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Phenotype Evolution and Surgical Burden Predict Outcomes in Refractory Trigeminal Neuralgia: Development of the TN-PPS Risk Score

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Abstract

Background

Refractory trigeminal neuralgia (TN) poses significant treatment challenges. While neurovascular compression is a classic etiology, its explanatory power for treatment resistance is limited. This study investigates the prognostic role of pain phenotype evolution and surgical history in refractory TN and develops a novel risk stratification tool.

Methods

We retrospectively analyzed 584 primary TN patients treated between 2023–2024. Clinical characteristics including pain phenotypes (background pain, trigger zone evolution, absence of refractory period) and surgical history were recorded. Multivariate Firth logistic regression identified independent predictors of poor outcome (defined as treatment failure or recurrence). A prognostic score (TN-PPS) was constructed and validated internally.

Results

Poor outcome occurred in 17.5% of patients. Independent predictors were: background pain (OR 19.88), trigger zone evolution (OR 15.58), history of ablative surgery (OR 7.01), and absence of refractory period (OR 4.73). These four factors formed the 8-point TN-PPS, stratifying patients into low (0 points), intermediate (1–3), and high-risk (≥ 4) groups. High-risk patients had 95.0% failure rate versus 2.5% in low-risk patients (validation AUC 0.914). Ablative procedures (PBC/RF) were strongly associated with subsequent phenotype evolution, mediating 14.0% of poor outcomes.

Conclusions

Dynamic pain phenotype evolution and prior ablative surgery are critical determinants of TN prognosis. The TN-PPS provides a simple, effective bedside tool for identifying truly refractory patients and guiding treatment decisions.

Introduction

Trigeminal neuralgia (TN) is a neuropathic pain syndrome characterized by sudden, brief, and severe electric shock-like or knife-like facial pain, which significantly impairs patients' quality of life [1]. For a long time, the diagnosis of TN has primarily relied on its distinctive clinical symptoms, while treatment options are diverse, mainly including pharmacotherapy, microvascular decompression of the trigeminal nerve, percutaneous balloon compression of the trigeminal ganglion, radiofrequency thermocoagulation of the trigeminal nerve, and stereotactic radiosurgery [2].

In recent years, advancements in the vascular compression theory and cerebrovascular imaging techniques have led some scholars to classify TN into typical and atypical forms, advancing our understanding of its etiology and treatment strategies [3]. However, discrepancies have been observed between imaging evidence of vascular compression and actual compression identified during surgery, suggesting that vascular compression does not have an absolute causal relationship with TN [4]. Furthermore, common clinical phenomena—such as trigger points, paroxysmal pain, migration or increase of trigger points, higher prevalence in women, kindling phenomena (the progressive amplification of pain response), and persistent background pain—remain difficult to explain [5-8]. More importantly, the overall efficacy of TN treatment remains suboptimal, with recurrent and refractory cases being far from rare. Clinical decision-making is particularly challenging for patients with refractory TN who have undergone multiple surgical treatments [9]. Although imaging-based classifications primarily focus on structural factors such as the root entry zone and vascular compression, their explanatory power for pain behavioral characteristics is limited. This limitation suggests that identifying new clinical evidence and further refining the classification and subtyping of TN may be crucial for improving treatment outcomes.

This study retrospectively analyzes a cohort of patients with refractory trigeminal neuralgia, focusing on their surgical history and clinical pain characteristics. Through statistical analysis, we aim to provide a novel perspective and preliminary clinical evidence for a new classification of refractory trigeminal neuralgia based on pain phenotypes and treatment burden.

Methods

Study Design and Population

This study is a single-center retrospective cohort study. It consecutively enrolled patients with trigeminal neuralgia (TN) who sought treatment and received care at the Department of Neurosurgery, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, from January 2023 to December 2024. The diagnosis of TN was based on the criteria of the International Classification of Headache Disorders (ICHD), combined with clinical manifestations and imaging findings [1].

This study was approved by the Ethics Committee of Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine (Approval No.: SH9H-2022-T258-2). Due to the retrospective design of the study and the anonymization of all data, the requirement for patient informed consent was waived.

Patient Selection

Inclusion criteria were: (1) diagnosis of primary trigeminal neuralgia meeting the ICHD criteria; (2) complete clinical data with a follow-up period of no less than 12 months.

Exclusion criteria were: (1) secondary trigeminal neuralgia; (2) co-existing major facial pain syndromes (e.g., atypical facial pain, postherpetic neuralgia); (3) severely deficient clinical data or incomplete follow-up information; (4) follow-up period less than 12 months.

Of the initially screened patients, 16 were excluded due to loss to follow-up or insufficient follow-up data, and 2 were excluded due to death during follow-up from causes unrelated to TN or its treatment. Ultimately, 584 patients with primary trigeminal neuralgia were included in the analysis.

Surgical Procedures:

Surgical procedures included microvascular decompression (MVD), percutaneous balloon compression (PBC) of the trigeminal ganglion, radiofrequency thermocoagulation (RF) of the trigeminal ganglion, and Gamma Knife radiosurgery (GK).

Prior Surgical Burden: For patients who had previously undergone surgical treatment, records of their 1st, 2nd, 3rd, or more prior surgeries were documented.

Combined Procedures: For some patients with refractory TN, our center empirically performed a combination of traditional surgeries during a single hospitalization, consisting of a primary procedure and a secondary procedure, aiming to improve pain control. Primary procedures mainly included MVD, PBC, and radiofrequency thermocoagulation (RF) of the trigeminal ganglion. Secondary treatments mainly included radiofrequency ablation of the supraorbital, infraorbital, and mental foramina, or Gamma Knife radiosurgery (GK).

Clinical Pain Characteristics:

Anatomical Site: Involvement of a single branch (V1, V2, or V3) or multiple branches (V1+V2, V1+V3, V2+V3, or V1+V2+V3).

Trigger Zone: Whether there was a precise anatomical location on the patient's face (e.g., nasal ala, oral commissure) where tactile stimulation could induce a paroxysmal, electric shock-like pain within the trigeminal nerve distribution.

Trigger Zone Evolution: Whether the location or number of trigger zones changed or migrated significantly over the patient's long-term disease course.

Paroxysmal Attacks: Whether pain attacks occurred in a repetitive, paroxysmal pattern.

Background Pain: Whether continuous or near-continuous pain persisted in the affected trigeminal region between paroxysmal attacks.

Absence of Refractory Period: Whether there was no distinct pain-free period following an attack, allowing for repeated re-induction shortly thereafter.

Outcome Definition

Patients meeting any of the following criteria were classified as having a poor outcome:

Requirement for further invasive intervention after initial treatment (e.g., repeat MVD, balloon compression, radiofrequency ablation, or Gamma Knife surgery), indicating failure of initial analgesia;

Explicit documentation of symptom persistence or recurrence during follow-up, leading to re-presentation for outpatient or inpatient treatment primarily for pain, or requiring escalation or modification of the treatment strategy.

Patients who did not experience the above situations, did not require further surgical intervention, and maintained symptom relief were classified as having a good outcome.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation or median (interquartile range). Categorical variables were expressed as counts and percentages. Due to the risk of sparse events and complete separation for some predictor variables, both univariate and multivariate analyses were performed using Firth's bias-reduced penalized-likelihood logistic regression to minimize small-sample bias and improve estimation stability.

In some analyses, multivariate models were constructed based on clinical relevance and statistical significance. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. The discriminative ability and clinical utility of the models were assessed using receiver operating characteristic (ROC) curves and decision curve analysis (DCA).

All statistical analyses were performed using R software. A two-tailed P-value < 0.05 was considered statistically significant.

Results

Between January 2023 and December 2024, a total of 602 patients with primary trigeminal neuralgia who met the inclusion criteria were initially screened for this study. After excluding 16 patients due to loss to follow-up or insufficient follow-up data, and 2 patients who died during follow-up from causes unrelated to TN or its treatment, a final total of 584 patients were included in the analysis (the inclusion process is detailed in Fig. 1). The baseline characteristics of all included patients are shown in Table 1.

Overall, the mean age of the patients was 64.5 ± 11.8 years, and 65.2% (381/584) were female. The median duration of pain was 24.0 months (interquartile range 65.0 months). Pain was predominantly unilateral (56.2% right-sided, 42.8% left-sided), with the most frequently involved branches being the V2 branch alone (47.6%) and the combined V2/V3 branches (29.8%). Regarding pain phenotypes, 29.8% (174/584) of patients exhibited at least one abnormal phenotype among background pain, trigger zone evolution, or absence of refractory period. The proportion of patients with these abnormal phenotypes and the mean number of abnormal phenotypes were significantly higher in the poor outcome group (77.5%; 1.1 ± 0.9) compared to the good outcome group (19.7%; 0.3 ± 0.5; both P < 0.001).

Radiologically, MRTA suggested vascular compression in 71.9% (420/584) of patients. Regarding treatment history, 43.8% (256/584) of patients had a history of prior surgery, with the majority having undergone one previous procedure (34.8%, 203/584). For the current treatment modality, microvascular decompression (29.8%), percutaneous balloon compression (31.8%), and radiofrequency ablation (25.3%) were the primary interventions.

Several characteristics differed significantly between the poor and good outcome groups, including the presence of background pain, trigger zone evolution, absence of refractory period, history of prior surgery, and the type of current surgical procedure (all

P < 0.05). However, no statistically significant differences were found between the two groups in age, sex, pain duration, pain laterality, specific branches involved, or the rate of positive MRTA findings (all P > 0.05).

Table 1
Baseline Characteristics of Patients with Trigeminal Neuralgia

Characteristic	Overall (n = 584)	Good Outcome (n = 482)	Poor Outcome (n = 102)	P Value
Demographics				
Age [years, mean ± SD]	64.5 ± 11.8	64.7 ± 11.8	63.9 ± 12.0	0.575
Sex [n (%)]				0.365
Female	381 (65.2)	310 (64.3)	71 (69.6)	
Male	203 (34.8)	172 (35.7)	31 (30.4)	
Clinical Features				
Disease Duration [months, M (IQR)]	24.0 (65.0)	24.0 (65.0)	12.0 (65.0)	0.203
Pain Side [n (%)]				0.490
Right	328 (56.2)	274 (56.8)	54 (52.9)	
Left	250 (42.8)	204 (42.3)	46 (45.1)	
Bilateral	6 (1.0)	4 (0.8)	2 (2.0)	
Trigeminal Nerve Branch Involvement [n (%)]				
V1	10 (1.7)	8 (1.7)	2 (2.0)	0.689
V2	278 (47.6)	236 (49.0)	42 (41.2)	0.186
V3	70 (12.0)	56 (11.6)	14 (13.7)	0.669
V1 + V2	30 (5.1)	24 (5.0)	6 (5.9)	0.629
V2 + V3	174 (29.8)	140 (29.0)	34 (33.3)	0.459
V1 + V2+V3	22 (3.8)	18 (3.7)	4 (3.9)	1.000
Pain Phenotype Features				
Background Pain [n (%)]	27 (4.6)	4 (0.8)	23 (22.5)	< 0.001
Trigger Zone Evolution [n (%)]	112 (19.2)	51 (10.6)	61 (59.8)	< 0.001
Absence of Refractory Period [n (%)]	81 (13.9)	53 (11.0)	28 (27.5)	< 0.001
Presence of Trigger Zone [n (%)]	535 (91.6)	439 (91.1)	96 (94.1)	0.418
Paroxysmal Attacks [n (%)]	481 (82.4)	398 (82.6)	83 (81.4)	0.884
Any Abnormal Phenotype* [n (%)]	174 (29.8)	95 (19.7)	79 (77.5)	< 0.001
Number of Abnormal Phenotypes [n, mean ± SD]	0.5 ± 0.7	0.3 ± 0.5	1.1 ± 0.9	< 0.001
Imaging Features				
Positive MRTA [n (%)]	420 (71.9)	354 (73.4)	66 (64.7)	0.096
Treatment-Related Features				
Prior Surgical History [n (%)]	256 (43.8)	172 (35.7)	84 (82.4)	< 0.001
Number of Prior Surgeries [n (%)]				< 0.001
0	328 (56.2)	310 (94.5)	18 (5.5)	

Characteristic	Overall (n = 584)	Good Outcome (n = 482)	Poor Outcome (n = 102)	P Value
1	203 (34.8)	131 (64.5)	72 (35.5)	
2	53 (9.1)	41 (77.4)	12 (22.6)	
Current Treatment [n (%)]				< 0.001
Microvascular Decompression (MVD)	174 (29.8)	170 (97.7)	4 (2.3)	
Percutaneous Balloon Compression (PBC)	186 (31.8)	174 (93.5)	12 (6.5)	
Radiofrequency Thermocoagulation (RF)	148 (25.3)	92 (62.2)	56 (37.8)	
Gamma Knife Radiosurgery (GK)	10 (1.7)	10 (100.0)	0 (0.0)	
Combined Surgery (Combi)	40 (6.8)	36 (90.0)	4 (10.0)	
Conservative Treatment	26 (4.5)	\	\	

Note

Continuous variables are presented as mean ± standard deviation or median (interquartile range). Categorical variables are presented as number (percentage).

P values: Continuous variables were compared using the t-test or Wilcoxon rank-sum test; categorical variables were compared using the Chi-square test or Fisher's exact test.

Any Abnormal Phenotype: Defined as the presence of at least one of the following: background pain, trigger zone evolution, or absence of a refractory period.

Bolded P values indicate statistical significance (P < 0.05).

Univariate and Multivariate Analysis of Prognostic Factors

To identify independent risk factors for poor prognosis, we first conducted a univariate analysis of all candidate variables (Table 2). Background pain, trigger zone evolution, absence of refractory period, history of prior surgery, and the type of current treatment were significantly associated with poor prognosis (all P < 0.001). In contrast, demographic characteristics, pain duration, pain laterality, specific branches involved, and positive MRTA findings showed no significant differences between the two groups (all P > 0.05).

To further control for confounding and identify independent predictors, we included variables with P < 0.10 in univariate analysis, along with clinically important variables (history of prior surgery, pain phenotypes, and current treatment modality), in a multivariate Firth penalized-likelihood logistic regression model. After adjusting for potential confounders, history of prior surgery, background pain, trigger zone evolution, and absence of refractory period remained independent predictors of poor prognosis (all P < 0.01) (Table 2). The adjusted odds ratio (OR) for history of prior surgery was exceptionally high, confirming its role as the strongest risk marker. Notably, when treatment modality was included in the model with microvascular decompression (MVD) as the reference, the ORs for other procedures (e.g., radiofrequency ablation and percutaneous balloon compression) were elevated but did not reach statistical significance (all P > 0.05). This finding suggests that the choice of treatment modality is profoundly influenced by patients' baseline characteristics (i.e., significant confounding bias).

These findings validate the core hypothesis of this study: compared with traditional static anatomical factors (e.g., vascular compression on MRTA), abnormal pain phenotypes reflecting the dynamic disease process (background pain, trigger zone evolution, absence of refractory period), along with a history of prior surgery representing treatment burden and disease

complexity, are more critical clinical features for distinguishing prognosis and identifying truly refractory cases. This provides a solid foundation for constructing a concise clinical prediction model based on these core characteristics.

Table 2
Univariate and Multivariable Analyses of Factors Associated with Poor Outcome in Trigeminal Neuralgia

Variable	Good Outcome (n = 482)	Poor Outcome (n = 102)	Univariate Analysis		Multivariable Analysis†	
			Statistic	P Value	Adjusted OR (95% CI)	P Value
Demographics						
Age, years, mean ± SD	64.66 ± 11.82	63.92 ± 12.00	t = 0.563	0.575		
Sex, n (%)			χ^2 = 0.820	0.365		
Female	310 (64.3)	71 (69.6)				
Male	172 (35.7)	31 (30.4)				
Clinical Features						
Disease duration, months, M (IQR)	24.00 (65.00)	12.00 (65.00)	W = 26552	0.203		
Pain Phenotype						
Background pain, n (%)	4 (0.8)	23 (22.5)	Fisher's	< 0.001	19.88 (4.27–237.63)	< 0.001
Trigger zone evolution, n (%)	51 (10.6)	61 (59.8)	χ^2 = 128.44	< 0.001	15.58 (7.18–36.24)	< 0.001
Absence of refractory period, n (%)	53 (11.0)	28 (27.5)	χ^2 = 17.73	< 0.001	4.73 (1.80–12.91)	0.002
Paroxysmal attacks, n (%)	398 (82.6)	83 (81.4)	χ^2 = 0.021	0.884		
Presence of trigger zone, n (%)	439 (91.1)	96 (94.1)	χ^2 = 0.655	0.418		
Imaging						
Positive MRTA, n (%)	354 (73.4)	66 (64.7)	χ^2 = 2.765	0.096	0.68 (0.28–1.66)	0.398
Treatment-Related						
Prior surgical history, n (%)	172 (35.7)	84 (82.4)	χ^2 = 72.588	< 0.001	148.52 (18.11–19517.96)‡	< 0.001
Current Treatment, n (%)			χ^2 = 212.700	< 0.001	§	
MVD	170 (35.3)	4 (3.9)			(Reference)	
PBC	174 (36.1)	12 (11.8)			0.81 (0.17–4.43)	0.795
RF	92 (19.1)	56 (54.9)			3.33 (0.86–16.08)	0.083
GK	10 (2.1)	0 (0.0)			0.46 (0.00–8.30)	0.631
Combin	34 (7.1)	4 (3.9)			4.18 (0.03–83.76)	0.460
Conservative¶	0 (0.0)	26 (25.5)			(Not included)	

Note

Data are presented as mean ± standard deviation (SD), median (interquartile range, IQR), or number (percentage).

Univariate Analysis: Continuous variables were compared using the t-test or Wilcoxon rank-sum test; categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate.

† Multivariable Analysis: Performed using Firth's penalized-likelihood logistic regression model to reduce small-sample bias. The model included all variables with P < 0.10 in univariate analysis or considered clinically relevant (prior surgery, pain phenotypes, current treatment). The reference category for current treatment was Microvascular Decompression (MVD).

‡ Wide Confidence Interval: The extremely wide 95% confidence interval for prior surgical history is due to quasi-complete separation in the data (most patients with poor outcome had prior surgery). The Firth method provides a stable but large estimate, confirming it as an exceptionally strong risk factor.

§ Current Treatment in Multivariable Model: The ORs for individual treatment modalities should be interpreted with caution due to the strong confounding effect of patient selection. The model indicates RF is associated with higher odds of poor outcome compared to MVD, but this did not reach conventional statistical significance after adjustment.

¶ Conservative Treatment: All 26 patients managed conservatively were classified into the poor outcome group per protocol (see Methods). They were excluded from the multivariable model examining treatment effects.

Bolded P values indicate statistical significance (P < 0.05). ** denotes P < 0.01.

Association Analysis between Pain Phenotype Characteristics and Prognosis

To delve deeper into the specific impact of pain phenotypes on prognosis, we conducted a detailed association analysis focusing on each phenotypic characteristic (Table 3). Univariate analysis confirmed that background pain, trigger zone evolution, and absence of refractory period were significantly associated with poor prognosis (all P < 0.001). In contrast, typical TN features (presence of a trigger zone, paroxysmal attacks) showed no significant association with prognosis (all P > 0.05). After adjusting for the mutual influences among other phenotypic traits, the multivariate Firth regression model revealed that background pain (adjusted OR = 15.95, 95% CI 5.50–56.16), trigger zone evolution (adjusted OR = 11.15, 95% CI 6.58–19.22), and absence of refractory period (adjusted OR = 3.22, 95% CI 1.70–6.04) remained independent risk factors for poor prognosis (all P < 0.001).

Crucially, the abnormal pain phenotypes exhibited a clear cumulative effect. As shown in Table 3, as the number of abnormal phenotypes present in a patient increased (0, 1, 2, or 3), the rate of poor prognosis demonstrated a significant dose-response increase (P for trend < 0.001). Patients with just one abnormal phenotype already had a significantly elevated risk of poor prognosis. For patients with two or three abnormal phenotypes simultaneously, the rates of poor prognosis reached 88.9% and 100%, respectively. Furthermore, combining these three features into a composite indicator, "presence of any abnormal phenotype," proved to be an extremely strong predictor of poor prognosis, with an adjusted OR of 9.87 (95% CI 6.11–15.96, P < 0.001).

These results not only quantify the independent risk associated with each abnormal pain phenotype but also reveal their synergistic and amplifying effect. From the perspective of clinical pain presentation, this provides deeper insight into the finding in Table 2 that "abnormal phenotypes" serve as core predictors. Given that "history of prior surgery" was also identified in Table 2 as one of the strongest risk factors, and clinical observations suggest that surgical history may be linked to the evolution of pain phenotypes, we subsequently conducted a focused analysis of the impact of different surgical burdens and the type of initial surgery.

Table 3
Association Between Pain Phenotype Features and Clinical Outcomes in Trigeminal Neuralgia

Pain Phenotype Feature	Good Outcome (n = 482)	Poor Outcome (n = 102)	Univariate P Value	Multivariable Analysis*	
				Adjusted OR (95% CI)*	P Value*
Phenotypes Associated with Poor Outcome					
Background pain, n (%)	4 (0.8)	23 (22.5)	< 0.001	15.95 (5.50–56.16)	< 0.001
Trigger zone evolution, n (%)	51 (10.6)	61 (59.8)	< 0.001	11.15 (6.58–19.22)	< 0.001
Absence of refractory period, n (%)	53 (11.0)	28 (27.5)	< 0.001	3.22 (1.70–6.04)	< 0.001
Typical TN Phenotype Features					
Presence of trigger zone, n (%)	439 (91.1)	96 (94.1)	0.418	1.42 (0.55–4.31)	0.494
Paroxysmal attacks, n (%)	398 (82.6)	83 (81.4)	0.884	0.64 (0.34–1.28)	0.204
Combined Phenotype Analysis					
Number of abnormal phenotypes†			< 0.001‡	–	–
0 (n = 406)	378 (93.1)	28 (6.9)			
1 (n = 139)	100 (71.9)	39 (28.1)			
2 (n = 36)	4 (11.1)	32 (88.9)			
3 (n = 3)	0 (0.0)	3 (100.0)			
Any Abnormal Phenotype§			< 0.001	9.87 (6.11–15.96)¶	< 0.001
Yes (n = 174)	95 (54.6)	79 (45.4)			
No (n = 410)	387 (94.4)	23 (5.6)			
Note:					

Multivariable Analysis: Performed using Firth's penalized-likelihood logistic regression. The model for individual phenotypes (rows 1–5) adjusted for all other pain phenotype variables listed in the table. The model for the composite “Any Abnormal Phenotype” variable adjusted for prior surgical history, treatment modality, and MRTA findings.

† Number of abnormal phenotypes: The sum of positive findings for background pain, trigger zone evolution, and absence of refractory period (range 0–3). To maintain consistency with Table 1, this term is used.

‡ P for trend: Cochran-Armitage test for trend, indicating a significant dose-response relationship between the number of abnormal phenotypes and the rate of poor outcome (P < 0.001).

§ Any Abnormal Phenotype: Defined as the presence of at least one of the following: background pain, trigger zone evolution, or absence of a refractory period. ¶ OR for Any Abnormal Phenotype: The adjusted OR of 9.87 indicates that patients with any abnormal phenotype had nearly 10 times higher odds of experiencing a poor outcome.

Bolded terms and P values indicate emphasis and statistical significance (P < 0.05), respectively.

Analysis of the Impact of Previous Surgical History on Prognosis

To further characterize the impact of prior surgical history—the strongest risk factor identified—we conducted a stratified quantitative analysis (Table 4). Compared with patients without prior surgery, those with a history of surgery had a significantly increased risk of poor prognosis. The poor outcome rate among patients with prior surgery was 32.8%, with an adjusted risk approximately 5.7 times that of surgery-naïve patients (adjusted OR, 5.69; 95% CI, 2.96–11.83).

Further analysis revealed a non-linear "dose-effect" relationship for surgical burden. Patients who had undergone one prior surgery had the highest risk (adjusted OR, 6.03; 95% CI, 3.14–12.14), while those with two prior surgeries still had a significantly higher risk than surgery-naïve patients (adjusted OR, 3.85; 95% CI, 1.67–8.85), but lower than that of the one-surgery group (P for trend < 0.001). This suggests that failure of the first surgery may be the strongest risk signal, and that some patients undergoing a second surgery may represent a selected subgroup with different characteristics.

More importantly, the type of first surgery was strongly associated with subsequent refractoriness. In analyses using surgery-naïve patients as the reference, those who underwent radiofrequency ablation (RF) or percutaneous balloon compression (PBC) as their first procedure had the highest risk of poor outcome (adjusted OR, 12.03; 95% CI, 4.78–30.26; and adjusted OR, 7.52; 95% CI, 3.41–16.58, respectively). Patients who underwent microvascular decompression (MVD) as their first procedure had a significantly lower risk (adjusted OR, 4.32; 95% CI, 2.14–8.71), while other modalities such as Gamma Knife did not show statistical significance, likely due to small sample size. The rate of poor outcome differed significantly across first surgery types (P < 0.001 for between-group comparison).

In conclusion, this study not only confirmed that prior surgical history as a whole is a powerful prognostic predictor but also quantitatively revealed its inherent heterogeneity: failure of the first surgery, particularly when the first procedure was an ablative surgery such as radiofrequency ablation or balloon compression, constitutes the most critical risk for subsequent refractoriness. This provides a new dimension for understanding the clinical significance of surgical burden.

Table 4
Impact of Prior Surgical History on Outcomes in Trigeminal Neuralgia

Category	Item	N	Patients with Poor Outcome	Poor Outcome Rate (%)	P Value vs. Reference	Relative Risk (RR)	Adjusted OR (95% CI)*
Overall							
	All Patients	584	102	17.5	–	–	–
	No Prior Surgery (Primary)	328	18	5.5	(Reference)	1.00	1.00 (Reference)
	Prior Surgery (Re-treatment)	256	84	32.8	< 0.001	5.96	5.69 (2.96–11.83)
Number of Prior Surgeries							
	0 Surgeries	328	18	5.5	(Reference)	1.00	1.00 (Reference)
	1 Surgery	203	72	35.5	< 0.001	6.45	6.03 (3.14–12.14)
	2 Surgeries	53	12	22.6	< 0.001	4.11	3.85 (1.67–8.85)
	P for trend†			< 0.001			
Type of First Surgery							
	Radiofrequency Thermocoagulation (RF)	26	18	69.2	< 0.001	12.58	12.03 (4.78–30.26)
	Percutaneous Balloon Compression (PBC)	50	22	44.0	< 0.001	8.00	7.52 (3.41–16.58)
	Microvascular Decompression (MVD)	168	42	25.0	< 0.001	4.55	4.32 (2.14–8.71)
	Gamma Knife Radiosurgery (GK)	4	1	25.0	0.135	4.55	4.21 (0.44–40.12)
	Other/Unknown	8	1	12.5	0.422	2.27	2.15 (0.26–17.83)
	P for between-group comparison‡			< 0.001			
Note:							

Adjusted OR: Derived from Firth's penalized-likelihood logistic regression analysis, adjusting for potential confounders including age, sex, disease duration, MRTA findings, background pain, trigger zone evolution, and absence of refractory period.

† P for trend: Calculated using the Cochran-Mantel-Haenszel test for trend.

‡ P for between-group comparison: Calculated using Fisher's exact test due to small cell counts (< 5) in some categories.

Relative Risk (RR): Calculated as the poor outcome rate of each group divided by the poor outcome rate of the reference group (5.5% for "0 Surgeries").

Reference Group: For the "Number of Prior Surgeries" and the "Overall" comparison, the group with "0 Surgeries" served as the reference. For the "Type of First Surgery," RR was calculated against the "No Prior Surgery" group rate (5.5%).

Bolded values indicate statistical significance (P < 0.05).

Association between previous surgical procedures and abnormal pain phenotypes

To explore potential reasons for the prognostic differences associated with different surgical procedures, we analyzed the association between prior surgery type and the development of new or exacerbated abnormal pain phenotypes (Table 5, Fig. 1). Compared with surgery-naïve patients, those with a history of surgery had a significantly higher risk of developing any abnormal phenotype, with distinct risk profiles across different surgical modalities.

The risk heatmap (Fig. 1) visually illustrates this association pattern. Percutaneous balloon compression (PBC) showed the strongest associations with all three abnormal phenotypes, appearing as a prominent "red cluster" in the heatmap, with the highest association strength for background pain (adjusted OR, 30.35; 95% CI, 8.10–113.78). Radiofrequency ablation (RF) demonstrated a specific strong association with trigger zone evolution (adjusted OR, 5.32; 95% CI, 2.20–12.88). In contrast, microvascular decompression (MVD) showed overall weaker associations with abnormal phenotypes, appearing as cooler colors in the heatmap; it was significantly associated with background pain (OR, 7.68; 95% CI, 2.10–28.11) and trigger zone evolution (OR, 2.45; 95% CI, 1.50–3.99), but did not increase the risk of absence of refractory period (OR, 1.08; 95% CI, 0.62–1.88; P > 0.05).

In summary, both the quantitative data and visual analysis indicate that ablative procedures such as PBC and RF—particularly PBC—are strongly associated with the key pain phenotypes (background pain and trigger zone evolution) that predict poor outcome. This suggests that the choice of surgical procedure not only affects immediate efficacy but may also shape specific pain phenotypes, thereby exerting a profound impact on the long-term disease trajectory.

Figure 1. Risk heatmap of abnormal pain phenotypes associated with different prior surgical procedures. The heatmap displays adjusted odds ratios (ORs) with 95% confidence intervals for the development of three abnormal pain phenotypes in patients with prior surgery compared with surgery-naïve patients (reference OR = 1.00). Color intensity represents log10-transformed OR values, with blue indicating lower risk and red indicating higher risk. Asterisks (*) denote statistically significant associations (P < 0.05) after adjustment for age, disease duration, and MRTA findings. PBC shows the strongest associations across all phenotypes, particularly for background pain (OR, 30.35). RF demonstrates a specific association with trigger zone evolution, while MVD shows relatively weaker associations.

Table 5
Association Between Different Prior Surgical Procedures and the Development of Abnormal Pain Phenotypes

Prior Surgical Procedure	N	Background Pain [n (%)]	OR (95% CI)†	Trigger Zone Evolution [n (%)]	OR (95% CI)†	Absence of Refractory Period [n (%)]	OR (95% CI)†	Any Abnormal Phenotype* [n (%)]	OR (95% CI)†
No Prior Surgery (Reference)	328	3 (0.9)	1.00	34 (10.4)	1.00	40 (12.2)	1.00	75 (22.9)	1.00
Microvascular Decompression (MVD)	168	11 (6.5)	7.68 (2.10–28.11)	37 (22.0)	2.45 (1.50–3.99)	22 (13.1)	1.08 (0.62–1.88)	52 (31.0)	1.52 (1.02–2.27)
Percutaneous Balloon Compression (PBC)	50	11 (22.0)	30.35 (8.10–113.78)	28 (56.0)	10.78 (5.63–20.65)	13 (26.0)	2.54 (1.28–5.05)	36 (72.0)	7.88 (4.08–15.22)
Radiofrequency Thermocoagulation (RF)	26	2 (7.7)	9.05 (1.69–48.55)	10 (38.5)	5.32 (2.20–12.88)	3 (11.5)	0.94 (0.27–3.25)	11 (42.3)	2.49 (1.08–5.72)
Gamma Knife Radiosurgery (GK)	4	0 (0)	–‡	2 (50.0)	8.04 (1.05–61.73)	2 (50.0)	6.96 (1.04–46.74)	2 (50.0)	3.41 (0.42–27.67)
Other/Unknown	8	0 (0)	–‡	1 (12.5)	1.23 (0.15–10.18)	1 (12.5)	1.03 (0.13–8.32)	2 (25.0)	1.12 (0.22–5.68)
P for between-group comparison§	–	< 0.001		< 0.001		0.063		< 0.001	

Note: Any abnormal phenotype is defined as the presence of at least one of the following: background pain, trigger zone evolution, or absence of refractory period.

† Adjusted odds ratios were derived from multivariable logistic regression adjusting for age, disease duration, and MRTA findings, with the no prior surgery group as the reference.

‡ Odds ratios could not be calculated for cells with 0% incidence.

§ Between-group comparisons were performed using Fisher's exact test.

Bolded values indicate statistical significance (P < 0.05) and an odds ratio ≥ 2.0, suggesting a clinically meaningful increased risk.

Mediation Analysis of the Role of Abnormal Pain Phenotypes in the Association Between Surgical History and Prognosis

To investigate whether abnormal pain phenotypes mediate the association between prior surgical procedures and poor prognosis, we conducted a causal mediation analysis (Table 6). The results revealed a clear trend of phenotypic mediation in the effect of prior surgery on prognosis, with varying magnitudes across different surgical modalities.

Percutaneous balloon compression (PBC) exhibited the strongest trend toward a mediating effect. An estimated 14.0% of its total effect on poor prognosis was attributable to the mediating role of abnormal pain phenotypes, a proportion that was statistically significant (bootstrap P < 0.001). This mediation pathway was primarily driven by background pain and trigger zone evolution, consistent with the finding that PBC was strongly associated with both phenotypes (adjusted OR, 30.35; 95% CI, 8.10–113.78; and adjusted OR, 10.78; 95% CI, 5.63–20.65, respectively). Radiofrequency ablation (RF) also showed a trend toward mediation through trigger zone evolution (mediation proportion, 7.5%; bootstrap P = 0.082) and was significantly associated with trigger zone evolution (adjusted OR, 5.32; 95% CI, 2.20–12.88), although the mediated effect did not reach conventional

statistical significance. In contrast, microvascular decompression (MVD) showed the weakest and non-significant trend toward mediation through abnormal phenotypes (mediation proportion, 3.7%; bootstrap P = 0.104).

In summary, the mediation analysis provides evidence that the increased risk of poor prognosis following PBC and RF, compared with MVD, is partially attributable to the new onset or exacerbation of abnormal pain phenotypes—particularly background pain and trigger zone evolution—after treatment. This offers important mechanistic insights into why ablative procedures such as PBC and RF are associated with higher rates of treatment failure during long-term follow-up.

Table 6
Mediation Analysis of the Effect of Prior Surgery on Outcome via Abnormal Pain Phenotypes

Analytical Dimension	Microvascular Decompression (MVD)	Percutaneous Balloon Compression (PBC)	Radiofrequency Thermocoagulation (RF)
1. Baseline Risk			
Poor Outcome Rate, % (n/N)	25.0 (42/168)	44.0 (22/50)	69.2 (18/26)
2. Total Effect (Surgery → Outcome)			
Crude OR (95% CI)	4.05 (2.14–8.71)	22.17 (3.41–16.58)	14.27 (4.78–30.26)
3. Path Decomposition: Direct vs. Indirect Effect			
Direct Effect OR (95% CI) †	3.85 (2.02–8.43)	18.91 (2.92–15.23)	14.27 (4.76–30.20)
Mediated Proportion, % (Bootstrap P value)	3.7 (0.104)	14.0 (< 0.001)	7.5 (0.082)
4. Key Mediating Pathway			
Primary Mediating Phenotype(s)	Minor Phenotype Alteration‡	Background Pain, Trigger Zone Evolution	Trigger Zone Evolution
5. Mechanistic Evidence: Strength of Phenotype Induction by Surgery §			
Background Pain, Adj. OR (95% CI)	7.68 (2.10–28.11)	30.35 (8.10–113.78)	9.05 (1.69–48.55)
Trigger Zone Evolution, Adj. OR (95% CI)	2.45 (1.50–3.99)	10.78 (5.63–20.65)	5.32 (2.20–12.88)
Absence of Refractory Period, Adj. OR (95% CI)	1.08 (0.62–1.88)	2.54 (1.28–5.05)	0.94 (0.27–3.25)
Note:			

† Direct Effect OR: The effect of prior surgery on poor outcome after statistically controlling for the mediating abnormal pain phenotypes.

‡ For MVD, the mediation effect was not statistically significant (P = 0.104), indicating that abnormal pain phenotypes played a minimal role in mediating its effect on outcome.

§ Adjusted odds ratios (Adj. OR) for the association between prior surgery (vs. no surgery) and the subsequent development of each abnormal pain phenotype. Bold values indicate statistical significance (P < 0.05). Data sourced from Table 5.

Bold values in the table highlight findings of primary importance, including the significant mediated proportion for PBC and the strongest phenotype-surgery associations.

Construction and Validation of the TN-PPS Scoring System

To integrate the independent risk factors identified above into a concise clinical tool, we developed the Trigeminal Neuralgia Prognostic and Phenotypic Score (TN-PPS) (Table 7).

This scoring system is based on four strong predictors derived from the multivariate Firth logistic regression model: background pain, trigger zone evolution, history of ablative surgery, and absence of refractory period. Based on their relative weights in the model, these factors were assigned additive integer scores of 3, 2, 2, and 1 point, respectively, yielding a total score range of 0–8 points (Table 7A, B).

Based on the total score, patients were stratified into three risk levels: low risk (0 points), intermediate risk (1–3 points), and high risk (≥ 4 points). This stratification demonstrated excellent and consistent predictive performance in both the training and independent validation cohorts (Table 7C). In the validation cohort, the rate of poor prognosis was only 2.5% among low-risk patients but reached 95.0% among high-risk patients. The model exhibited excellent discriminative ability in the validation cohort (AUC, 0.914; 95% CI, 0.844–0.985), good calibration (Hosmer–Lemeshow P = 0.42), and a favorable negative predictive value (97.5%) for low-risk patients (Table 7D).

The TN-PPS successfully transforms complex clinical pain phenotypes and treatment history into an integer score that can be rapidly calculated at the bedside, providing an efficient and objective risk stratification tool for identifying truly refractory patients who are likely to fail standard treatments.

Table 7
Predictors, Points Assignment, and Risk Stratification of the TN-PPS Score

Variable	Adjusted OR (95% CI)	P Value	Points Assigned	TN-PPS Risk Category (Total Points)
Background pain	13.50 (2.51–107.41)	0.005	3	Low Risk: 0 points
Trigger zone evolution	8.11 (4.32–15.47)	< 0.001	2	Intermediate Risk: 1–3 points
History of ablative surgery †	7.01 (3.31–15.05)	< 0.001	2	High Risk: ≥4 points
Absence of refractory period	2.62 (1.18–5.69)	0.016	1	(Total Range: 0–8 points)

Note: † History of ablative surgery is defined as prior radiofrequency thermocoagulation (RF) or percutaneous balloon compression (PBC). The TN-PPS score is the sum of points for each predictor present.

Table 8
Predictive Performance of the TN-PPS Score in Training and Validation Cohorts

TN-PPS Risk Category	Score	Training Cohort (n = 409)		Validation Cohort (n = 175)	
		n (%)	Poor Outcome Rate, % (n/N)	n (%)	Poor Outcome Rate, % (n/N)
Low Risk	0	257 (62.8)	7.4 (19/257)	120 (68.6)	2.5 (3/120)
Intermediate Risk	1–3	121 (29.6)	21.5 (26/121)	35 (20.0)	17.1 (6/35)
High Risk	≥ 4	31 (7.6)	93.5 (29/31)	20 (11.4)	95.0 (19/20)
Overall model performance in the validation cohort:					
Discrimination: area under the ROC curve (AUC), 0.914 (95% CI, 0.844–0.985)					
Calibration: Hosmer–Lemeshow test, P = 0.42					
Key predictive values:					
Negative predictive value (for low risk): 97.5%					
Positive predictive value (for high risk): 95.0%					
Operational performance (cut-off ≥ 2 points):					
Sensitivity: 85.7%					
Specificity: 87.1%					

(A) Receiver operating characteristic (ROC) curve for the TN-PPS score. The area under the curve (AUC) is 0.914 (95% CI, 0.844–0.985). The diagonal line represents chance performance (AUC = 0.5). (B) Decision curve analysis (DCA) comparing the net benefit of using the TN-PPS score (red line) against the strategies of treating all (gray line) and treating none (black line) across a range of threshold probabilities. The shaded area indicates where the TN-PPS score provides a positive net benefit.

Clinical Utility of the TN-PPS in Guiding Treatment Decisions: A Case Study of Combined Surgery

To evaluate the clinical utility of the TN-PPS, we used it to retrospectively analyze the heterogeneity in treatment outcomes among patients who underwent combined surgery—an intervention typically reserved for complex or refractory cases (Table 9).

Among the 40 patients who underwent combined surgery, the overall rate of poor prognosis was 10.0%. However, when stratified by TN-PPS score, outcomes varied dramatically: low-risk and intermediate-risk patients (accounting for 95% of the cohort) achieved favorable outcomes (poor prognosis rates, 4.0% and 7.7%, respectively), whereas both high-risk patients (TN-PPS ≥ 4) experienced treatment failure (poor prognosis rate, 100%). High-risk patients had a 25-fold higher risk of poor prognosis compared with low-risk patients (Fisher's exact test, P = 0.0085).

This finding carries dual significance. First, it confirms that combined surgery is an effective strategy for selected complex cases —primarily those at low-to-intermediate risk. More importantly, it reveals that without risk stratification, the overall efficacy rate (10%) would obscure the fact that this surgical approach is ineffective for truly high-risk patients (TN-PPS ≥ 4). The TN-PPS successfully quantifies the clinical impression of case complexity, precisely identifying truly refractory patients who are highly likely to fail even with aggressive combined interventions.

Table 9
Heterogeneity in Outcomes of Combined Surgery Stratified by the TN-PPS Score

Patient Subgroup (by TN-PPS)	N	Patients with Poor Outcome	Observed Poor Outcome Rate
All Patients Undergoing Combined Surgery	40	4	10.0%
Low Risk (TN-PPS = 0)	25	1	4.0%
Intermediate Risk (TN-PPS = 1–3)	13	1	7.7%
High Risk (TN-PPS ≥ 4)	2	2	100.0%

Note: This analysis demonstrates the critical importance of case selection. The favorable overall outcome of combined surgery is predominantly driven by its application in low-risk patients. Both high-risk patients, each with a prior history of PBC, experienced treatment failure.

Discussion

This retrospective study sought to elucidate the potential relationships among pain phenotypes, surgical burden, and refractory trigeminal neuralgia, and to develop the TN-PPS scoring system.

1. Pain Phenotypes, the TN-PPS, and Trigeminal Neuralgia

The classic diagnosis and description of trigeminal neuralgia (TN) have long revolved around a core clinical feature: the presence of a trigger point or trigger zone—typically activated by innocuous stimuli, relatively fixed in location, and followed by a distinct refractory period after an attack [10–12]. This characteristic forms a cornerstone of diagnostic criteria such as the International Classification of Headache Disorders (ICHD) and has shaped the clinical understanding of classic TN. However, long-term clinical observations suggest that this seemingly stable pain pattern is not immutable [13]. With natural disease progression or following various interventions, the pain characteristics in some patients undergo profound evolution. Examples include migration or an increase in the number of trigger zones, disappearance of the refractory period following attacks, and the emergence of continuous background pain in the interictal phase [14]. These manifestations, which deviate from the classic pattern, are often broadly categorized as atypical TN. However, their specific prognostic significance and association with treatment response have long lacked systematic quantitative evaluation [15].

Through a systematic analysis of 584 TN patients, this study confirms for the first time in a large sample that these dynamic evolutionary characteristics of pain phenotypes are independent and powerful risk factors for predicting long-term treatment outcomes. Multivariate regression analysis revealed that background pain, trigger zone evolution (migration or increase), and absence of refractory period were all significantly associated with poor prognosis (adjusted ORs, 19.88, 15.58, and 4.73, respectively; all $P < 0.01$). More importantly, these abnormal phenotypes exhibited a clear dose-response relationship: as the number of abnormal phenotypes present in a patient increased, the rate of poor prognosis rose sharply in a stepwise manner. For instance, patients with two abnormal phenotypes had a treatment failure rate as high as 88.9%, while those with all three were uniformly classified into the poor prognosis group. These objective data clearly indicate that the transition of pain phenotypes from fixed, intermittent, and predictable to migratory, persistent, and uncontrollable is not a trivial clinical detail but a critical signal marking the disease's entry into a more aggressive and refractory stage. Therefore, in clinical practice and research, beyond documenting classic trigger zone features, systematically assessing background pain, trigger zone evolution, and the refractory period should become an indispensable component of baseline evaluation and follow-up for TN patients.

Based on these findings, we developed the Trigeminal Neuralgia Prognostic and Phenotypic Score (TN-PPS). This scoring system integrates four independent predictors—background pain (3 points), trigger zone evolution (2 points), history of ablative surgery (2 points), and absence of refractory period (1 point)—forming a 0–8 point scale. In the validation cohort, the TN-PPS demonstrated excellent discriminative ability (AUC, 0.914) and effectively stratified patients into low-, intermediate-, and high-risk groups. This tool may help clinicians move beyond the traditional classic/atypical dichotomy, enabling more refined patient risk stratification. Admittedly, such a scoring system has inherent limitations, but its greater significance lies in alerting clinicians to these important pain phenotypes.

However, this study shows that when all patients undergoing combined surgery were considered as a whole, their outcomes were not significantly superior to those of other strategies—seemingly contradicting clinical intuition. Yet, this paradox was clarified upon introducing the TN-PPS for risk stratification. For the very rare subset of patients with refractory trigeminal neuralgia facing clinical dilemmas, combined surgery showed a trend toward better efficacy, but its indications require strict definition.

2. Surgical Burden and Trigeminal Neuralgia

The patient cohort in this study profoundly reflects the complexity of TN diagnosis and treatment in the real world. The mean disease duration was 24 months, and 43.8% of patients had undergone at least one surgical intervention prior to enrollment, with 9.1% having experienced two or more surgical procedures. This composition not only highlights the chronic and recurrence-prone nature of TN but also reveals a common clinical dilemma: following initial treatment failure, the selection of subsequent treatment strategies often lacks clear evidence-based guidance, easily falling into an empirical cycle of trial and error [17]. Unlike prospective randomized trials that typically employ strict variable control, this study incorporates such complex and overlapping prior treatment histories as a core analytical dimension, systematically exploring the potential impact of different treatment burdens and modalities on the long-term disease trajectory.

A history of prior surgery itself emerged as one of the strongest risk factors for poor prognosis [18–20]. Compared with treatment-naïve patients, those with a history of surgery had a nearly 6-fold increased risk of poor prognosis (adjusted OR, 5.69; 95% CI, 2.96–11.83). More nuanced analysis revealed heterogeneity in this risk: patients who had undergone one prior surgery had the highest risk (adjusted OR, 6.03; 95% CI, 3.14–12.14), while those with two prior surgeries—although still at significantly higher risk than treatment-naïve patients—showed a somewhat reduced risk compared with those with a single prior surgery (adjusted OR, 3.85; 95% CI, 1.67–8.85).

The choice of initial surgical modality had a profound impact on the subsequent development of refractoriness [7, 21, 22]. In analyses using treatment-naïve patients as the reference, those whose initial surgery was percutaneous balloon compression or radiofrequency ablation had a substantially higher risk of progressing to a poor outcome compared with those whose initial surgery was microvascular decompression (adjusted ORs, 7.52 and 12.03 vs. 4.32, respectively). This difference cannot be simply attributed to variations in baseline disease severity, as the multivariate model adjusted for known clinical and phenotypic variables. This strongly suggests that the treatment modality itself—particularly ablative interventions targeting the trigeminal ganglion or peripheral branches—may actively alter the natural history of the disease.

This study provides potential mechanistic explanations for these associations. Mediation analysis indicated that a considerable proportion of the risk for poor prognosis following PBC and RF (14.0% and 7.5%, respectively) was attributable to abnormal pain phenotypes induced or exacerbated by these procedures. Specifically, PBC was strongly associated with the postoperative emergence of background pain and trigger zone evolution (adjusted ORs, 30.35 and 10.78, respectively), while RF was significantly associated with trigger zone evolution (adjusted OR, 5.32; 95% CI, 2.20–12.88). In other words, while ablative procedures achieve short-term analgesic effects, they may simultaneously reshape the pathophysiological basis of pain through direct nerve injury, secondary inflammatory responses, or aberrant nerve regeneration, thereby inducing clinical features indicative of central sensitization or disrupted neuroplasticity and laying the groundwork for long-term treatment resistance and recurrence.

This phenomenon can be understood from a more continuous pathophysiological perspective. The traditional vascular compression theory focuses on the root entry zone as a critical node, successfully explaining many classic cases and providing a theoretical foundation for the efficacy of microvascular decompression [23, 24]. However, the generation, transmission, and perception of pain signals in trigeminal neuralgia involve a complete functional pathway extending from peripheral sensory terminals and nerve fibers through the trigeminal ganglion and root entry zone to the central sensory processing network [18, 25–31]. The findings of this study suggest that, for some patients who eventually become refractory, the pathological process may not be static at a single focal lesion at the root entry zone.

Specifically, ablative procedures targeting the trigeminal ganglion or peripheral branches can be viewed as intense interventions targeting the peripheral segment nodes within this continuous pathway. While interrupting pain transmission, they may also

cause direct injury and secondary inflammation at these nodes. Such interventions may trigger not merely functional silencing but a series of complex neuroplastic reactions. Aberrant nerve repair, sensitization, or regeneration processes could potentially induce lasting alterations in the functional state of local and even upstream (central) neural circuits. Clinically, such alterations manifest as a remodeling of pain phenotypes, characterized by the emergence of background pain, trigger zone evolution, and other features. When this aberrant functional state becomes consolidated and extends along the neural pathway, it may form a refractory condition that responds poorly to conventional treatments (including interventions targeting other nodes) and becomes difficult to reverse.

Therefore, a history of prior surgery—particularly ablative surgery—may be understood as a marker indicating that the patient's pain pathway has sustained a specific type of injury. The consequence of such injury is not merely a historical record of treatment failure but potentially a clue that the pain maintenance mechanisms have become more complex and intractable. This analytical perspective, based on a continuous pathway model, helps explain why focusing solely on radiographic evidence of vascular compression at the root entry zone sometimes fails to predict long-term outcomes in such complex patients. It also underscores the importance, in treatment decision-making, of assessing not only local etiological factors but also the functional integrity and plasticity of the entire sensory pathway.

3. Re-evaluating the Efficacy of MVD and Its Unique Value

Microvascular decompression (MVD), as an etiological treatment targeting neurovascular compression, has been widely established as a first-line and durable therapeutic option for primary trigeminal neuralgia, particularly in patients with clear radiographic evidence of vascular compression [32]. However, in this retrospective cohort, MVD did not demonstrate the high success rates reported in some prospective studies or highly selected cohorts. This finding does not negate the core value of MVD but rather reflects the complexity of real-world clinical practice and the heterogeneity of the patient population.

First, treatment decision-making in the real world involves a multifactorial process. Not all patients with positive magnetic resonance tomographic angiography findings ultimately undergo MVD; factors such as patient age, overall health status, surgical preference, fear of craniotomy, and inclination toward other minimally invasive treatments all influence the final treatment pathway. Conversely, in some experienced centers, a subset of patients with highly typical clinical presentations but negative MRTA findings may undergo exploratory MVD after comprehensive evaluation. Among these, some are found intraoperatively to have vascular contact or compression and benefit from decompression, while others may achieve pain relief through intraoperative nerve combing. This individualized decision-making based on clinical judgment means that the patient population actually receiving MVD differs from the ideal population suitable for MVD, thereby affecting the overall efficacy observed in large real-world samples.

Second, this study reveals a unique advantage of MVD from a novel perspective. Compared with ablative procedures such as percutaneous balloon compression and radiofrequency ablation, patients who underwent MVD had a significantly lower risk of developing new or exacerbated abnormal pain phenotypes (e.g., background pain or trigger zone evolution). Multivariate analysis showed strong associations between PBC or RF and the occurrence of abnormal phenotypes (significantly elevated ORs), whereas the association for MVD was much weaker and non-significant. This suggests that MVD, while relieving vascular compression, maximally preserves the anatomical integrity and physiological function of the trigeminal nerve. Its therapeutic goal is to remove the etiological factor and restore a normal neuroelectrophysiological environment, rather than to block pain transmission by creating controlled nerve injury. Consequently, MVD not only provides pain relief but, more importantly, avoids the aberrant neuroplastic changes that may be triggered by nerve damage—changes that can lead to pain chronification and complexification. In the long term, this preservation of neurological function may be the underlying reason why MVD achieves more stable and durable efficacy, and it explains why MVD is considered the gold standard treatment for suitable patients.

In summary, within the real-world context reflected in this study, the efficacy data for MVD can be viewed as an objective representation of its practical application across diverse clinical scenarios. Although its overall success rate is influenced by factors such as patient selection bias, this study, through comparative analysis, strongly corroborates the fundamental advantage of MVD as an etiological and nerve-sparing procedure from the perspective of long-term impact on pain phenotypes.

This reinforces the clinical consensus: for suitable patients, MVD should be prioritized, not only because of its higher curative potential but also because of the superior long-term neurological health outcomes it may afford.

4. Study Limitations

Although this study provides new perspectives and tools for the clinical classification and prognostic assessment of trigeminal neuralgia, its limitations must be acknowledged. These limitations also chart a course for future research.

First, the single-center retrospective design constitutes a fundamental methodological limitation. While standardized diagnostic and treatment processes at a single center facilitate consistency in collecting clinical data such as pain phenotypes and minimize inter-rater variability, retrospective studies are subject to selection bias and information bias. The non-random nature of patient enrollment and reliance on the completeness of historical data may affect the generalizability of the conclusions. Future multicenter prospective cohort studies are needed to validate the external validity and stability of these findings.

Second, challenges exist regarding the quality of data on prior treatment history. Except for patients who received continuous care at our center, most patients' history of prior surgeries relied on recall and verbal reports from the patients themselves or their family members. For patients with disease courses spanning a decade or longer, the accuracy and completeness of their memories are inevitably subject to bias, which may introduce error in the analysis of key variables such as prior surgical burden and initial surgical modality.

Third, the cornerstone of the TN-PPS developed in this study—pain phenotype characteristics—relies primarily on subjective patient descriptions. Although core definitions such as background pain, trigger zone evolution, and absence of refractory period have clear clinical indications and are common in clinical practice, they lack objective, quantifiable biomarkers or neurophysiological correlates for verification. This subjectivity may affect the reproducibility and precision of the assessment. This fundamentally reflects a pervasive challenge in the current field of neuropathic pain: the scarcity of clinical-pathological correlations and the shortage of objective assessment tools. In the future, electrophysiology, magnetic resonance imaging, pathology, and artificial intelligence may help address this challenge.

5. Conclusion

This retrospective study reveals the critical role of dynamic pain phenotype evolution and history of ablative surgery in the prognostic assessment of TN. The TN-PPS provides a preliminary quantitative tool to facilitate more refined patient risk stratification and clinical decision-making. For the rare clinical scenario of refractory trigeminal neuralgia, combined surgery demonstrates feasibility but requires strict case selection.

Abbreviations

SD
Standard Deviation
M (IQR)
Median (Interquartile Range)
V1, V2, V3
Ophthalmic, Maxillary, and Mandibular divisions of the trigeminal nerve, respectively
MRTA
Magnetic Resonance Tomographic Angiography
MVD
Microvascular Decompression
PBC
Percutaneous Balloon Compression
RF
Radiofrequency Thermocoagulation
GK

Gamma Knife Radiosurgery
Combi
Combined Surgical Procedure

Declarations

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Conflict of interest/Competing interests

The authors declare that they have no conflict of interest.

Ethics approval

This study was performed in accordance with the ethical standards of the Declaration of Helsinki and its later amendments. The study protocol was approved by the Institutional Ethics Committee of Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine (Approval No. SH9H-2022-T258-2).

Consent to participate

Given the retrospective design of this study and the use of fully anonymized data, the requirement for written informed consent was waived by the Institutional Ethics Committee of Shanghai Ninth People's Hospital.

Consent for publication

As this manuscript does not contain any individual person's data in any form (e.g., individual details, images, or videos), a specific consent for publication from participants is not applicable.

Authors' contributions

Xiangrong Chen: Conceptualization, Literature search and analysis, Writing original draft. Weihan Wu: Literature search and analysis, Writing review & editing. Zongtao Wu: Literature search, Data visualization. Xin Xu: Methodology, Supervision, Writing review & editing. Wenchuan Zhang: Conceptualization, Project administration, Supervision, Writing review & editing. All authors read and approved the final manuscript.

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Figures

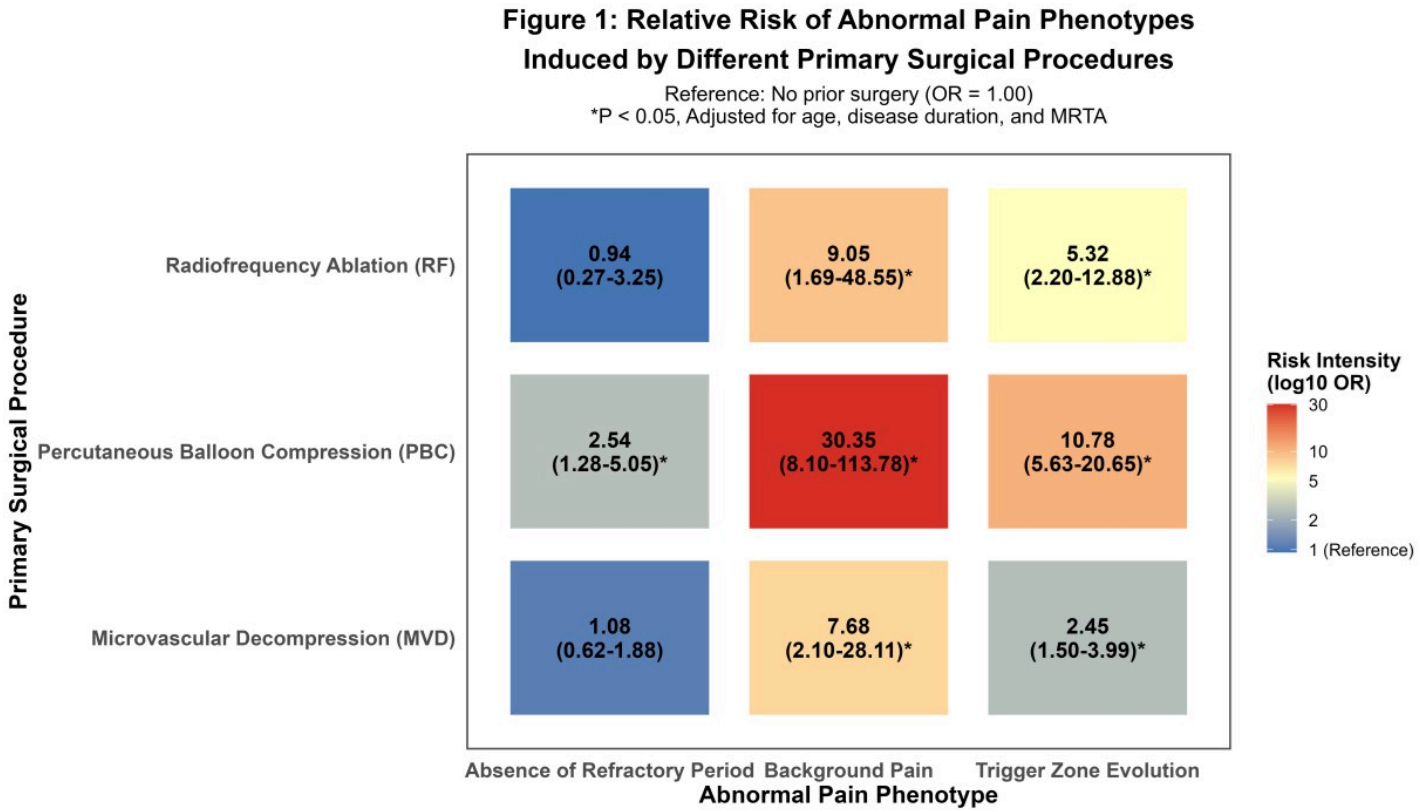


Figure 1

Risk heatmap of abnormal pain phenotypes associated with different prior surgical procedures. The heatmap displays adjusted odds ratios (ORs) with 95% confidence intervals for the development of three abnormal pain phenotypes in patients with prior surgery compared with surgery-naïve patients (reference OR = 1.00). Color intensity represents log10-transformed OR values, with blue indicating lower risk and red indicating higher risk. Asterisks (*) denote statistically significant associations (P < 0.05) after adjustment for age, disease duration, and MRTA findings. PBC shows the strongest associations across all phenotypes, particularly for background pain (OR, 30.35). RF demonstrates a specific association with trigger zone evolution, while MVD shows relatively weaker associations.

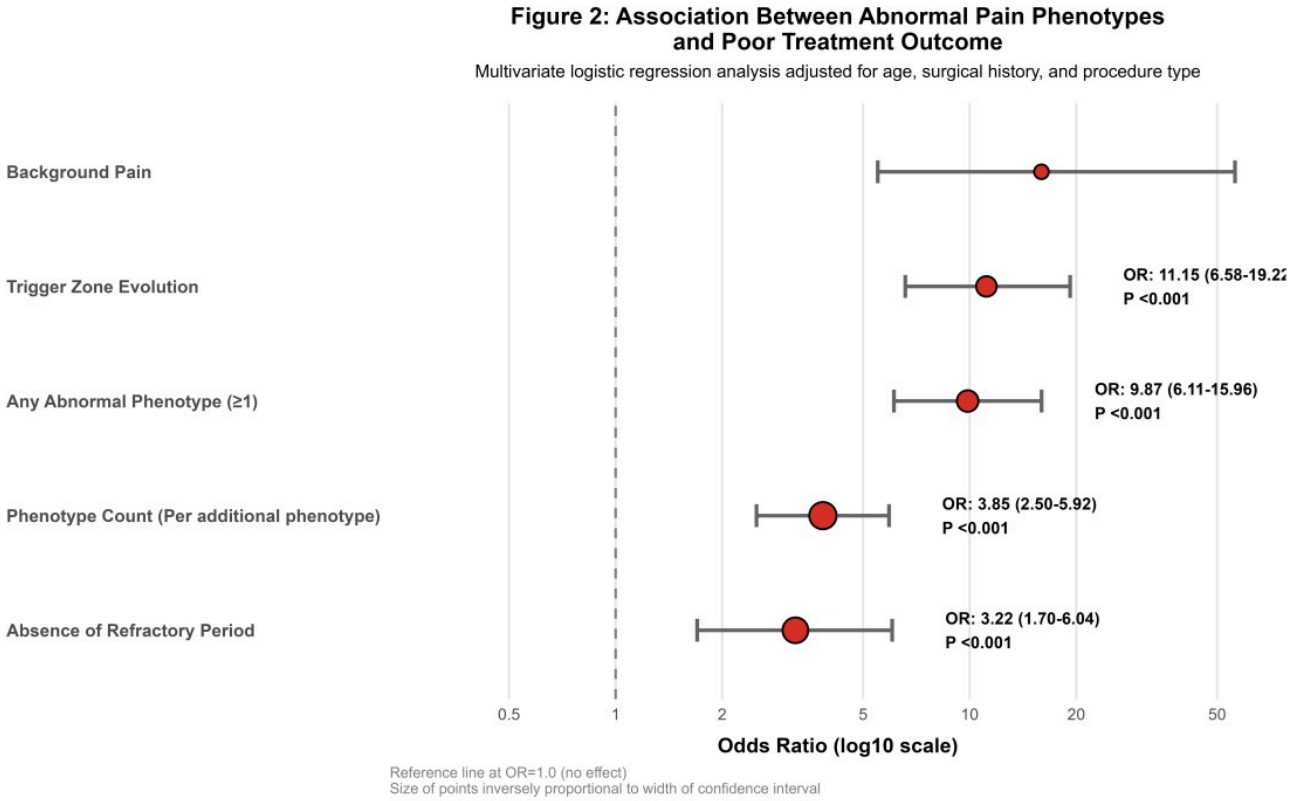


Figure 2

Dose-Response Relationship Between the TN-PPS Score and the Risk of Poor Outcome in the Validation Cohort.

(A) Bar plot showing the observed rate of poor outcome for each TN-PPS score (0 to 8) in the validation cohort (n = 175). The dashed vertical line indicates the high-risk threshold (≥4 points). (B) Stacked bar chart showing the proportion of patients with good versus poor outcome within each TN-PPS risk category (low: 0 points; intermediate: 1–3 points; high: ≥4 points), with actual rates labeled.

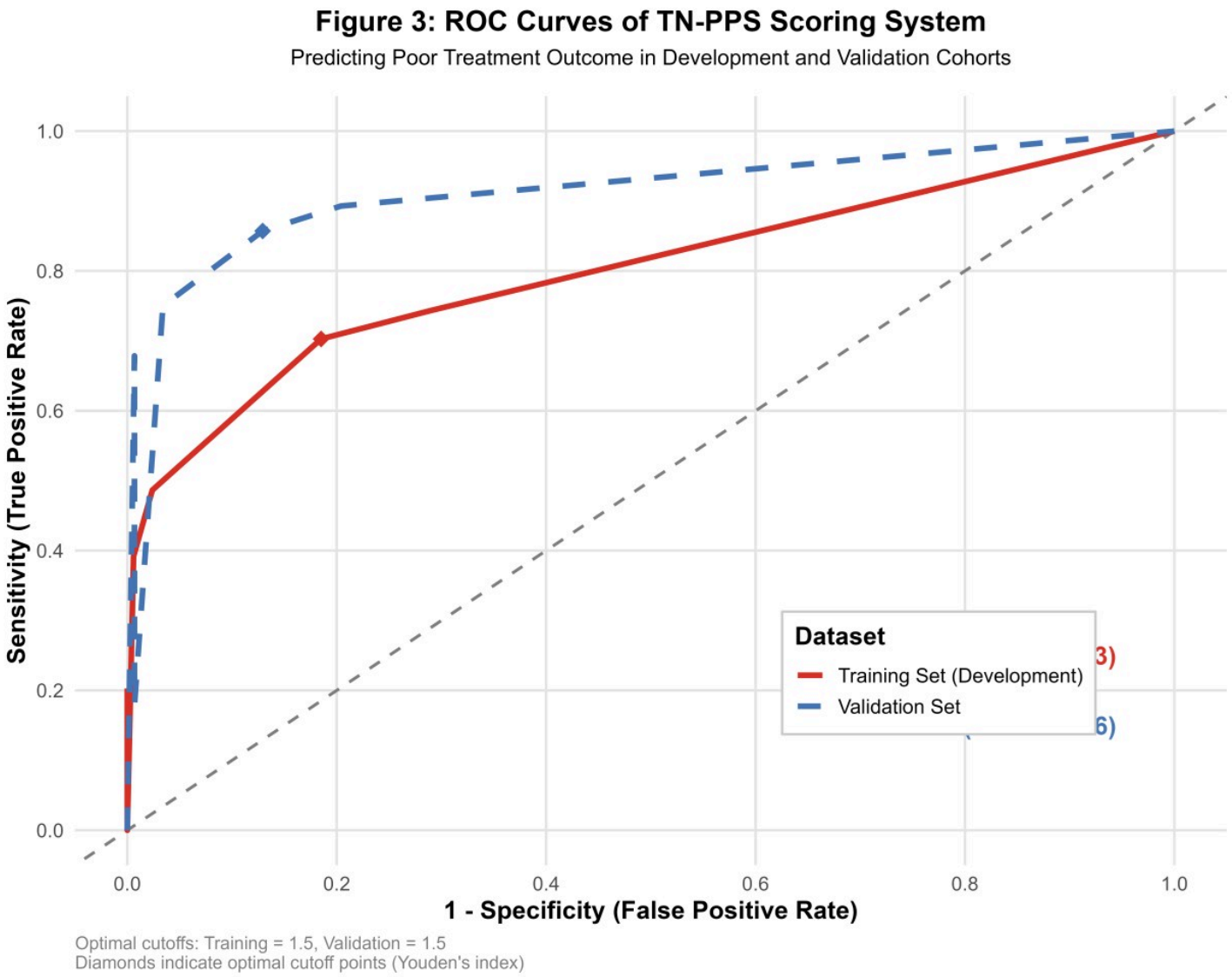


Figure 3

Discriminatory Performance and Clinical Utility of the TN-PPS Score in the Independent Validation Cohort.

(A) Receiver operating characteristic (ROC) curve for the TN-PPS score. The area under the curve (AUC) is 0.914 (95% CI, 0.844–0.985). The diagonal line represents chance performance (AUC = 0.5). (B) Decision curve analysis (DCA) comparing the net benefit of using the TN-PPS score (red line) against the strategies of treating all (gray line) and treating none (black line) across a range of threshold probabilities. The shaded area indicates where the TN-PPS score provides a positive net benefit.