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Original Article / Araştırma Makalesi

PREDICTIVE VALUE OF C-REACTIVE PROTEIN/ALBUMİN RATIO IN THE DEVELOPMENT OF CONTRAST-INDUCED NEPHROPATHY IN PATIENTS WITH ACUTE ISCHEMIC STROKE TREATED PERCUTANEOUSLY

Perkutan Olarak Tedavi Edilen Akut İskemik İnme'li Hastalarda Kontrast Kaynaklı Nefropati Gelişiminde C-Reaktif Protein /Albumin Oranının Öngörü Değeri

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ABSTRACT

Contrast induced nephropathy (CIN) is known to play an important role in acute kidney injury. The purpose of this study was to determine the predictive effect of the CRP/albumin ratio (CAR) in the detection of CIN in patients with acute ischemic stroke (AIS) treated percutaneously. A total of 148 acute stroke patients treated percutaneously were included in the study. In the study population, groups were determined according to the development of CIN. The CAR value was calculated by dividing the CRP value by the albumin value. CIN developed in 26 (17%) patients. DM (p=0.031) and HT (p=0.014) diseases were observed at higher rate in the CIN group. Glucose (p<0.001), contrast amount (p<0.001), WBC (p=0.020), NIHSS0 score (p=0.001), and CAR (p<0.001) were higher in the CIN (+) group compared to the CIN (-) group. A cutoff point of 0.393 for CAR was identified with 80.7% sensitivity and 92.6% specificity to predict CIN. The CAR was found to be significantly higher in CIN patients and was also identified as an independent predictor of the development of CIN.

Keywords: Acute ischemic stroke, C-reactive protein to albumin ratio, Contrast induced nephropathy.

ÖZ

Kontrast kaynaklı nefropatinin (KKN) akut böbrek hasarında önemli rolü olduğu bilinmektedir. Çalışmamızda, perkütan olarak tedavi edilen akut iskemik inmeli hastalarda KKN tespitinde CRP/albümin oranının (CAO) tahmin edici etkisini ortaya koymak amaçlanmıştır. Perkütan olarak tedavi edilen toplam 148 akut inme hastası çalışmaya dahil edilmiştir. Çalışma popülasyonunda gruplar KKN gelişimine göre iki gruba ayrıldı. CAO değeri, CRP değerinin albümin değerine bölünmesiyle elde edildi. 26 (%17) hastada KKN gelişti. DM (p=0.031) ve HT (p=0.014) hastalıkları KKN grubunda daha yüksek oranda izlendi. Glikoz (p<0.001), kontrast miktarı (p<0.001), WBC (p=0.020), NIHSS0 skoru (p=0.001) ve CAO (p<0.001) KKN (+) grubunda KKN (-)'e göre daha yüksekti. CAO için 0.393'lük bir eşik değeri, KKN'yi tahmin etmek için %80.7 duyarlılık ve %92.6 özgüllük ile belirlendi. CAO, KKN hastalarında anlamlı olarak daha yüksek bulundu ve ayrıca KKN gelişiminin bağımsız bir öngörücüsü olarak tanımlandı.

Anahtar kelimeler: Akut iskemik inme, C-reaktif protein/albümin oranı, Kontrast kaynaklı nefropati.

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INTRODUCTION

In developed countries, the majority of deaths are due to stroke, ischemic heart disease and cancer. Of these, stroke is the first cause of infirmity (Yang et al., 2017). In the age of revascularization, percutaneous endovascular intervention is the main treatment for eligible patients with ischemic stroke.

Contrast induced nephropathy (CIN) is defined as an increase in serum creatinine (SCr) ≥0.5 mg/dL or an increase in SCr to ≥25% from its initial value within 48-72 hours of contrast exposure (Solomon et al., 2007). CIN causes an extended hospital stay, increased costs, and is also a predictor of morbidity and mortality (McCullough, Wolyn, Rocher, Levin, & O'Neill, 1997). Previous researches have reported higher incidences of CIN in patients with acute coronary syndrome who were treated by an endovascular approach (McCullough et al., 1997; Mehran et al., 2004). Therefore, determining patients at risk for the development of CIN before the procedure is very important to take preventive measures and improve clinical outcomes.

The effect of inflammation on the development of CIN is known (Kwasa, Vinayak, & Armstrong, 2014). There are studies showing that inflammation indicators such as white blood cell, fibrinogen, neutrophil, procalcitonin, C-reactive protein (CRP) value are linked with the development of CIN (Kwasa et al., 2014). Also, some researchers have claimed that low albumin levels are linked with the development of CIN (Li et al., 2017). Recent studies have indicated that CRP/albumin ratio (CAR), as an inflammation score, is an important prognostic marker in cardiac and non-cardiac conditions (Li et al., 2017; Wei et al., 2015). Although the effect of CAR on the development of CIN has been investigated in many conditions (Murat, Kurtul, & Yarlioglues, 2015; Satılmış & Karabulut, 2020), it has not been studied in patients with acute ischemic stroke treated percutaneously.

Therefore, we aimed to determine whether there is a relationship between CAR and CIN in patients with acute ischemic stroke treated percutaneously.

MATERIAL AND METHOD

This retrospective, single center study used the data of 157 consecutive patients with acute ischemic stroke (AIS) treated percutaneously. The patients were 18 years of age or older and admitted to our emergency department from October 2020 through September 2021. Patients who were admitted within 4.5 h of symptom onset and who had no contraindications underwent percutaneous endovascular intervention after administration of intravenous tissue

plasminogen activator (tPA) in accordance with current guidelines (Powers et al., 2019). In the study population, groups were determined according to the development of CIN (CIN +, and CIN -). Causes that may affect inflammatory response, such as active infection, rheumatic diseases, congestive dilated heart failure, acute and chronic liver disease, and also end-stage renal disease (GFR <30 mL / min or hemodialysis) were determined as exclusion criteria. Four patients who died within three days after the procedure and five other patients were excluded as sufficient data could not be obtained.

Patients who met the following criteria were eligible for mechanical endovascular thrombectomy: a clinical diagnosis of acute stroke; age ≥ 18 years; a National Institutes of Health Stroke Scale (NIHSS) score ≥ 6 at admission; an Alberta Stroke Program Early CT Score (ASPECTS) ≥ 6 based on non-contrast brain CT or diffusion-weighted magnetic resonance imaging (MRI) (Barber, Demchuk, Zhang, & Buchan, 2000 ; Barber et al., 2005); a brain MRI and/or CT ruling out intracranial hemorrhage; and intracranial major arterial occlusion demonstrated by CT angiography or MRA.

Endovascular treatment was done by using the femoral route with a Solitaire stent retriever placed in the thrombus via a micro-catheter. A nonionic, low-osmolality contrast agent (Iohexol-Omnipaque) was used in the catheterization laboratory and the amount was noted. Since endovascular treatment for acute stroke is an emergency procedure, no treatment was given to prevent nephropathy before the procedure. 0.9% saline was administered intravenously at a rate of 1 mL/kg/h for 24 hours after contrast exposure. Medical records and laboratory values of each patient were obtained. SCr, CRP, glucose and albumin levels were measured before and within 48-72 hours after the procedure.

CIN was determined by the 0.5 mg/dL or 25% increase in SCr levels compared to the baseline value, 48-72 hours after contrast agent administration (Solomon et al., 2007). The glomerular filtration rate (GFR) was evaluated according to the modification of diet in renal disease (MDRD) formula (Hojs, Bevc, Ekart, Gorenjak, & Puklavec, 2011). The standart values for albumin and CRP levels were accepted as 3.5 to 5.5 g/dL and 0 to 19 mg/L, respectively. The CAR value was obtained by multiplying the ratio of the CRP value to the albumin value by 10 (Karabağ et al., 2019). Diseases such as diabetes mellitus (DM), hypertension (HT) were recorded. DM was considered as receiving medical treatment or a fasting glucose level higher 126 mg/dL (American Diabetes Association, 2014). HT was considered as antihypertensive drug use or systolic blood pressure higher than 140 mmHg and diastolic pressure higher than 90 mmHg in repeated office measurements (Mancia et al,

2014). Heart failure was accepted as a systolic ejection fraction of ≤40% during hospitalization or in a previous echocardiography.

Our study was approved by the local ethics committee (Malatya Turgut Ozal University, no: 2021-93) and was also conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

Data were analyzed by using MedCalc statistics software (12.7.8, Mariakerke, Belgium) and SPSS (22.0, SPSS Inc., Chicago IL). Categorical variables were evaluated using Chi-square or Fisher's exact tests and expressed as percentages. Continuous variable data were presented as mean ± standard deviation. The distribution of continuous variables was compared using the Kolmogorov-Smirnov test. The groups were compared using MannWhitney U tests and Pearson analysis. The univariate analysis was performed to identify the predictors of CIN and variables with a p value of less than 0.05 were included in the multivariate analysis. Receiver operating characteristic (ROC) curves were used to predict the future incidence of CIN using the MedCalc statistical software. P value <0.05 was considered statistically significant.

RESULTS

A total of 148 patients were included in the analysis between October 2020 through September 2021. CIN developed in 26 (17%) patients. Clinical, laboratuary and demographic characteristics are shown in Table 1. Age, gender, smoking, diastolic blood pressure, EF, platelet, total cholesterol, LDL, HDL, triglyceride, serum albumin value, basal creatinine and GFR were similar between the two groups. DM (p=0.031) and HT (p=0.014) diseases had a higher rate in the CIN group. Glucose (p<0.001), contrast amount (p<0.001), WBC (p=0.020), NIHSS0 score (p=0.001), and CAR (p<0.001) were higher in the CIN (+) group compared to the CIN (-) group.

Table 1. Clinical and Demographic Characteristics of Groups

	CIN(-) (n=122)	**CIN(+) (n=26)**	**p**
Age, years	70.4 ± 10.9	67.6 ± 11.7	0.245
Female Sex, n(%)	66(54.1)	18(69.2)	0.157
Diabetes Mellitus, n(%)	47(38.5)	16 (61.5)	0.031
Hypertension, n(%)	72(59.0)	22(84.6)	0.014
Smoking, n(%)	57 (46.7)	10(38.5)	0.442
Systolic BP (mmHg)	137 ± 14.8	146 ± 20.5	0.034

Diastolic BP (mmHg)	90.3 ± 6.9	96.6 ± 13.2	0.218
Baseline creatinine (mg/dL)	0.88 ± 0.34	0.90 ± 0.25	0.761
Baseline GFR (mL/min)	78±16	73±19	0.170
Contrast volüme (mL)	219.1 ± 82.4	289.2 ± 77.5	<0.001
NIHSS0 score	12.8 ± 2.8	14.9 ± 2.1	0.001
Ejection Fraction, (%)	51.6 ± 11.3	53.0 ± 9.2	0.559
Hemoglobin, g/dl	13.6±1.0	13.4±2.0	0.778
CRP (mg/dL)(median)	12.0 (9.1-13.1)	19 (16.0-21.5)	<0.001
Serum albümin (g/dL)	3.80 ± 0.5	3.69 ± 0.5	0.341
CRP/albümin ratio (median)	0.30(0.14-0.44)	0.52 (0.24-0.87)	<0.001
WBC, 103/mL	7.9±2.0	9.1±2.7	0.020
Total cholesterol (mg/dL)	198 ± 18	202 ± 13	0.322
Low density lipoprotein cholesterol (mg/dL)	151 ± 21	157 ± 12	0.211
High density lipoprotein cholesterol (mg/dL)	37±4	37±5	0.903
Triglyceride (mg/dL)	170±34	181±22	0.122

(BP, blood pressure; CRP, C-reactive protein; NIHSS0, national institutes of health stroke scale at admission; WBC, white blood cell)

Univariate and multivariate regression analysis results are given in Table 2. In the multivariate regression analysis, it was observed that the NIHSS0 (p=0.005) and CAR (p<0.001) was indepented predictors of CIN.

Table 2. Univariate and Multivariate Analysis for Prediction of CIN

	Univariate analysis		**Multivariate analysis**	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**
NIHSS0	1.403 (1.143-1.722)	0.001	1.736 (1.184-2.544)	0.005
Contrast volume	1.011 (1.005-1.017)	<0.001	1.007 (0.998-1.016)	0.148
CRP/albumin ratio	2.444 (1.699-3.516)	<0.001	2.848 (1.814-4.470)	<0.001
WBC	1.214 (1.024-1.438)	0.025	1.382 (1.045-1.829)	0.023
Diabetes Mellitus	2.553 (1.069-6.095)	0.035	1.245 (0.329-4.709)	0.747
Hypertension	3.819 (1.240-11.762)	0.020	0.191 (1.184-2.544)	0.082

(CI, confidence interval; OR, odds ratio; NIHSS0, national institutes of health stroke scale at admission; WBC, white blood cell)

The optimal threshold CAR for predicting CIN was >0.393, with a 80.7% sensitivity and 92.6% specificity (area under the curve [AUC]: 0.898, 95%CI: 0.838- 0.942, $p< 0.001$) (Figure 1).

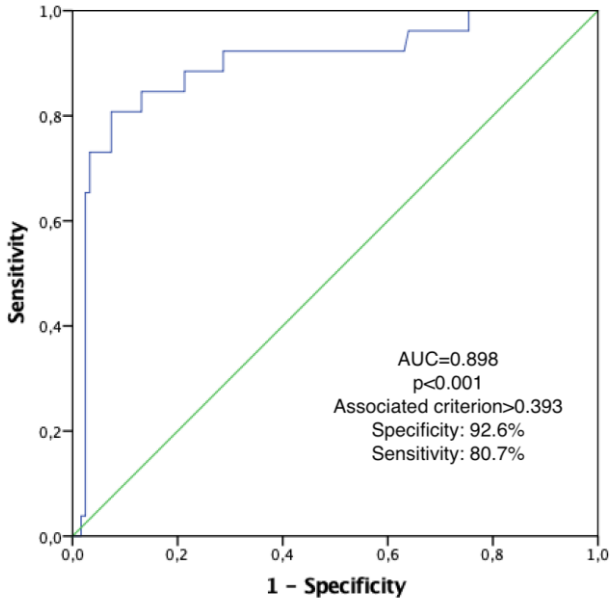

Figure 1: ROC Curve Plots to Determine the Best Cut-Off Value for CAR in Estimating the CIN in Percutaneously Treated Stroke Patients. AUC Shows the Area Under the Curve

DISCUSSION

We showed that the CAR is associated with CIN in patients with acute ischemic stroke undergoing percutaneous endovascular intervention and is also an independent predictor of the development of CIN.

Although thrombolytic therapy has been the only option until recently in acute ischemic stroke, significant mortality and morbidity reduction has been achieved in patients who have been treated early with newly developed endovascular thrombus aspiration devices. However, these methods, which require the use of contrast agents, have side effects such as CIN, especially in elderly patients. It is known that CIN is associated with long hospital stay, poor clinical outcomes, and increased hospital mortality (Finn, 2006).

The pathophysiology of CIN is still unclear and many underlying factors have been suggested. Increased use of interventional procedures in various clinical situations (especially complex and prolonged vascular interventions) leads to the use of larger value of contrast agent, which has a major effect on the occurrence of CIN (Connolly, McEneaney, Menown, Morgan, & Harbinson, 2015). The possible mechanisms of acute kidney injury include harmful effects of contrast media, ischemic damage, oxidative stress and acute inflammation. Several clinical and laboratory data can be used to identify patients at risk of developing CIN. (Connolly et al., 2015). Old age, diabetic nephropathy, congestive heart failure, low glomerular filtration rate (<60 mL/ min/1.73 m2), dehydration, anemia, use of non-iso-

osmolar contrast agents and the use of higher amounts of contrast agent are identified risk factors for the development of CIN (Connolly et al., 2015).

Basal creatinine values and GFR are known to be predictors of CIN (Connolly et al., 2015). Since serum creatinine levels are affected by many conditions (age, hydration status, gender, etc.), its' sensitivity is limited in the earlier diagnosis of CIN. In our study, basal SCr levels and GFR were not significant in determining the development of CIN. In our study, similar with Parfrey et al's study, diabetes, hypertension and contrast volume were found to be predictors for the development of CIN (Parfrey et al., 1989).

Connolly et al. showed that white blood cell count, neutrophil count, neutrophil lenfosit ratio (NLR), and CRP are linked with the development of CIN (Connolly et al., 2015). These findings also support that the basal inflammatory state can be a-substantial determinant of the development of CIN. The ratio of CRP and albumin has been defined as a useful predictor of the inflammatory response (Kwasa et al., 2014; Li et al., 2017). C-reactive protein, a positive acute phase reactant, is a useful classification tool for the inflammatory status. Gao et al. showed strong link between high CRP levels and CIN (Gao et al, 2011). Consistent with previous publications, in our study, CRP was found to be higher in patients with CIN. Serum albumin, a negative acute phase reactant, is inversely proportional to the inflammatory response and has antioxidant activity (Roche, Rondeau, Singh, Tarnus, & Bourdon, 2008). The decrease in the albumin level may increase blood viscosity and impair the endothelial function (Joles, Willekes-Koolschijn, & Koomans, 1997). Although some studies have shown that a lower albumin level is a predictor for the development of CIN (Murat et al., 2015), in our study, albumin levels were found to be similar between groups.

The use of a combination of biomarkers such as NLR, platelet to lymphocyte ratio (PLR) and CAR for more sensitive risk assessment of acute kidney injury has been demonstrated in various studies (Aşkın, Tanrıverdi, Tibilli, & Türkmen, 2019; Kaya et al, 2014). Many studies have shown the usefulness of CAR, which is calculated by using simple, widely available and inexpensive CRP and albumin levels, in risk stratification (Aşkın et al, 2019; Ranzani, Zampieri, Forte, Azevedo, & Park, 2013). Park et al. showed that a higher CAR ratio is associated with increased mortality in ICU patients (Park et al, 2018). There are also studies showing that CAR value is associated with the presence of coronary artery disease and autoimmune diseases (Tsai, Yu, Tang, Huang, & Kuo, 2020). Çınar et al. showed the prognostic efficacy of CAR in patients with ST-segment elevated myocardial infarction (STEMI) (Çınar et al, 2019). In addition, CAR value is also used as a predictor of mortality in

stroke patients. Kocaturk et al. demonstrated that a high CAR value is an independent predictor of 90-day mortality in patients with AIS (M. Kocatürk, & O. Kocatürk, 2019). A recent study showed that CAR is a strong predictor of CIN development in patients with STEMI undergoing primary PCI (Satılmış & Karabulut, 2020). Similarly, in our study, we found that CAR is a more sensitive marker for detecting the development of CIN compared to albumin and CRP alone, and higher CAR is a strong predictor of CIN development.

The CAR was significantly higher in CIN patients and was an independent predictor of CIN development. The ratio of CRP to albumin, both of which responded adversely to each other in terms of inflammation, increased the diagnostic value compared to CRP and albumin alone. With the CAR value, it will be possible; to identify the patients who may develop CIN and start the treatment for this situation early, to reduce the length of hospital stay and treatment costs, as well as to reduce mortality and morbidity.

The limitations in this study included; the small number of patients, single-center and retrospective study design. Larger, prospective and randomized clinical studies are needed to confirm the clinical applicability of our findings.

CONCLUSIONS

We have shown that preprocedural high CAR value could be associated with the development of CIN in patients with acute ischemic stroke treated percutaneously. Accordingly, in patients with high CAR values, pre- and post-procedure precautions may reduce poor outcomes.**Acknowledgements**

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