RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2019, Volume 53, no. 3, pages: 205–211
DOI: 10.5603/PJNNS.a2019.0020

ISSN 0028–3843

Assessment of relationship between C-reactive protein to albumin ratio and 90-day mortality in patients with acute ischaemic stroke

Mehtap Kocatürk[1], Özcan Kocatürk[1]

[1]Department of Neurology, Harran University, Şanlıurfa, TURKEY

Abstract

Aim and clinical rationale for the study. It is now known that inflammation is involved in the pathophysiology of acute ischaemic stroke (AIS). It has been proven that CRP and albumin alone are useful in predicting a prognosis for stroke patients. A combination of these two parameters, namely the ratio of CRP to albumin (CAR), is believed to be a more accurate indicator of inflammatory status than CRP or albumin alone, and may be more valuable than either of them separately in predicting the prognosis of ischaemic stroke patients. However, the role of CAR as a predictor of mortality in patients with AIS remains unclear.

Materials and methods. We retrospectively enrolled 260 patients who were referred to our clinic within the first 24 hours of symptom presentation and who were diagnosed with AIS between January 2015 and December 2018. The patient group was classified into two groups according to 90-day mortality. These groups were compared in terms of C-reactive protein, albumin, and CAR.

Results. The C-reactive protein and CAR values were higher, and the albumin level was lower, in non-surviving patients. The CAR value was also found to be a significant independent variable of 90-day mortality in patients with AIS ($p < 0.001$). The optimum cut-off value of CAR in predicting the 90-day mortality for patients with AIS was 0.50, with 64.1% sensitivity and 56.2% specificity.

Conclusions and clinical implications. Our study demonstrated that a high CAR value is an independent predictor of 90-day mortality in patients with AIS.

Key words: stroke, C-reactive protein to albumin ratio, mortality

(*Neurol Neurochir Pol 2019; 53 (3): 205–211*)

Introduction

Acute Ischaemic Stroke (AIS) has a high rate of worldwide mortality and disability. Intravenous rtPA and endovascular therapy, which are effective treatments for ischaemic stroke, have narrow therapeutic windows and therefore patient selection criteria are important for these treatments. Also, there is as yet no treatment known to have neuroprotective properties. This situation prompted us to search for a biomarker to accelerate the diagnosis, predict the prognosis for patient selection, better understand the pathophysiology, and offer new treatment options.

Inflammation is known to occur in the pathophysiology of ischaemic stroke [1, 2]. Necrotic cells, which are formed in the brain due to vascular occlusion, trigger inflammation. CRP and albumin is an acute phase protein. CRP is increased in inflammation, while albumin is decreased in inflammation as a negative phase reactant.

Many studies have investigated the relationship between CRP and disease severity, functional outcome, in-hospital mortality, long-term mortality, and infarct volume in patients with ischaemic stroke [3–6]. Increased plasma levels of CRP may affect coagulation by inducing tissue factor expression

Address for correspondence: Özcan Kocatürk, Osman Bey Campus, Mardin Yolu, Şanlıurfa, TURKEY tel.: +905074191621 e-mail: ozcankocaturk@gmail.com

[7]. Activation of coagulation in patients with ischaemic stroke may increase mortality [8]. In addition to that, post-ischaemic inflammation increases neuronal injury [9], which may explain the poor outcome in patients with high CRP.

Albumin, which is synthesised from the liver, acts as a carrier of endogenous and exogenous substances in the blood. The neuroprotective properties of albumin have been shown in animal models of ischaemic stroke [10]. It has also been reported to be an important inhibitor of platelet aggregation, scavenging free oxygen radicals, and acting as an antioxidant [11]. Albumin, like CRP, has been shown to be an independent prognostic factor, and has been used to predict recurrence, prognosis and mortality in ischaemic stroke [10, 12, 13].

Clinical rationale for the study

Although it has been shown that CRP and albumin individually are useful in predicting prognosis [14, 15], the combination of these two parameters, namely the ratio of CRP to albumin (CAR), has not been studied in detail. CAR may be a more accurate indicator of inflammatory status than CRP or albumin alone, and it may be of greatervalue than either of them separately in predicting the prognosis of ıschaemic stroke patients. Although CRP and albumin have been separately demonstrated to be associated with increased poor prognostic events in patients with ischaemic stroke, no study to date has investigated the prognostic importance of the CRP to albumin ratio in patients with ischaemic stroke. In this study, we hypothesise that an elevated CAR increases the risk of mortality in patients with ischaemic stroke. We assessed the association between the CAR at admission and 90-day mortality in patients with ischaemic stroke.

Methods

Study design and data collectionThe files of patients who were admitted to the neurology clinic of Harran University Faculty of Medicine Training and Research Hospital, Sanlıurfa, Turkey between January 2015 and December 2018 with the diagnosis of acute ischaemic stroke (AIS) were retrospectively screened from electronic medical records. The diagnosis of AIS was based on the World Health Organisation definition [16]. Patients were aetiologically classified according to the Trial of Org 10,172 in Acute Stroke Treatment (TOAST) criteria: cardioembolic, atherosclerotic, small vessel/lacunar, and cryptogenic/others [17].

Exclusion criteria for the patients were the following: 1) those patients with trauma or a history of surgery within the previous 12 months; 2) those with an active infection before stroke onset or within 72 h after admission; 3) previously known haematological disorders (e.g. anaemia, bleeding disorder, leukaemia); 4) pre-existing kidney disease with serum creatinine > 1.5 mg/dL and pre-existing liver disease with abnormal liver function test; 5) intoxication; 6) patients with previous history of cerebrovascular diseases (ıschaemic and haemorrhagic); 7) a history of cancer at any time or the use of steroids or immunosuppressant agents within the previous 12 months; and 8) an absence of medical, demographic, clinical, laboratory, and/or radiological data. Our study was conducted in full accordance with the Declaration of Helsinki and was approved by the local ethics committee. Informed consent was not required due to its retrospective design.

Baseline clinical data including age, gender, and risk factors such as hypertension (HT), diabetes mellitus (DM), hyperlipidemia (HL), heart failure, and atrial fibrillation (AF) were recorded from patients' medical records for all patients. HT was defined as systolic blood pressure (BP) ≥ 140 mmHg, and/or diastolic BP ≥ 90 mmHg, taking anti-hypertensive medications, and/or previously diagnosed hypertension. DM was defined as fasting serum glucose of ≥ 126 mg/dL (7 mmol/L), non-fasting glucose of ≥ 200 mg/dL (11.1 mmol/L), use of anti-diabetic medications, or a previously established diagnosis. HL was diagnosed if low-density lipoproteins (LDL)-cholesterol level was ≥ 100 mg/dL or in cases of the use of lipid-lowering agents after being diagnosed with HL. Congestive heart failure was defined as left ventricular ejection fraction (LVEF) < 40% and typical symptoms e.g. breathlessness, ankle swelling, and fatigue [18]. Atrial fibrillation was defined as AF recorded at the time of the electrocardiography, or any previously known episode of AF.

Laboratory measurements

Venous blood samples for a complete blood count and serum chemistry, including serum albumin and CRP levels, were drawn when admitted to our hospital emergency service in all patients with a suspicion of acute ischaemic stroke. CAR was calculated by dividing the serum CRP level by the serum albumin level, while the neutrophil to lymphocyte ratio (NLR) was calculated by dividing the neutrophil count by the lymphocyte count. CAR, NLR, CRP, albumin, neutrophil, lymphocyte, and thrombocyte levels were recorded.

Statistical analysis

Data was expressed as the median for continuous variables and percentages for categorical variables. Mann-Whitney U test for continuous variables and x2 test for categorical variables were performed. To determine the factors associated with 90-day mortality, univariate analyses were performed firstly, followed by multivariate logistic regression analysis. Variables with P-values < 0.05 were put into the multivariate logistic regression model. To assess the association of the CRP/albumin ratio with mortality outcome, the CRP/albumin ratio was examined as a continuous variable. To determine the best cutoff values for the albumin and CRP levels and CRP/albumin ratio, a receiver operating characteristic curve was generated and Youden's index was calculated; sensitivities, specificities,

Table 1A. Baseline characteristics and laboratory data of categorical variables of patients with or without 90-day mortality

	Death at 90 days n: 45 (17.3%)	Surviving patient n: 215 (82.6%)	p
Male, n (%)	15 (33.3)	129 (60)	0.028
Hypertension, n (%)	17 (37.8)	131 (60.9)	0.0047
DM, n (%)	11 (24.4)	62 (28.8)	0.295
Hyperlipidemia, n (%)	4 (8.9)	65 (30.2)	0.029
Heart failure, n (%)	9 (20)	12 (6)	0.000
Coronary artery disease	4 (7)	14 (7)	0.326
Atrial fibrillation, n (%)	13 (28.9)	31 (14.1)	0.011
Stroke aetiologic subtypes, n (%)			
Cardioembolic	24 (53.3)	52 (24.2)	0.001
Atherosclerotic	4 (9)	39 (18)	
Small vessel/ lacunar	3 (6.7)	34 (16)	
Cryptogenic/others	14 (31)	90 (41.9)	
Therapy strategy			
Endovascular / thrombolitic	10 (22.2)	33 (15.3)	0.188
Antiaggregant only	35 (77.8)	182 (84.7)	
Anterior circulation, (%)	34 (75.6)	155 (72.1)	0.635
Stroke severity (NIHSS)			
Mild (0–4)	2 (4)	55 (26)	< 0,001
Moderate (5–15)	29 (64)	143 (67)	
Severe (> 16)	14 (31.1)	17 (8)	

Values are shown as median (interquartile range) or number (%) DM – diabetes mellitus; NIHSS – National Institutes of Health Stroke Scale

Table 1B. Baseline characteristics and laboratory data of continuous variables of patients with or without 90-day mortality

	Death at 90 days n: 45 (17.3%)	Surviving patient n: 215 (82.6)	p
Age, years	75 (15)	66 (17)	< 0.001
Albumin, g/dL	3.40 (0.4)	3.80 (0.6)	< 0.001
CRP	1.32 (2.99)	0.53 (1.13)	< 0.001
CRP / albumin	0.40 (0.87)	0.14 (0.31)	< 0.001
NIHSS	7 (6)	13 (9)	< 0.001
LDL, mg/dL	141 (108.05)	117 (72)	0.20
HDL, mg/dL	39.3 (11)	39 (11)	0.117
Triglyceride, mg/dL	133 (41.46)	169 (80)	0.016
Total cholesterol, mg/dL	183 (24.6)	183 (46)	0.875
Creatinine	0.75 (0.3)	0.81 (0.27)	0.875
Glucose, mg/dL	151 (50)	123 (58)	0.022
White blood cell, 10^3/mc	11.5 (4.56)	10.1 (3.63)	0.006
Platelet, 10^3/mc	240 (108)	256 (105)	0.263
Haemoglobin, g/dL	13.4 (2.34)	14 (2.97)	0.014
Neurophil / lymphocyte	5.51 (5.67)	3.8 (3.12)	< 0.001
Platelet / lymphocyte	152.27 (142.87)	129.5 (90.62)	0.088

Values are shown as median (interquartile range) LDL – low density lipoprotein; HDL – high density lipoprotein; CRP – C-reactive protein; NIHSS – National Institutes of Health Stroke Scale

positive and negative predictive values, and their 95% CIs were also calculated. We determined predictive performance using receiver operating characteristic curves with logistic regression models to compare and assess for equality of the area under the curve using the DeLong test. Statistical analyses were performed by the use of SPSS, NSCC, Stata, and Gretl. P values ≤ 0.05 were considered statistically significant.

Results

A total of 413 patients with suspected acute ischaemic stroke were admitted to our hospital during the study period. Of those, 153 were excluded because they had a history of previous stroke (n: 19), had liver or kidney disease (n: 20), were admitted more than 24 hours after the onset of symptoms (n: 52), had a recent history of surgery, acute infection and malignancy (n: 14), or had missing data (n: 48).

The remaining 260 patients were finally included in this study. The median age was 68 (18) years and 144 patients (55.4%) were male. Forty-five patients (17.3%) died within 90 days. Female were more common in the non-survivor group. Hypertension was the most common comorbidity. A history of atrial fibrillation and heart failure were more common among non-survivors, while hypertension was more common among survivors. There was no association between CAR and stroke subtypes. Baseline characteristics and laboratory data of categorical variables are set out in Table 1A and continuous variables are set out in Table 1B.

The CAR ranged from zero to 3.47 [0.170 (0.36)]. The CAR was higher in non-survivors than in survivors [0.40 (0.87) *vs* 0.14 (0.31)]. In the univariate analyses, age, female sex, hypertension, hyperlipidemia, atrial fibrillation, congestive heart failure, stroke severity, triglyceride, white blood cell count, haemoglobin level, neutrophil count, total cholesterol, CRP, albumin, CAR, neutrophil to lymphocyte ratio, and platelet to lymphocyte ratio revealed statistically significant associations with 90-day mortality. After adjusting for all these variables, the CAR still revealed an association with 90-mortality of

Table 2. Odds ratios for all-cause 90 day mortality events

	Univariate			p	Multivariate			p
	Odds ratio	CI lower	CI upper		Odds ratio	CI lower	CI upper	
Age	1.067	1.033	1.101	0.000	1.064	1.010	1.122	0.020
Sex, female	3	0.0681	0.1985	0.000	4.437	1.265	15.560	0.020
Diabetes mellitus	0.798	0.3805	1.675	0.552				
Hypertension	0.389	0.2008	0.755	0.005	0.891	0.282	2.820	0.844
Hyperlipidemia	0.225	0.078	0.655	0.006	0.524	0.086	3.180	0.482
Coronary artery disease	1.401	0.439	4.472	0.569				
Atrial fibrillation	2.41	1.140	5.097	0.021	0.160	0.022	1.169	0.071
Congestive heart failure	8.323	3.254	21.289	0.000	3.176	0.464	21.734	0.239
NIHSS	1.201	1.131	1.291	0.000	1.257	1.113	1.419	< 0.001
Stroke severity (NIHSS)	1			–				
Mild (0–4)								
Stroke severity (NIHSS)	5.577	1.29	24.16	0.022	13.918	1.591	121.744	0.017
Moderate (5–15)								
Stroke severity (NIHSS)	22.647	4.672	109.760	0.000	57.907	5.061	662.580	< 0.001
Severe (> 16)								
Stroke aetiology (cardio-embolic)	1			–				
Stroke aetiology (athero-sclerotic)	0.440	0.149	1.301	0.138				
Stroke aetiology (small vessel/lacunar)	0.380	0.149	1.301	0.123				
Stroke aetiology (crypto-genic/other)	0.627	0.316	1.247	0.183				
LDL cholesterol, mg/dL	1.001	0.998	1.012	0.155				
HDL cholesterol, mg/dL	1.010	0.985	1.037	0.448				
Triglyceride, mg/dL	0.994	0.988	0.999	0.018	0.996	0.807	1.009	0.664
White blood cell, 103/mL	1.199	1.05	1.367	0.006	1.749	0.997	4.335	0.227
Haemoglobin, g/dL	0.837	0.721	0.973	0.020	1.110	0.629	1.527	0.522
Platelet count, 103/mL	1.000	0.997	1.003	0.931				
Mean platelet volume, fL	1.016	0.838	1.233	0.869				
Neutrophil count, 103/mL	1.226	1.085	1.385	0.001	0.652	0.995	1.513	0.320
Lymphocyte count, 103/mL	0.725	0.508	1.035	0.077				
Glucose, mg/dL	1.003	0.998	1.007	0.297				
Creatinine, mg/dL	1.351	0.457	3.995	0.586				
Total cholesterol, mg/dL	0.991	0.983	0.999	0.026	0.975	0.098	1.007	0.055
CRP	1.672	1.355	2.064	0.000	1.771	1.010	2.486	0.001
Albumin	0.279	0.138	0.566	0.000	0.325	0 .996	1.075	0.066
CRP/albumin	4.998	2.497	10.005	0.000	6.345	2.201	18.295	0.001
Neutrophil to lymphocyte ratio	1.138	1.059	1.223	0.000	0.835	0.660	1.057	0.134

CRP – C-reactive protein; CI – confidence interval

Table 3. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of albumin, CRP, and CRP / albumin ratio (CAR)

	Cutoff	Sensitivity	Specificity	PPV	NPV
Albumin	2.2	0.366 (0.225–0.069)	0.501 (0.362–0.068)	0.101 (0.081–0.122)	0.771 (0.743–0.800)
CRP	1.92	0.560 (0.525–0.018)	0.656 (0.616–0.020)	0.362 (0.331–0.394)	0.883 (0.880–0.886)
CRP / albumin ratio	0.50	0.641 (0.609–0.016)	0.562 (0.525–0.019)	0.431 (0.386–0.477)	0.878 (0.874–0.883)

Table 4. Area under curve of CRP, albumin, and CRP / albumin ratio

	Area	Std. Error	p	95% Lower Bound	95% Upper Bound
CRP	0.689	0.048	0.000	0.595	0.783
Albumin	0.694	0.041	0.000	0.614	0.775
CRP / albumin ratio	0.696	0.047	0.000	0.604	0.788

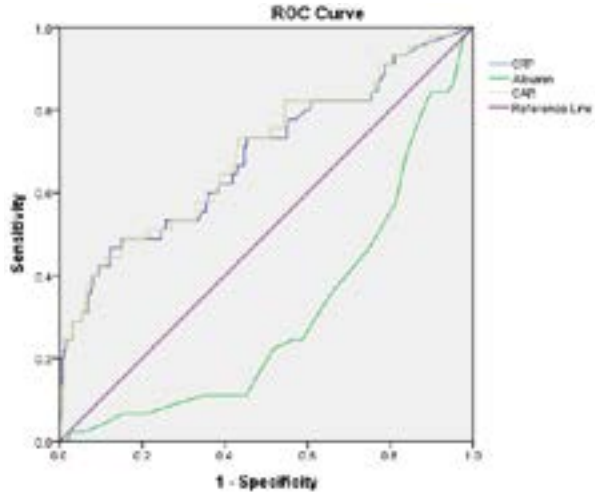

Figure 1. Receiver operating curve of CRP, albumin level and CAR in predicting 90-day mortality

stroke patients. The CAR showed an association with 90-day mortality (odds ratio, 6.345; 95% CI, 2.201 to 18.295) (Tab. 2).

Table 3 reveals the sensitivity, specificity, positive and negative predictive values of the albumin level, CRP level and CAR. The best cutoff value of the CAR was 0.50, with 64.1% sensitivity and 56.2% specificity. The area under the curve of the CAR was greater than that of albumin and CRP alone (Tab. 4, Fig. 1).

Discussion

Ourstudy showed that CAR at the time of admission is an independent predictor of mortality in the third month of acute ischaemic stroke patients. To the best of our knowledge, CAR has not been previously evaluated in predicting prognosis in patients with acute ischaemic stroke. The present study is the first to show that CAR is an independent predictor of three--month mortality of ischaemic stroke patients. In addition, CAR may have a greater prognostic value than CRP and albumin alone. The odds ratio of CAR (6.35) was higher than the CRP's odds ratio (1.8) for predicting three month mortality. For intance, after adjusting for all confounding factors, every whole-number increase in CAR increased by 6.35 the probability of mortality in the third month. On the other hand, while each whole-number increase in CRP increased by 1.8, each whole number decrease in albumin level affected mortality by 3.07 (Tab. 2).

If a patient had a CAR of > 0.5, the risk of 90-day mortality was 43.1%. If a patient had a CAR of < 0.5, the probability of survival at 90 days was 87.8% (Tab. 3).

CRP and albumin are both independently affected by inflammatory conditions, As CRP increases in inflammation, albumin metabolism increases and synthesis decreases [19]. Albumin is also affected by nutritional deficiency. With increasing age, malnutrition increases and this causes albumin deficiency [20]. We tried to exclude conditions that might affect CRP and albumin, but we could not exclude chronic hypoalbumin due to a lack of information about the nutritional status of patients. In our study, similar to previous studies, elevated CRP level was statistically significant at 90-day mortality (p: 0.001), and decreasing albumin did not reach significance but trended toward significance at three month mortality (p: 0.06) (Tab. 2). CAR, which collects CRP and albumin under a single index, has been recently considered as a novel marker. In different disease groups, especially in prognostic predictive studies, some have used CAR as only one marker, while others have compared the values of CAR to those of albumin and CRP alone to predict prognosis.

In our study, CRP was found to be statistically significant. Albumin did not reach significance but trended toward significance. As shown in ROC analysis, we found CAR was more significant compared to the area under the curve (Tab. 4). The fact that albumin was not statistically significant may be due to the limited number of patients. Furthermore, although albumin is an acute phase reactant, its response is slightly delayed. In this study, we obtained albumin at the time of admission, and this may be another reason why albumin did not reach statistical significance.

In a systematic review of five studies, CRP elevation was significantly related to functional outcome in ischaemic stroke [21]. One study found that follow-up CRP had a greater predictive value than that of CRP on admission [22]. In another study, CRP taken within two weeks of admission to hospital was associated with poor functional disability at one year [5]. We thought that the marker (CAR) obtained at the time of admission could be more useful in making a quick decision about the treatment to be chosen. So in this study we used admission CRP and albumin to predict 90-day mortality.

CAR is a new inflammation marker and is believed to reflect inflammatory status better than albumin and CRP alone. In our study, the predictive accuracy of CAR was better than that of CRP and albumin, according to the comparison of ROC curves. Recently, the relationship between CAR and critical diseases, malignancy, post-op patients, and cardiovascular diseases has been studied [23, 24]. CAR has emerged as an independent indicator of poor prognosis in various malignancies, including liver, lung, pancreatic, oesophageal and cervical malignancies [25]. A significant relationship was found between the CAR and the severity of coronary artery disease in patients with acute coronary syndrome [26]. One study showed that CAR measured after admission to the intensive care unit was an independent risk factor for 30-day and one-year mortality in postoperative patients [27]. To the best of our knowledge, no previous study has investigated the relationship between prognosis, disease severity or mortality, and CAR in stroke patients.

Neutrophil to lymphocyte ratio (NLR) has emerged as a novel marker of systemic inflammation. Previous studies have reported that NLR was associated with poor outcomes and predicted short-term mortality in patients with AIS [28]. In our study, although NLR was associated with an increased risk of mortality in univariate analysis, it did not reach statistical significance in multivariate analysis. However, CAR was an independent predictor of mortality in multivariate analysis. Therefore, CAR may be more valuable than NRL in predicting prognosis in acute ischaemic stroke. In accordance with the previous report, age, sex (female) and stroke severity also affected 90-day mortality independently ın our study [29] (Tab. 2).

In this study, we could not detect a relationship between stroke subtypes and CAR. For this reason, it is not yet clear how CAR works in each stroke subtype. In order to clarify the relationship between CAR and stroke subtypes, we think that there is a need for further studies with broader participation.

The primary limitation of this study is its retrospective observational design from a single centre. We do not know the exact cause of death of our study population, and cannot provide serial measurements of CRP and albumin. Also in our study we used conventional CRP rather than hsCRP, which can detect smaller changes in inflammation.

In conclusion, CAR at admission to hospital was associated with 90-day mortality among stroke patients. CAR may serve as a surrogate marker of disease severity. Moreover, CAR at the time of admission may be more helpful in predicting mortality at three months compared to CRP. A high CAR at initial presentation to the hospital in a stroke patient may aid decision making regarding treatment. However, the prognostic value of CAR needs to be verified by larger studies with different populations.

Conflict of interest: *The authors declare no conflict of interest.*
Funding information: *The authors received no external sources of funding for the research or authorship of this publication.*
Ethical statement: *This study was approved by the Institutional Review Boards and Ethical Committee.*

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