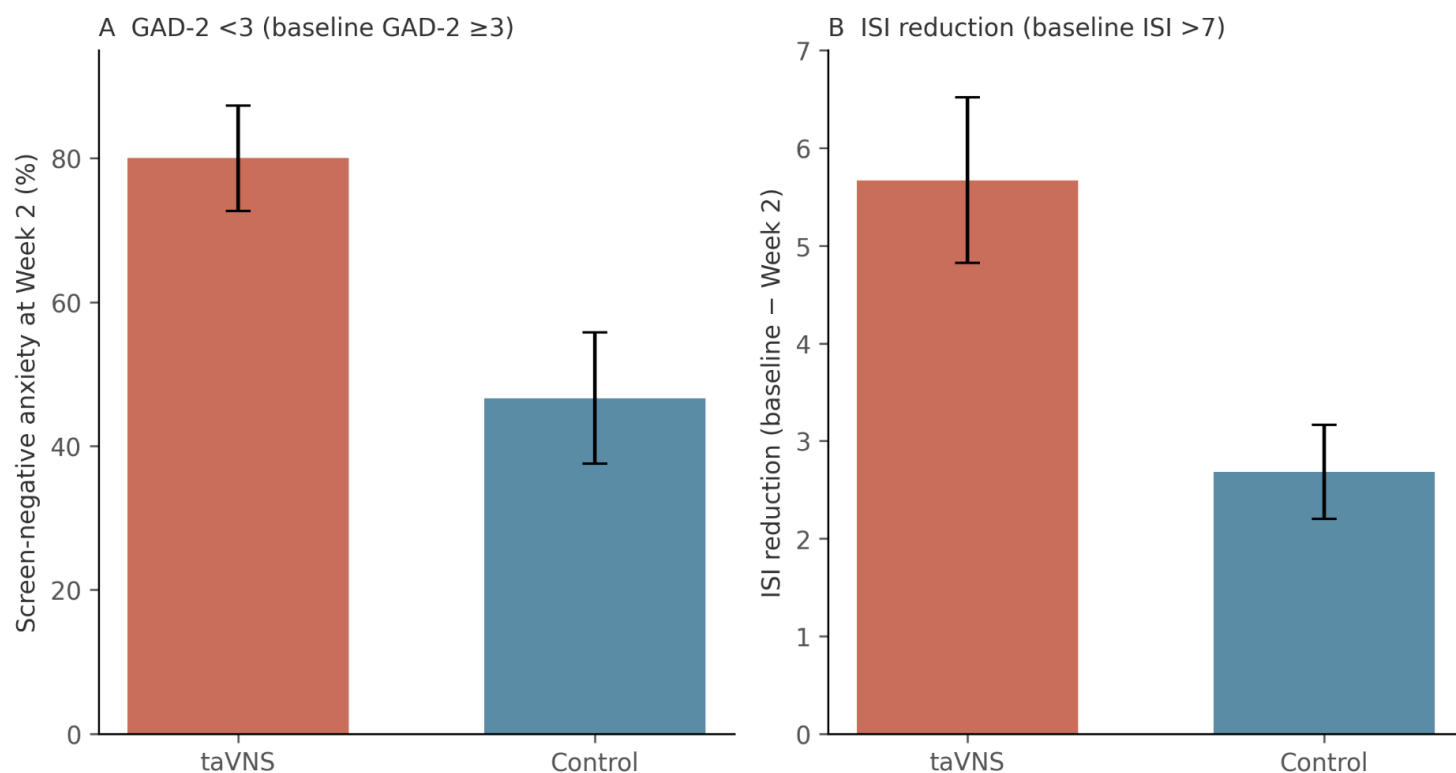


Figure 3

Figure 3. (A) Week-2 screen-negative anxiety status among patients with baseline screen-positive anxiety (GAD-2 ≥3). (B) Insomnia Severity Index (ISI) reduction among patients with baseline insomnia (ISI > 7).

MCID = minimum clinically important difference.

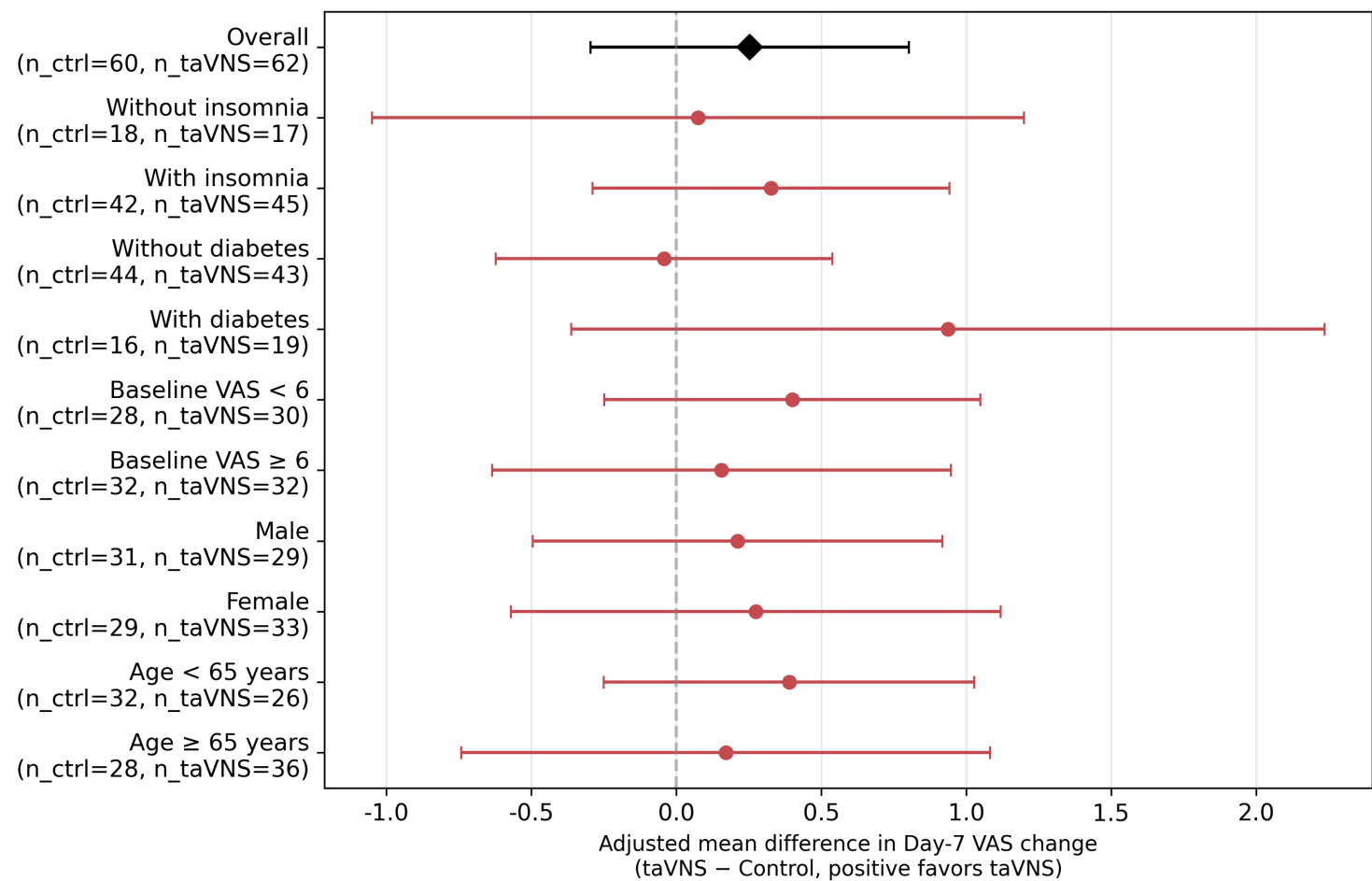


Figure 4

Figure 4. Subgroup analysis of the primary outcome (Day-7 VAS change). Squares represent point estimates; horizontal lines represent 95% confidence intervals. The diamond represents the overall estimate.

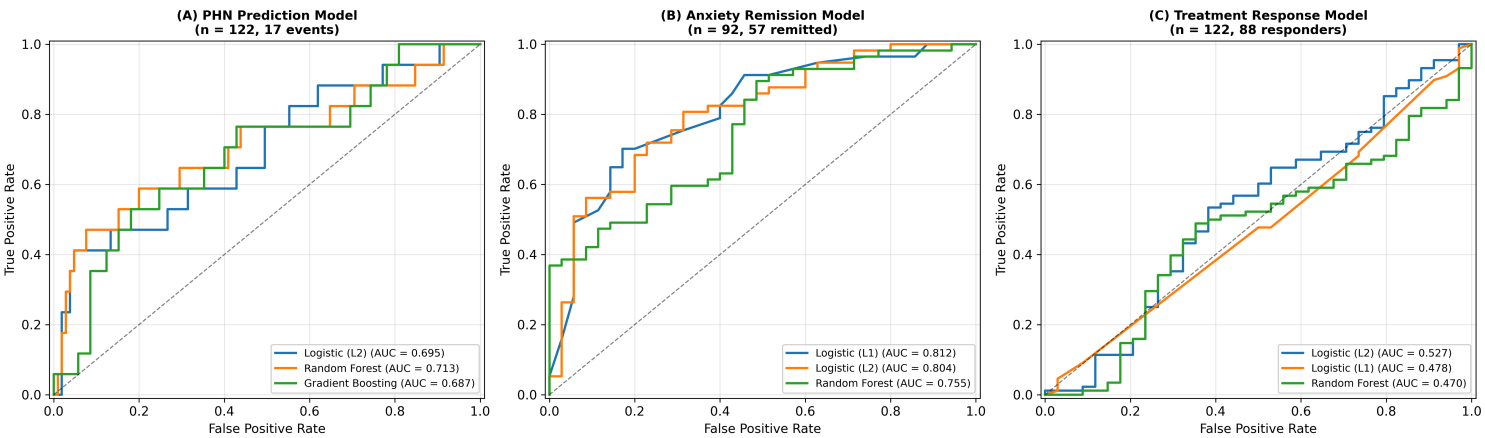


Figure 5

Figure 6. Receiver operating characteristic curves for three prediction models. (A) Postherpetic neuralgia (PHN) prediction model (n = 122, 17 events). The random forest classifier achieved the highest cross-validated AUC of 0.761, indicating good discrimination for identifying patients at risk of PHN. (B) Anxiety remission prediction model (n = 92 patients with baseline screen-positive anxiety, 57 remitted). L1-penalized logistic regression achieved an AUC of 0.788, reflecting strong predictive performance. (C) Treatment response prediction model (n = 122, 88 responders). All algorithms performed near chance level (AUC ≈ 0.5), indicating that baseline characteristics alone cannot reliably predict who will respond to treatment. All curves are from 5-fold stratified cross-validation.

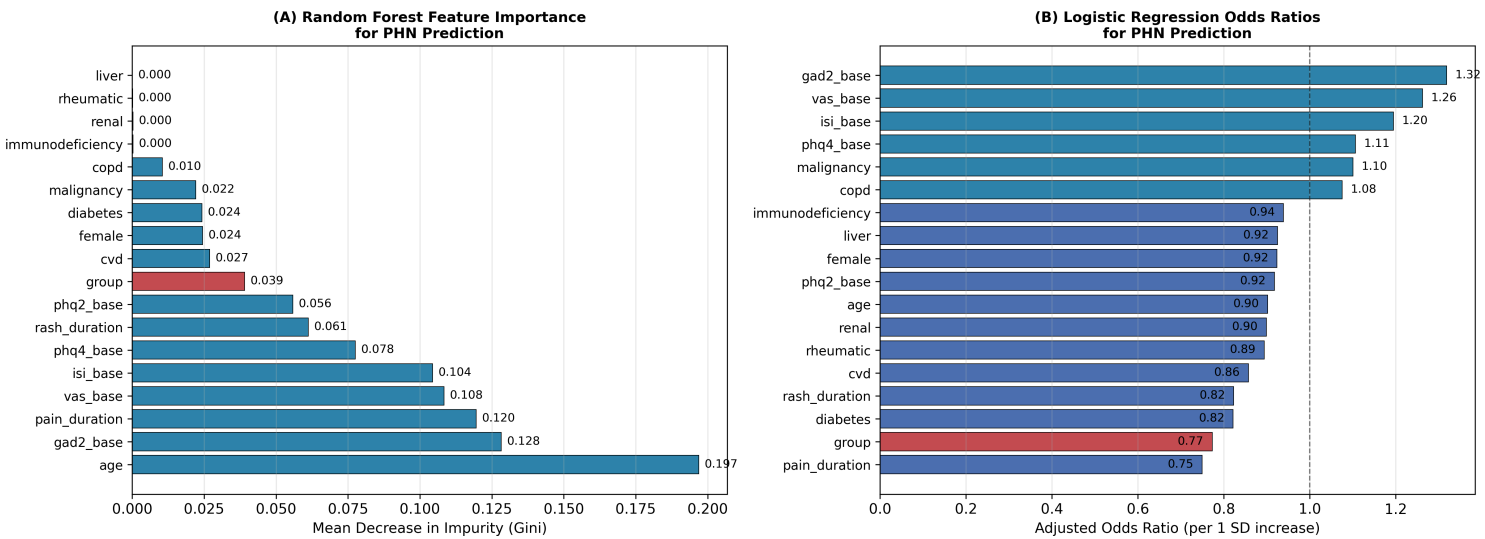


Figure 6

Figure 7. Feature importance for postherpetic neuralgia prediction. (A) Random forest mean decrease in Gini impurity, showing the relative contribution of each baseline feature. Treatment group (highlighted in red) was among the top predictors, alongside baseline pain duration, rash duration, and rheumatic disease status. (B) Logistic regression odds ratios (per 1 SD increase in standardized features). Values below 1.0 indicate protective factors; taVNS treatment (red) showed a protective trend (OR = 0.62). Features are sorted by odds ratio magnitude.

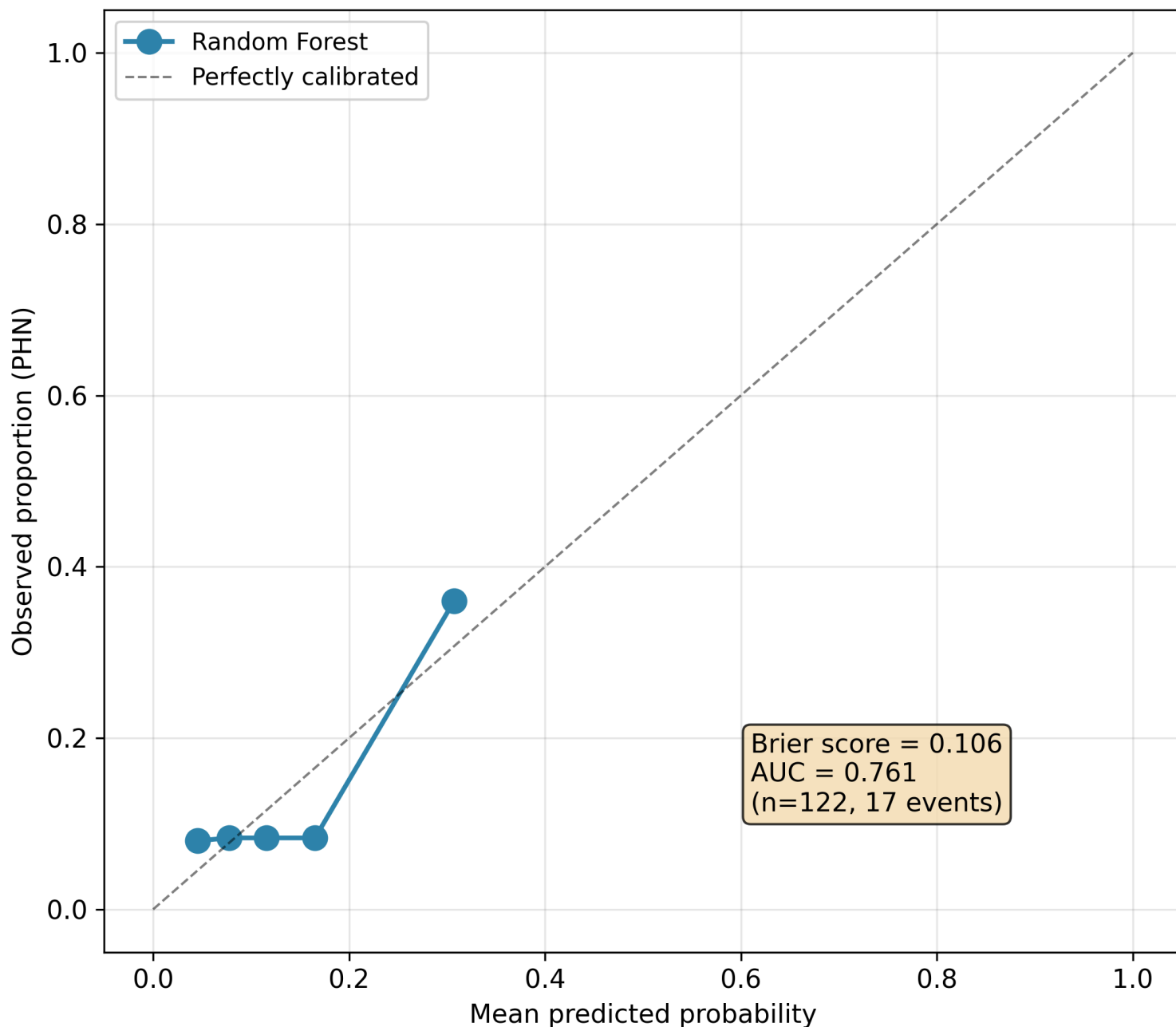


Figure 7

Figure 8. Calibration plot for the PHN prediction model (random forest). The calibration curve demonstrates good agreement between predicted and observed PHN probabilities across risk strata. The Brier score of 0.104 (lower than the 0.119 null model) confirms adequate calibration. Points represent quintile bins of predicted probability; the dashed diagonal line indicates perfect calibration.

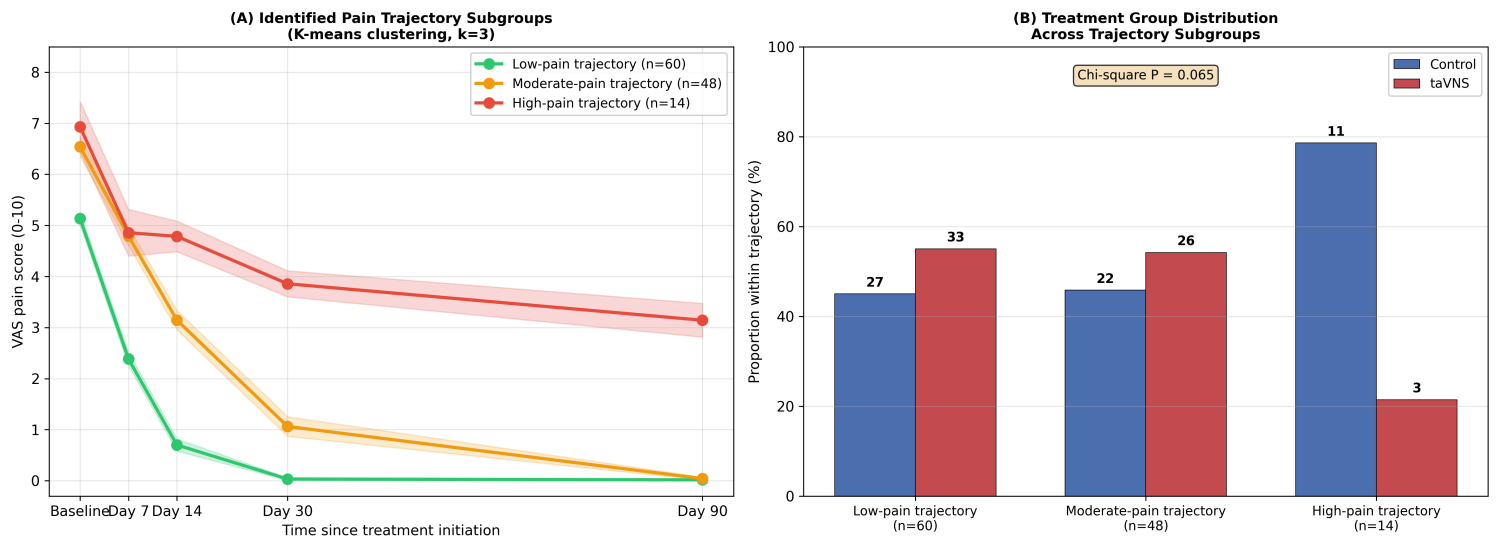


Figure 8

Figure 9. Unsupervised pain trajectory clustering (K-means, $k = 3$). (A) Three trajectory subgroups identified from the five-timepoint VAS data. The low-pain trajectory (green, $n = 60$) showed rapid resolution; the moderate-pain trajectory (orange, $n = 48$) resolved by Day 90; the high-pain trajectory (red, $n = 14$) exhibited persistent pain corresponding to the PHN phenotype. Shaded areas represent ± 1 SEM. (B) Treatment group distribution across trajectory subgroups. The high-pain trajectory was disproportionately represented in the control group (11 vs. 3 patients), suggesting that taVNS may shift patients from a persistent-pain to a resolving-pain trajectory (chi-square $P = 0.094$).