The Predictive Value of C-Reactive Protein-Albumin Ratio in Long-Term Mortality Among Patients Undergoing Carotid Artery Stenting

Cüneyt Toprak(İD)

Clinic of Cardiology, Kartal Koşuyolu High Specialization Training and Research Hospital, İstanbul, Türkiye

ABSTRACT

Introduction: Several inflammatory biomarkers reported in previous research have been associated with the severity of carotid artery stenosis, symptomatic carotid lesions, and carotid stent restenosis. The C-reactive protein (CRP)-to-serum albumin ratio (CAR) has been shown to predict peripheral artery disease severity in patients with carotid artery disease (CAD). However, the relationship between CAR and long-term mortality in CAD patients following carotid artery stenting (CAS) remains uncertain. The goal of this study was to investigate the ability of CAR to predict long-term mortality in patients with CAS.

Patients and Methods: A total of 998 CAD patients who had percutaneous carotid artery intervention were reviewed retrospectively, and 482 of them without follow-up data were excluded from this study. The study included patients who had percutaneous carotid artery intervention between 2012 and 2018. Before the procedure, serum CRP, complete blood counts, and albumin levels were measured. The relationships between patients' characteristics, procedural details, and CAR with all-cause mortality were evaluated in the long-term follow-up after CAS.

Results: Older age (HR= 1.044; 95% CI= 1.001-1.089; p= 0.046), smoking (HR= 2.636; 95% CI= 1.213-5.728; p= 0.014), blood urea (HR= 1.017; 95% CI= 1.002-1.033; p= 0.025), albumin (HR= 0.252; 95% CI= 0.132-0.480; p< 0.001), CRP levels (HR= 1.336; 95% CI= 1.055-1.691; p= 0.016) and CAR (HR= 1.012; 95% CI= 1.003-1.022; p= 0.008) were statistically associated with all-cause mortality at 55.2 ± 12.4 months follow-up after CAS in multivariate COX regression analysis.

Conclusion: In patients undergoing CAS, CAR was independently related to long-term mortality. CAR could be used in this population for risk stratification to achieve closer follow-up and optimize treatment.

Key Words: C-reactive protein; carotid artery stenosis; mortality; serum albumin; stents

Karotis Arter Stentleme Uygulanan Hastalarda Uzun Vadeli Mortalitede C-Reaktif Protein-Albümin Oranının Prediktif Değeri

ÖZET

Giriş: Daha önceki araştırmalarda bildirilen karotis arter darlığı, semptomatik karotis lezyonları ve karotis stent restenozu şiddeti ile ilişkili birkaç enflamatuvar biyobelirteç vardır. C-reaktif protein (CRP)-serum albümin oranının (CAO), karotis arter hastalığı (KAH) olan hastalarda periferik arter hastalığı şiddetini öngördüğü gösterilmiştir. Ancak, karotis arter stentleme (KAS) sonrası KAH hastalarında CAO ve uzun vadeli mortalite arasındaki ilişki belirsizliğini korumaktadır. Bu çalışmanın amacı, KAS'lı hastalarda CAO'nun uzun vadeli mortaliteyi öngörme yeteneğini araştırmaktır.

Hastalar ve Yöntem: Perkütan karotid arter müdahalesi olan toplam 998 KAH hastası geriye dönük olarak incelendi ve bunlardan 482 kişi takip verileri olmadığı için bu çalışmaya dahil edilmedi. Çalışmaya 2012-2018 yılları arasında perkütan karotis arter müdahalesi olan hastalar dahil edildi. İşlem öncesi serum CRP, tam kan sayımı ve albümin düzeyleri ölçüldü. KAS sonrası uzun dönem takipte hastaların özellikleri, işlem detayları ve CAO ile tüm nedenlere bağlı mortalite arasındaki ilişkiler değerlendirildi.

Bulgular: İleri yaş (HR= 1.044; %95 CI= 1.001-1.089; p= 0.046), sigara kullanımı (HR= 2.636; %95 CI= 1.213-5.728; p= 0.014), kan üre (HR= 1.017; %95 CI= 1.002-1.033 ; p= 0.025), albümin (HR= 0.252; %95 CI= 0.132-0.480; p< 0.001), CRP seviyeleri (HR= 1.336; %95 CI= 1.055-1.691; p= 0.016) ve CAO'nun (HR= 1.012; 95% CI= 1.003-1.022; p= 0.008), çok değişkenli Cox regresyon analizinde KAS sonrası 55.2 ± 12.4 aylık takipte tüm nedenlere bağlı mortalite ile istatistiksel olarak ilişkili oldugu saptandı.

Sonuç: KAS uygulanan hastalarda CAO, bağımsız olarak uzun vadeli mortalite ile ilişkiliydi. CAO, daha yakın takip uygulamak ve tedaviyi optimize etmek için bu popülasyonda risk sınıflandırması için kullanılabilir.

Anahtar Kelimeler: C-reaktif protein; carotis arter stenozu; mortalite; serum albumin; stentler

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Correspondence

Cüneyt Toprak

E-mail: cuneytoprak@hotmail.com
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INTRODUCTION

One of the leading causes of morbidity and mortality is ischemic stroke, and approximately 20% of all ischemic strokes are caused by carotid artery atherosclerosis[1,2]. Current interventional therapeutic methods for individuals with carotid artery stenosis include carotid artery stenting (CAS) and carotid endarterectomy (CEA)[3,4]. Because CAS is less invasive in nature than CEA, it is typically used in patients who are at high surgical risk[5,6]. Many clinical factors, including age, diabetes, smoking, coronary artery disease, chronic lung diseases, kidney failure, and symptomatic carotid artery stenosis, may impact morbidity and mortality in patients undergoing CAS. Furthermore, mortality and ischemic stroke in these patients are associated with procedural issues as well as lesion morphology, which include ulcerated and calcified plaques, lesion length, osteal lesions, lesion severity, type III aortic arch, pre-dilatation, and post-dilatation[7-10]. Although carotid atherosclerosis progresses similarly to other arterial beds, the relationship between plaque growth and cerebral infarction is complicated. Inflammation is well known to play a role in the pathogenesis of carotid atherosclerosis, and the roles of several inflammatory cells and mediators in carotid artery disease and stroke should be explored to better predict or identify patients at high risk[11-13].

Nevertheless, pathophysiological changes might affect only a single biomarker. CAR, which combines CRP and albumin, may provide more comprehensive information to better predict the outcomes in CAS patients. Previous studies have shown that CAR is a novel inflammatory prognostic factor for cardiovascular disease outcomes[14-15]. As a result, CAR might be a more sensitive indicator of the inflammatory process, morbidity, and mortality. The goal of this study was to investigate the ability of CAR to predict long-term mortality in patients with CAS.

PATIENTS and METHODS

Study Patients

A total of 998 CAD participants with percutaneous carotid artery intervention were evaluated retrospectively, and 516 of them were included in this study. Patients who underwent percutaneous carotid artery intervention from 2012 to 2018 were included in the study. Four hundred eighty-two patients whose follow-up data could not be collected were excluded from the study. Before the procedure, serum CRP, complete blood counts, and albumin levels were measured. A retrospective chart review was conducted to assess the demographic and clinical features of the patients (age, gender, smoking history, diabetes mellitus, hyperlipidemia, hypertension, peripheral arterial disease, and chronic kidney disease).

Patients with chronic renal failure, acute coronary syndrome in the last six months, congestive heart failure, atrial fibrillation, active or chronic infection, and malignancy were not included in the study. The North American Symptomatic Carotid Endarterectomy Study (NASCET) criteria were used to measure carotid artery stenosis[3]. Total occluded carotid artery lesions were not intervened in. Our study adhered to the Helsinki Declaration, and all patients provided written informed consent. The Ethics Commission of Kartal Koşuyolu High Specialty Training and Research Hospital approved the study in İstanbul, Türkiye.

Carotid Artery Stenting Protocol

The patients were given a daily dose of 75 mg of clopidogrel and 100 mg of aspirin for at least seven days prior to the CAS. This treatment regimen was followed for at least three months following CAS. Under local anesthesia, diagnostic cerebral angiography was conducted exclusively through the femoral artery. In all cases, digital subtraction angiography was performed prior to CAS. Digital subtraction angiography was used to assess the diameters of the internal carotid artery, the common carotid artery, and the stenotic portion of the internal carotid artery. The internal carotid artery (ICA) to common carotid artery (CCA) diameter ratio was established as the ratio of the normal segment diameters of these two arteries. The North American Symptomatic Carotid Endarterectomy Trial (NASCET) technique was used to quantify the percentage of diameter stenosis [diameter stenosis %= (1-diameter of the stenotic segment/distal normal segment of the internal carotid artery) × 100%][3]. In addition, all patients had coronary artery angiography. An 8F introducer catheter was employed for carotid artery stenting. Heparin was administered in standard fashion. The target for activated clotting time was 250 s. During the procedures, the patients' arterial pressure and electrocardiograms were monitored. The 8F JR4 guiding catheter (Launcher, Medtronic Inc, Minneapolis ABD) was placed proximally to the lesion via a 0.035 hydrophilic guidewire. Severe carotid artery stenosis was predilated with a balloon. An embolic protection device was used for neuroprotection in all patients. A self-expanding carotid stent was performed. Post-dilatation was performed in patients who did not achieve optimal results. One mg of intravenous atropine was given 30 seconds before post-dilatation to prevent hypotension and bradycardia. A final cerebral angiography was performed to confirm the lack of distant embolism. Residual diameter stenosis of less than 20% was evaluated as successful.

Statistical Analysis

First, the normally distributed continuous variables were tested using the Kolmogorov-Smirnov or Shapiro-Wilk tests, as appropriate. While mean ± standard deviation formation

was used for the expression of normally distributed continuous variables, median (inter-quartile ranges) formation was preferred for skew-distributed continuous variables. Categorical variables were expressed as numbers and percentages. To compare categorical variables, the chi-square test and Fisher's exact test were used. The variables that satisfied parametric variable criteria were tested by the 2-tailed independent sample t-test, whereas the Mann-Whitney U test was used to examine non-parametric variables. A univariate logistic regression model included factors that were significantly different for patients with and without mortality. The variables whose non-adjusted p-value was under 0.1 were included in the full model of Cox regression analysis, which was used to identify independent predictors of mortality. The cut-off value of CAR was calculated using an area under the receiver operating characteristic (ROC) curve study. A p-value of under 0.05 (2-tailed) was recognized to be statistically significant. The SPSS software (Version 21.0, SPSS, Inc., Chicago, IL) was used to evaluate the obtained data.

RESULTS

The study population had a median age of 67 (60-75) years, with 137 (26.5%) patients being female. Patients with and without all-cause mortality were divided into two groups for the study. Table 1 summarizes the demographic features, stent type, and laboratory parameters of all patients. Comorbidities

Table 1. Baseline characteristics, laboratory parameters, and angiographic characteristics of the study population

Variables	Mortality (-) (n= 423)	Mortality (+) (n= 93)	p
Gender (female), n (%)	109 (25.8)	28 (30.1)	0.437
Age (years) median IQR	66 (60-72)	70 (65-75)	0.001
Hypertension, n (%)	324 (76.6)	81 (87.1)	0.026
Smoking, n (%)	105 (25.3)	40 (43.2)	0.001
Hyperlipidemia, n (%)	246 (58.3)	48 (52.7)	0.351
Diabetes mellitus, n (%)	161 (38.1)	36 (40)	0.722
Symptomatic disease, n (%)	148 (35)	42 (45.2)	0.169
Previous MI, n (%)	130 (31)	26 (28.3)	0.708
Previous PCI, n (%)	159 (37.9)	32 (34.8)	0.635
Stent length (mm) mean ± SD	36.4 ± 7.7	36.8 ± 6.7	0.369
Stent type, n (%)			
XACT	277 (65.4)	48 (51.6)	
ACCULINK	40 (9.5)	8 (8.6)	
WALLSENT	16 (3.8)	8 (8.6)	0.059
EV3	89 (21)	28 (30.1)	
CRYSTALLO	1 (0.2)	1 (0.2)	
Pre-dilatation, n (%)	60 (14.2)	11 (11.8)	0.621
Post-dilatation, n (%)	356 (84.8)	86 (93.5)	0.029
Open-cell Stents, n (%)	132 (31.2)	36 (39.1)	0.143
WBC ($10^3/\mu$L) median IQR	4.77 (2.7-7.8)	9.6 (7.4-15.7)	0.001
Hemoglobin (gr/dL) median IQR	12.8 (11.3-14.1)	12.3 (108-13.9)	0.34
Fasting glucose (mg/dL) median IQR	110 (95-144)	111 (96.5-148.5)	0.665
Urea (mg/dL) median IQR	39 (31.7-49)	42 (33-52.5)	0.026
Creatinine (mg/dL) median IQR	0.78 (0.09-0.99)	0.76 (0.09-1.06)	0.591
Platelet ($10^3/\mu$L) mean ± SD	248 ± 79.1	273.3 ± 100.3	0.010
Albumin (mg/dL) mean ± SD	4.07 ± 0.49	3.79 ± 0.48	<0.001
CRP (mg/L) median IQR	0.34 (0.08-0.75)	0.56 (0.12-1.4)	0.010
CAR median IQR	8.95 (2.01-18.74)	14.88 (3.78-39.45)	0.005

CAR: C-reactive protein/albumin ratio, MI: Myocardial infarction, PCI: Percutaneous coronary interventions, Median IQR: Median value (25-75% value), WBC: White blood cell, CRP: C-reactive protein.

Table 2. Cox regression analysis for independent predictors of all-cause mortality

	Univariate			Multivariate		
Variables	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
Gender (female)	1.241	0.757-2.033	0.757			
Age (years)	1.050	1.022-1.079	<0.001	1.044	1.001-1.089	0.046
Smoking	2.251	1.351-3.751	0.002	2.636	1.213-5.728	0.014
Hypertension	2.062	1.080-3.938	0.028			
Stent type	1.231	1.044-1.450	0.013			
WBC	1.001	1.001-1.002	<0.001			
Urea	1.006	1.001-1.011	0.022	1.017	1.002-1.033	0.025
Platelet	1.003	1.001-1.006	0.011			
Albumin	0.329	0.194-0.556	<0.001	0.252	0.132-0.480	<0.001
CRP	1.308	1.067-1.602	0.010	1.336	1.055-1.691	0.016
CAR[¥]	1.012	1.004-1.021	0.005	1.012	1.003-1.022	0.008

CAR: C-reactive protein/albumin ratio, HR: Heart rate, CI: Confidence interval, WBC: White blood cell, CRP: C-reactive protein.
Model 1: Age, smoking, urea, albumin, CRP.
Model 2: Age, smoking, urea, CAR.
[¥]: Model 2.

such as hypertension, diabetes, hyperlipidemia, and coronary disease history were not different in both groups. Fasting blood glucose, creatinine, and hemoglobin counts were comparable in both groups in terms of laboratory markers (Table 1). Additionally, the carotid stent type, including stent trademark, stent length, and open-cell or closed-cell type, was similar between groups.

Patients with all-cause mortality had greater urea levels, CRP, white blood cell, and platelet counts, according to our findings. Inversely, in individuals with all-cause mortality, plasma albumin levels were lower. Remarkably, patients with all-cause mortality also had higher CAR than those without all-cause mortality [8.95 IQR (2.01-18.74) vs. 14.88 IQR (3.78-39.45), p= 0.005, respectively]. We used both univariable and multivariable Cox regression models to establish the determinants of all-cause mortality. Advanced age, smoking, CAR, CRP, albumin, and urea were found to be predictors of all-cause mortality in a multivariate Cox regression analysis (Table 2).

According to the ROC-Curve analysis, the most appropriate cut-off value for CAR to predict all causes of mortality was 11.1%, with a sensitivity of 57.4% and a specificity of 59.5% (AUC= 0.617, 95 CI%= 0.535-0.700, p= 0.005) (Figure 1). Furthermore, demographic characteristics, stent type, and laboratory parameters of all patients were presented by dividing them into two groups based on the determined cut-off CAR value (Supplementary Table 1). Higher CAR was associated with worse long-term survival in Kaplan-Meier curves (CRP/Albumin ratio was associated with worse survival in the 75-100 percentile range) (Figure 2).

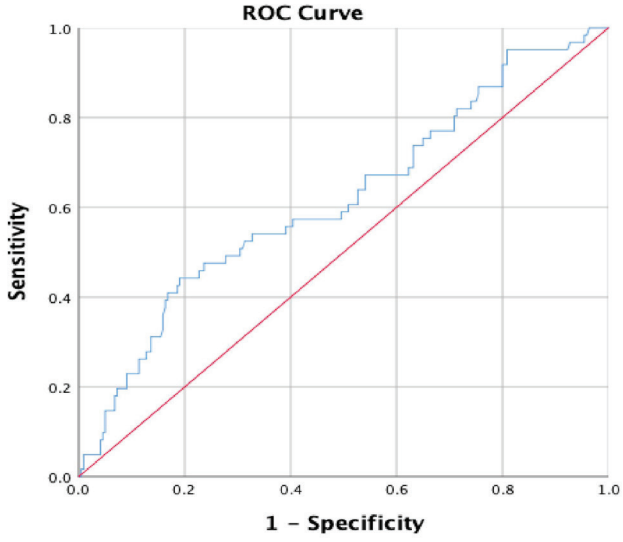

Figure 1. Receiver operating characteristic (ROC) curve for the value of C-reactive protein to albumin ratio (CAR) to predict long-term mortality.

DISCUSSION

CAR was shown in this study to be a reliable marker in the prediction of all-cause mortality in CAS patients, and this is the first study to reveal the results in this patient population in the literature.

Supplementary Table 1. Demographic and laboratory values according to CAR classification as lower and higher than CAR median value of 11.1

Variable	CAR lower (n= 158)	CAR higher (n= 124)	p
Gender (female) (%)	42 (26.6)	33 (26.6)	0.995
Age (year) median IQR	66 (61-72)	67 (62-78)	0.110
Hypertension, n (%)	124 (78.5)	105 (84.7)	0.183
Current smoker, n (%)	45 (28.5)	48 (39.7)	0.055
Hyperlipidemia, n (%)	91 (57.6)	64 (52.5)	0.399
Diabetes mellitus, n (%)	61 (38.6)	46 (38)	0.920
Symptomatic disease	53 (33.5)	49 (39.5)	0.424
Previous MI, n (%)	27 (17.2)	41 (33.9)	0.002
Previous coronary PCI, n (%)	59 (37.8)	52 (42.3)	0.462
Stenosis significance (%)	83 ± 10.8	82.2 ± 11.5	0.586
Stent length (mm) mean ± SD	37.8 ± 8.9	36.3 ± 7.2	0.125
Stent type, n (%)			
XACT	90 (57)	70 (56.5)	
ACCULINK	11 (7)	10 (8.1)	
WALLSENT	6 (3.8)	9 (7.3)	0.819
EV3	49 (31)	34 (27.3)	
CRYSTALLO	2 (1.3)	0 (0)	
KORONER	0 (0)	1 (0.8)	
Pre-dilatation, n (%)	15 (9.5)	15 (12.1)	0.561
Post-dilatation, n (%)	138 (87.3)	105 (85.4)	0.726
Open-cell stent, n (%)	61 (38.6)	44 (35.5)	0.621
WBC ($10^3/\mu$L) median IQR	37.8 (7.5-74.6)	41.7 (7.8-76.5)	0.569
Hemoglobin (gr/dL) median IQR	12.7 (11.3-14.1)	12.6 (10.8-14.1)	0.722
Fasting glucose (mg/dL) median IQR	107 (92.5-140.7)	109 (96-146)	0.213
Urea (mg/dL) median IQR	38.5 (31-50.2)	40 (32-50)	0.791
Cr (mg/dL) median IQR	0.72 (0.08-0.96)	0.79 (0.09-1.07)	0.121
Platelet ($10^3/\mu$L) mean ± SD	243 ± 67	269 ± 97	0.011
Albumin (mg/dL) mean ± SD	4.07 ± 0.54	3.97 ± 0.48	0.107
CRP (mg/L) median IQR	0.11 (0.04-0.28)	1.11 (0.68-2.1)	<0.001

MI: Myocardial infarction, PCI: Percutaneous coronary interventions, CAR: C-reactive protein/albumin ratio, WBC: White blood cell, CRP: C-reactive protein. Median value (25-75% value).

Although carotid atherosclerosis progresses similarly to other arterial beds, the relationship between plaque growth and cerebral infarction is complicated. Inflammation is well known to play a role in the pathogenesis of carotid atherosclerosis, and the roles of several inflammatory cells and mediators in carotid artery disease and stroke should be explored to better predict/identify patients at high risk[11-13]. Research suggests that inflammation occurs prior to the onset of stroke and could also contribute to the development of stroke[16]. Restoring carotid lumen patency and decreasing the risk of plaque embolism are the main goals of CAS[17]. After the stent implantation, inflammatory processes are still being studied and are linked to plaque progression, stent restenosis, and stroke. Many clinical factors, including age, diabetes, and symptomatic carotid artery stenosis, may impact mortality in patients undergoing CAS[7-9]. Furthermore, mortality and ischemic stroke in these patients are associated with procedural issues as well as lesion morphology, which includes ulcerated and calcified plaques[10]. In contrast to patients with stable plaques, patients with unstable plaques had significantly higher levels of inflammatory markers, which implies a connection between atherosclerotic unstable carotid artery lesions and the activity of the selected inflammatory indices in serum[18,19].

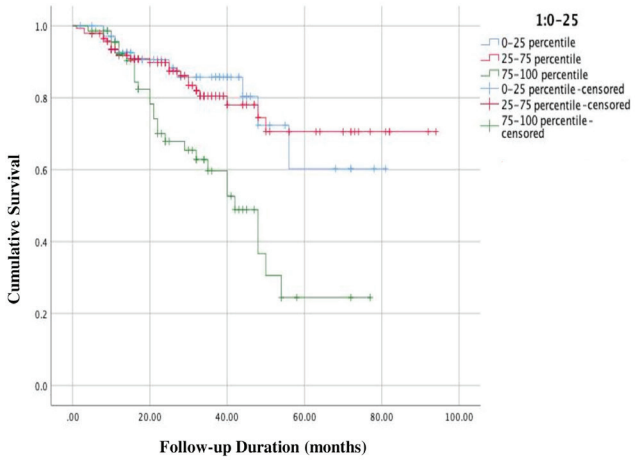

Figure 2. The Kaplan-Meier curve for overall survival in CAS patients was stratified by C-reactive protein to albumin ratio (CAR) level.

CRP and albumin are two acute phase reactants (APRs) that can be used to assess inflammatory status[20,21]. CRP, one of the most important APRs, may be more than just a marker of systemic inflammation; it may also be a direct, active contributor to atherogenesis, the development of atherosclerosis, and its destabilization[20,22]. CRP is widely acknowledged as a powerful risk indicator capable of predicting future cerebrovascular events. Elevated CRP serum levels have been reported in some studies of carotid arteriosclerotic disease[13,17,23]. Furthermore, previous research found that patients with acute ischemic stroke had larger infarct volumes when their CRP levels were higher[24,25]. CRP may be used as a valuable indicator to assess the probability and course of atherosclerotic cerebral infarction. Albumin, on the other hand, is a negative APR, and its serum levels are expected to fall in pro-inflammatory conditions like atherosclerotic heart disease. Previous studies found a link between low albumin concentrations and an increased risk of adverse cardiovascular outcomes in the general population[26-29]. The association between high serum albumin levels and lower mortality and better functional status in ischemic stroke demonstrated Alb's neuroprotective effect[30]. Furthermore, as an anti-inflammatory agent, albumin is thought to reduce microglial and T-cell activation[31].

Nevertheless, pathophysiological changes might affect only a single biomarker. CAR, which combines CRP and albumin, may provide more comprehensive information to better predict the outcomes of CAS patients. The CAR, developed by Fairclough et al., is thought to have higher prognostic accuracy than albumin and CRP concentrations in predicting poor prognosis in patients admitted with seriously ill status[32]. CAR has been linked to the severity of carotid atherosclerosis, which is related to the size and prognosis of stroke[33]. In-hospital mortality in patients with intracerebral hemorrhage, a different type of stroke, was recently reported to be significantly correlated with high CAR levels at presentation[34]. CAR has been investigated in the context of carotid artery stenosis and has been associated with an increased risk of restenosis after carotid artery stenting[35]. However, the value of CAR in predicting long-term mortality in CAS patients has yet to be investigated. Our study combines these ratios by developing the CAR and demonstrating its utility in long-term clinical outcomes.

Limitations

This study was based on a retrospective analysis in a single center. We could not evaluate the potential prognostic role of the CAR with respect to future adverse events. Some inflammatory markers were not evaluated in this study. Multicenter and prospective studies are needed to ascertain the definitive role of CAR in CAS mortality.

CONCLUSION

The results of the current study suggest that routine blood test findings in patients undergoing CAS may provide valuable prognostic information. This study showed that high CAR at admission was independently associated with long-term mortality in CAS patients. CAR could be used in this population for risk stratification to achieve closer follow-up and optimize treatment. Further research on independent multicenter cohorts is needed to validate our results.

Ethics Committee Approval: This study was approved by Kartal Koşuyolu High Specialization Training and Research Hospital Ethics Committee (Decision no: 2022/11/611, Date: 09.08.2022).

Informed Consent: This is retrospective study, we could not obtain written informed consent from the participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept/Design - CT; Analysis/Interpretation - CT; Data Collection - CT; Writing - CT; Critical Revision - CT; Final Approval - CT; Statistical Analysis - CT; Overall Responsibility - CT.

Conflict of Interest: The authors have no conflicts of interest to declare.

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