KAROTİD ARTER STENTLEME SONRASI GELİŞEN STENT-İÇİ RESTENOZUN YENİ BİR ÖNGÖRDÜRÜCÜSÜ: CRP/ALBUMİN ORANI

The CRP/Albumin Ratio: A Novel Predictor of In-stent Restenosis After Carotid Artery Stenting

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ÖZET

Amaç: Çalışmamızda, karotid arter stentleme (KAS) işlemi öncesi bakılan C-reaktif protein/albumin oranının (CAO) stent içi restenozu (SİR) öngördürme potansiyelini araştırmayı amaçladık.

Gereç ve Yöntem: Retrospektif olarak dizayn edilen bu çalışmaya tersiyer merkezimizde başarılı bir şekilde karotid arter stentleme yapılan toplam 206 hasta alındı. İşlem öncesi her hastanın C-reaktif protein (CRP) ve serum albumin değerleri çalışıldı. CAO değeri, CRP değeri serum albumin değerine bölünerek hesaplandı. Çalışmanın primer sonlamın noktası takip sırasında gelişen SİR olarak belirlendi.

Bulgular: 206 hastanın ortalama 24.2 ± 1.5 ay takibi sonunda SİR toplam 34 (%16.5) hastada izlendi. SİR gelişmeyen hastalarla karşılaştırıldığında, CAO, SİR gelişen hastalarda anlamlı olarak daha yüksek saptandı (0.15 [0.2] vs. 0.99 [1.3], p < 0.01, sırasıyla). Çok değişkenli COX analizinde, CAO, SİR 'un bağımsız öngördürücüsü olarak saptandı (HR: 1.85, %95 CI: 1.29 – 2.64, p < 0.01). ROC eğrisi analizinde CAO değerinin > 0.53 olması, SİR 'u %100 duyarlılık ve %97.1 özgüllük ile öngördürmekteydi (AUC) 0.98, p < 0.01).

Sonuç: Çalışmamızın sonuçları göstermiştir ki, inflamatuar bazlı yeni bir belirteç olan CAO KAS işlemi yapılan hastaların takiplerinde gelişen SİR 'un güçlü ve bağımsız bir öngördürücüsüdür. Hızlı ve kolayca bakılabilen bu parametre, KAS işlemi yapılan hastalarda SİR gelişimini değerlendirmek için kullanılabilir.

Anahtar kelimeler: *CAO; Stent içi restenoz; Karotis arter stentleme; İnflamasyon*

ABSTRACT

Objective: The present study aimed to assess the predictive value of preprocedural C-reactive protein/albumin ratio (CAR) for in-stent restenosis (ISR) after carotid artery stenting (CAS).

Materials and Method: In this retrospective study, 206 patients who underwent successful CAS procedure in a tertiary heart centre were included. For each patient, both C-reactive protein (CRP) and serum albumin were determined before the index procedure. The CAR was calculated by dividing serum CRP by serum albumin level. The main end-point of the study was ISR during long-term follow-up.

Results: ISR developed in 34 (16.5%) out of 206 patients after a mean follow-up of 24.2 ± 1.5 months. The CAR was significantly elevated in patients with ISR compared to those who were not (0.99 [1.3] vs. 0.15 [0.2], p < 0.01, respectively). In a multivariate Cox regression analysis, the CAR was an independent predictor of ISR (HR: 1.85, %95 CI: 1.29 – 2.64, p < 0.01). A ROC curve analysis revealed that the optimal value of CAR in predicting ISR was > 0.53 with a sensitivity of 100 % and a specificity of 97.1 % [area under curve (AUC) 0.98, p < 0.001].

Conclusion: The present study demonstrated that CAR, a new inflammatory-based index, is a strong independent predictor of ISR after CAS. As a simple and easily accessible parameter, this index may be used for the assessment of ISR in patients who are treated with CAS.

Keywords: *CAR; In-stent restenosis; Carotid artery stenting; Inflammation*

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INTRODUCTION

Extracranial carotid arteries, particularly carotid artery bifurcations, are the most frequent locations of the atherosclerotic involvement due to their unique geometric profiles (1). Atherosclerotic occlusion of carotid bifurcations is responsible for 7-20 % of all ischemic stroke cases which result in major disability and death (2,3). Even though the carotid endarterectomy is accepted as the gold standard treatment for stenotic carotid artery disease (4), carotid artery angioplasty and stenting (CAS) have emerged as an alternative treatment option providing a less invasive approach, better tolerability and patient comfort as well as potentially fewer complications and shorter hospital stay (5). However, despite significant advances in stent technology and even, we have several different types of stents at our disposal, in-stent restenosis (ISR) remains as a potential problem and raises concerns about the long-term safety and efficacy of CAS. The documented ISR rates after CAS range from 3-16% depending on its definition (6-11). Because an evidence-based treatment for ISR after CAS has not been elucidated yet, predicting ISR by identifying its potential causes still has the utmost importance.

It is well known that inflammation has a pivotal role in the pathogenesis of ISR (12). C-reactive protein (CRP) is an established marker of systemic inflammation, and it is a positive acute phase reactant, while serum albumin is a negative phase reactant which tends to decrease in inflammatory disorders. Hence, the CRP/albumin ratio (CAR) may be suggested as a more sensitive marker of the inflammatory process and progression of the disease. Even though the current evidence in the literature point out the association of increased baseline CRP levels and poor prognosis after endovascular treatment of peripheral artery disease (13-15), the data in respect to the relation of CAR with ISR after CAS is limited. In this study, our objective was to investigate the association of preprocedural CAR and ISR development in patients who underwent CAS procedure.

METHODS

Study Population and Data collection

This was a retrospective study which included a total of 206 patients who underwent successful CAS procedure in Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital from April 2016 to April 2019. Our institution is a tertiary referral cardiovascular centre with a high-volume of endovascular interventions mostly performed by interventional cardiologists. Our institution has a detailed clinical recording system for patients with atherosclerotic carotid artery disease. Also, all patients are evaluated by a consultant neurologist before and after the CAS procedure. All data including the demographic and clinical characteristic of the subjects as well as the laboratory findings and the details of interventional procedures were obtained from the hospital's medical records. Patients with incomplete data in the hospital database were excluded from the study. The exclusion criteria in our study were; patients who had CAS due to aetiology other than atherosclerosis (e.g. vasculitis and dissection), undergoing chronic renal replacement therapy (any type of dialysis) and had acute coronary syndrome in last 6 months. Moreover, patients with congestive heart failure, atrial fibrillation, active systemic organ disease, active or chronic infection, and malignancy were excluded from the study. Besides, patients who had overlapping stents in their carotid segments were not included in the study to preclude confounding bias. The degree of stenosis was calculated according to the method of the North American Symptomatic Carotid Endarterectomy Trial (16). The symptomatic presentation was defined as ipsilateral symptoms such as ischemic stroke, transient ischemic attack, or amaurosis fugax within the past 6 months before neurological assessment. All procedures were performed after obtaining an inform consent form. The study was approved by the local ethics committee, and it was performed according to the principles of the Declaration of Helsinki.

Carotid Artery Angioplasty and Stenting Procedure

All CAS interventions were performed by experienced operators according to the European Society of Vascular Surgery guidelines (17). All patients were treated with a regular dose of 100 mg aspirin and 75 mg clopidogrel daily before the procedure. Patients with hypercholesterolemia or symptomatic carotid stenosis or relevant coronary and peripheral arterial

disease were treated with statin therapy at least one week before the index procedure. After discharge, statin medication was continued until an adverse effect occurred. In terms of antiplatelet therapy, 75 mg clopidogrel daily was prescribed at least one month and 100 mg aspirin daily were given lifelong. On the day of the procedure, all patients were taken to the catheterization laboratory and 8 Fr. sheath was placed into the femoral artery under local anaesthesia. Intravenous unfractionated heparin was administered at the beginning of all procedures (100 units/kg), and additional doses were given as needed to achieve a target activated clotting time between 250 to 350. Once an 8 Fr. guiding catheter or a shuttle sheath was safely located proximal to the stenosis, a distal cerebral protection system (Emboshield, Abbott Vascular) was routinely delivered by crossing the stenotic lesion. Self-expandable stents such as Xact (Abbott Vascular), Protege (Ev3) and Precise (Cordis) of suitable sizes were implanted. In patients with sub-occlusive stenosis, pre-dilatation was performed to diminish the plaque protrusion into the stent scaffold which was shown to be correlated with perioperative ischemic stroke (18). Technical success was defined as the ability to treat stenosis with < 30 % residual stenosis. In cases with > %50 residual stenosis, post-dilatation was usually performed to achieve an optimal result.

Follow-up and Definition of ISR

After a successful revascularization procedure, patients with carotid stents were regularly evaluated at 1, 6, 12 months and then every 12 months. Besides a clinic evaluation, Doppler ultrasound was performed at 1 and 6 months, and then, repeated annually after the index procedure. Further radiographic evaluations such as computed tomography angiography and/or digital subtraction angiography were performed in case if indicated. Patients who described new neurological symptoms during the follow-up period were reevaluated by clinical and radiological assessment. In-stent restenosis was defined as ≥ 50 % stenosis or occlusion in the location of the target lesion.

Laboratory Analyses

All blood samples were obtained in the morning before the procedure for the measurement of serum albumin, CRP, and other hematologic and biochemical parameters. CRP and serum albumin levels were measured by using the Roche Cobas 6000 biochemistry auto-analyzer device (Indianapolis, USA). In our institution, the normal range for CRP and serum albumin levels are 0-5 mg/L and 3.5-5.5 g/dL, respectively. The CAR was calculated by dividing serum CRP by serum albumin level. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

Statistical Analyses

The data were presented as a mean ± SD for parametric or a median [interquartile range] for non-parametric variables and as percentages (%) for categorical variables. Continuous variables were assessed for the normal distribution using Kolmogorov-Smirnov statistics. Differences between ISR (+) and ISR (-) subjects were evaluated using two-sample t-tests. Categorical variables were tested by Pearson's $\chi 2$ test or Fisher's Exact Test. A receiver operating curve (ROC) was generated to define the cut-off values of the CAR for ISR. Using these cut-off values of the CAR, Kaplan-Meier curves were developed, and the groups were compared using log-rank tests. Multivariate Cox regression analyses were used to investigate the independent predictors of ISR. Also, multicollinearity analysis was performed for the parameters of the regression model to assess whether there is multicollinearity or not. P-values were two-sided, and values < 0.05 were considered statistically significant. All statistical studies were carried out using Statistical Package for Social Sciences software (SPSS 22.0 for Windows).

RESULTS

The study population consisted of 206 patients who underwent successful carotid artery stenting. The patients were classified into two groups as having ISR or not. ISR was developed in 34 (16.5%) out of 206 patients after a mean follow-up of 24.2 ± 1.5 months. Baseline demographic and laboratory findings, as well as angiographical and interventional details of all patients, were depicted in Table 1.

Table 1. Baseline clinical, interventional details and laboratory findings of all patients.

	Overall (n=206)	ISR (-) (n=172)	ISR (+) (n=34)	P value
Age, y, mean ± SD	69.6 ± 7.9	69.1 ± 7.8	70.8 ± 7.2	0.35
Male, n (%)	174 (84.5)	146 (84.9)	28 (82.4)	0.71
BMI, kg/m2	23.3 ± 2.9	23.2 ± 2.6	23.5 ± 2.7	0.65
Hypertension, n (%)	189 (91.7)	157 (91.3)	32 (94.1)	0.58
Diabetes mellitus, n (%)	116 (56.3)	95 (55.2)	21 (61.8)	0.48
Dyslipidemia, n (%)	157 (77)	125 (73.5)	32 (94.1)	0.01
Smoking, n (%)	109 (52.9)	89 (51.7)	20 (58.8)	0.45
CAD, n (%)	172 (83.5)	141 (82)	31 (91.2)	0.18
Symptomatic admission, n (%)	73 (35.4)	57 (33.1)	16 (47.1)	0.12
Follow-up time, month	24.2 ± 1.5	23.8 ± 1.8	25.4 ± 1.6	0.48
Lesion				
Lesion length, mm	26.2 ± 6.3	26.3 ± 5.9	25.5 ± 8.2	0.51
Lesion stenosis, %	85.74 ± 5.1	84.3 ± 4.6	87.1 ± 6.3	0.19
Stenting				
Left carotid, n (%)	102 (49.5)	84 (48.8)	18 (52.9)	0.36
Pre-dilatation, n (%)	18 (8.7)	16 (9.3)	2 (5.9)	0.53
Post-dilatation, n (%)	188 (91.3)	158 (91.9)	30 (88.2)	0.49
Stent length, mm	36.9 ± 6.1	37.1 ± 5.6	35.8 ± 8	0.25
Stent diameter, mm	8.03 ± 1.2	8.1 ± 1.3	7.6 ± 0.8	0.05
Residual stenosis, n (%)	45 (21.8)	23 (13.4)	22 (64.7)	< 0.01
Laboratory parameters				
Hemoglobin, mg/dL,	13.8 ± 1.4	14.1 ± 1.3	13.1 ± 1.6	0.33
Leukocyte, x109/L	8.4 ± 2.19	8.3 ± 2.04	8.89 ± 2.79	0.78
Neutrophil count x 109/L	5.20 ± 2.06	5.04 ± 1.75	6.02 ± 3.12	0.01
Lymphocyte count x 109/L	2.27 ± 0.78	2.35 ± 0.79	1.85 ± 0.59	< 0.01
NLR	2.7 ± 0.9	2.4 ± 1.3	3.9 ± 1.5	< 0.01
Platelet count x109/L	242.1 ± 36.2	239.6 ± 35.3	248.5 ± 39.8	0.49
eGFR, mL/min/1.73 m2	87.9 ± 14.4	89.4 ± 13.2	85.4 ± 14.5	0.21
Uric acid, mg/dL	5.9 ± 1.3	5.9 ± 1.2	6.2 ± 1.4	0.19
HbA1c, (%)	7.3 ± 1.5	7.2 ± 1.4	7.7 ± 1.7	0.07
CRP/Albumin Ratio (CAR)	0.18 [0.33]	0.15 [0.2]	0.99 [1.3]	< 0.01

BMI, body mass index; CAD, coronary artery disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ISR, in-stent restenosis; NLR, neutrophil to lymphocyte ratio.

The mean age of the sample cohort was 69.6 ± 7.9, and the vast majority of the subjects were male (84.5 %). Although the frequency of risk factors such as hypertension, diabetes mellitus, smoking, and history of coronary artery disease was similar between the groups (p > 0.05 for each), dyslipidemia was more frequently observed in the ISR (+) group (p = 0.01). We noted that the lesion length, the degree

of stenosis, pre-dilatation, and post-dilatation rates were not different ($p > 0.05$ for each) between the groups. On the other hand, the stent length, clinical status (whether symptomatic or asymptomatic), the stent diameter, and residual stenosis rates reached statistical significance between the groups ($p < 0.05$ for each). In terms of laboratory findings, neutrophil and lymphocyte count, as well as the neutrophil to lymphocyte ratio (NLR) and CAR, were significantly different ($p < 0.05$ for each) in each group, while other laboratory parameters were similar between the groups ($p > 0.05$ for each). The type of medications after discharge and the mean follow-up time after the index procedure was similar for both groups.

In univariate Cox regression analysis; dyslipidemia, stent diameter, NLR, CAR, and residual stenosis were found to be correlated with ISR. After applying these parameters to the multivariable Cox analysis; stent diameter (HR: 0.57, %95 CI: 0.41–0.80, $p < 0.01$), NLR (HR: 1.27, %95 CI: 1.12–1.45, $p < 0.01$), CAR (HR: 1.85, %95 CI: 1.29–2.64, $p < 0.01$) and residual stenosis (HR: 3.96, %95 CI: 1.64–9.56, $p < 0.01$) were found to be independent predictors of ISR (Table 2).

Table 2. Predictors of ISR in multivariable analysis.

	Multivariate HR (95% CI)	**P value**
Dyslipidemia	1.68 (0.37 – 7.58)	0.49
Stent diameter	0.57 (0.41 – 0.80)	< 0.01
NLR	1.27 (1.12 – 1.45)	< 0.01
CRP/Albumin Ratio (CAR)	1.85 (1.29 – 2.64)	< 0.01
Residual stenosis	3.96 (1.64 – 9.56)	< 0.01
NLR, neutrophil to lymphocyte ratio; CRP, C-reactive protein.		

The tolerance and variance inflation factor (VIF) were determined to access the multicollinearity of parameters in the model. Because of all values had a tolerance > 0.1 and VIF < 10, we accepted that there was no multicollinearity between each parameter in the model. In ROC analysis, the CAR value of > 0.53 predicted ISR with a sensitivity of 100 % and a specificity of 97.1 % (AUC 0.98, $p < 0.001$) (Figure 1).

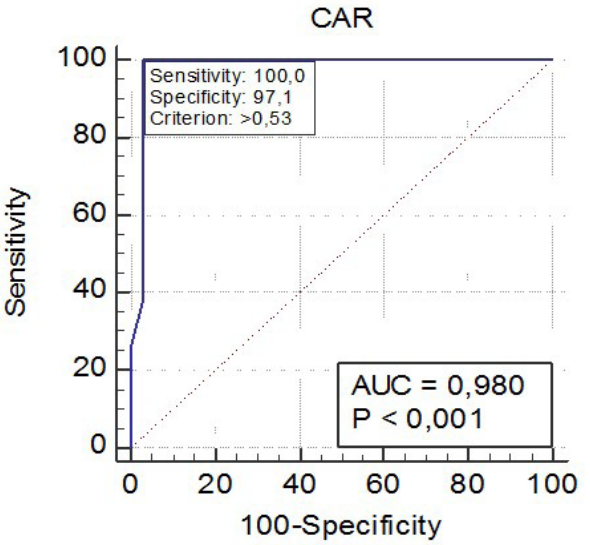

Figure 1. ROC curve analysis of the association between the CAR and ISR in patients undergoing CAS.
ROC: Receiver operating characteristic; AUC: Area under the curve; CAR: CRP to albumin ratio;
CAS: carotid artery stenting.

In Kaplan-Meier curves, patients with CAR value above the cut-off value had a significantly higher risk for ISR during follow-up (long-rank $p < 0.01$) (Figure 2).

DISCUSSION

In the present research, we showed that elevated preprocedural CAR levels are related to the development of ISR after CAS. To the best of our knowledge, this is the first study to demonstrate a significant correlation between CAR and ISR after CAS. Also, similar to published previous studies, we noted that stent diameter, residual stenosis after the index procedure, and elevated NLR were independent predictors of ISR.

ISR, which is one of the Achilles' heels of the percutaneous vascular interventions, increases the risk of long-term vascular complications even after a successful procedure. Recent studies have documented the main role of vascular inflammation in the development of ISR in patients with coronary artery disease who are treated with stenting (19,20). ISR is usually initiated by vascular injury due to balloon inflation and stent deployment (21). This vascular

injury causes the release of various substances, all of which leads to adhesion of various inflammatory cells including neutrophils, monocytes, and thrombocytes. These cells secrete various types of vasoactive, thrombogenic, and mitogen cytokines, which cause the development of vascular remodelling, neointimal proliferation and inflammation resulting in ISR. Since ISR within the carotid arteries might have a similar underlying pathophysiologic mechanism, a preprocedural evaluation of the inflammatory status may be useful to identify patients who are at risk for ISR.

Previous studies have demonstrated the relationship between systemic inflammation and ISR after CAS. In a recent study, conducted by Wasser et al., has shown that periprocedural inflammatory status during CAS may play a crucial role in the development of the carotid artery ISR (22). Another study reported that CRP levels two days after the index carotid artery intervention was associated with ISR during six months period following CAS (23). In addition to the role of elevated CRP levels, preprocedural NLR, mean platelet volume, and the neutrophil and albumin ratio was found to be associated with the occurrence of ISR following CAS (24-26). In this study, we also found that a higher ratio of CAR, a new inflammatory-based index, is a strong predictor of ISR development after CAS. The possible underlying mechanism of this relationship may be explained as follows. Firstly, serum albumin is a potential extracellular antioxidant and its reduced levels cause an increase of reactive oxygen species which lead to vascular muscle cell apoptosis, and trigger proliferation, migration and remodelling of adventitial myofibroblasts that are responsible for ISR (27,28). Secondly, preprocedural higher levels of the inflammatory substance, namely CRP, might cause an aggregated vessel response to balloon injury (29).

Accuracy and predictive value of CAR have been recently investigated in patients with cardiovascular disease. The elevated levels of CAR have found to be associated with a poor long-term prognosis in patients with acute coronary syndrome (30,31). Besides that, it was reported that elevated CAR is correlated with ISR development in patients with acute coronary syndrome (32). However, the predictive value of preprocedural CAR has not been assessed for ISR following CAS. Our study might be the first study to demonstrate a significant relationship between ISR and CAR levels.

In terms of clinical applicability, our study findings may be valuable because a risk stratification system using CAR may be a more affordable method comparing to more specific but expensive biomarkers. Moreover, both CRP and albumin analysis are simple and inexpensive parameters which are widely available in the most clinical centre. Also, we considered that since statins can significantly decrease systemic inflammation, patients with elevated preprocedural CAR levels may need a more aggressive statin treatment during the follow-up period to decrease the development of ISR.

Study limitations

Our study has the following limitations. First, the study had a non-randomized retrospective design. Second, this research had a relatively small patient size even though we tried to enrol all consecutive patients. Third, we did not assess other well-known inflammatory and prognostic biomarkers like interleukins in our study. Finally, multicenter and prospective studies are needed to ascertain the definitive role of CAR for ISR following CAS.

CONCLUSION

ISR is a frustrating complication of percutaneous vascular intervention. As shown in our study, the combination of two inflammatory markers, namely CAR, can accurately predict the risk of ISR development after CAS.

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