



Prognostic nomogram for microvascular decompression–treated trigeminal neuralgia

Wen-Bo Zhang¹ · Ya-Ying Zeng² · Bo-Wen Chang¹ · Ling-Zhao Min¹ · Qiu-Yang Sun¹ · Bin Li¹ · Bang-Bao Tao¹ · Xiao-Qiang Wang¹

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Abstract

This study aimed to establish an effective prognostic nomogram for microvascular decompression (MVD)–treated trigeminal neuralgia (TN). The nomogram was based on a retrospective cohort study of 1054 patients with TN. During the period 2005–2014, 845 patients at our department treated TN with MVD and served as a development cohort. The predictive accuracy and discriminative ability of the nomogram were determined by concordance index (C-index) and calibration curve. The model was externally validated by 209 TN patients during 2014–2016. Multivariate cox analysis suggested that the patient’s age, atypical pain, vascular type, number of offending vessels, and second MVD were significant factors influencing the prognosis of MVD-treated TN. The C index of nomogram in the development cohort was 0.767 (95% CI, 0.739–0.794), and 0.749 (95% CI, 0.688–0.810) in the validation cohort. We developed and validated a nomogram to predict 3-year overall remission rate after MVD treatment of TN. The nomogram can be used in clinical trials to determine the likelihood of pain recurrence in TN patients treated with MVD for 3 years to aid in the comprehensive treatment of TN.

Keywords Trigeminal neuralgia · Remission rate · Microvascular decompression · Nomogram · Predictive model

Introduction

The incidence of idiopathic TN is reported as 1 to 2/10000 [1], and oral carbamazepine usually relieves the onset of pain, but its strong side effects force patients to abandon medication. Since Dandy [2] first described TN as a result of vascular compression of the trigeminal nerve, this neurovascular conflict theory has been widely accepted. According to this theory, microvascular decompression (MVD) has become one of the most effective ways to treat TN. Although MVD is more effective in treating TN than stereotactic radiation surgery (SRS) and balloon compression and other treatments, the recurrence of TN is not uncommon; it has been reported that its

annual recurrence rate reached 1–5% [3–6], and 5-year recurrence rate reached 22–42% [7, 8]. According to our previous study, the vast majority of recurrences occurred within 3 years after surgery and the 3-year recurrence rate was 27.1% [9]. According to the literature, many factors affect the prognosis of TN, including the gender of the patient, the duration of pain, whether the pain is typical, and whether it is venous compression [10–12]. However, current studies are single-factor studies, isolating the relationship between various factors. The authors suggest that one factor is a significant factor for the recurrence of TN, but they do not integrate these factors in the recurrence of the TN. The development of nomogram makes up for this deficiency; it can integrate a variety of significant factors to model and predict the patient’s survival rate (remission rate). Currently, nomograms have been developed in the majority of cancer types and it has been proposed as an alternative or even a new standard. However, this model is rare in TN. John [13] developed a nomogram based on the prognosis of patients with TN in 2014; although it is a good predictive model, the nomogram is based on TN treated by SRS; it is questionable whether this nomogram can be applied to MVD-treated of TN. At present, we have not found any nomogram based on MVD treatment of TN; the purpose of

Wen-Bo Zhang, Ya-Ying Zeng, and Bo-Wen Chang are co-first authors to the article.

✉ Xiao-Qiang Wang
wangxiaoqiang@xinhumed.com.cn

¹ Department of Neurosurgery, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

² Department of Neurology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China

this paper is to develop and validate the nomogram of MVD-treated TN, and predict the 3-year remission rate of patients.

Patients and methods

Patients and study design

A retrospective study was conducted on a primary cohort of patients who underwent MVD for TN between 2005 and 2016 at the Xinhua Hospital (Shanghai, China). The study was approved by the Xinhua Ethics Committee; since the study is a retrospective study, no informed consent is required. Among them, 845 TN patients were used as development cohort between 2005 and 2014, and 209 TN patients served as external validation cohort between 2014 and 2016. Exclusion criteria were as follows: (1) TN was secondary to tumor, vascular malformation, and demyelinating disease; (2) other treatment other than MVD in this hospitalization; (3) patients who lost follow-up. The database reviewed retrospectively consisted of patients' age, sex, gender, hypertension, diabetes, duration of onset, typical or not (according to Burchiel's classification [14], TN is divided into typical pain and atypical pain), whether V2 related (V1, V3 or V2, V1–2, V2–3, V1–3), compression vessel type (including simple arteries, simple veins, arteriovenous mixture), the number of compression vessels (1, 2, ≥ 3), the disease side, the number of compression zones (according to Feng's theory [15], we divide the trigeminal nerve into zone 1–5, and judge the "zone number" of vascular compression), whether second MVD surgery, whether SRS before surgery, and follow-up period with remission status: followed up every 3 months in the first year, every half year in 1–3 years, and every 1 year after 3 years. We evaluated the surgical outcome according to the BNI [16], and considered patients with postoperative pain BNI grade I and II as remission, and III–V as non-response. All follow-up and pain assessments were performed by independent third parties.

Statistical analysis

The Cox proportional hazard regression model was used to estimate the risk ratio for each potential risk factor (and the corresponding 95% CI), and single-factor and multi-factor Cox regression analysis was performed on patient baseline data using Empowerstats and R. Calibration demonstrates the consistency of the predicted results with the actual results and accurately evaluates the predictive power of the model. The C index is a measure of a consistency similar to the area under the receiver operating characteristic (ROC) curve. The discrimination ability of the developed model is verified by using C index. Discrimination refers to distinguishing whether an event occurs or not; the larger the C index, the more

accurate the model is; and quantitative evaluation can be done by calculating the C index developed for the model. A nomogram was formulated based on the results of multivariate analysis and by using the package of rms in R version 3.6.1. *P* values were two-sided; *P* < 0.05 was considered to have statistical significance.

Results

Clinical characteristics of the development and validation sets

There were 845 patients in the development sets and 209 patients in the validation sets. The database included patients' age, sex, gender, hypertension, diabetes, duration of onset, typical or not, whether V2 related, compression vessel type, the number of compression vessels, the disease side, the number of compression zones, whether second MVD surgery, and whether SRS before surgery, a total of 13 variables (Table 1).

Risk factors for overall remission rate and development of the nomogram

In the development sets, the mean follow-up time was 35.3 months and a total of 255 (30.2%) patients had no pain relief during follow-up. In the univariate analysis, the patient's age, length of onset, typical or not, compression vessel type, the number of compression vessels, and whether second MVD surgery were significantly associated with overall remission rate (*P* < 0.1). After multivariate COX regression analysis excluded confounding factors, the patient's age, typical or not, compression vessel type, the number of compression vessels, and whether second MVD surgery were independent predictors; in contrast, the duration of onset was not an independent predictor (Table 2).

Based on these results, we developed a predictive model and generated a nomogram that predicts the 3-year overall remission rate. Each clinical factor corresponds to a specific score, and the straight line is drawn up to the point axis to calculate the total score, which corresponds to a 3-year remission axis with a 3-year remission probability. The C-index for TN prediction was 0.767 (95% CI, 0.739–0.794); the calibration plot of the 3-year remission probability after MVD shows the best agreement between the nomogram and the actual observation (Figs. 1 and 2).

External validation set and performance

Evaluate the model's ability to identify and calibrate through external validation. The C-index, which indicated discrimination ability, was 0.749 (95% CI, 0.688–0.810). The calibration plot of the 3-year remission probability is shown in Fig. 2; we

Table 1 Baseline characteristics in modeling cohort and validation cohort

Factors	Development (<i>n</i> = 849)	Validation (<i>n</i> = 209)
Vessel type		
Artery	404 (51.83%)	90 (43.06%)
Vein	153 (18.11%)	52 (24.88%)
Mixed	288 (34.08%)	67 (32.06%)
Vessel number		
1	465 (55.03%)	120 (57.42%)
2	325 (38.46%)	76 (36.36%)
≥ 3	55 (6.51%)	13 (6.22%)
Zone number		
1	438 (51.83%)	110 (52.63%)
2	324 (38.34%)	73 (34.93%)
3	52 (6.15%)	14 (6.70%)
4	31 (3.67%)	12 (5.74%)
Second MVD		
No	735 (86.98%)	179 (85.65%)
Yes	110 (13.02%)	30 (14.35%)
SRS treatment		
No	785 (92.90%)	192 (91.87%)
Yes	60 (7.10%)	17 (8.13%)
Sex		
Male	300 (35.50%)	78 (37.32%)
Female	545 (64.50%)	131 (62.68%)
Age (years)		
< 50	85 (10.06%)	17 (8.13%)
50–59	220 (26.04%)	56 (26.79%)
60–69	340 (40.24%)	90 (43.06%)
≥ 70	200 (23.67%)	46 (22.01%)
Time of onset (months)		
< 36	363 (42.96%)	92 (44.02%)
36–96	259 (30.65%)	65 (31.10%)
> 96	223 (26.39%)	52 (24.88%)
Side		
Left	340 (40.24%)	81 (38.76%)
Right	505 (59.76%)	128 (64.24%)
HP		
No	595 (70.41%)	152 (72.73%)
Yes	250 (29.59%)	57 (27.27%)
DM		
No	755 (89.35%)	194 (92.73%)
Yes	90 (10.65%)	15 (7.18%)
V2-related		
No	80 (9.47%)	16 (7.66%)
Yes	765 (90.35%)	193 (92.34%)
Type		
Typical	575 (68.05%)	144 (68.90%)
Atypical	270 (31.95%)	65 (31.10%)

MVD, microvascular decompression; HP, hypertension; DM, diabetes mellitus; SRS, stereotactic radiation surgery

can see that in the verification queue, the calibration curve almost perfectly fits the actual situation.

Discussion

MVD is the first-line treatment of choice for patients with idiopathic TN; Dandy [2] assumes that trigeminal nerve root compression by the superior cerebellar artery is the main cause of TN; Gardner [17] first performed surgery to

perform vascular decompression; Jannetta [18] and Barker et al. [3] introduced microsurgical methods and promoted MVD as the main treatment for idiopathic TN. Although some people have questioned that neurovascular compression is the cause of TN [19], now that vascular compression causes TN to be an overwhelming consensus, neurologists and neurosurgeons now believe that neurovascular compression assumptions are correct and explain most TN patients with facial pain without tumor or demyelinating disease. MVD is a non-destructive technique, and pain relief after MVD treatment protects trigeminal nerve and does not damage it [20]. The large series shows that 65 to 70% of patients still have no pain after ≥ 10 years [3, 21]; also, the incidence of complications of this procedure is very low when performed by experienced surgeons [22]. Therefore, MVD is a safe and effective procedure that eliminates facial pain and retains most of the trigeminal nerve function.

Although MVD is a highly successful surgery, its immediate remission rate reached 91.7% in our development population; however, MVD treatment of TN is not satisfactory in terms of long-term remission rate. It has been reported that the 3-year recurrence rate of MVD is 27.1% [9], and the 5-year recurrence rate is 22–42% [7, 8]. In our study, the 3-year recurrence rate was 26.6%, and the probability of recurrence was significantly reduced after 3 years. This is a frustrating phenomenon; can we seek other treatments to avoid craniotomy for patients with a high risk of potential recurrence? Currently, neurosurgeons have identified several risk factors that affect the effectiveness of MVD surgery: Zhong found in nearly 3000 operations that venous compression is the main cause of MVD recurrence [23], while Lee et al. found that 75% of patients with TN who have simple venous compression will relapse within 1 year [24]; younger patients have worse outcomes than older patients [25–27]; Barker et al. found that the 10-year effective rate of secondary MVD was 42%, which was much lower than 64% of the first MVD operation [3]; atypical pain is worse than typical prognosis [12, 28]. According to Sindou et al.'s research [29], patients' pain branches and the degree of compression of nerve by blood vessels had a significant impact on prognosis. Besides, the patient's gender, hypertension, diabetes, whether SRS before surgery, duration of disease, and so on have also been reported to be related to the prognosis of TN treated by MVD [10–12, 30, 31].

However, even if the patient has the same risk factor, the remission rate is quite different. MVD failure caused by a multi-factorial cause, and the single-factor analysis may affect the prognosis of one-sidedness, and often miss other important influencing factors, thus losing accurate judgment on the prognosis of patients. Nomogram is a good tool for predicting patient survival; it can integrate

Table 2 Risk factors for overall survival according to Cox proportional hazards regression model

Factors	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	<i>P</i> value	Hazard ratio	95% CI	<i>P</i> value
Vessel type						
Artery	1			1		
Vein	4.43	(3.24, 6.04)	< 0.01	3.37	(2.42, 4.70)	< 0.01
Mixed	1.90	(1.39, 2.59)	< 0.01	1.13	(0.76, 1.67)	0.55
Vessel number						
1	1			1		
2	1.10	(0.84, 1.43)	0.50	1.99	(1.34, 2.96)	< 0.01
≥ 3	2.39	(1.60, 3.56)	< 0.01	3.01	(1.92, 4.73)	< 0.01
Zone number						
1	1					
2	1.25	(0.96, 1.62)	0.10			
3	1.15	(0.69, 1.91)	0.59			
4	1.18	(0.63, 2.18)	0.60			
Second MVD						
No	1			1		
Yes	2.44	(1.81, 3.30)	< 0.01	1.52	(1.07, 2.16)	0.02
SRS treatment						
No	1					
Yes	0.91	(0.54, 1.54)	0.73			
Sex						
Male	1					
Female	1.01	(0.78, 1.31)	0.95			
Age (years)						
< 50	1			1		
50–59	1.60	(1.07, 2.39)	0.02	1.47	(0.97, 2.22)	0.07
60–69	0.55	(0.36, 0.84)	0.006	0.64	(0.42, 1.00)	0.05
≥ 70	0.53	(0.33, 0.85)	0.008	0.57	(0.36, 0.92)	0.02
Time of onset (months)						
< 36	1					
36–96	0.82	(0.61, 1.09)	0.17			
> 96	0.74	(0.54, 1.02)	0.06			
Side						
Left	1					
Right	1.00	(0.77, 1.28)	0.97			
HP						
No	1					
Yes	1.16	(0.89, 1.51)	0.27			
DM						
No	1					
Yes	0.76	(0.48, 1.18)	0.22			
V2-related						
No	1					
Yes	1.18	(0.74, 1.86)	0.49			
Type						
Typical	1			1		
Atypical	2.51	(1.96, 3.23)	< 0.01	2.42	(1.83, 3.19)	< 0.01

MVD, microvascular decompression; *HP*, hypertension; *DM*, diabetes mellitus; *SRS*, stereotactic radiation surgery

In univariate analysis, we found that the patient's age, length of onset, typical or not, compression vessel type, the number of compression vessels, and whether second MVD surgery were significantly associated with overall remission rate ($P < 0.1$). After multivariate analysis, we found that the patient's age, typical or not, compression vessel type, the number of compression vessels, and whether second MVD surgery are independent risk factors affecting patient prognosis. Therefore, we incorporate these 5 factors into the nomogram model

the influence of various factors on patient survival rate, and has been widely used in the survival analysis of cancer patients and gradually replaces the traditional prediction model. It is a pity that this predictive model is rarely used in TN patients. Currently, only John [13] developed a nomogram based on the prognosis of patients with TN in 2014; a predictive model was included in 446 patients,

which is a good predictor of long-term remission probability. However, the model still has shortcomings: first, the model is based on a predictive model of 446 patients with TN who have been treated with SRS. The effect of MVD in the treatment of TN is superior to that of SRS, and this model cannot be applied to patients with TN treated with MVD; second, after the model passed the standard, only

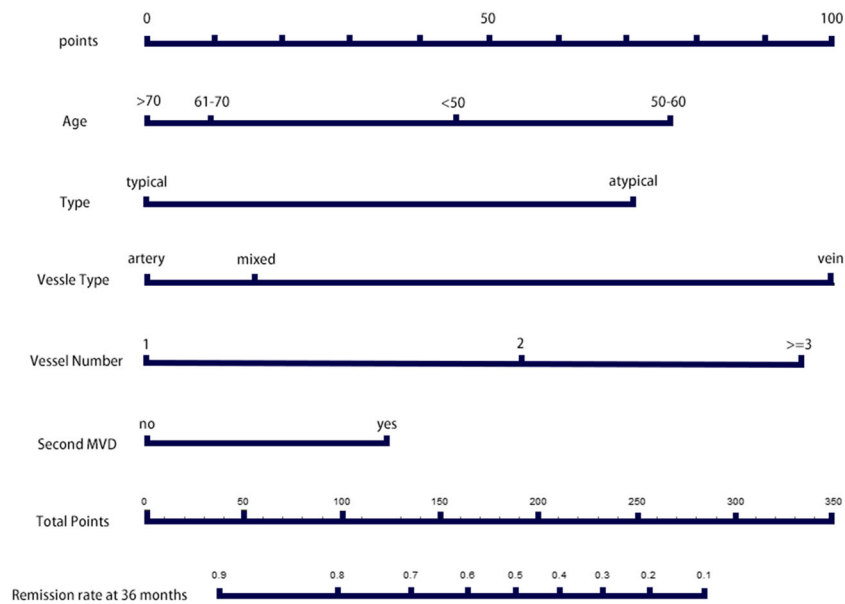


Fig. 1 Nomogram to predict 3-year overall remission after MVD for TN. Clinical factor corresponds to a specific point by drawing a line straight upward to the points axis. After the sum of the points is located on the

total points axis, the sum represents the probability of 3-year remission rate by drawing straight down to the 3-year survival axis. MVD, microvascular decompression; TN, trigeminal neuralgia

446 patients were included in the model, and the smaller number of patients made the results less credible; thirdly, due to the improvement of technology and the change of operation concept, we should update different predictors to build a new model. In 2005–2016, we included 1054 patients into the model and constructed the first nomogram model based on MVD for TN. A large number of patients and the latest MVD concept make the model accurate. After multivariate Cox survival analysis, we included age, typical or not, compression vessel type, the number of compression vessels, and whether second MVD surgery, a total of five factors, as nomogram score points. The results also support our view that older

patients, typical pain, arterial compression, and patients with first surgery have a better prognosis [32, 33, 24]. The model has good prediction ability; C index is 0.767 (95% CI, 0.739–0.794), while in the validation queue, C index is 0.749 (95% CI, 0.688–0.810). The calibration plot in the validation queue almost perfectly fits the actual situation (Fig. 2).

Finally, the study still has several shortcomings. Firstly, this study is based on a single-center study. Although this research center is one of the most frequently operated institutions for TN, it is unclear whether ethnicity, diet, climate, and other factors affect the prognosis. Whether the model can be used in primary hospitals or other areas has

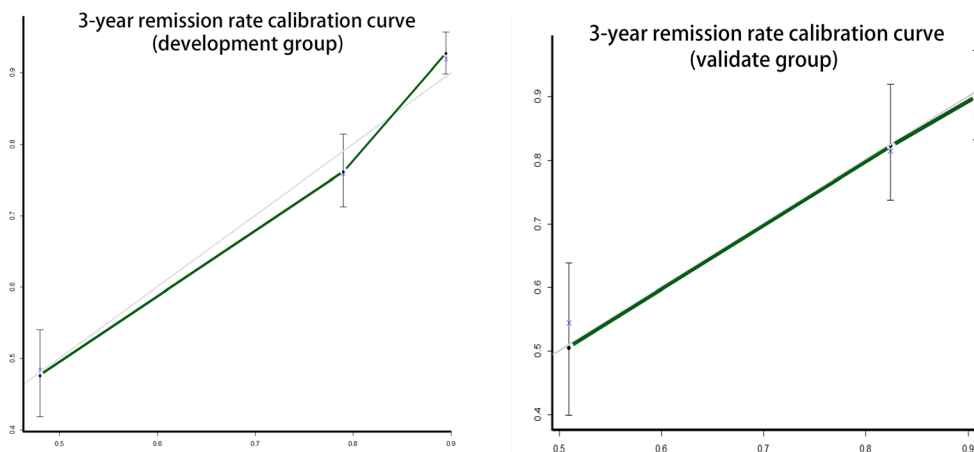


Fig. 2 Nomogram-predicted probability of 3-year remission rate. The calibration curve for predicting patient remission rate at 3 years in the development cohort (a) and at 3 years in the validation cohort (b).

Nomogram-predicted probability of overall remission rate is plotted on the x-axis; actual overall remission rate is plotted on the y-axis

not been verified. In the next step of preparation, we will adopt multi-center cooperation and randomly select TN patients from other centers as external validation. Secondly, this paper is a retrospective cohort study, and the bias generated during the follow-up is unavoidable. Thirdly, there may be selection bias when excluding some patients with missing data.

Conclusions

In conclusion, we have developed a nomogram to predict the 3-year remission rate of TN patients treated with MVD, which can be used to provide advice for patients after MVD. It is also possible to determine adjuvant therapies such as SRS and balloon compression, based on the results of this nomogram.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study has been approved by the Institutional Ethics Committee of Xinhua Hospital and was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. For this retrospective study, formal consent was not required.

Informed consent Informed consent was obtained from all individual participants who were included in the study.

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