Original Article

Cerebral collateral circulation as an independent predictor for in-stent restenosis after carotid artery stenting

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Background: In-stent restenosis is a crucial problem after carotid artery stenting, but the exact predictors of in-stent restenosis remain unclear. We aimed to evaluate the effect of cerebral collateral circulation on in-stent restenosis after carotid artery stenting and to establish a clinical prediction model for in-stent restenosis.

Methods: This retrospective case-control study enrolled 296 patients with severe carotid artery stenosis of C1 segment (≥70%) who underwent stent therapy from June 2015 to December 2018. Based on follow-up data, the patients were divided into the in-stent restenosis and no in-stent restenosis groups. The collateral circulation of the brain was graded according to the criteria of the American Society for Interventional and Therapy Neuroradiology/Society for Interventional Radiology (ASITN/SIR). Clinical data were collected, such as age, sex, traditional vascular risk factors, blood cell count, high-sensitivity C-reactive protein, uric acid, stenosis degree before stenting and residual stenosis rate, and medication after stenting. Binary logistic regression analysis was performed to identify potential predictors of in-stent restenosis, and a clinical prediction model for in-stent restenosis after carotid artery stenting was established.

Results: Binary logistic regression analysis showed that poor collateral circulation was an independent predictor of in-stent restenosis (P=0.003). We also found that a 1% increase in residual stenosis rate was associated with a 9% increase in the risk of in-stent restenosis (P=0.02). Ischemic stroke history (P=0.03), family history of ischemic stroke (P<0.001), in-stent restenosis history (P<0.001), and nonstandard medication after stenting (P=0.04) were predictors of in-stent restenosis. The risk of in-stent restenosis was lowest when the residual stenosis rate was 12.5% after carotid artery stenting. Furthermore, we used some significant parameters to construct a binary logistic regression prediction model for in-stent restenosis after carotid artery stenting in the form of a nomogram.

Conclusions: Collateral circulation is an independent predictor of in-stent restenosis after successful carotid artery stenting, and the residual stenosis rate tends to be below 12.5% to reduce restenosis risk. The standard medication should be strictly carried out for patients after stenting to prevent in-stent restenosis.

Keywords: Carotid artery stenosis; collateral circulation; stenting; in-stent restenosis

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Introduction

Carotid artery stenosis is a well-documented risk factor for cerebrovascular disease, and significant carotid artery stenosis is responsible for approximately 7% of all cases of ischemic stroke (1). de Weerd *et al.* (2) found that the risk of severe carotid artery stenosis (≥70%) increased from 0.1% in men and 0% in women aged <50 years to 3.1% in men and 0.9% in women over 80 years of age. Patients with significant carotid stenosis need effective interventions to reduce the risk of stroke. Carotid angioplasty with stenting (CAS) is an effective method to remodel the vascular structure and restore the blood flow for patients with symptomatic carotid stenosis >50% or asymptomatic carotid stenosis >70% (3). However, in-stent restenosis (ISR) is a significant clinical issue in long-term follow-up after CAS and the main reason for stroke recurrence. Many clinical trials have reported that the risk of ISR after CAS is diverse (4,5), with many possible risk factors being identified for ISR in previous investigations, including smoking, hypertension, diabetes mellitus, and hyperlipidemia (6). However, the exact risk factors remain controversial, and some studies report opposing results for the same factors (7-10).

Brain collateral circulation determines the heterogeneity of stroke, and abundant collateral circulation could improve the long-term prognosis. Some studies have revealed that good collateral circulation reduces the incidence of ISR after percutaneous coronary intervention (PCI) (11-13). However, other studies have reached the opposite conclusion (8,14). Thus far, there has been no explicit conclusion concerning the relationship between cerebral collateral circulation and ISR after CAS. This study thus analyzed the influence of collateral circulation on ISR after CAS and provided further evidence for the choice of effective measures in avoiding ISR. We present the following article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-22-975/rc).

Methods

Study population

This retrospective case-control study recruited 296 patients who were treated in the second hospital of Hebei Medical University from June 2015 to December 2018. These patients satisfied the following inclusion criteria: (I) severe stenosis of the internal carotid artery (ICA) atherosclerosis (C1 segment ≥70%) with stent therapy; (II) willingness to be followed up, including undergoing a carotid Doppler ultrasound; (III) a modified Rankin scale (mRS) ≤2 before stenting; and (IV) not in the acute phase of ischemic stroke (more than 2 weeks after onset). The exclusion criteria were as follows: (I) ICA stenosis caused by nonatherosclerotic factors, such as cardioembolic stroke, arterial dissection, vasculitis, fibromuscular dystrophy, or moyamoya disease; (II) carotid artery interventional treatment; (III) cancer, autoimmune disease, severe liver or kidney dysfunction, or other serious diseases; (IV) acute or chronic infection; and (V) death that occurred during follow-up. There were 89 patients excluded from the study: 14 patients had nonatherosclerotic stenosis; 35 patients had received carotid artery interventional treatment; 34 patients had cancer, autoimmune disease, severe liver or kidney dysfunction, or other serious diseases; 3 patients had an acute or chronic infection; 1 patient had stent crushes; and 2 patients died during the follow-up. The flow diagram of participant selection at each stage is shown in *Figure 1*. Simultaneously, we collected relevant clinical data, including age, sex, traditional vascular risk factors (including hypertension, diabetes mellitus, coronary artery disease, current smoking, current drinking, total cholesterol, triglyceride, low-density lipoprotein cholesterol), blood cell count, homocysteine, high-sensitivity C-reactive protein, uric acid, stenosis degree before stenting and residual stenosis rate, and drug therapy after stenting. This retrospective study was approved by the Institutional Ethics Committee of the Second Hospital of Hebei Medical University (No. 2020-R384), and all patients or their families signed an informed consent form. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Follow-up and grouping

The follow-up was performed with in-clinic visits at 1, 6, and 12 months and yearly thereafter. According to the follow-up results of the carotid Doppler ultrasound, the enrolled patients were divided into the ISR group (n=28) and the no-ISR group (n=268).

Definition of ISR

The restenosis at each visit was determined centrally based on the ultrasound flow velocities recorded at the stenting site (15). The criteria for developing restenosis involved a narrowing of the lumen by 50% or greater as indicated by the carotid Doppler ultrasound (15). The peak systolic

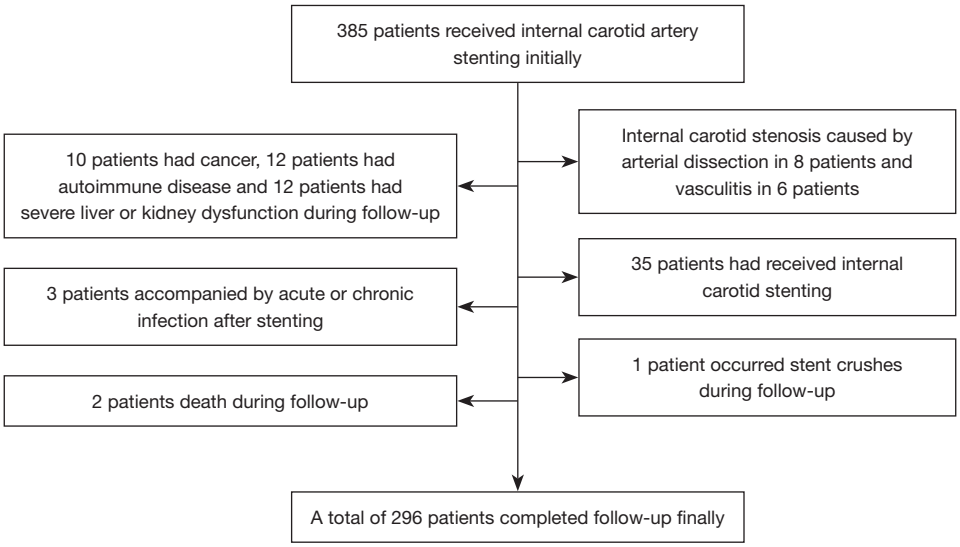

Figure 1 The flow diagram of participant selection at each stage.

velocities (PSVs) of the common carotid artery (CCA), ICA, and the end-diastolic velocity of the ICA were recorded. The PSV ICA cutoff values used to quantify the severity of stenosis were >130 cm/s for ≥50% stenosis, but the end-diastolic velocity ICA and the PSV ICA to PSV CCA ratio were also considered (2,16,17). ISR was diagnosed if any of the following criteria were met: PSV ICA >130–210 cm/s, end-diastolic velocity in ICA >40 cm/s, or PSV ICA:PSV CCA >3.2 (16).

Stenting procedure and medication after stenting

Stenting was performed by a well-trained neurointerventional specialists team with more than 10 years of experience in .the second hospital of Hebei Medical University. Four professional neurointerventionists completed all the stents in this study, and their specialty was neurointerventional therapy. All enrolled patients were managed with dual antiplatelet therapy (aspirin 100 mg and clopidogrel 75 mg daily) for at least 3 days before stenting. A bolus of intravenous heparin (50 IU/kg of body weight, 3,000–5,000 IU) was injected after the guide catheter. The intervention therapy was performed via the femoral artery route, a guiding catheter was placed into the CCA, and a suitable size of stent was implanted. In our study, the closed stents included Wallstent and Enterprise, and the opened stents included EV3 and Acculink. The open stent was preferred for vessel tortuosity and angulation, and the closed stent was preferred for significant ulcerative plaques or unstable soft plaques. In the absence of these conditions, the surgeon determined the stent type. After successful stent implantation, the residual stenosis rate was evaluated with cerebral angiography. Angiography of the C1 segment of the ICA before and after stenting is shown in *Figure 2*.

All patients were recommended to receive drug care and control traditional vascular risk factors after stenting. Aspirin (100 mg/day) and clopidogrel (75 mg/day) were administered orally for 90 days after stenting and then switched to monoplatelet therapy for lifelong treatment. Statins were also taken orally after stenting. The above measures were defined as standard medication (18). However, any deviation from the listed measures was defined as nonstandard medication. In addition, all patients were administered a standardized prevention program to control traditional vascular risk factors.

Grading of collateral circulation

According to the criteria of the American Society for Interventional and Therapy Neuroradiology/Society for Interventional Radiology (ASITN/SIR), the collateral circulation was divided into 5 levels according to cerebral angiography: level 0, no collateral visible to the ischemic site; level 1, slow collateral to the periphery of the ischemic site with the persistence of defect; level 2, rapid collateral to the periphery of the ischemic site with the persistence of

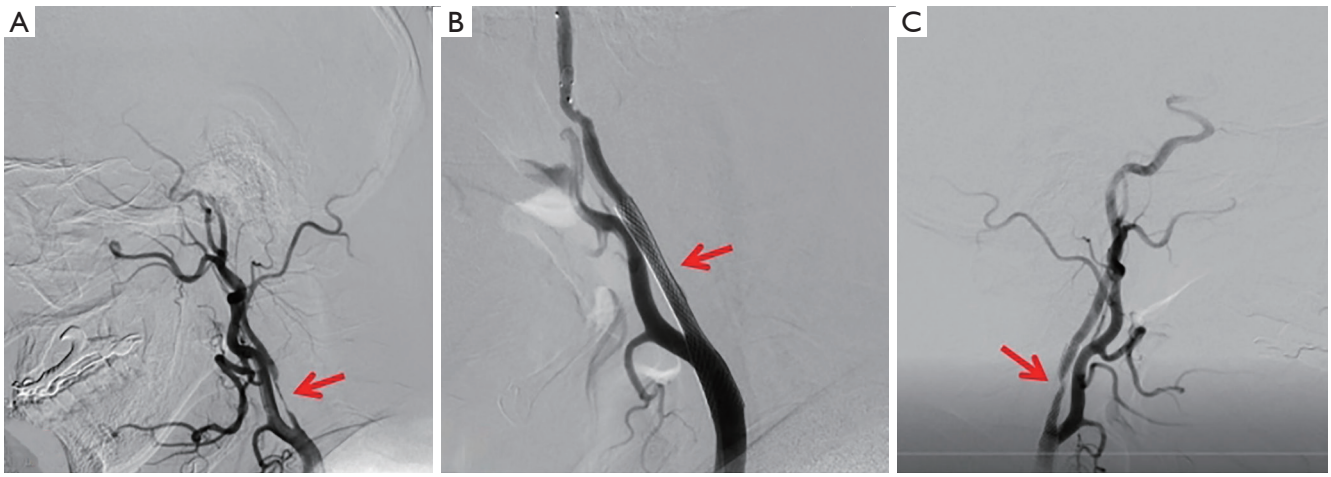

Figure 2 A 66-year-old woman who had ISR within 12 months after CAS. (A) Severe stenosis in the C1 segment of the right carotid artery (arrow). (B) There was no obvious stenosis after stenting (arrow). (C) Restenosis occurred in the stent (arrow). CAS, carotid angioplasty with stenting; ISR, in-stent restenosis.

defect and to only a portion of the ischemic territory; level 3, collateral with slow but complete angiographic blood flow of the ischemic bed by the late venous phase; and level 4, complete and rapid collateral blood flow to the vascular bed in the entire ischemic territory by retrograde perfusion (19). Levels 0–1 were defined as poor collateral circulation, and levels 2–4 were defined as good collateral circulation (20). We performed the stenosis side and contralateral cerebral angiography, and all images were reviewed by two experienced independent observers who were blinded to the patients' information. If the conclusions were controversial, a third observer was invited to draw a final decision.

Statistical analysis

Statistical analysis was performed using SPSS 25.0.0 (IBM Corp, Armonk, NY, USA). Data are expressed as the mean ± standard deviation, median with interquartile range, or numbers with percentages. Categorical variables were analyzed using the chi-squared or Fisher exact test, as appropriate. Normality was assessed for continuous variables using the Kolmogorov-Smirnov test. Continuous variables were compared using an independent Student *t*-test. If the variable distributions were not normal, a nonparametric Mann-Whitney test was used.

To determine the independent predictors for ISR, according to the results of univariate analysis, the statistically significant factors ($P<0.05$) in the univariate analysis were subsequently entered into the multivariate logistic regression model. The preoperative stenosis rate, residual stenosis rate, diabetes mellitus history, ischemic stroke history, family history of ischemic stroke, history of ISR, collateral circulation, and medication after operation were further entered into the binary logistic regression analysis. Statistical significance was defined as a P value <0.05, and the strength of influence was estimated according to odds ratios (OR). The optimal residual stenosis rate was calculated according to the receiver operating characteristic (ROC) curve, and the sensitivity, specificity, and Youden index were calculated. According to the Kaplan-Meier curve, we analyzed the cumulative risk of ISR during follow-up in the ISR group using the log-rank test. The clinical prediction model for ISR after CAS was constructed with RStudio (Boston, MA, USA). A nomogram was constructed based on a binary logistic regression model, and the concordance index (C-index) and calibration curves were used to assess the discrimination and calibration of the nomogram.

Results

Baseline characteristics

In our study, the enrolled patients were divided into the ISR (n=28) and no-ISR (n=268) groups. The cumulative rate of restenosis during follow-up was 9.5% (28/296 patients). The mean follow-up duration was 48 months, ranging from a minimum of 3 months to a maximum of 72 months.

There were 24 men (85%) in the ISR group and 223 men (83%) in the no-ISR group (P=0.94). The mean age was 62±6 years in the ISR group and 64±8 years in the no-ISR group (P=0.20). Compared to that in the no-ISR group, the collateral circulation was poorer (75% *vs.* 59%; P=0.001) in the ISR group. The prevalence of diabetes mellitus was higher in the ISR group (53% *vs.* 28%; P=0.007). Ischemic stroke history (64% *vs.* 31%; P<0.001), family history of ischemic stroke (25% *vs.* 0.7%; P<0.001), and a history of ISR (28% *vs.* 0.7%; P<0.001) were more common in the ISR group than in the no-ISR group. Furthermore, in the ISR group, the preoperative stenosis rate was higher (86±7 *vs.* 82±6; P=0.01); however, the residual stenosis rate was lower in the no-ISR group (median, 12 *vs.* 8; P=0.01). We also found that, in the ISR group, the recurrence rate of ischemic stroke was higher (18% *vs.* 4%; P=0.005), and more patients did not take standardized medication (22% *vs.* 8%; P=0.03). Based on stent types, the ISR rate was 12.0% (16/133) in EV3, 4.9% (4/81) in Acculink, 14.3% (5/35) in Wallstent, and 6.3% (3/47) in Enterprise. The above results are listed in *Table 1*.

The predictor of ISR

According to the univariate analysis results, we chose the preoperative stenosis rate, residual stenosis rate, diabetes mellitus history, ischemic stroke history, family history of ischemic stroke, history of ISR, collateral circulation, and medication after operation for binary logistic regression analysis. We found that poor collateral circulation was associated with an 8.61-fold increased risk of ISR compared with good collateral circulation [OR =8.61; 95% confidence interval (CI): 2.12–34.94; P=0.003]. The results also implied that a 1% increase in residual stenosis rate was associated with a 9% increase in the risk of ISR (OR =1.09; 95% CI: 1.01–1.15; P=0.02). No ischemic stroke history (OR =0.31; 95% CI: 0.10–0.92; P=0.03), no family history of ischemic stroke (OR =0.01; 95% CI: 0.001–0.12; P<0.001), and no ISR history (OR =0.01; 95% CI: 0.001–0.09; P<0.001) was associated with a reduced occurrence of ISR. Nonstandard medication after the operation was associated with a 4.68-fold increased risk of ISR compared with standard medication after the operation (OR =4.68; 95% CI: 1.01–21.95; P=0.04). The results are listed in *Table 2*. The risk of ISR was lowest when the residual stenosis rate was 12.5% after CAS (sensitivity 42.9%; specificity 82.8%; Youden index 0.26), and the area under the curve (AUC) was 0.63 (95% CI: 0.51–0.75; P=0.02; *Figure 3*). According to the Kaplan-Meier curve, the patients with good collateral circulation had a lower risk of ISR during follow-up (χ^2=11.03; P<0.001). ISR mainly occurred within 12 months after stent therapy for patients with poor collateral circulation and within 18 months for patients with good collateral circulation (*Figure 4*).

Clinical prediction model for ISR

We used several significant parameters, including ischemic stroke history, family history of ischemic stroke, ISR history, residual stenosis rate, collateral circulation, and postoperative medication to construct a binary logistic regression prediction model for ISR after CAS in the form of a nomogram (*Figure 5*). The C-index and calibration curves were used to assess the discrimination and calibration of the nomogram. The C-index was 0.89 (95% CI: 0.83–0.97), and the nomogram showed a satisfactory calibration for ISR (*Figure 6*).

Discussion

The pathophysiological mechanisms of ISR include many factors, such as elastic retraction of the vessel wall at the stent and inflammation-induced neointimal hyperplasia (21-24). Stents destroy vascular endothelial cells and make vascular wall remodeling (25). On the other hand, some studies have recently demonstrated that neoatherosclerosis is related to incomplete endothelial regeneration, resulting in incomplete stent strut coverage (26) and acceleration of the atherosclerotic process (27,28). After stenting, chronic mechanical stimulation of the vessel wall promotes vascular smooth muscle cell proliferation, contributes to extracellular matrix formation (24), and ultimately leads to ISR. Our study found that inflammatory markers, including high-sensitivity C-reactive protein, were higher in the ISR group. In addition, our study on carotid artery balloon injury in rats demonstrated that endothelial cell injury, oxidative stress, apoptosis, and proline-rich tyrosine kinase 2/mitochondrial calcium uniporter (PyK2/MCU) regulation of Ca^{2+} balance were involved in the pathological process of restenosis after vascular injury (29), which indicated that many factors are involved in the pathogenesis of ISR. The reported incidence of ISR following CAS varies widely, from 3% to 20% (30), and in our study was 9.5% (28/296), which was consistent with the literature.

Patients who had at least moderate (≥50%) or severe (≥70%) restenosis after stenting had a significantly increased

Table 1 The baseline characteristics of the ISR and the no-ISR groups

Characteristics	ISR group (n=28)	No-ISR group (n=268)	P value
Age (years)	62±6	64±8	0.20
Sex (male)	24 [85]	223 [83]	0.94
Medical history			
Hypertension	18 [64]	207 [77]	0.12
Diabetes mellitus	15 [53]	77 [28]	0.007
CAD	10 [35]	79 [29]	0.49
Ischemic stroke	18 [64]	83 [31]	<0.001
FHIS	7 [25]	2 [1]	<0.001
History of ISR	8 [28]	2 [1]	<0.001
Current smoking	11 [39]	84 [31]	0.39
Current drinking	8 [28]	75 [28]	0.94
TC (mmol/L)	3.63±0.75	3.93±0.95	0.10
TG (mmol/L)	1.65±0.84	1.47±0.95	0.32
LDL-C (mmol/L)	2.12±0.67	2.43±0.82	0.06
HDL-C (mmol/L)	1.02±0.22	1.06±0.38	0.66
Platelet ($\times10^9$/L)	225±78	215±59	0.41
Leukocytes ($\times10^9$/L)	6.13±1.10	6.76±1.70	0.06
Neutrophils ($\times10^9$/L)	3.82±0.95	4.22±1.40	0.14
Homocysteine (μmol/L)	11 [8, 14]	13 [8, 16]	0.08
hs-CRP (mg/L)	8 [1, 11]	6 [1, 10]	0.28
Uric acid (μmol/L)	312±87	312±78	>0.99
Stent type			0.91
Opened stent	20 [71]	194 [72]	
Closed stent	8 [29]	74 [28]	
SRP	82±6	86±7	0.01
Residual stenosis rate	12 [6, 20]	8 [5, 10]	0.01
RIS	5 [18]	10 [4]	0.005
MO			0.03
Standard	22 [78]	248 [92]	
Non-standard	6 [22]	20 [8]	
Collateral circulation			0.001
Poor	21 [75]	157 [59]	
Good	7 [25]	111 [41]	

Date are expressed as the mean ± standard deviation, median [interquartile range], or n [%]. ISR, in-stent restenosis; CAD, coronary artery disease; FHIS, family history of ischemic stroke; TC, total cholesterol; TG, triglyceride, LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; SRP, stenosis rate preoperatively; RIS, recurrence of ischemic stroke; MO, medication after the operation.

Table 2 Analysis of risk factors for ISR after carotid artery stenting according to binary logistic regression analysis

Variables	B value	OR value (95% CI)	P value
Stenosis rate preoperative	–0.01	0.98 (0.92–1.05)	0.68
Residual stenosis rate	0.09	1.09 (1.01–1.15)	0.02
No diabetes mellitus history	–0.95	0.38 (0.13–1.13)	0.08
No ischemic stroke history	–1.17	0.31 (0.10–0.92)	0.03
No FHIS	–4.17	0.01 (0.001–0.12)	<0.001
No history of ISR	–4.49	0.01 (0.001–0.09)	<0.001
Poor collateral circulation	2.15	8.61 (2.12–34.94)	0.003
Nonstandard MO	1.54	4.68 (1.01–21.59)	0.04

ISR, in-stent restenosis; OR, odds ratio; CI, confidence interval; FHIS, family history of ischemic stroke; MO, medication after the operation.

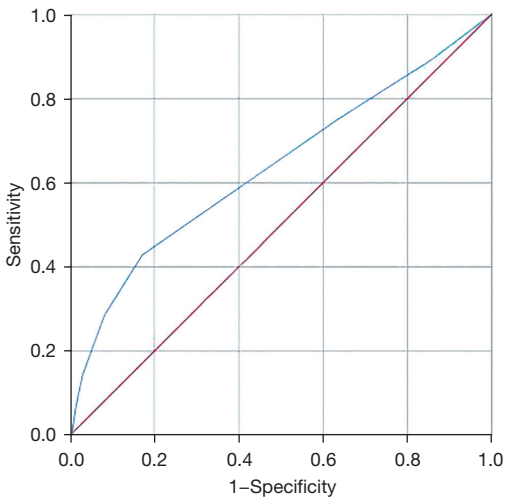

Figure 3 The risk of ISR was lowest when the residual stenosis rate was 12.5% after CAS (sensitivity, 42.9%; specificity, 82.8%; Youden index, 0.26) and the area under AUC curve was 0.63 (95% CI: 0.51–0.75; P=0.02). ROC, receiver operating characteristic; ISR, in-stent restenosis; CAS, carotid angioplasty with stenting; AUC, area under the curve; CI, confidence interval.

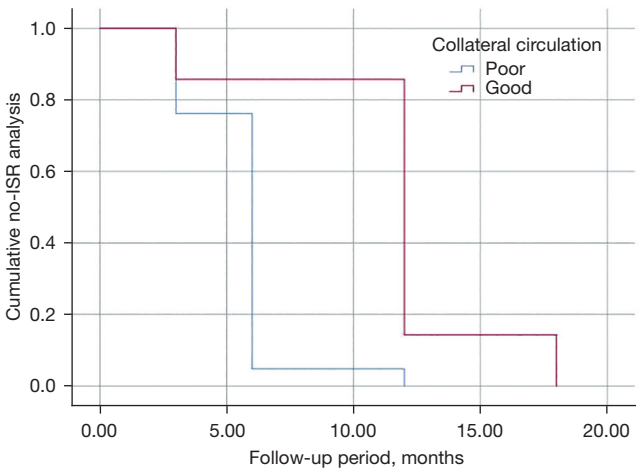

Figure 4 Kaplan-Meier curve. The patients with good collateral circulation had a lower risk of ISR during follow-up (log-rank, χ^2=11.03; P<0.01). ISR occurred mainly within 12 months after stent therapy for patients with poor collateral circulation. ISR occurred within 18 months after stent therapy for patients with good collateral circulation. ISR, in-stent restenosis.

risk of subsequent ipsilateral ischemic stroke compared with those without restenosis (31,32). Our study found that long-term and standardized medication therapy can reduce the incidence of restenosis. Therefore, appropriate oral medications are important to prevent restenosis after CAS, including antiplatelet aggregation, lower low-density lipoprotein, and control of traditional vascular risk factors. The dual antiplatelet therapy plays an important role in the inhibition of neointimal hyperplasia (33,34), which leads to an enhanced antithrombotic and antiproliferative effect through the concurrent inhibition of both thromboxane A2 and adenosine diphosphate pathways. Additionally, dual antiplatelet therapy reduces in-stent neointimal formation by persistently inhibiting platelet aggregation and smooth muscle hyperplasia. Moreover, statins can also lower the risk of ISR by inhibiting the proliferation and migration

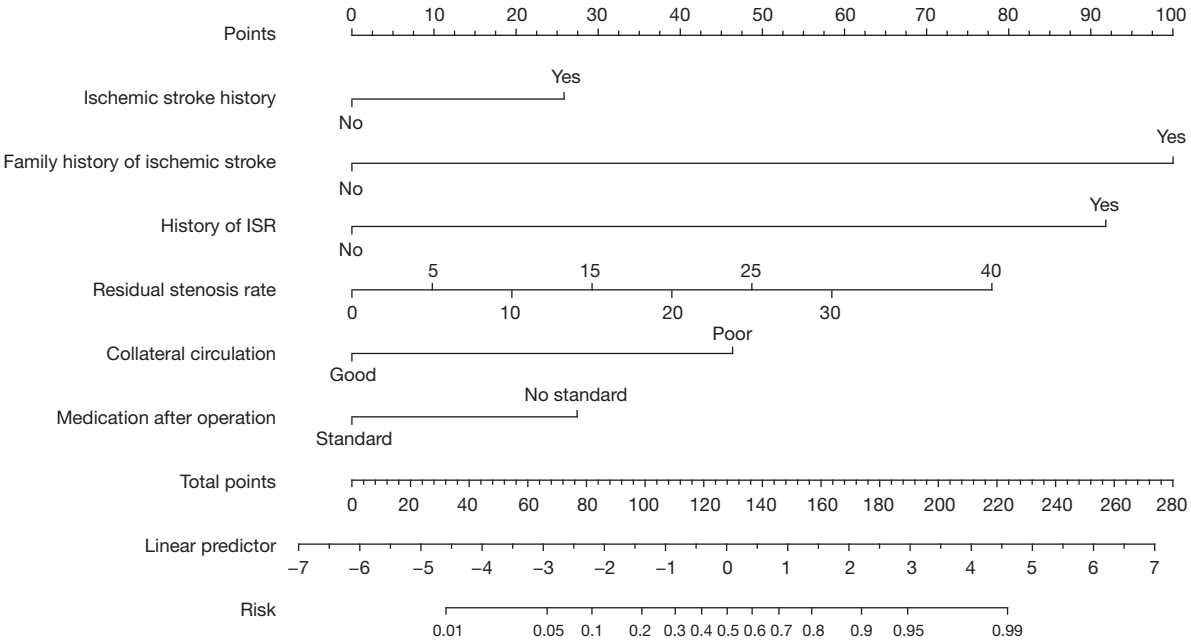

Figure 5 The nomogram to predict ISR after CAS. ISR, in-stent restenosis; CAS, carotid angioplasty with stenting.

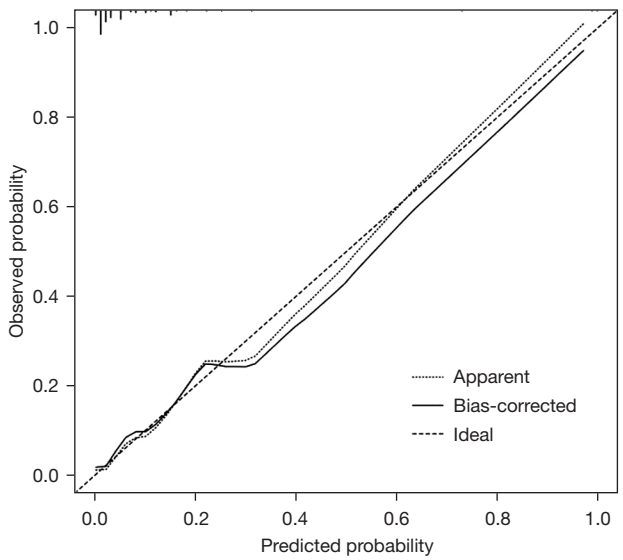

Figure 6 The calibration of the nomogram for ISR. ISR, in-stent restenosis.

of vascular smooth muscle cells and stabilizing endothelial plaques (35,36). Therefore, medication should be taken regularly for an extended period after CAS to reduce the risk of ISR. The combination of antiplatelet drugs and statins is the keystone, and not a single one can be omitted.

The risk of ISR is particularly high among patients with diabetes mellitus, which is consistent with our results, and may be associated with metabolic alterations that promote endothelial dysfunction, accelerate intimal hyperplasia, and increase platelet aggregability and thrombogenicity (37). In our research, ISR history refers to stenting performed in the contralateral carotid artery or posterior circulation artery. Compared with the no-ISR group, the incidence of family history of ischemic stroke and frequency with ISR history were significantly higher in the ISR group in our study, so the influence of these two factors was greater in the nomogram. In addition, we found that the patients with a family history of ischemic stroke or ISR history were more likely to develop restenosis, which suggested that the occurrence of ISR may have more risk factors or a genetic predisposition (38-42), such as *CDKN1B*, *CCNB1*, and *VEGF* gene polymorphism. We observed that 64.0% of patients in the ISR group had a history of ischemic stroke, compared with 31.0% in the no-ISR group. The patients with a history of ischemic stroke in the ISR group had a higher rate of diabetes (61.1% *vs.* 34.9%; P=0.04) and smoking (50.0% *vs.* 25.3%; P=0.03) than did those in the no-ISR group. In the ISR group, 28.6% (8/28) of patients had a history of ISR, compared with only 0.7% (2/268) in the no-ISR group. These previous ISR sites were

located in the contralateral carotid artery, vertebral artery, or basilar artery. Furthermore, the higher residual stenosis rate after stenting promotes local thrombosis formation, and it has been reported that a target of less than 30% residual stenosis has been recommended (43,44). However, this cutoff value was derived from patients with moderate or higher stenosis before stenting, and some only involved intracranial arteries or terminal ICA. Our study found that the residual stenosis of <12.5% after CAS was appropriate; however, the sensitivity of the ROC curve was a little low, which may be related to the small sample size in the ISR group. Meanwhile, we speculate from the ROC curve that the less residual stenosis rate after CAS is, the better. Oteros *et al.* (45) suggested that the lower the rate of residual stenosis is, the lower the risk of restenosis in CAS, which is consistent with our hypothesis.

Collateral circulation is an important prognostic factor for acute cerebrovascular disease. Abundant collateral circulation could lower the severity of stroke and reduce the infarct area. According to our knowledge, the relationship between collateral circulation and ISR has not been investigated in CAS. However, some studies have revealed that poor collateral circulation is a predictor of ISR after PCI, while others have reported the opposite conclusion (8,11). We speculate that the phenomenon is due to the different evaluation methods used for collateral circulation. Vascular perfusion pressure has been used to evaluate the grade of collateral circulation in the coronary artery; however, according to the latest opinion, this method is indirect and imprecise (14,44). The elevated perfusion pressure may be related to the recanalization of occluded vessels, but it does not exactly refer to the abundant collateral circulation. Our study found that poor collateral circulation, evaluated by cerebral angiography, was an independent risk factor for ISR after CAS. We speculate that the related mechanisms may be the following: first, the vascular wall shear stress dramatically declines in patients with poor collateral circulation after stenting, which increases the expression of pro-inflammatory genes and leads to intimal hyperplasia (24); second, patients with poor collateral circulation have a greater change in blood flow at the stenosis after stenting, which could further stimulate the vascular endothelial cell proliferation (46). Therefore, we consider that evaluating collateral circulation may help to predict the risk of ISR after CAS.

In this study, carotid Doppler ultrasound was used to evaluate ISR during follow-up, and PSV was used as a major parameter for evaluating ISR after CAS. Digital subtraction angiography (DSA) is the gold standard for the evaluation of ISR. However, it has many defects, such as radiation damage and contrast agent allergy. Some studies found that carotid Doppler is a readily available and noninvasive diagnostic tool for the evaluation of ISR (18,47,48). The accuracy of Doppler ultrasound compared with DSA is very clear, and Doppler ultrasound has been proven to have a high sensitivity (100%) and specificity (93.3%) in the detection of ISR (18).

There were also some limitations to our study. First, it involved a retrospective, observational design, and the materials were collected in a predetermined manner; therefore, information bias cannot be ruled out. Second, this was a single-center study, and selection bias might have affected the reliability of our conclusion. Third, a relatively limited number of patients were included in our trial, especially in the ISR group. A prospective and systemic observational study would obtain further results based on our preliminary conclusions. Fourth, although they underwent uniform training, and the related evaluation parameters were also consistent, carotid Doppler ultrasound was performed by two different clinicians, which might have affected the homogeneity of the results.

Conclusions

Our study found collateral circulation to be independently associated with ISR in patients with CAS. Controlling the residual stenosis rate and regularly administering oral antiplatelets and statins over a long period could effectively reduce the odds of ISR.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-22-975/rc

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uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-22-975/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Institutional Ethics Committee of the Second Hospital of Hebei Medical University (ethics grant No. 2020-R384). Informed consent was obtained from all patients or their families.

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