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ORIGINAL RESEARCH

Development and Validation of a Nomogram for Predicting Poor Outcome in Spontaneous Cervical Artery Dissection

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Objective: This exploratory study aimed to develop a preliminary nomogram for risk assessment of poor prognosis in spontaneous cervical artery dissection (sCAD) and evaluate its statistical performance using internal validation.

Methods: We retrospectively analyzed 75 patients with sCAD (mean age 51.8 ± 14.0 years; 41 males [55%] and 34 females [45%]) diagnosed between November 2013 and April 2024. Poor prognosis was defined as imaging-confirmed acute cerebral infarction or hemorrhage (n=38); the remaining 37 patients comprised the good prognosis group. Due to the small sample size, variables with $p<0.2$ in univariate analysis (sex, extracranial CAD type, hypertension, hyperhomocysteinemia) were considered for multivariate modeling, though none were statistically significant predictors (all $p>0.05$). A multivariate logistic regression-based nomogram was constructed and internally validated using 1000 bootstrap resamples.

Results: The final model included the four variables above. Only non-intramural hematoma (other) CAD type showed statistical significance in the multivariate model (OR=13.41, 95% CI: 2.89–62.17, $P<0.01$), while sex, hypertension, and hyperhomocysteinemia did not, likely reflecting statistical instability from inadequate power. In bootstrap internal validation, the model demonstrated moderate discrimination (AUC=0.788, 95% CI: 0.686–0.891) with a Brier score of 0.185. Hosmer-Lemeshow test indicated acceptable calibration ($\chi^2=8.11$, $P=0.23$). Mean AUC across bootstrap samples was 0.763 (95% CI: 0.662–0.863), suggesting minimal overfitting within this dataset, though this does not imply generalizability.

Conclusion: This pilot study generates the hypothesis that ultrasonographic CAD type, combined with clinical variables, may aid in predicting sCAD outcomes. However, due to the small sample size (9.5 events/variable), lack of external validation, and inclusion of non-significant predictors, this model is not ready for clinical application. Multi-center prospective validation in a cohort of at least 400 patients is required before any clinical utility can be claimed.

Keywords: cervical artery dissection, poor prognosis, nomogram, risk prediction, pilot study

Introduction

In recent years, cervical artery dissection (CAD), as one of the main causes of stroke in young and middle-aged individuals, has received increasing clinical attention.[1] CAD accounts for a proportion (25%) of ischemic strokes in patients under 50 years of age.[2,3] CAD, including carotid artery dissection and vertebral artery dissection, can be roughly divided into extracranial artery dissection and intracranial artery dissection based on the range of lesion involvement. According to the cause, CAD is classified into three categories: spontaneous cervical artery dissection, traumatic cervical artery dissection, and iatrogenic cervical artery dissection. This study mainly focuses on the extracranial spontaneous cervical artery dissection.

The clinical presentation of spontaneous CAD is highly variable and often subtle at onset, making early recognition difficult, with many patients initially presenting with mild and non-specific symptoms such as neck pain, headache,

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cervical stiffness, or Horner's syndrome.[4] These symptoms lack specificity and are easily overlooked or misdiagnosed by clinicians, leading to missed optimal treatment opportunities and result in irreversible neurological deficits in some patients, or even be life-threatening. Therefore, there is an urgent clinical need for an effective tool that can accurately identify high-risk patients in the early stage of the disease. This study conducted a retrospective analysis of patients with spontaneous CAD, collecting detailed clinical and imaging examination data, aiming to construct an individualized risk prediction model. Nomograms translate complex regression coefficients into an intuitive, graphical format that clinicians can use at the bedside without specialized statistical software, facilitating real-time decision-making. We contrast nomograms with alternative approaches: while machine learning models may achieve marginally higher discrimination, they often sacrifice transparency and require "black box" implementations unsuitable for many clinical settings. Traditional logistic regression, though statistically valid, lacks the visual interface that promotes clinical adoption and communication with patients. Given our explicit goal of creating a "practical tool for personalized risk stratification," the nomogram's unique capacity to bridge statistical modeling and clinical utility makes it the most appropriate choice for translating research findings into actionable clinical information.

Material and Methods

Patients Selection

This retrospective study was conducted at Baotou Central Hospital using the clinical data of patients diagnosed with spontaneous CAD between March 2014 and May 2023. The study protocol was approved by the Ethics Committee of Baotou Central Hospital (approval number: 20024). Given the retrospective design of the study, which relied exclusively on anonymized data extracted from electronic medical records without any direct patient contact or intervention, the requirement for individual informed consent was formally waived by the Institutional Review Board.

Participants were included based on the following criteria: (1) aged 18 years or older; (2) availability of complete medical Patients were included if they met the following criteria: (1) age ≥18 years; (2) availability of complete medical records; and (3) diagnosis of spontaneous CAD without an identifiable underlying cause. Exclusion criteria were: (1) cervical artery dissection secondary to aortic dissection; and (2) missing or incomplete clinical data.

Following this, patients were stratified into two groups according to clinical outcomes: those without poor outcomes (ie, no acute stroke) and those with poor outcomes (ie, occurrence of acute stroke, including ischemic or hemorrhagic stroke).

Data Collection

The following variables were collected from the patient records: (1) demographic information, including age and sex; (2) vascular risk factors, including hypertension, diabetes, hyperlipidemia, and hyperhomocysteinemia; and (3) ultrasonographic features, with particular attention to intramural hematoma, those with intramural hematoma were classified as intramural hematoma-type dissection, and those without were classified as other types dissection.

Image Evaluation (Diagnostic Criteria)

At present, the commonly used imaging modalities for diagnosing CAD include magnetic resonance angiography or imaging (MRA/MRI), digital subtraction angiography (DSA), and computed tomography angiography (CTA). The diagnostic criteria applied in this study were based on the *2015 Chinese Guidelines for the Diagnosis and Treatment of Cervical Artery Dissection*,[5] and are summarized as follows: (1) on axial MRI, a curved or crescent-shaped eccentric hematoma typically shows isointensity on both T1- and T2-weighted images during the early stage, whereas in the subacute stage, it appears hyperintense on both sequences; (2) characteristic features on MRA or CTA include linear signs, double-lumen signs, and aneurysmal dilatation, all of which suggest the presence of dissection; and (3) typical DSA findings include beaded arterial stenosis or "flame sign" occlusion, while irregular or smooth tapering of the vessel, referred to as the "rat tail sign" or "line sign", also supports the diagnosis of arterial dissection.

Ultrasonographic diagnostic criteria followed the 2015 Chinese guidelines and relevant literature,[5] and included the following features: (1) A double-lumen structure or floating membranous echoes within the lumen; (2) Irregular arterial

stenosis; (3) Segmental thickening of the arterial wall; (4) Partial or continuous lumen dilation; (5) Presence of membranous echoes within an occluded lumen. According to ultrasonographic features, extracranial cervical artery dissection is classified into four types: (1) intramural hematoma type dissection; (2) double-lumen artery type dissection; (3) aneurysmal type dissection; (4) occlusive type artery dissection.[6] Since there are more intramural hematoma-type dissections and fewer other types of arterial dissections, the types of extracranial cervical arterial dissections in this study are divided into intramural hematoma-type and other types of arterial dissections.

The diagnosis of acute stroke was made by experienced clinicians based on patients' clinical symptoms, physical signs, and neuroimaging findings. Imaging results were interpreted independently by two experienced radiologists to ensure diagnostic accuracy.

Statistical Analysis

All data analyses were performed using R software (version 4.3.1). Continuous variables are expressed as mean ± standard deviation (SD), and comparisons between groups were conducted using the independent samples *t*-test. Categorical variables are presented as frequencies, and intergroup differences were assessed using the χ^2-test. A multivariate logistic regression model was used to construct the nomogram. The discriminative ability of the model is evaluated using the receiver operating characteristic curve (ROC curve) and its area under the curve (AUC). The closer the AUC value is to 1, the stronger the model's ability to distinguish between high-risk and low-risk patients. The calibration of the model is assessed through the Hosmer-Lemeshow (HL) test and calibration curves. A P-value from the HL test greater than 0.05 (typically the significance level) indicates no significant difference between the model's predicted probabilities and the actual observed event rates; the closer the calibration curve is to the ideal 45° diagonal line, the better the model's calibration performance. The Brier score is used to measure the model's predictive accuracy, with a Brier score closer to 0 indicating higher overall predictive accuracy of the model. Model validation was performed using the bootstrap method with 1000 resampling iterations. Considering the effective sample size and the clinical relevance of the variables, those with a P-value < 0.2 in the univariate analysis were included in the multivariate regression model. A two-tailed P-value < 0.05 was considered statistically significant.

Result

Demographic and Clinical Data

A total of 75 patients were included in the study. Their age ranged from 27 to 85 years and had a mean age of 51.81 ± 13.99 years. Of them, 41 patients (55%) were male. The cohort included 14 cases of carotid artery dissection and 61 cases of vertebral artery dissection. According to ultrasound findings, intramural hematoma was detected in 10 cases of carotid artery dissection and 46 cases of vertebral artery dissection.

Among the 38 patients classified in the poor outcome group, 2 experienced hemorrhagic stroke and 36 experienced ischemic stroke. The remaining 37 patients were included in the good outcome group. No statistically significant differences were observed between the two groups in terms of age, sex, hypertension, diabetes mellitus, hyperlipidemia, hyperhomocysteinemia and external cervical artery dissection type (eCAD-type) (P > 0.05) (Table 1).

Variable Screening and Model Construction

The variables with p < 0.2 in univariate logistic regression analysis were selected into multivariate logistic regression analyses. Results showed sex, eCAD-type, hypertension and hyperhomocysteinemia were included in the nomogram model, among which other types dissection was an independent risk factors for poor outcome (Table 2). The total score of the nomogram ranged up to 240, corresponding to a predicted probability of poor outcome between 0.20 and 0.95 (Figure 1). The area under the receiver operating characteristic curve (AUC) for the model was 0.788, indicating good discriminative ability. Furthermore, Hosmer–Lemeshow test's p-value was 0.2305, indicating a satisfactory goodness-of-fit. The calibration curve demonstrated strong agreement between the predicted probabilities and actual clinical outcomes (Figure 2). Brier score of the nomogram model was 0.185, suggesting the model has high predictive accuracy. The

Table 1 Characteristics of the Two Groups

Variables	Good Prognosis Group (n=37)	Poor Prognosis Group (n=38)	*P* Value
Age (years)	52.6±13.8	51.0±14.5	0.627
Sex			
Male (n, %)	17(46%)	24(63%)	0.206
Female (n, %)	20(54%)	14(37%)	
Hypertension (n, %)	13(35%)	21(55%)	0.128
Diabetic Mellitus (n, %)	3(8%)	7(18%)	0.330
Hyperlipidemia	7(19%)	8(21%)	1.000
Hyperhomocysteinemia	7(19%)	13(34%)	0.216
eCAD-type			
Intramural hematoma-type	34(92%)	22(58%)	0.002
Other types	3(8%)	16(42%)	

Table 2 Univariate and Multivariate Binary Logistic Regression Analyses of Predictors for Poor Prognosis

Variables	Univariate Analysis		Multivariate Analysis	
	p Value	OR (95% CI)	*p* Value	OR (95% CI)
Age	0.622	0.99 (0.96–1.02)		
Sex				
Female	Reference			
Male	0.136	0.49 (0.19–1.23)	0.095	2.56 (0.85–7.70)
Hypertension				
None	Reference			
Yes	0.082	2.28 (0.90–5.89)	0.058	2.86 (0.97–8.50)
Diabetic Mellitus				
None	Reference			
Yes	0.200	2.56 (0.61–10.77)		
Hyperlipidemia				
None	Reference			
Yes	0.817	1.14 (0.37–3.64)		
Hyperhomocysteinemia	0.139	2.23 (0.37–3.64)	0.065	3.15 (0.93–10.70)
None	Reference			
Yes	0.139	2.23 (0.37–3.64)	0.065	3.15 (0.93–10.70)
eCAD-type				
Intramurl hematoma-type	Reference			
Other types	0.002	8.24 (2.40–38.47)	<0.001	13.41 (2.89–62.17)

decision curve analysis showed that within a specific threshold range, the nomogram provided a higher net clinical benefit for predicting adverse outcomes in cervical artery dissection (Figure 3).

Model Verification

In this study, internal validation of the model was performed using the bootstrap method with 1000 resampling iterations. The ROC curve for the validation set demonstrated an average area under the curve (AUC) of 0.763, with a 95% CI of 0.662–0.863. In the original dataset, the AUC of the nomogram was 0.788, with a 95% CI of 0.686–0.891. The similarity between the AUC values and corresponding confidence intervals of the original dataset and validation set suggests that the model exhibits good discriminative ability and stability on the present study dataset. While the close alignment

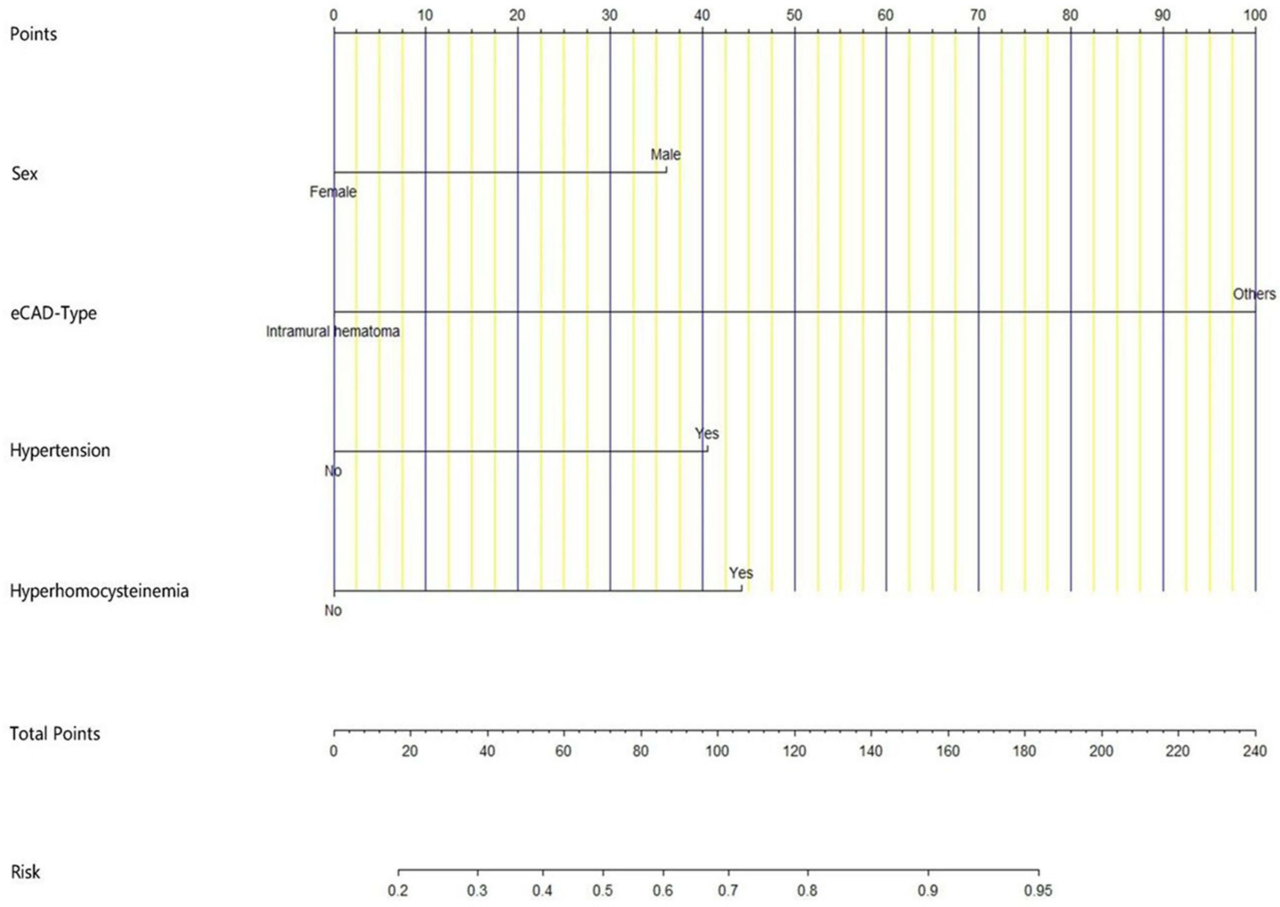

Figure 1 The nomogram to predict poor outcome of cervical artery.

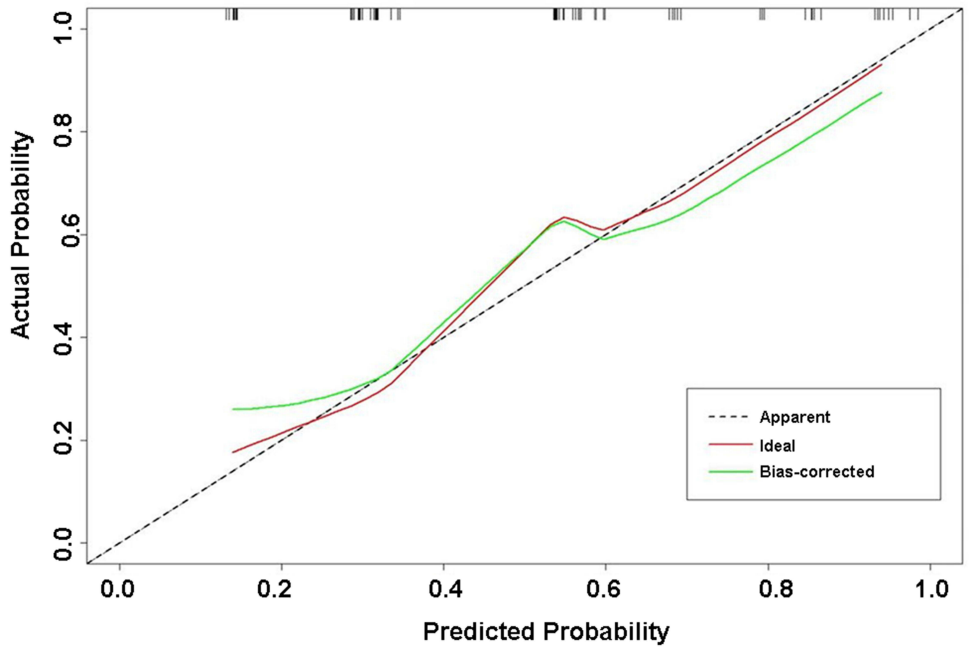

Figure 2 Calibration curves of the nomogram.

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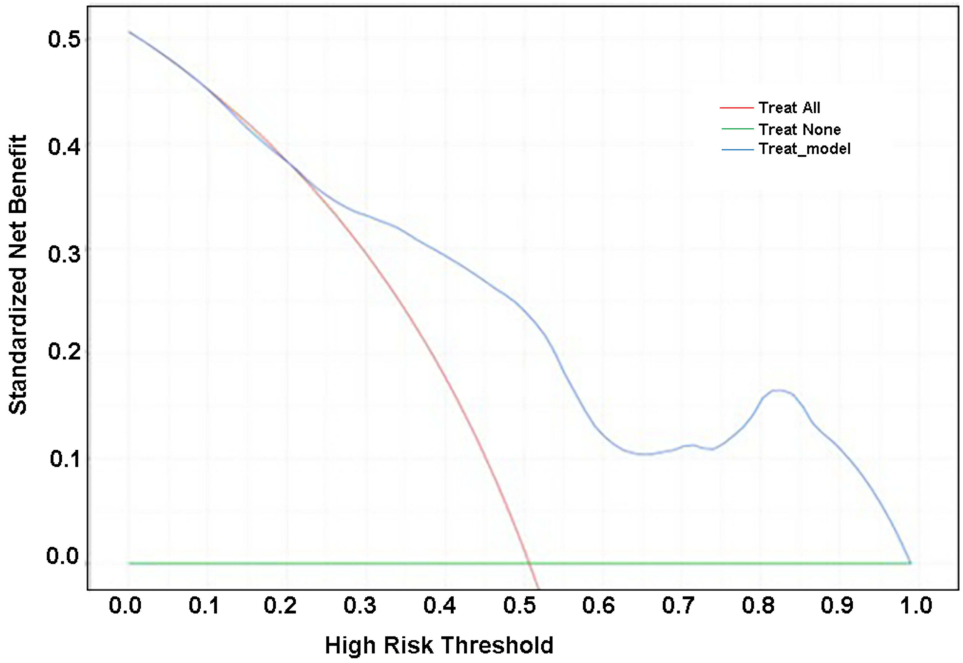

Figure 3 Decision curve analysis (DCA) for the clinical-ultrasonographic nomogram.

between development and bootstrap validation suggests minimal overfitting in internal resampling, these metrics are likely optimistic and cannot be extrapolated to external populations.

Discussion

In this study, we developed a clinical-ultrasonographic features based model for predicting poor outcomes of cervical artery dissection, including sex, eCAD-type, hypertension and hyperhomocysteinemia. This model performs well on existing dataset, with its AUC and Brier scores being 0.788 and 0.185 respectively. The Hosmer-Lemeshow test result was a chi-squared value of 8.1054 and a p-value of 0.2305.

The results of the multivariate regression analysis showed that, after excluding confounding effects between variables, other types of dissection are an important risk factor for adverse outcomes of CAD, with an OR (95% CI) of 13.41 (2.89–62.17). This indicates that, under other equal conditions, patients with other types arterial dissection have a 13.41 times higher risk of adverse outcomes compared to those with intramural hematoma-type arterial dissection. In the present study, the intramural hematoma-type arterial dissection represents the main form of spontaneous CAD as it accounts for approximately 63%–70% of all cases.[7] In the present study, intramural hematoma type dissection accounts for 74% (56 out of 75) of all dissections. In the group with a good outcome, intramural hematoma-type dissection accounted for 92% (34 out of 37), while in the group with a poor outcome, it accounted for 58% (22 out of 38). Our previous research confirmed that intramural hematoma is the most common type of extracranial vertebral artery dissection,[6] and most cases of cervical artery dissection can be managed conservatively, often achieving favorable clinical and anatomical outcomes.[8] This is consistent with the conclusion of this study. While the underlying mechanisms require further investigation, it is plausible that the presence of an intramural hematoma, as opposed to other pathological features, might be associated with a more stable arterial wall condition or a lower likelihood of complications such as thromboembolism. Other types arterial dissection, including double-lumen arterial dissection, aneurysm-type arterial dissection, and occlusion-type arterial dissection. In the acute phase, other types arterial dissection was often accompanied by instability of the vascular state, leading to embolic events or more severe strokes. According to a study by Keser et al.[9] CAD accounts for approximately 25% of ischemic strokes in individuals under 50 years of age. In the present nomogram model, other types arterial dissection was associated with a higher contribution score and

demonstrated strong predictive value for poor outcomes, but in fact the results should be interpreted with caution given the small sample size of our study, and validated in larger, independent cohorts.

An earlier Italian case-control study reported that hypertension, a well-established risk factor for atherosclerosis, was more prevalent in patients with non-CAD ischemic stroke than in those with CAD or in a reference control group composed of practitioners without vascular disease.[5] However, when compared specifically with the reference group, the CAD cohort showed a significantly higher prevalence of hypertension, thereby supporting its identification as a risk factor for cervical artery dissection. Similarly, a French case-control study found no significant differences in major vascular risk factors, including hypertension, between patients with sCAD and controls.[10] A meta-analysis of risk factors for cervical artery dissection, which included 17 case-control studies and data from 2185 patients with sCAD, demonstrated a significant association between hypertension and spontaneous CAD.[11] Further subgroup analysis in stroke-related cervical artery dissection research revealed that this association was more pronounced among spontaneous CAD patients with confirmed cerebral infarction compared to those without infarction.[5] Taken together, these results support the inference that hypertension may contribute to the occurrence of stroke in patients with cervical artery dissection, in accordance with previously published evidence.[12]

Sex was also identified as a predictor in the present nomogram model. Arnold et al reported sex-related differences in CAD, observing a higher prevalence among men. A recent review further highlighted geographic variability in sex distribution, with North American data indicating a higher incidence of CAD in women, whereas European studies reported a greater incidence in men.[1] A separate study focusing on vertebral artery dissection-related stroke also demonstrated a clear male predominance among affected patients, suggesting that men may be at increased risk for ischemic events.

Hyperhomocysteinemia (HHcy) has been recognized as an independent risk factor for stroke. A meta-analysis comprising eight case-control studies with a total of 2146 individuals demonstrated a significant association between HHcy and CAD.[10] Similarly, a study from Switzerland reported that even mild hyperhomocysteinemia may be a risk factor for sCAD leading to ischemic stroke.[13] A systematic review further supported the role of HHcy in promoting vascular damage and tissue ischemia, contributing to both CAD and ischemic stroke.[14] Notably, the C677T polymorphism in the methylenetetrahydrofolate reductase (MTHFR) gene is strongly associated with elevated homocysteine levels. This genetic variant contributes to hyperhomocysteinemia but can be modulated through supplementation with vitamin B12 and folic acid, which may serve as a practical approach for primary prevention.

Taking the above into account, male sex, hypertension, hyperhomocysteinemia have been linked to stroke and spontaneous CAD in previous studies. It is worth noting that in the nomogram model of this study, although gender, hypertension, and hyperhomocysteinemia were included as predictor variables, their p-values were all >0.05. From a statistical perspective, they were not independent predictors of adverse outcomes in cervical artery dissection, meaning there were no significant statistical association between them and adverse outcomes of cervical artery dissection. Their potential risk of adverse outcomes with cervical artery dissection still needs to be validated in large-scale independent cohort studies. From a clinical perspective, they have stronger biological rationality and clinical practicality as predictive factors for the model, making the model results easier for clinicians to understand and accept. In addition, as predictive factors, they enhance the overall predictive performance of the model, with the model's AUC reaching 0.803, helping accurately identify high-risk patients and also provide valuable reference for the assessment of clinical risk factors in the future. Based on the above analysis, while sex, hypertension, and hyperhomocysteinemia were not statistically significant in the model, they can enhance the overall predictive ability of the model, which is more important than the statistical significance of individual variables.

This study has several limitations. First, the sample size is relatively small, which may significantly reduce statistical power. Second, external validation was not conducted in this study, limiting the model's generalizability and extrapolation ability. The good discriminative ability and calibration of the model on the existing dataset may be an overfitting to specific sample characteristics. When applying this model directly to other clinical scenarios or patient populations, its predictive performance may significantly decline. In future research, we plan to include a larger sample size and conduct external validation to further evaluate the model's robustness and clinical applicability.

This pilot study's value lies not in providing a ready-to-use nomogram, but in identifying ultrasonographic CAD type as a candidate predictor that deserves prioritization in larger, multi-center studies. The profound limitations we have acknowledged—small sample size, non-significant predictors, and lack of external validation—mean that attempting clinical implementation would be premature and potentially harmful. We hope that by transparently reporting these limitations, this study can serve as a methodological cautionary tale and a stimulus for more robust investigations. Despite the aforementioned limitations, this study still has certain advantages. This study integrates multiple clinically routinely available variables into a nomogram model, ensuring the model's good clinical practicality and popularity. Moreover, strict adherence to standardized procedures for model development was followed during the model construction process, including variable selection, model fitting, and internal validation, which to some extent guarantees the model's internal validity and reliability. It provides a preliminary research basis and reference framework for future exploration of risk factors for adverse outcomes in cervical artery dissection.

Data Sharing Statement

The datasets generated and analyzed during the present study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

This study was approved by the ethics committee of Baotou Central Hospital (approval number: 20024). Given the retrospective design of the study, which relied exclusively on anonymized data extracted from electronic medical records without any direct patient contact or intervention, the requirement for individual informed consent was formally waived by the Institutional Review Board. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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This paper has been uploaded to Research Square as a preprint: https://www.researchsquare.com/article/rs-4880114/v1.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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