Online dynamic nomogram for predicting pain recurrence after microvascular decompression in trigeminal neuralgia

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Received February 24, 2023; Accepted July 5, 2023

DOI: 10.3892/etm.2023.12130

Abstract. Trigeminal neuralgia (TN) is one of the most common causes of facial pain. Microvascular decompression (MVD) is the first-choice surgical treatment. The present study aimed to develop a novel practical assessment system based on preoperative clinical and imaging factors for clinicians to predict the likelihood of pain recurrence following MVD in TN. A total of 56 patients with primary unilateral TN who underwent MVD were retrospectively analyzed. Patients were followed up to observe pain recurrence 1 year after MVD. An online dynamic nomogram was constructed for predicting the probability of pain recurrence after MVD in patients with TN based on multivariate logistic model. The concordance index (C-index) and receiver operating characteristic (ROC) were used to measure model discrimination. Bootstrap resampling was used for internal validation of the model and calibration curve was constructed. Decision curve analysis (DCA) was used to assess clinical applicability. Factors such as numeric rating scale (to score pain degree of patients with TN), response to neuroanalgesic drugs and neurovascular contact on magnetic resonance imaging were independent risk factors affecting the pain recurrence rate (all $P<0.05$).C-index was 0.973 (95%CI, 0.938-1.000) and the area under the ROC was 0.973 (95%CI, 0.938-1.000). Calibration curve with a 1,000 bootstrap resampling showed a good fit between dynamic nomogram prediction and actual observations. The DCA showed that at a threshold probability between 0 and 100%, this model can achieve a greater net benefit than if all patients had surgery or none had surgery. In conclusion, this online dynamic nomogram reliably predicted risk of pain recurrence in patients with TN following MVD.

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Key words: microvascular decompression, trigeminal neuralgia, nomogram, pain recurrence

Introduction

Trigeminal neuralgia (TN) is one of the most common causes of facial pain. It is characterized by intermittent transient (lasting seconds to minutes), electrocution- or needle-like pain in trigeminal nerve distribution area induced by minor mechanical stimuli such as brushing and chewing (1). Despite the unclear pathogenesis in TN, neurovascular compression is considered to be an important cause of TN and microvascular decompression (MVD) is widely recognized as the first-choice surgical treatment (2,3). Compared with drug therapy, radiofrequency ablation, percutaneous balloon compression (PBC) and other methods, MVD results in longer pain-free periods and fewer side effects or complications, such as postoperative facial spasms and hearing loss (2,3). However, 3-31% of patients experience pain recurrence, which affects the quality of life and prognosis of these patients (4-6).

Neurosurgeons have studied prognostic prediction systems for MVD, some of which originated from internationally renowned medical centers (7,8). Previous research has reported prognostic factors for MVD, including sex, age, symptomatic side, trigeminal nerve branches, sensitivity to carbamazepine, type 1 or 2 TN (TN1 or TN2), severity and site of neurovascular compression, and type of vessels involved (9-16). To the best of our knowledge, however, most studies use univariate or multivariate correlation analyses and there is no recognized prognostic prediction system for MVD. More importantly, the independent risk factors in the aforementioned MVD prognostic models of TN all included TN type (TN1 or TN2), but the latest international TN diagnostic guidelines [the International Classification of Headache Disorders, 3rd edition (ICHD-3); the 11th Revision of the International Classification of Diseases (ICD-11)] classify TN as classic, secondary and idiopathic, so these models are not suiTable for the current status of clinical diagnosis and treatment (17-19). In addition,

previous studies only provided static prognostic models (7,8), which made it inconvenient for clinicians or patients to access the predicted results of the model at any time. It was hypothesized that a reliable and accurate prediction model could be constructed based on preoperative clinical and imaging factors. To test this hypothesis, univariate and multifactor logistic regression statistical analysis methods were used to analyze the included preoperative clinical and imaging factors, and a model was constructed. The present study aimed to combine the current prognostic factors for MVD and construct a new practical predictive assessment systems to evaluate the risk of pain recurrence in patients with TN after MVD based on preoperative clinical and imaging factors. This may provide a reference for patient consultation and choice of surgical plan.

Materials and methods

Clinical case data and characteristics. Clinical data of 56 patients diagnosed with primary unilateral TN at the Second Affiliated Hospital of Anhui Medical University (Hefei, China) from August 2011 to October 2021 were retrospectively reviewed. None of the patients underwent any invasive intervention before surgery, such as MVD, PBC, radiofrequency ablation or trigeminal sensory rhizotomy. The characteristics of the study patients are shown in Table I. The retrospective study was approved (approval no. 202115) by the Ethics Committee of the Second Affiliated Hospital at Anhui Medical University. All patients provided written informed consent. The diagnosis and subtyping of TN were performed according to the latest criteria [ICHD-3 (17) and ICD-11 (19)] established by the International Headache Society and the World Health Organization. All patients underwent uniform clinical and radiographic assessments, including symptomatic and medical history, numeric rating scale, response to medication and tolerability and retrospective analysis of trigeminal magnetic resonance imaging (MRI) (20) before MVD, including conventional 3.0-Tesla MRI plain scans, three-dimensional time of light MR angiography and 3D-FIESTA sequence. Based on these assessments, surgical treatment was determined and performed by the same team of experienced neurosurgeons. In addition, patients were excluded if they had never been treated with carbamazepine or oxcarbazepine. Patients were excluded if they had incomplete or missing data, including medical history, MR images or long-term clinical follow-up.

Postoperative follow-up. The outcome of MVD was assessed immediately after surgery, before discharge and 1 year after surgery by outpatient or telephone follow-up. This follow-up assessed postoperative pain, degree of pain, need for medication, clinical improvement following drug use and complications. Pain was assessed with the Barrow Neurological Institute (BNI) pain intensity score: I indicated no pain recurrence after MVD, whereas BNI pain score II-V (from BNI level II to V, the pain severity gradually increases. BNI levels III and IV require medication for pain relief, while BNI level V indicates that medication is ineffective in alleviating the pain) indicated pain recurrence after MVD (21).

Statistical analysis. Statistical analysis was performed using R language, version 4.2.0 (http://www.Rproject.org). Data are presented as mean ± standard deviation, percentages or odds ratio (OR) with 95% confidence interval (CI). Univariate and multivariate logistic regression analysis were used to determine risk factors of pain recurrence and OR was calculated. According to these independent risk factors, an online dynamic nomogram was constructed with R language, version 4.2.0 (http://www.Rproject.org) At https://www.shinyapps.io, this nomogram was transformed into a web server to facilitate use. Model performance was assessed in terms of discrimination and calibration. The concordance index (C-index) and receiver operating characteristic (ROC) were used to measure model discrimination. Bootstrap resampling was used for internal validation and calibration curve was constructed, which graphically represents the association between actual and predicted probabilities. Presenting the P-values of the Hosmer-Lemeshow goodness-of-fit test on the calibration curve can increase the rigor and objectivity of the model evaluation by providing an additional quantitative assessment. Decision curve analysis (DCA) was used to evaluate the clinical applicability of the model. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Characteristics of 56 patients with MVD. The present study included a total of 56 patients who met the inclusion criteria and conducted follow-up evaluations. Patients were aged 25-77 years with a mean age of onset 55 years and mean age at surgery of 59 years. The mean disease duration was 4 years. Women were more common, accounting for 58.93% (n=33); Right side pain was more common, accounting for 53.57% (n=30). Among the 56 patients with MVD, pain involved the second and third branches of trigeminal nerve (V2+V3) in 75.00% (n=42) of cases. NoTable neurovascular compression or deformation on MRI was observed in 58.93% (n=33) of cases, pain scores ranging from 4 to 10 accounted for 82.14% (n=46), vascular compression at the trigeminal nerve root exiting the brainstem zone (REZ) occurred in 92.86% (n=52) of cases and neuroanalgesic drug treatment was effective in 73.21% (n=41) of cases. One year after MVD, pain recurrence occurred in 23.21% (n=13) of patients (Table I).

Establishment of the nomogram. Univariate and multivariate logistic regression analysis showed that numeric rating scale (NRS; OR=58.50, 95%CI: 4.71-2,349.77, P=0.007), response to neuroanalgesic drugs (OR=60.35, 95%CI: 4.84-2,661.18, P=0.007) and neurovascular contact on MRI (OR=98.55, 95%CI: 5.39-10,642.56, P=0.014) were independent risk factors for pain recurrence in patients with TN after MVD (Table II). On the basis of these results, R software version 4.2.0 was used to develop an online dynamic nomogram (Fig. 1). Each clinical factor is given a score; total score represents probability of pain recurrence in patients with TN after MVD. To visualize the nomogram and make the clinical application more convenient, this nomogram was created by web server (ppramvdftn.shinyapps.io/DynNomapp/). After entering the predictive variables of the model in the left panel, the predicted value of pain recurrence in patients with TN after MVD will

Table I. Characteristics of patients with MVD (n=56).

Characteristic	Value
Mean age of onset, years	54.81±11.09
Mean age at surgery, years	58.67±10.82
Mean duration between onset and surgery, years	3.86±3.26
Sex, n (%)	
Female	33 (58.93)
Male	23 (41.07)
Symptomatic side, n (%)	
Left	26 (46.43)
Right	30 (53.57)
Trigeminal nerve branches, n (%)	
V2 + V3	42 (75.00)
Other	14 (25.00)
Neurovascular contact on MRI, n (%)	
Vascular deformity	33 (58.93)
Vascular contact	19 (33.93)
Absent vascular proximity	4 (7.14)
NRS, n (%)	
0-3	10 (17.86)
4-10	46 (82.14)
REZ, n (%)	
Yes	52 (92.86)
No	4 (7.14)
Response to neuroanalgesic drugs, n (%)	
Yes	41 (73.21)
No	15 (26.79)
Recurrence 1-year post-MVD, n (%)	
Yes	13 (23.21)
No	43 (76.79)

MVD, microvascular decompression; MRI, magnetic resonance imaging; NRS, numeric rating scale; REZ, root exiting brainstem zone.

be displayed in the right panel (Fig. 2). The prediction model had good discriminative ability and area under the ROC curve was 0.973 (Fig. 3A). When the optimal cutoff value for model scoring was 0.820, the sensitivity was 0.923 and the specificity was 0.953 (Fig. 3A). Furthermore, the ROC curve demonstrated a 95% confidence interval of 0.938-1.000 (Fig. 3B). The C-index was 0.973 (95% CI, 0.938-1.000).

Validation of the nomogram. The bootstrap verification method was used to verify the generated model internally and the C-index of internal validation was 0.97. Calibration curve (Fig. 4) showed that predicted and actual probability of pain recurrence was close to x=y. Hosmer-Lemeshow goodness-of-fit test yielded P=1, which also indicates that the model had a good calibration degree. DCA (Fig. 5) indicated the clinical usefulness. When the probability of high-risk threshold was between 0 and 100%, the model can achieve a greater net benefit than if all patients had surgery or none had surgery (Fig. 5A). The net reduction of MVD cases likely to be unsuccessful increased to >75 per 100 patients when applied to patients with a perceived likelihood of success after MVD of 87.5% (Fig. 5B).

Discussion

MVD is currently recognized as the first choice for treatment of TN and its effectiveness has been confirmed (2). Nevertheless, 3-31% of patients with TN experience pain recurrence (4-6). The present study showed a 1-year recurrence rate of 23.21%. Independent risk factors associated with prognosis of MVD have been reported (7,8,22), such as TN1 or TN2 status, sensitivity to carbamazepine and severity of neurovascular compression. Prognostic prediction systems for MVD have been developed based on these independent risk factors by different methods (7,8). The aforementioned studies all reported TN1 or TN2 as an independent risk factor related to the prognosis of MVD. However, the latest classification of TN by the International Headache Association in 2019 abandoned the traditional TN1 and TN2 classification method (18,19). According to the latest international pain classification guidelines (ICHD-3 and ICD-11) (17-19), previous evaluation and prediction models are not suiTable for the current clinical diagnosis and treatment. Therefore, the present study was based on previous literature and the latest international pain guidelines. The present study developed a novel practical prognosis prediction system in patients with TN after MVD.

R language was used to program the model and the experimental design method was more novel, the technology was more comprehensive and the results were more reliable than other statistical analysis software such as SPSS. Univariate and multivariate logistic regression analysis showed that NRS, response to neuroanalgesic drugs and neurovascular contact on MRI were associated with good prognosis of MVD. Other factors, including sex, the side of pain, age of onset and disease duration, did not affect the prognosis of MVD. After long-term follow-up, the effectiveness of MVD as a surgical method for treating drug-refractory TN has been proven, and these findings are consistent with the previous literature (17,23,24). In the present study, no significant difference was seen between sexes; however, there were more female than male patients and women still account for the majority of patients with pain recurrence following MVD. Therefore, based on these findings, it can be concluded that men may have a more favorable prognosis. At present, the causal connection between sex and the rate of pain recurrence in patients with TN after MVD remains unclear and it is not known if sex is a risk factor for TN. Female patients exhibit a higher incidence of TN, which may be due to hormone secretion and gene expression differences. For example, migraine and menstrual pain are more common in female patients, and female patients are more sensitive to pain (9,17,25). NRS is a more detailed numerical pain score that accurately represents the preoperative pain degree of patients with TN compared with other pain scores such as the McGill Pain Questionnaire (23,24). Generally, the more severe trigeminal nerve compression and stimulation response, the more severe the pain and relief of neurovascular compression is associated with patient prognosis. Studies have reported that the molecular mechanisms underlying the pathogenesis

Table II. Univariate and multivariate logistic regression analysis.

	Univariate analysis			Multivariate analysis		
Characteristic	OR	95%CI	P-value	OR	95%CI	P-value
Age at onset, years						
<55	1.00			-		
≥55	0.24	0.06-0.86	0.035	-	-	-
Duration of illness	0.99	0.78-1.19	0.889	-	-	-
Sex						
Female	1.00			-	-	-
Male	1.31	0.37-4.62	0.671	-	-	-
Symptomatic side						
Left	1.00			-	-	-
Right	0.29	0.07-1.04	0.068	-	-	-
Trigeminal nerve branches						
V2 + V3	1.00			-	-	-
Other	0.19	0.01-1.14	0.131	-	-	-
Neurovascular contact on MRI						
Vascular deformity	1.00			1.00		
Absent vascular proximity or vascular contact only	34.91	5.89-674.28	0.001	98.55	5.39-10642.56	0.014
NRS						
4-10	1.00			1.00		
0-3	32.80	6.29-265.27	<0.001	58.50	4.71-2349.77	0.007
REZ						
Yes	1.00			-		
No	12.60	1.45-270.27	0.036	-	-	-
Response to neuroanalgesic drugs						
Yes	1.00			1.00		
No	13.88	3.45-66.90	<0.001	60.35	4.84-2661.18	0.007

NRS, numeric rating scale; MRI, magnetic resonance imaging.

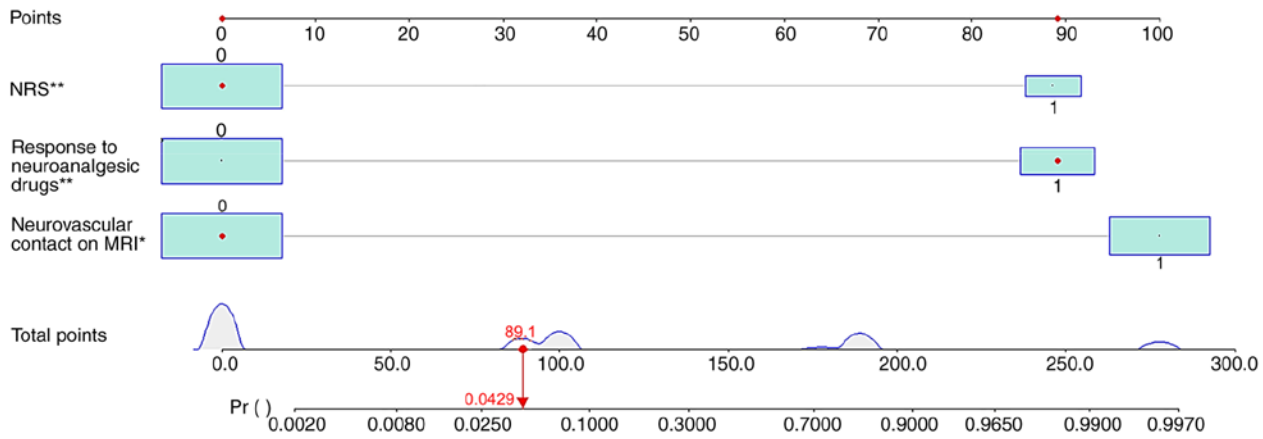

Figure 1. Nomogram to predict pain recurrence rate after MVD for TN. The nomogram was developed by incorporating the following three parameters: NRS (0=0-3;1=4-10), neurovascular contact on MRI (0=Vascular deformity; 1=Absent vascular proximity or vascular contact only) and response to neuroanalgesic drugs (0=Yes, 1=No). The red text/arrow indicates an example for predicting the probability of pain recurrence for a patient with TN after MVD with low NRS, response to neuroanalgesic drugs and vascular deformity. *P<0.05, **P<0.01 (significance of variable in the multivariate logistic regression analysis). NRS, numeric rating scale; MRI, magnetic resonance imaging; MVD, microvascular decompression; TN, trigeminal neuralgia; Pr, predict.

of TN involve changes in various pain-associated neuropeptides, inflammatory mediators and ion channels (26,27). The neuroanalgesic drugs, such as carbamazepine, have membrane-stabilizing effects, which decrease permeability of

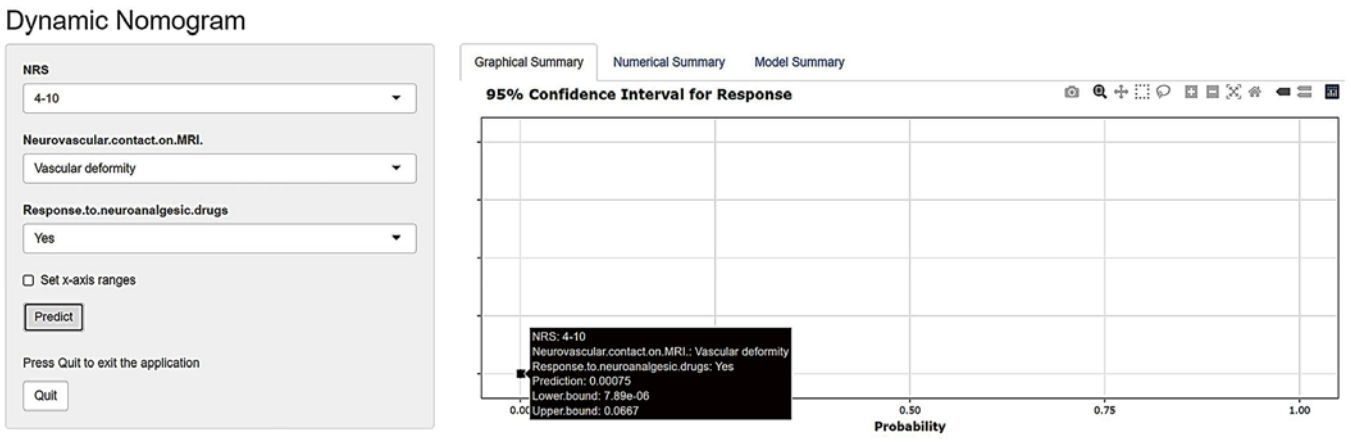

Figure 2. Dynamic nomogram for the probability of pain recurrence in patients with TN after MVD. Predicted probability of pain recurrence after MVD in patients with TN and NRS score of 4-10 and vascular deformity who responded to neuroanalgesic drugs. NRS, numeric rating scale; MRI, magnetic resonance imaging; MVD, microvascular decompression; TN, trigeminal neuralgia.

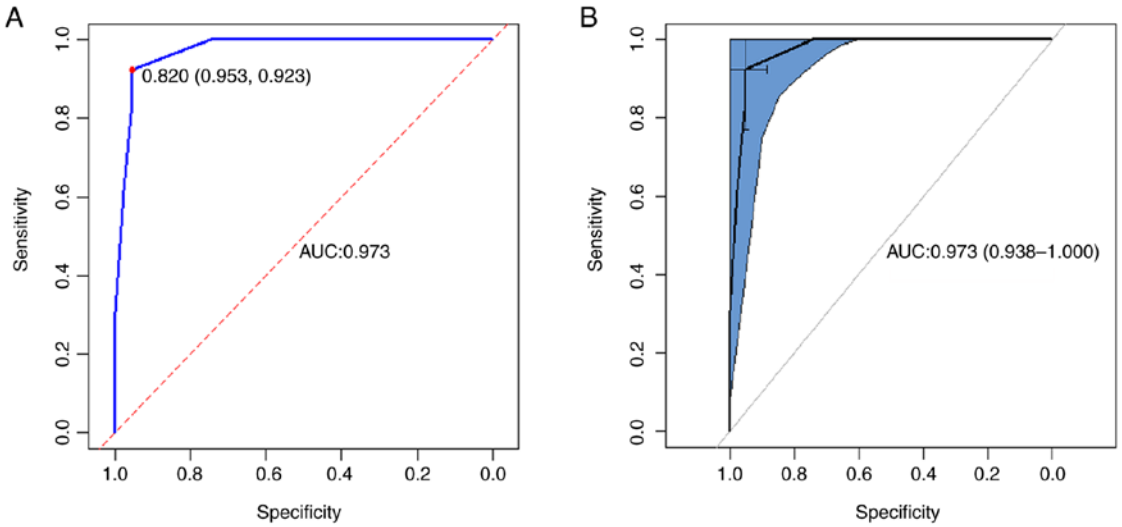

Figure 3. ROC curves. (A) ROC curve evaluation of discrimination power. (B) Confidence interval of AUC. ROC, receiver operating characteristic; AUC, area under the curve.

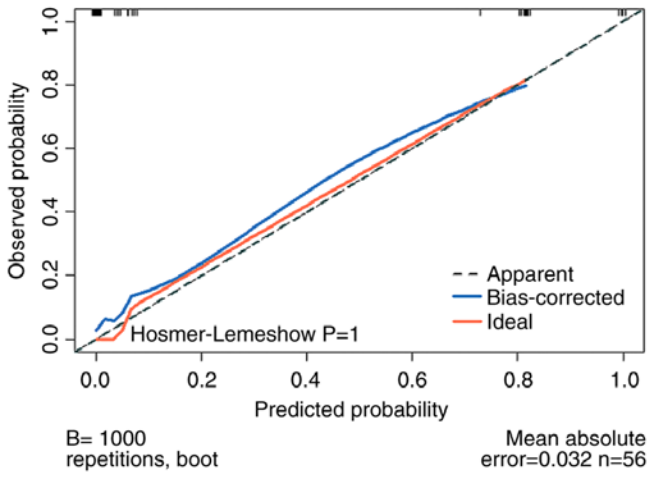

Figure 4. Calibration curve for the nomogram. The x-axis represents the predicted probability and the y-axis denotes the observed probability. Black dashed line indicates perfect prediction. The red solid line represents the entire cohort (n=56) and the blue solid line is bias-corrected by bootstrap (1,000 repetitions), indicating observed nomogram performance.

nerve cell membrane to Na^+ and Ca^{2+}, thereby decreasing the cell excitability and prolonging the refractory period. They may also enhance synaptic transmission function of γ-aminobutyric acid. Neuroanalgesic drugs are widely accepted as a classical conservative treatments of TN (1,17). Patients who respond to drug therapy have better prognosis. Effective drug treatment may be influenced by factors such as vascular compression and compression deformation. When the vascular compression is relieved, the effect of MVD is excellent. However, if the nerve has no obvious vascular compression, stimulation injury is severe or the postoperative compression is relieved but the function does not recover due to severe injury, MVD does not improve pain and the prognosis is poor. The presence of neurovascular contact on MRI is identified as a standalone risk factor for pain recurrence following MVD. The level of neurovascular compression indicated by this independent risk factor plays a key role in classical theories of etiology. Basic and clinical evidence support the hypothesis of demyelination (1,28), which suggests the trigeminal nerve is compressed

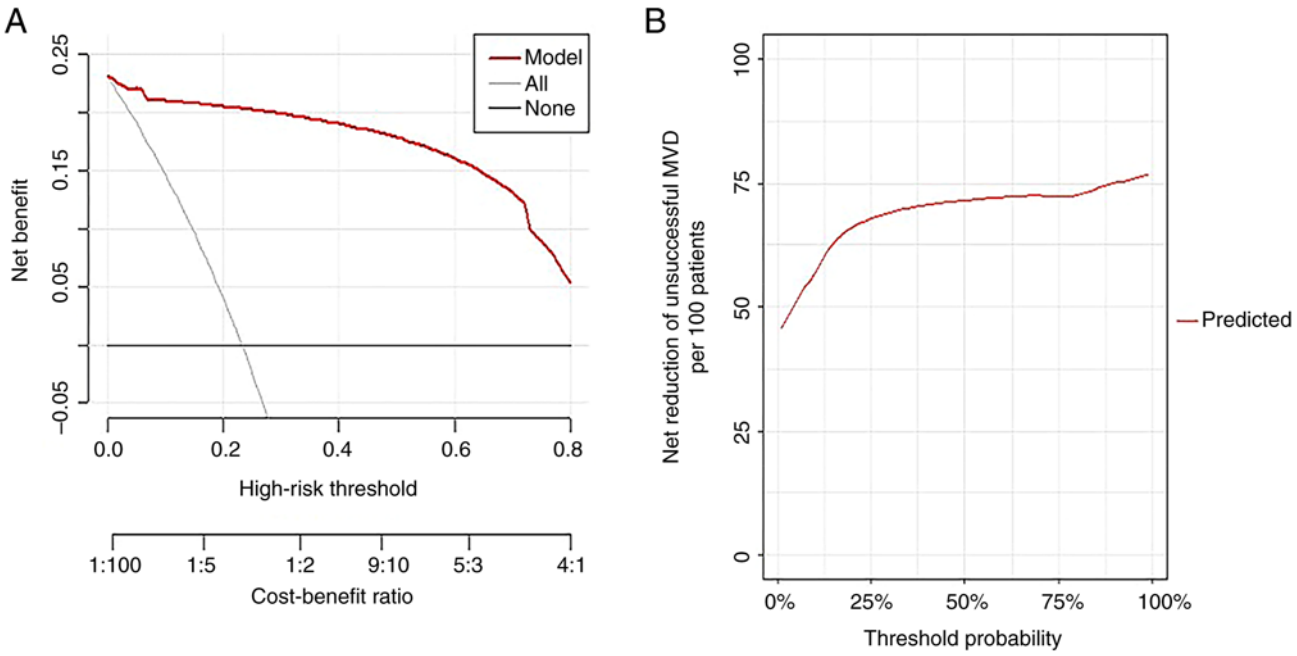

Figure 5. Decision-curve analyses of the predictive ability of the nomogram for pain recurrence rate following MVD. (A) When the high-risk threshold probability is 0-100%, the model can achieve a greater net benefit than if all or no patients had surgery. (B) The X-axis represents the net reduction of unsuccessful MVD per 100 patients, while the Y-axis represents the threshold probability. DCA depicts that this model offers net reduction of 75 cases likely to be unsuccessful per 100 patients undergoing MVD above a decision threshold of 87.5%. DCA, decision curve analysis; MVD, microvascular decompression.

by blood vessels, especially the superior and anterior inferior cerebellar arteries and the trigeminal nerve is stimulated by pulsating blood vessels (26,27). Therefore, demyelination of the sensory branches of the trigeminal nerve is the primary driver of the pathogenesis and pathophysiology of TN. This pathological demyelination can result from physical compression of the trigeminal ganglion or other primary demyelinating diseases. Studies in patients with TN and animal models have revealed significant molecular changes, channel lesions and electrophysiological abnormalities in affected trigeminal nerves (12,26-28). Therefore, neurovascular contact on MRI is an independent risk factor for pain recurrence after MVD.

Based on the aforementioned independent risk factors, an online dynamic nomogram was developed. C-index and ROC were used to measure model discrimination. Bootstrap resampling was used for internal validation and calibration curve was constructed to assess calibration of the proposed model. DCA was used to evaluate the clinical applicability of the model. The aforementioned indexes showed that the model had good discrimination and calibration and clinical applicability. Patient data was input into the web version of the model to obtain the predicted recurrence probability. According to preoperative clinical and imaging findings, patients with TN with high NRS, response to neuroanalgesic drugs and severe neurovascular compression had the lowest probability of pain recurrence after MVD. The present prediction model demonstrated a net benefit compared with if all patients had surgery or none had surgery when the high-risk threshold probability was between 0 and 100%. The present model would reduce the risk of surgical failure by >75%, even in cases where the neurosurgeon believes likelihood of success is >90%. Other studies have included more clinical features in the assessment of pain outcomes in patients with TN after MVD to improve overall management (7,8). Among them, the classical typing method of TN (TN1 and TN2) was not included in this study (15) because the International Headache Society published a new classification in its 2019 guidelines (19). The most representative studies in assessing pain outcomes with TN after MVD are those by Hardaway *et al* (7) and Panczykowski *et al* (8). The aforementioned studies provide important guidance and reference the study of a prediction pain recurrence model in patients with TN after MVD. However, the aforementioned models all adopted the classical TN classification (15) and the latest TN classification (19) was not used, which could not well apply to the current clinical diagnosis and treatment practices. The present study used a numerical rating scale to assess severity of TN, which is the primary symptom of this condition. There are four categories of digital pain score: 0, no; 1-3, mild; 4-6, moderate; and 7-10, severe pain. A previous study showed that when the NRS score iss >4, the quality of life, sleep and diet are affected. In such cases, the standard clinical diagnosis and treatment protocols typically involve the use of medications or surgical interventions (29). Based on this, the present study divided patients into NRS0-3 and NRS4-10 categories. Univariate and multivariate analyses demonstrated that NRS was associated with the risk of recurrence after MVD, as previously reported (23,24). NRS is commonly used in chronic pain scoring systems and is similar to Visual Analog Scale, being less affected by non-pain intensity factors than VRS or Faces Pain Scale-Revised (24). Therefore, the present study simulated clinical practice. The present study showed that NRS, response to neuroanalgesic drugs and neurovascular contact on MRI predicted the recurrence rate of pain following MVD in patients with TN.

Nomogram is used to analyze the prognosis of patients with brain injury (30) and cancer (31,32) and replace traditional prediction models. In previous studies, such as that

by Hardaway *et al* (7) and Panczykowski *et al* (8), it was suggested that prognostic models incorporating multiple independent risk factors can effectively predict the outcome of patients undergoing MVD. This approach helps provide valuable guidance to clinicians and patients in making preoperative decisions and reduce the incidence of unnecessary surgeries. However, the previous studies only used univariate or multivariate analysis, or the key factors in the model did not use the latest trigeminal pain diagnosis and treatment guidelines (such as TN classification), or only provided a static prognostic scoring system which is not helpful for clinicians or patients to refer to (7,8,33) The present study used R language software, to establish a user-friendly prediction model web version, more convenient to use, more accurate data display. As shown in Fig. 2 (available at ppramvdftn.shinyapps.io/DynNomapp/pages), the personalized information allows for the selection of appropriate independent risk factors based on individual patients. The prognostic system then provides real-time probability predictions accordingly. For example, for a patient with 4-10 based on NRS, response to neuroanalgesic drugs and vascular deformity, the predicted value of the system is 0.00075, the recurrence rate is low and surgery is recommended. The system is easy to use and the data is comprehensible and accurate.

The present study has limitations. First, a single-center study with a relatively small sample size introduces selection bias. In addition, the present study did not elucidate whether race, location, lifestyle habits, depression and anxiety or other factors influence the likelihood of better pain improvement (34,35). Future studies should expand the single-center sample size to refine the model and conduct multicenter studies that will allow random selection of patients with TN from other centers for external validation. In addition, because of the retrospective cohort nature of the study, biases during follow-up are inevitable. Physicians should consider other relevant factors, including patient overall health, comorbidities and preferences, alongside the predictive model results when deciding on the appropriate course of treatment. The present cohort was followed up for 1 year; longer follow-up is needed to test the prognostic risk model and effect of MVD on the risk of pain recurrence in patients with TN.

In summary, the present study developed an online dynamic nomogram to predict the likelihood of pain recurrence in patients with TN after MVD. The analysis of ROC, calibration and DCA curve showed that nomogram had good prediction and calibration performance. The model is valuable for predicting pain improvement in patients with TN after MVD, reducing the incidence of unnecessary MVD; it is a new practical prognostic prediction system for TN MVD, which is worthy of being used by clinical doctors and patients, providing them with valuable references when making decisions regarding treatment options.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HW designed the study, collected data and wrote the manuscript. SL analyzed the data and constructed the model. ZW collected clinical case data, conducted follow-ups with patients after discharge, and performed preliminary organization and analyzed of case data. BZ, DW and ZG performed MVD. JW designed the study. HW and SL confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the ethics committee of the Second Affiliated Hospital at Anhui Medical University (Hefei, China; approval no. 202115). The Helsinki Declaration was followed. All patients provided written informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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