Preprocedural Neutrophil to Albumin Ratio Predicts In-Stent Restenosis Following Carotid Angioplasty and Stenting

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Background and purpose: In-stent restenosis (ISR) is unfavorable to the long-term efficacy of carotid angioplasty and stenting (CAS). Inflammation plays a critical role in the development of ISR. The aim of the study was to investigate whether neutrophil to albumin ratio (NAR) is a predictor of ISR in patients undergoing CAS. *Methods:* We retrospectively recruited patients who underwent CAS. These patients were divided into restenosis group and nonrestenosis group. NAR was examined prior to the CAS procedure. Clinical and radiographic assessments were performed at 6 months and annually after the procedure. ISR was defined as greater than or equal to 50% stenosis in the treated lesion. Cox regression was used to identify predictors of ISR following CAS. *Results:* During a mean follow-up period of 14.6 months, a total of 459 treated arteries (in 427 participants) were enrolled, among which 72 (15.7%) developed ISR. On multivariate analysis, baseline NAR greater than or equal to13.4, residual stenosis, lesion length, and baseline glucose level were associated with ISR (hazard ratio 1.94 [95% confidence interval (CI), 1.08-3.49], 1.09[95% CI, 1.07-1.12], 1.04[95% CI, 1.01-1.06], and 1.01[95% CI, 1.00-1.02], respectively). *Conclusion:* Elevated preprocedural NAR may be a predictor of ISR in patients undergoing CAS.

Key Words: Angioplasty—Stenting—Restenosis—Neutrophil to albumin ratio

Introduction

Ischemic stroke is the leading cause of death and disability in the adult population globally. Atherosclerotic stenosis in carotid artery is well known as a major risk factor of ischemic stroke. Vascular recanalization can alleviate ischemic symptoms and decrease the risk of cerebrovascular events. Although carotid endarterectomy (CEA) is still recommended to the standard of care for patients with severe symptomatic and asymptomatic carotid stenosis, carotid angioplasty and stenting (CAS) has emerged as an effective and less invasive alternative to CEA with regard to stroke prevention.[1,2] Furthermore, CAS is a preferable treatment for patients with restenosis after CEA. However, the occurrence of in-stent restenosis (ISR) endangers the long-term efficacy and safety of CAS.[3-6] Thus, identification of predictive

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factors associated with restenosis is beneficial to screen the patients with high risk of ISR and allows for early intervention.

Previous studies confirmed that inflammation played a vital role in the development of ISR.[7] Some inflammatory indicators such as leukocyte counts and C-reactive protein (CRP) were well established to be related to ISR.[8,9] Meanwhile, high neutrophil level increased the risk of ischemic stroke and poor outcome.[10-12] As a serum indicator of inflammation, low preprocedural albumin level is involved in the development of ISR after coronary stenting,[13] and elevates the morbidity and mortality of cardiovascular disease.[14] A recent study reported that pretreatment neutrophil to albumin ratio (NAR), a novel inflammatory biomarker, was able to predict pathological complete response to neoadjuvant chemoradiotherapy.[15] However, no data to date are available on the association between NAR and ISR after CAS. The present study was aimed to investigate the predictive value of preprocedural NAR on the development of ISR in patients undergoing CAS during follow-up.

Methods

Subjects

All patients who successfully underwent CAS were extracted consecutively from the Nanjing Stroke Registry System[16] between March 2004 and December 2016. The degree of lumen stenosis was accessed according to the criterion of the North American Symptomatic Carotid Endarterectomy trial.[17] We excluded the patients who (1) underwent CAS due to nonatherosclerosis etiology; (2) had unavailable images of the treated artery during follow-up; (3) presented acute infection, such as fever, cough, or diarrhea; (4) developed chronic inflammatory disease or malignancy; (5) suffered severe liver or kidney disease. Informed consents were obtained from all patients, and this study was approved by the ethical committee of Jinling Hospital.

Data Collection

Patients' data on demographics, main vascular risk factors, laboratory examinations, and imaging results were recorded. Venous blood was collected prior to stent implantation. Hematological parameters including total leukocyte, neutrophil, lymphocyte, and platelet counts were examined before CAS procedure. Simultaneously, biochemical values such as albumin, CRP, globulin, creatinine, uric acid, glucose, total cholesterol, triglyceride, high-density lipoprotein, and low-density lipoprotein were detected using standard laboratory techniques. The NAR was calculated as the ratio of neutrophil to albumin.

CAS Procedure

CAS was performed by digital subtraction angiography under local anesthesia. After determining the location of groin puncture, we inserted an 8F sheath into the femoral artery to establish a vascular passage. Intravenous heparin (70 IU/kg) was then routinely administered to prevent thromboembolic events. After an 8F guiding catheter was navigated proximal to the stenosis, a distal embolic protective device was released crossing the stenosis lesion. The subocclusive vessels were generally dilated before stent implantation. A self-expandable and size-suitable stent such as Acculink (Abbott Vascular, Redwood City, CA), Wallstent (Boston Scientific, Natick, MA), or Precise (Cordis, Miami Lakes, FL) was implanted at the stenosis lesion. The treated lumens which had over 50% residual stenosis after stent implantation were received supplemental dilation. A final angiography was performed to determine the residual stenosis. Double antiplatelet therapy with aspirin and clopidogrel was rendered for at least 90 days after the procedure and then monotherapy (commonly aspirin) proceeded for lifetime.

Follow-Up Assessments

All patients were followed with clinical and radiographic inspection such as digital subtraction angiography, computed tomography angiography, or Doppler ultrasound that was performed at 6 months and annually after CAS, unless they deceased or were lost within 6 months of the procedure. Additional imaging assessment was utilized in patients who suffered recurrent neurological symptoms during follow-up. ISR was defined as greater than or equal to 50% stenosis in stented segment. The diagnosis of in-stent restenosis was implemented by two experienced neurologists who were blinded to the clinical and laboratory findings.

Statistical Analysis

All data were statistically analyzed using SPSS 22.0 (IBM, Armonk, NY). Categorical variables were expressed as counts and percentage, and continuous parameters were presented as mean ± standard deviation. Cox regression was used to identify the predictors associated ISR. The variables with P values less than .10 in univariate analysis were entered into multivariate analysis. Kaplan-Meier analysis was employed to compare cumulative risk of ISR between groups. A value of P less than .05 was considered to be statistically significant.

Results

A total of 427 patients (459 arteries) were lastly enrolled in the study. The recruited arteries were classified into restenosis group (n = 72) and nonrestenosis group (n = 387). The baseline clinical and demographic characteristics between groups are present in Table 1. The average age of the included participants was 66.0 ± 8.0 years. The male proportion of total population was 85.8%. In-stent restenosis was recognized in 72 (15.7%) treated

Table 1. *Baseline characteristics of the participants by restenosis*

Characteristics	All lesions(n = 459)	Restenosis (n = 72)	No restenosis (n = 387)	*P* value
Age, y	66.0±8.0	66.4±7.0	65.9±8.2	.617
Male, n (%)	394 (85.8)	66 (91.7)	328 (84.8)	.187
BMI, kg/m^2	24.5±2.7	24.6±2.8	24.4±2.7	.267
Smoking, n (%)	180 (39.2)	30 (41.7)	150 (38.8)	.410
Hypertension, n (%)	380 (82.8)	57 (79.2)	323 (83.5)	.160
DM, n (%)	170 (37.0)	40 (55.6)	130 (33.6)	.001
Hyperlipidemia, n (%)	202 (44.0)	32 (44.4)	170 (43.9)	.136
CAD, n (%)	61 (13.3)	12 (16.7)	49 (12.7)	.577
Lesion				
Length, mm	18.6±8.9	20.8±9.4	18.2±8.8	.003
stenosis, %	72.4±15.4	76.1±15.7	71.7±15.3	.001
Stenting				
Left carotid, n (%)	217 (47.3)	39 (54.2)	178 (46.0)	.207
Open cell stent, n (%)	397 (86.5)	61 (84.7)	336 (86.8)	.582
Pre-dilation, n (%)	329 (71.7)	55 (76.4)	274 (70.8)	.038
Post-dilation, n (%)	121 (26.4)	15 (20.8)	106 (27.4)	.464
Residual stenosis, %	27.7±11.0	35.5±12.3	26.3±10.1	<.001
Hematological parameters				
Leukocyte, × 109/L	6.82±1.89	6.94±1.88	6.79±1.89	.274
Neutrophil, × 109/L	4.24±1.64	4.45±1.67	4.21±1.63	.113
Monocyte, × 109/L	0.46±0.20	0.45±0.14	0.46±0.21	.781
Lymphocyte, × 109/L	1.90±0.63	1.85±0.52	1.91±0.65	.574
NAR ≥ 13.4, n (%)	301(65.6)	58 (80.6)	243 (62.8)	.011
Biochemical parameters				
CRP, mg/L	6.17±10.88	6.49±10.17	6.11±11.02	.892
ALT, U/L	24.30±15.60	25.38±14.08	24.09±15.87	.142
AST, U/L	21.90±9.14	22.01±9.49	21.88±9.09	.659
Total protein, g/dL	6.67±0.52	6.63±0.52	6.67±0.52	.093
Albumin, g/dL	4.27±0.35	4.27±0.38	4.27±0.35	.203
Globulin, g/dL	2.39±0.41	2.36±0.40	2.40±0.41	.291
Cr, mg/dL	0.83±0.22	0.85±0.23	0.82±0.22	.897
UA, mg/dL	5.43±1.48	5.36±1.39	5.44±1.49	.910
Glu, mg/dL	102.1±31.17	113.1±44.70	100.1±27.55	<.001
TC, mg/dL	156.9±37.94	154.6±34.92	157.3±38.51	.261
TG, mg/dL	137.1±80.00	126.8±57.17	139.0±83.48	.257
HDL, mg/dL	39.55±8.21	40.02±9.99	39.46±7.85	.824
LDL, mg/dL, mean±SD	94.19±31.02	91.28±30.98	94.73±31.03	.107

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CAD, coronary artery disease; CRP, C-reactive protein; Cr, creatinine; DM, diabetes mellitus; Glu, glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NAR, neutrophil-to-albumin ratio; TC, total cholesterol; TG, triglyceride; UA, uric acid.

arteries during a mean follow-up of 14.6 ± 19.1 months (range, .7-120.7; Table 1).

In the univariate analysis, diabetes mellitus ($P = .001$), residual stenosis ($P < .001$), predilation ($P = .038$), NAR greater than or equal to 13.4 ($P = .011$), high serum glucose level ($P < .001$), longer lesion ($P = .003$), and more severe stenosis ($P = .001$) were significantly associated with ISR. Association of age, gender, BMI, hypertension, and coronary artery disease with ISR was not observed. Except for NAR and serum glucose, we did not find apparently relationship between other hematology parameters and ISR, although baseline total protein ($P = .093$) tended to be associated with ISR. Also, the location of the stent implantation and presence of post-dilation was not associated with ISR. In the multivariate cox regression analysis, preprocedural NAR value greater than or equal to 13.4 (hazard ratio [HR], 1.94; 95% confidence interval[CI], 1.08-3.49), lesion length (HR, 1.04; 95% CI, 1.01-1.06), residual stenosis (HR, 1.09; 95% CI, 1.07-1.12), and serum glucose level (HR, 1.01; 95% CI, 1.00-1.02) were related to ISR after CAS (Table 2).

The Kaplan-Meier analysis of cumulative freedom from ISR based on NAR value (≥13.4 or <13.4) was present in the Figure 1. According to the log-rank test, the risk of ISR was significantly higher in patients with NAR greater than or equal to 13.4 than in patients with NAR less than 13.4 ($P = .009$).

Table 2. *Multivariate analysis of predictors of ISR after CAS*

Variables	Multivariate HR (95% CI)	*P*
Lesion length	1.04 (1.01-1.06)	.002
Residual stenosis	1.09 (1.07-1.12)	<.001
NAR ≥ 13.4	1.94 (1.08-3.49)	.028
Serum glucose	1.01 (1.01-1.02)	<.001

Abbreviations: CAS, carotid angioplasty and stenting; CI, confidence interval; HR, hazard ratio; ISR, in-stent restenosis; NAR, neutrophil-to-albumin ratio.

Discussion

In the study, our data showed that patients with high preoperative NAR (≥13.4) were associated with 1.94-fold increased risk for ISR after CAS. The present report is the first to indicate a correlation between NAR and ISR after CAS.

ISR is one of the major concerns for the therapy of CAS, and augments recurrent vascular events. There are accumulating data showing that inflammation is not only involved in the pathogenesis of atherosclerosis,[18,19] but also a major contributor for ISR.[7,20] A previous investigation demonstrated that high neutrophil numbers in the resected plaques were associated with the features of rupture-prone atherosclerotic plaques.[21] It is suggested that the intense inflammatory response in plaque increased the risk of carotid plaque destabilization. Postprocedural leukocyte count was reported to be an independent predictor of ISR after CAS.[9] Another study revealed that CRP level at 48 hours after intervention was associated with ISR in 6 months following CAS.[8] A coronary stent analysis confirmed an association of high baseline CRP levels with risk of ISR.[22] These studies indicated the critical role of periprocedural inflammatory response in the occurrence of ISR. In our study, a relationship between preprocedural NAR and ISR was analyzed, showing that high baseline NAR level prior to intervention was associated with increased risk of ISR after CAS.

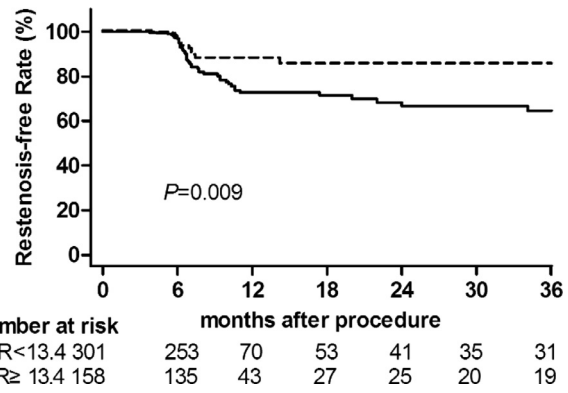

Figure 1. *Kaplan-Meier analysis for cumulative freedom from in-stent restenosis in patients who underwent CAS. Patients with neutrophil to albumin ratio (NAR) greater than or equal to 13.4 are illustrated with solid line; patients with NAR less than 13.4 are illustrated with dotted line. Cumulative rates of freedom from in-stent restenosis were compared with log-rank test.log-rank P = .009.*

Several possible mechanisms may interpret the association between NAR and ISR. Serum albumin is known as one of major plasma antioxidant components.[23] Reactive oxygen species has been evidenced to trigger vascular smooth muscle cells apoptosis, and stimulate proliferation, migration, and remodeling of adventitial myofibroblasts or medial vascular smooth muscle cells which are responsible for ISR.[24] Reduced serum albumin level reflecting intense reactive oxygen species, therefore, maybe place patients with CAS at raised risk of ISR. The predictive capacity of lower preprocedural serum albumin level has been confirmed in ISR after coronary stent implantation with bare-metal stent.[13] Additionally, lower serum albumin raised the risk of coronary disease and all-cause mortality.[25] A connection between high serum albumin and reduced mortality as well as better functional outcome in ischemic stroke suggested the neuroprotective effect of albumin.[26] Another possible underlying mechanism is inflammatory response related to vascular trauma after balloon angioplasty and stent implantation. This vascular trauma caused by operation attracted adhesion of inflammatory cells and platelets to the injury site.[27] After resident in the arterial wall, the circulating inflammatory cells such as neutrophil participated and aggravated the local inflammatory response to damaged segment. The activated neutrophils can intensify the endothelial injury and stimulate platelets, subsequently resulting in neointimal hyperplasia and smooth muscle cell proliferation, finally developing restenosis.[28] Although no significant association between neutrophil or serum albumin level and ISR was observed in our analyses, the indicator of NAR combining neutrophil with albumin may be a sensitive marker of predicting ISR after CAS. Based on the relationship between NAR and ISR, we speculate that the large number of neutrophils and simultaneous lower serum albumin which represent distinct mechanisms may have synergistic effect to result in ISR. Considering the possible mechanisms of NAR referring to ISR, nutritional interventions which increase and at least stabilize the concentration of serum albumin are possible avenues to reduce the risk of ISR in patients with high NAR. Another combined strategy is the modulation of inflammatory state such as early and high dose statin which is capable to attenuate systemic and local inflammation.

Moreover, this work ascertained that residual stenosis, lesion length, and serum glucose significantly contributed to the development of ISR following CAS. These results bear similarities with findings in an early study.[29] It is suggested that adequate vessel recanalization by reducing residual stenosis is necessary to attenuate occurrence of ISR. To target vessel with long lesion, decline of residual stenosis should be stressed so as to prevent ISR. The relationship between serum glucose and ISR emphasizes the fundamentality of controlling serum glucose especially in patients

with diabetes. As an important inflammatory marker, the role of CRP in predicting ISR has been addressed in multiple studies. However, we failed to hunt for the association between CRP and ISR after CAS in the observation.

Of note, the overall incidence of ISR (15.7%) in our population is high. The rate of ISR after CAS has been reported to range from 1.6% to 24%, depending on restenosis threshold and follow-up duration.[30] Commonly, the ISR rate of stenosis greater than or equal to 50% is higher than that of stenosis greater than or equal to 70%. The threshold of stenosis greater than or equal to 50% in our study maybe a contributor to the high rate of ISR, and similar incidences of restenosis after CAS were reported in some studies.[31,32] Diabetes mellitus has been associated with higher risk of restenosis.[33] The prevalence of diabetes mellitus (37%) was relatively high in our study, and 55.6% of patients who developed ISR had diabetes mellitus. This might be one of the reasons for the high rate of restenosis. The diagnoses of ISR were partially made through Doppler ultrasound which may overestimate stenosis degree.[34]

Study Limitations

Main limitations need to be mentioned in the current study. First, this was designed to be a retrospective study in a single-center with a relatively minor sample size. Second, in light of a fluctuation of NAR over time, the dynamic alteration of NAR might be a more valuable parameter displaying the association with ISR; however, dynamic NAR was not included due to the retrospective data collection. Third, some factors affecting neutrophil or albumin like nutritional status, trauma, and drugs were not assessed in the study.

Conclusion

The present study showed that preprocedural NAR may be a predictor of ISR in patients treated with CAS. Further prospective, randomized, and controlled clinical trials are required to verify the clinical implication of NAR.

Conflicts of interest

The authors declare no conflicts of interest.

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