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The Relationship of CRP/Albumin Ratio with Etiology and Prognosis in Acute Ischemic Stroke

Akut İskemik İnmede C-Reaktif Protein/Albümin Oranlarının Etyoloji ve Prognozla İlişkisi

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ABSTRACT

Objectives: Inflammation has a role in both the onset and progression of atherosclerosis. C-reactive protein (CRP) and albumin are indicators of inflammation and related to atherosclerosis and stroke. The ratio of CRP to albumin (CAR) is thought to have prognostic significance in systemic inflammation. However, the relationship between CAR and acute ischemic stroke (AIS) is yet to be clarified.

Methods: Between January 2016 and January 2018, 477 patients who were hospitalized in the Neurology Department with a diagnosis of AIS and 189 control cases were examined. Stroke severity of patients who admitted in first 24 h were evaluated with the National Institute of Health Stroke Scale (NIHSS) score. The relationship between CAR and stroke severity, early prognosis, and etiologic subtypes was evaluated.

Results: The mean age of patients was 69.54±12.8. While 52.2% of patients were male, 47.8% were female. The mean CAR values were 66.79±9.02 in the patient group and 36.19±3.56 in the control group. There was significant difference between the two groups (p<0.0001). With regard to NIHSS scores, there was significant difference between the mild (score <8), moderate (score 8–14), and severe (score >14) groups in terms of CAR values (60.7±8.5; 87.7±9.53; and 89.04±12.02) (p=0.0019). The mean CAR values in the atherothrombotic and cardioembolic groups were 94.553±9.36 and 60.974±9.36, respectively, and there was significant difference between the two groups (p=0.004). In terms of early prognosis, the mean CAR value of good prognosis (mRS: 0–2) and poor prognosis (mRS: 3–6) patients was 60.72±8.86 and 85.16±9.33, respectively. There was a strong statistical relationship between the CAR values and early prognosis (p<0.001). No statistically significant relationship was found according to either age or gender.

Conclusion: The strong relationship between high CAR values and stroke severity, bad early prognosis, and atherothrombotic stroke raises the question of whether or not the CAR value can be used as a predictive marker for the prognosis and etiologic subtype of stroke.

Keywords: Acute ischemic stroke; CRP/Albumin ratio; Prognosis.

ÖZET

Amaç: İnflamasyonun, aterosklerozda hem başlangıçta hem de progresyonda rolü olduğu bilinmektedir. C-reaktif protein ve albüminin her ikisi de inflamasyonun bir göstergesidir ve ateroskleroz ile bağlantılıdır. C-reaktif proteinin albümine oranının (CAR), C-reaktif protein ve albümin arasındaki dengeyi yansıttığı ve sistemik inflamasyonda prognostik önemi olduğu düşünülmektedir. CAR ile akut iskemik inme arasındaki ilişki henüz bilinmemektedir.

Yöntem: Ocak 2016-Ocak 2018 tarihleri arasında hastanemiz nöroloji bölümünde yatan 477 hasta ile enfeksiyonu ve bilinen tiroid hastalığı olmayan 189 kontrol olgusu incelendi. İlk 24 saat içinde başvuran hastaların inme şiddeti Ulusal Sağlık Enstitüsü İnme Ölçeği (NIHSS) puanı ile değerlendirildi. CAR ile inme şiddeti, erken prognoz ve etyolojik alt tipler arasındaki ilişki değerlendirildi.

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Bulgular: Hastaların ortalama yaşı 69.54±12.8 yıl, %52.2'si erkek ve %47.8'i kadındı. Ortalama CAR değerleri hasta grubunda 66.79±9.0, kontrol grubunda 36.19±3.56 idi. İki grup arasında anlamlı fark vardı (p<0.001). NIHSS'ye göre sınıflandırılan hafif, orta ve ağır gruplarda (<8, 8-14, >14) CAR değerleri açısından belirgin farklılık vardı (60.7±8.5; 87.7±9.53; 89.04±12.02) (p=0.0019). Aterotrombotik grupta ve kardiyoembolik grupta ortalama CAR değeri sırasıyla 94.553±9.36 ve 60.974±9.36 idi ve iki grup arasında anlamlı fark vardı (p=0.004). Erken prognoz açısından, iyi prognozlu hastaların (mRS= 0-2) ve kötü prognozlu (mRS= 3-6) hastaların ortalama CAR değerleri sırasıyla 60.72±8.86 ve 85.16±9.33 idi. CAR değerleri ile erken prognoz arasında güçlü bir istatistiksel ilişki vardı (p<0.001). Yaş ve cinsiyete göre istatistiksel olarak anlamlı bir ilişki bulunamadı.

Sonuç: Yüksek CAR değerlerinin inme şiddeti, kötü erken prognoz ve aterotrombotik inme ile ilişkili olduğunu gösteren bulgular, bu değerlerin inmenin prognozu ve etyolojik alt tipleri için öngörücü bir belirteç olarak kullanılabileceğini düşündürmektedir.

Anahtar sözcükler: C-reaktif protein/albümin oranı; akut iskemik inme; prognoz.

Stroke is regarded as the most damaging neurological disease, often resulting in death or physical impairment and disability.[1] Ischemic stroke (IS) is the most common type of stroke and accounts for about 80–85% of stroke cases.[2] C-reactive protein (CRP) is an acute-phase reactant and a marker of acute and chronic inflammation.[3] The CRP level is a marker for predicting the risk or prognosis of various diseases including AIS.[4-9] Increased serum C-reactive protein (CRP) levels have been found in AIS patients.[10-19] This finding may probably be related to systemic inflammatory response following stroke.[10] It has been suggested that increased CRP may have a relation with the severity of cerebral damage.[11] Studies on the correlation between elevated CRP levels with stroke severity and stroke subtype are limited.

Serum albumin is a negative acute phase protein, the serum levels of which decrease 1 week after AIS. In a study of AIS patients by Alvarez-Perez et al.,[20] 2011, serum albumin levels in cardioembolic stroke patients were found to be lower compared to the other etiologic subtypes.

In the light of these findings, it can be postulated that the ratio of serum CRP to albumin concentration may be more sensitive than either of them individually for predicting prognosis in AIS. This study aims to investigate the hypothesis that an elevated CRP/albumin ratio (CAR) in AIS is related to more severe clinical neurological findings in the acute setting and worse early prognosis. We assessed the association between the CAR value at admission with stroke severity, early prognosis, and etiologic subtypes which were either atherothrombotic or cardioembolic.

Methods

Between January 2016 and January 2018, 563 patients who were hospitalized with a diagnosis of acute IS (AIS) in the Neurology Department have been examined. Ninety-six patients not meeting the inclusion criteria have been excluded. A total of 477 patients and 189 control cases without a history of hemorrhagic stroke, hemorrhagic transformation, venous sinus thrombosis, any history of malignity, renal, rheumatological, immunological, infectious diseases, or malabsorption were included in the study. A written informed consent was obtained from the patients or their relatives on admission. The study was carried out in accordance with the Helsinki Declaration after the approval of the Ethical Committee of Erenkoy Mental Health and Disease Research and Training Hospital; the approval date and number were December 14, 2020-50.

Cerebral infarction was defined as a focal neurological deficit of sudden onset that persisted beyond 24 h and was documented by diffusion magnetic resonance imaging scan. Patients aged 18 years or older with acute IS who were admitted in the first 24 h after stroke onset were included in the study. The presence of hemorrhagic stroke, hemorrhagic transformation, venous sinus thrombosis, any history of malignity, renal, rheumatological, immunological, infectious diseases, or malabsorption was regarded as exclusion criteria for both the patient and control groups. Patients whose blood samples could not be collected in the first 24 h of stroke onset or whose prognosis could not be evaluated at the 10th day of the stroke were also not included in the study.

Demographic features and risk factors for IS were noted. Stroke subtype was determined as atherothrombotic, cardioembolic, lacunar, other, and undefined etiologic subgroups according to TOAST classification. Stroke severity on admission was assessed using the National Institute of Health Stroke Scale (NIHSS), and the distribution of NIHSS scores was classified into three categories: Mild for scores <8; moderate 8–14; and severe >14. The scores of NIHHS for

clinical stroke severity and modified Rankin Scale (mRS) for early stage prognosis were noted on the 10th day. The degree of disability or dependence was grouped into two according to the mRS; good prognosis, 0–2 points and poor prognosis, 3–6 points.

Blood samples were collected after an overnight fasting and analyzed in the first 24 h of stroke initiation. The analysis included fasting blood sugar, lipid profile, hemogram, sedimentation rate, CRP, and albumin levels. Cobas 8000 c502 (Roche Diagnostics, Tokyo, Japan) analyser was used to measure albumin and CRP levels. Normal ranges were 0.0–0.80 mg/dL for CRP and 3.5–5.3 g/dL for albumin. CAR was calculated as the ratio of CRP to the albumin level multiplied by 100. The relationship of CAR with stroke severity and early prognosis were investigated. CAR values were also studied to reveal any relation to the etiologic subtypes – the atherothrombotic versus the cardioembolic groups.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 20. Values for CRP and albumin showed a non-normal distributed pattern according to the Kolmogorov–Smirnov test; they were log transformed; and consequently Mann–Whitney-U test was further applied. Independent-sample t-tests were performed for variables with normal distribution. Categorical data were presented as percentage and continuous data as mean standard deviation. We investigated the associations of stroke severity on admission (NIHSS score) and functional outcome (mRS) with levels of CAR by performing Spearman's correlation. Multivariate logistic regression (step-wise backward conditional) analysis was used to determine independent predictors of early prognosis group using variables that were found to be significant in the univariate analysis ($p<0.05$). In the statistical analysis, $p<0.05$ with 95% confidence interval and 5% margin of error were considered statistically significant.

Results

Four hundred and seventy-seven patients with AIS and 189 control patients were included in the study. The mean ages of the patients and controls were 69.54±12.8 and 67.51±14.09, respectively. Male to female (M/F) percentages of the patient and control groups were 52.8/47.2 and 49.4/50.6, respectively. Female/male ratio was 0.89 in AIS group and 1.01 in the control group. There was no statistically significant difference in terms of gender and age ($p>0.05$). The mean CAR values were 66.79±9.02 in the stroke group and 36.19±3.56 in the control. There was a significant difference between the two groups in terms of mean CAR values ($p<0.001$) (Table 1).

The mean CAR values in the atherothrombotic group (n=178) were 94.55±9.36 and the mean CAR value was found to be 60.97±9.36 in the cardioembolic group (n=106). Mean CAR ratios in the lacunar (n=65), other (n=56), and undefined (n=72) groups were 46.5±4.8, 25.3±2.8, and 33.65±2.13, respectively. CAR values were significantly higher in the atherothrombotic group compared to the other groups ($p<0.001$) (Table 2 and Fig. 1).

Table 1. Demographic data and mean CRP/albumin ratio (CAR) values

Variables	Acute ischemic stroke patients n=477	Control group n=189	p
Gender Ratio (Female/Male) (n)	0.89 F:225 M:252	1.01 F:95 M:94	0.08
Age (years)	69.54±12.8	67.51±14.09	0.14
CRP/Albumin Ratio (CAR)	66.79±9.0	36.19±3.56	<0.001[a]

[a]Mann–Whitney U Test.

Table 2. Mean CRP/albumin ratio (CAR) values according to etiology

Variables	Atherothrombotic n=178	Cardioembolic n=106	Lacunar n=65	Other n=56	Undefined n=72	p
CRP/Albumin Ratio (CAR)	94.553±9.36	60.97±9.36	46.5±4.80	25.3±2.80	33.65±2.13	<0.001[a]

[a]ANOVA.

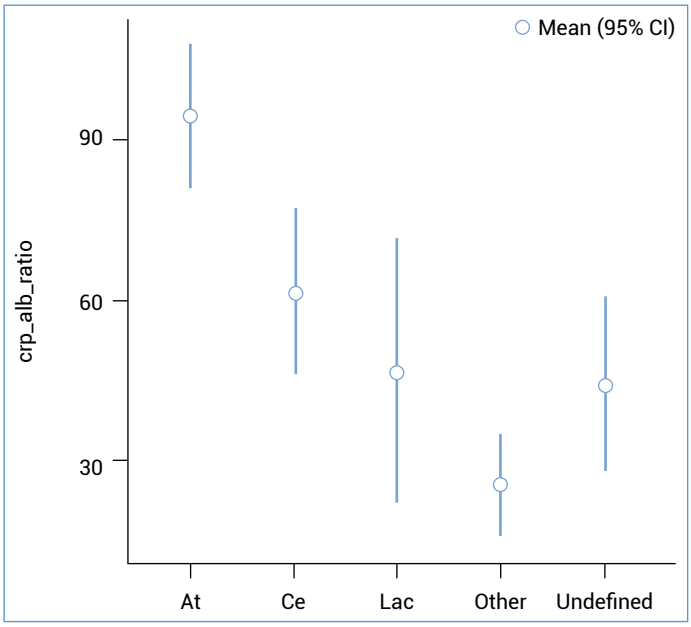

Figure 1. CAR ratio and etiological subtypes.

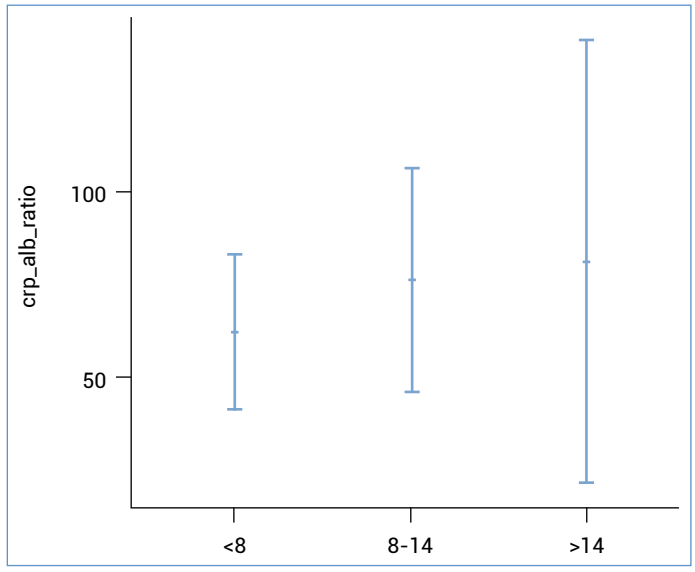

Figure 2. NIHSS and CAR ratio.

In the classification according to the NIHSS scores (NIHSS score <8, 8–14, >14), the mean CAR values were 60.7±8.5; 87.7±9.53; and 89.04±12.02 in the mild, moderate, and severe groups, respectively. There was a significant difference between NIHSS groups according to CAR (p=0.0019) (Table 3 and Fig. 2).

In terms of early-state prognosis, the mean CAR value was 60.72±8.86 in the good prognosis group (mRS=0–2, n=358), and 85.16±9.33 in the poor prognosis (mRS=3–6, n=118) group. There was a strong relationship between CAR values and early-state prognosis (p<0.001, rho=0.204) (Table 4 and Fig. 3).

In a univariate logistic regression analysis, age (Odds ratios [OR]=1.04 95% confidence interval [CI] [1.02–1.06], p<0.001), gender (OR=0.384 95% C.I. [0.25–0.59], p<0.001), localization of artery (OR=1.94 95% CI. [1.16–3.22], p=0.01), CRP/albumin ratio (OR=1.003 95% CI. [1.0–1.005], p=0.015), and NIHSS (OR=1.003 95% C.I. [1.0–1.005], p=0.015) were significantly associated with prognosis. Furthermore, in a multivariate logistic regression analysis; only gender (OR=0.54 95% CI [0.30–0.97] p=0.04) and NIHSS (OR=1.44 95% C.I. [1.33–1.56] p<0.001) were independent predictors of prognosis (Table 5).

Discussion

Values of CAR at admission were found to be associated with stroke severity, etiologic subtypes of stroke, and early prognosis in this study. To the best of our knowledge, this is one of the first reports describing the association of CAR values to etiology, severity and early prognosis in AIS patients.

Serum albumin levels are an indicator of nutritional status. The catabolic state may emerge following AIS and this may give rise to reduced serum albumin concentration.[21] Several studies have shown the role of low concentrations of albumin in atherosclerosis development by means of platelet hyperactivity, elevation of blood viscosity, endothelial dysfunction, and disinhibition of adhesion molecules predicting inflammation.[22-24]

Table 4. Mean CRP/albumin ratio (CAR) values according to prognosis

Variables	Good Prognosis n=358	Poor Prognosis n=119	p
CRP/Albumin Ratio (CAR)	60.72±8.86	85.16±9.33	<0.001[a] rho:0.204

Table 3. Mean CRP/albumin ratio (CAR) values according to National Institute of Health Stroke Scale (NIHSS) score groups

Variables	Mild NIHSS n=364	Moderate NIHSS n=88	Severe NIHSS n=25	p
Age (years) (±SD)	68.56 (±12.87)	72.54 (±11.9)	71.92 (±14.4)	0.021
CRP/Albumin Ratio (CAR)	60.7±8.5	87.7±9.53	89.04±12.02	0.00190.019[a]

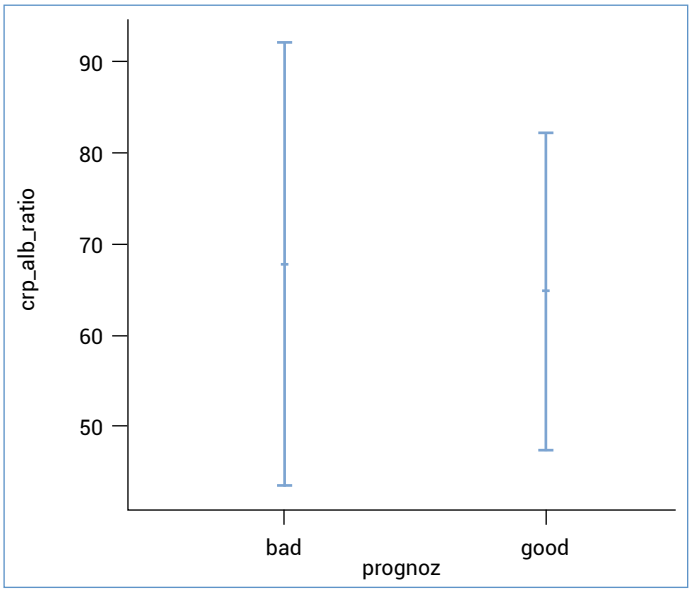

Figure 3. CAR values and early prognosis.

Serum albumin levels were examined in patients with AIS to find out whether there were alterations in different stroke subtypes and also its relationship to neurological status.[25-29] Alvarez-Perez et al.[20] investigated 200 patients with AIS and found lower levels of albumin in the atherothrombotic group than the other subtypes. Some authors have found a negative correlation of serum albumin levels to initial NIHSS scores while some others have not.[25,26] In some studies, it has been found that lower albumin levels were associated with worse outcome.[25,27-29] It was shown that severe hypoalbuminemia (serum albumin <2 mg/dL) at admission was associated with a poorer outcome as well as mortality and serum albumin level was suggested to be an independent indicator for poor prognosis.[28,30,31,32]

CRP is an acute-phase reactant and a non-specific marker in the diagnosis of various medical conditions such as infectious, immunologic, and rheumatologic disorders. CRP also takes part in atherogenesis by promoting an inflammatory state through complement regulation, producing prothrombotic processes by inducing tissue factor release and pro-inflammatory chemokines and adhesion molecules.[33,34] Carotid intima media thickness or carotid stenosis were found in association with higher levels of CRP in AIS patients.[35,36] Higher CRP values in AIS patients at admission are found to be correlated with stroke severity[37] and elevated levels of CRP are associated with more severe short-term and long-term prognosis.[6,7,10-19] Therefore, CRP may be accepted as a non-specific marker of the severity of ischemic damage.[38,39]

Although CRP and albumin may be accepted as prognostic markers in various clinical settings, the combination of both may provide more well-directed foresight than either one alone because this combination gives more information about both the inflammatory and metabolic status of the patient.[40] In recent studies, CAR ratio was found to be increased in patients with coronary artery sclerosis and restenosis[41,42] and also in association with disease severity.[43] In our study, the CAR ratio at admission being higher in the patients with atherothrombotic stroke than the other subtypes suggests that CAR ratio may be a marker of atherosclerosis.

We believe that CAR ratio in stroke patients is not yet well-studied. Kocatürk and Kocatürk have investigated 260 patients with AIS and found an association of CAR values with prognosis and mortality at the 90th day of stroke. Stroke survivors had lower levels of CAR than the ones who have died.[44] Our study found CAR values to be statistically higher in acute stroke patients than the control group. We have investigated the relationship of the admission NIHSS score and early prognosis at the 10th day of the stroke. We have found an association between stroke severity and poor prognosis and CAR value; the higher the ratio, the most severe the stroke, and the worse the outcome.

Table 5. Univariate and multivariate logistic regression analysis of prognosis

	Univariate OR, 95 CI%			Multivariate OR, 95 CI%		
	Odd ratio	95% C.I.	p	Odd ratio	95% C.I.	p
Age	1.04	1.02–1.06	<0.001	1.02	0.99–1.05	0.13
Gender	0.384	0.25–0.59	<0.001	0.54	0.30–0.97	0.04
Artery lolocalization	1.94	1.16–3.22	0.01	0.88	0.44–1.76	0.73
CAR	1.003	1.0–1.005	0.015	1.00	0.99–1.00	0.87
NIHSS	1.45	1.35–1.57	<0.001	1.44	1.33–1.56	<0.001
Stroke Type CE-AT	1,306	0.79–2.14	0.29	0.71	0.35–1.42	0.34

Conclusion

Serum albumin and CRP levels can easily be examined and CAR at admission may serve as an easy and early predictor marker for atherothrombotic etiologic subtype and early prognosis of patients with AIS.

There are some limitations in our study. The most important one is that the study was designed retrospectively at a single center, which may give rise to questions about the unknown influencing factors on the evaluation of the investigated parameters that limits the validity of its results.

Disclosures

Ethics Committee Approval: The study was carried out in accordance with the Helsinki Declaration after the approval of the Ethical Committee of Erenkoy Mental Health and Disease Research and Training Hospital; the approval date and number were December 14, 2020-50.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – M.Ü.; Design – M.Ü.; Supervision – F.D.; Materials – M.D.; Data collection &/or processing – M.Ü., R.K.; Analysis and/or interpretation – M.D., M.Ü.; Literature search – M.Ü., R.K.; Writing – M.Ü.; Critical review – F.D.

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