Risk Factors for Recurrence of Trigeminal Neuralgia After Percutaneous Balloon Compression

--------Development and Validation of a Machine Learning-Based Risk Prediction Model for Recurrence After Percutaneous Balloon Compression in Trigeminal Neuralgia Patients: A Retrospective Cohort Study

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1. Research Background and Rationale

Trigeminal Neuralgia (TN) is a disorder characterized by recurrent paroxysmal severe pain within the distribution area of the trigeminal nerve, with diagnosis confirmed in accordance with the criteria of the International Classification of Headache Disorders, 3rd edition (ICHD-3) [1]. Epidemiological studies have shown that the annual incidence of TN ranges from 4.3 to 28.9 per 100,000 population, and the prevalence can reach 10 to 30 per 100,000 population. Middle-aged and elderly individuals are the main affected group, with a slightly higher incidence in women. This disease causes severe impairment to patients' quality of life, mental health, and social functioning [2, 3].

For TN patients who are unresponsive to drug therapy or unable to tolerate drug adverse reactions, surgical intervention becomes a necessary treatment option. Among various interventional treatment methods, Percutaneous Balloon Compression (PBC), first reported by Mullan and Lichtor in 1983 [4], has become the preferred minimally invasive treatment for elderly patients, those with multiple comorbidities, or those who refuse craniotomy, due to its advantages such as relatively simple operation, short anesthesia time, and avoidance of craniotomy-related risks [5]. Studies have confirmed that the immediate pain relief rate (BNI Grade I-III) after PBC can exceed 90% [6].

However, the long-term efficacy of PBC is limited by pain recurrence. Long-term follow-up studies have revealed that pain recurrence after PBC exhibits a significant time-dependent pattern: the 1-year recurrence rate is 8%-15%, the 3-year recurrence rate increases to 22%-30%, and the 5-year cumulative recurrence rate reaches 20%-35% [7, 8]. The mechanism of recurrence involves the combined action of multiple factors, mainly including: (1) Baseline patient characteristics: Comorbid multiple sclerosis (HR = 3.21) [9], long-term hypertension (HR = 1.87) [10], long disease duration (>5 years), and non-classical TN are all important risk factors [11]; (2) Surgical operation parameters: The formation of an "ideal pear-shaped" balloon [12] and appropriate balloon compression parameters (volume ratio 1.5-1.8, pressure 138-154 kPa, duration 60-120 seconds) [13] are critical for prognosis; (3) Anatomical factors: Narrow foramen ovale (long diameter <7 mm) and abnormal Meckel's cave volume also significantly affect treatment outcomes [14].

Despite numerous studies investigating the influencing factors of recurrence after PBC, existing studies have obvious limitations: Firstly, the sample size is generally small. Most single-center studies have a sample size of less than 200 cases, lacking statistical power to examine complex relationships in high-dimensional data [17, 18]; Secondly, the construction of prediction models is incomplete. Traditional statistical methods such as Cox regression have limitations in handling complex non-linear relationships and interaction effects between variables [19]; Thirdly, external validation is insufficient. Most existing prediction models only undergo internal validation in the development cohort, lacking external validation in independent cohorts, which affects the generalization ability of the models [20]; Finally, the integration of predictors is inadequate. Most studies fail to systematically integrate multi-dimensional information such as clinical characteristics, imaging parameters, and surgical operation variables [21].

Compared with traditional statistical methods, machine learning algorithms can better handle high-dimensional data, automatically capture complex relationships between predictors and outcomes, and show significant advantages in large-sample data [22]. Ensemble learning methods such as Random Forest and Gradient Boosting Machine are particularly suitable for addressing non-linear relationships and interaction effects in clinical data [23].

The research center where the authors are located has performed nearly 700 cases of balloon compression surgery for trigeminal neuralgia and possesses rich clinical data. Therefore, based on a large-sample cohort of 700 cases, this study aims to systematically develop and validate a prediction model for recurrence after PBC using machine learning methods, so as to make up for the deficiencies of existing studies, provide a personalized risk assessment tool for clinical practice, and promote the development of PBC treatment towards precision medicine.

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2. Research Objectives

2.1 Primary Objective

To develop a clinical prediction model based on machine learning algorithms for individualized prediction of pain recurrence risk in patients with primary trigeminal neuralgia after PBC.

2.2 Secondary Objectives

(1) Identify and evaluate key predictors influencing recurrence after PBC.

(2) Compare the predictive performance of different machine learning algorithms with the traditional Cox proportional hazards regression model.

(3) Transform the final model into a clinically applicable Nomogram or online risk calculator.

3. Study Design

Study Type: Single-center, retrospective, observational cohort study.

Guideline Compliance: This study will adhere to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement.

Study Population: All patients with primary TN who met the inclusion criteria and underwent their first PBC treatment in the Department of Pain Medicine, the Second Xiangya Hospital of Central South University, from January 1, 2018, to June 30, 2025.

Sample Size: A total of 700 patients are expected to be included. With recurrence as the endpoint event, the expected number of events will be more than 175, which meets the requirement for the number of events in machine learning model development.

4. Study Subjects

4.1 Inclusion Criteria

(1) Aged ≥ 18 years.

(2) Meet the diagnostic criteria for primary trigeminal neuralgia according to the International Classification of Headache Disorders, 3rd edition (ICHD-3).

(3) Undergo the first PBC treatment.

(4) Have complete preoperative clinical data, imaging data, and intraoperative records.

(5) Have at least one postoperative follow-up record available for determining the recurrence status.

4.2 Exclusion Criteria

(1) Secondary trigeminal neuralgia (e.g., caused by cerebellopontine angle tumors, multiple sclerosis, etc.).

(2) Missing rate of key predictor variables (e.g., balloon shape) or outcome variables > 15%.

(3) Postoperative loss to follow-up (defined as no follow-up records available).

5. Study Variables and Definitions

5.1 Outcome Variable (Dependent Variable)

Definition: Pain recurrence (dichotomous variable: Yes/No).

Recurrence Criteria: Postoperative Barrow Neurological Institute (BNI) pain intensity score returns to Grade IV ("persistent pain, controllable with medication") or Grade V ("severe pain, uncontrollable with medication"), lasting for ≥ 1 week, and requiring an increase in medication dose or reoperation.

Time Indicator: From the date of surgery to the date of recurrence or the date of the last follow-up. For patients without recurrence, data will be censored at the date of their last follow-up.

Recurrence-Free Survival (RFS): Recurrence-free survival will be calculated.

5.2 Predictor Variables (Independent Variables)

Data will be extracted from the electronic medical record system, covering the following dimensions:

(1) **Demographic Data**: Age, gender.

(2) **Baseline Clinical Characteristics**: Disease duration, affected side of pain, involved branches, preoperative BNI score, presence of trigger points, presence of persistent background pain, comorbidities (diabetes, hypertension, etc.), preoperative biochemical indicators (inflammatory factors), preoperative sleep score, and anxiety scale score.

(3) **Imaging Anatomical Parameters**: Measured based on preoperative images (MRI/CT), such as foramen ovale size (long diameter, area), Meckel's cave volume and shape, and presence of neurovascular compression.

(4) **Surgical Operation Parameters**: Balloon shape (standard pear-shaped/non-standard pear-shaped), balloon inflation volume, balloon compression time, number of punctures, and guidance method (C-arm fluoroscopy/3D-CT navigation).

(5) **Postoperative Management**: Postoperative medication tapering strategy.

6. Data Collection and Management

(1) **Data Sources**: Hospital Information System (HIS), Picture Archiving and Communication System (PACS), surgical anesthesia system, and outpatient follow-up system.

(2) **Data Extraction**: Trained researchers will extract data using a standardized Case Report Form (CRF).

(3) **Data Anonymization**: All patient identifiers will be removed and replaced with unique study numbers.

(4) **Data Management**: Data entry and storage will be conducted using data collection systems such as Epidata, with logical verification functions set to ensure data quality.

7. Statistical Analysis Plan

7.1 Descriptive Statistical Analysis

For continuous variables, those conforming to a normal distribution will be described using mean ± standard deviation, while those not conforming to a normal distribution will be described using median (interquartile range). For categorical variables, frequency (percentage) will be used for description. Patients will be grouped by recurrence status, and inter-group differences will be compared. For continuous variables, t-test or Mann-Whitney U test will be used based on data distribution; for categorical variables, chi-square test or Fisher's exact test will be used.

7.2 Data Processing

Missing Value Handling: For continuous variables, if the missing rate is low (<5%), median or mean will be used for imputation; if the missing rate is high (≥5%), multiple imputation will be used. For categorical variables, the mode category will be used for imputation, or "missing" will be set as a separate category.

Data Splitting: The total dataset will be randomly divided into a training set and a test set at a ratio of 7:3. The training set will be used for model development and tuning, and the test set will be used for verifying the final model performance.

7.3 Model Development and Comparison

Baseline Model: The Cox proportional hazards regression model will first be used as the baseline model. Variable selection will be based on clinical importance and univariate analysis results, and stepwise regression (forward/backward) will be used to construct the multivariable model.

Machine Learning Models: The following machine learning survival analysis models will be trained on the training set:

Random Survival Forest

Gradient Boosting Machine (using Cox proportional hazards loss function)

CoxBoost

Survival Support Vector Machine

Model Training and Tuning: 5-fold or 10-fold cross-validation will be used to adjust the hyperparameters (e.g., learning rate, tree depth, node size) of each machine learning model to optimize model performance and prevent overfitting.

7.4 Model Performance Evaluation

The performance of all models will be evaluated on the independent test set.

Discrimination: The main evaluation indicator is the **Concordance Index (C-index)**. For time-dependent discrimination, the **Time-dependent Area Under the Receiver Operating**

Characteristic Curve (Time-dependent AUC) at 1 year, 2 years, and 3 years will be calculated.

Calibration: Calibration curves will be plotted to compare the consistency between the predicted recurrence probability and the actually observed recurrence probability. The Brier score will be calculated as a comprehensive evaluation indicator.

Clinical Utility: Decision Curve Analysis (DCA) plots will be drawn to evaluate the clinical net benefit of the model at different threshold probabilities and determine its clinical applicability.

7.5 Model Interpretation and Visualization

For the model with the best performance, SHapley Additive exPlanations (SHAP) values will be used for interpretation to assess the direction and magnitude of the contribution of each predictor to the individual prediction result. SHAP summary plots and SHAP dependence plots will be drawn to visualize the global and local effects of key predictors. Finally, a Nomogram will be plotted based on the results of the optimal model (or Cox model) for direct clinical use.

7.6 Software

All statistical analyses will be performed using R language (version 4.3.0 or higher). The main R packages used will include: survival, randomForestSRC, gbm, CoxBoost, rms, timeROC, ggDCA, shap, etc.

8. Ethics and Confidentiality

This study has been approved by the Ethics Review Committee of the Second Xiangya Hospital of Central South University (Approval No. LYF2022139). As a retrospective study, no additional intervention will be performed on patients, and a waiver of informed consent has been applied for. All study data will undergo strict de-identification, and only analyzed in the form of serial numbers. Data access rights will be restricted to members of the research team, and all data will be stored on an institutional encrypted server.

9. Research Plan

October 2025 - November 2025: Data extraction and cleaning.

November 2025 - December 2025: Descriptive analysis, model development and training, model validation and performance evaluation.

January 2026 - February 2026: Result interpretation, manuscript writing and submission.

10. Expected Outcomes and Dissemination

The research results are expected to be published in international peer-reviewed journals and presented at relevant academic conferences. The developed prediction model will be transformed into an online clinical calculator for use and validation by peers.

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