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Assessment of the relationship between C-Reactive Protein/Albumin ratio and 28-day mortality in critically very elderly patients (≥ 85 years) with acute ischemic stroke

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Abstract

Background & Objectives: The aim of this study is investigate the relationship of C-reactive protein, albumin, C-reactive protein/albumin ratio with prognosis and 28-day mortality in critically ill patients over 85 years of age with acute ıschaemic stroke. *Methods:* This study is a retrospective and observational study. A total of 189 patients aged 85 years and older who were followed up in the intensive care unit between 2017 and 2020 were included in the study. Demographic data of the patients included in the study, length of stay in the intensive care unit, comorbidities, laboratory data of hospitalization in the intensive care unit, C-reactive protein, albumin, C-reactive protein/albumin ratio, neutrophil/lymphocyte ratios, thrombocyte/lymphocyte ratios, APACHE II, SAPS II values of intensive care admissions were recorded. *Results:* In the statistical analysis performed for C-reactive protein, albumin, C-reactive protein/albumin ratio between survival and non-survival groups, a statistically significant difference was found between the groups (For C-reactive protein, p = 0.03; for albumin, p = 0.02; for C-reactive protein/albumin ratio, p= 0.03). The logistic regression model was applied to investigate the independent risk factors affecting the patients' mortality at 28 days. Albumin, CRP , C-reactive protein/albumin ratio was found to be associated with 28-day mortality according to the logistic regression analysis. (For albumin; p= 0.04, for C-reactive protein; p= 0.04, for C-reactive protein/albumin ratio; p= 0.04). According to the ROC curve analysis result, Cut-off value was found to be 2.47 for C-reactive protein/albumin ratio.
Conclusion: The CRP/albumin ratio is a valuable parameter that can be used to predict 28-day mortality in critically ill very elderly patients with acute ischemic stroke.

Keywords: Very elderly patient, intensıve care, 28-day mortality, C-reactive protein, albumin, C-reactive protein/albumin ratio

INTRODUCTION

Acute ischaemic stroke (AIS) has a high rate of worldwide mortality and disability. AIS is the third leading cause of death after heart disease and cancer and a leading cause of serious long-term disability in adults.[1] Age is a risk factor for acute ischemic stroke, and those over the age of 65 years are more likely to have an acute ischemic stroke, and the risk increases as age increases.[2]

Inflammation is known to occur in the pathophysiology of ischaemic stroke. Necrotic cells, which are formed in the brain due to vascular occlusion, trigger inflammation in AIS.[3] As a result, changes occur in acute inflammatory markers in the blood. The physiology of the inflammatory response is altered by the aging process and is significantly affected by multiple morbidity and disability. With aging, the immune response to inflammation decreases.[4]

C-reactive protein (CRP) is an acute-phase reactant that is synthesized in the liver and increases inflammation. With the expectation of a slight crp height with age; Studies conducted with geriatric patients have shown that the CRP value at the time of admission to the hospital is associated with the prognosis of the patient.[5]

Albumin is synthesized in the liver and acts as a carrier of endogenous-exogenous substances

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in the blood. It is a negative acute-phase reaction and a decrease in albumin values is expected in inflammation. In the elderly population, the albumin level is lower than the expected values.[6]

CRP/albumin ratio (CAR) is included in the literature as a new prognostic marker in inflammatory diseases, especially sepsis.[7]

CRP, albumin, and CRP/albumin ratio values are independent risk factors in the prognosis and mortality of acute ischemic stroke patients.[8] However, as far as we know, there is no dedicated study with a critical data very elder patient group (over 85 years old). Since the response of the elderly patient group to inflammation may be different, we aimed to investigate the relationship of CRP, albumin, CRP/albumin ratio with prognosis and 28-day mortality in this patient group in critically ill patients over 85 years of age with AIS.

METHODS

The electronic medical records of patients aged 85 years and older who were treated for acute ischemic stroke (AIS) in the intensive care clinic of Kastamonu University Medical Faculty Training and Research Hospital, which has 45 intensive care beds, between March 2017 and December 2020 were evaluated retrospectively. The diagnosis of AIS was based on the World Health Organization definition.[9]

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 hematological disorders (e.g. anaemia, bleeding disorder, leukemia); 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 a previous history of cerebrovascular diseases (ischaemic and hemorrhagic); 7. A history of cancer at any time or the use of steroids or immunosuppressant agents within the previous 12 months; 8. An absence of medical, demographic, clinical, laboratory, and/or radiological data.

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.[10] Atrial fibrillation was defined as AF recorded at the time of the electrocardiography, or any previously known episode of AF.

When admitted to the intensive care unit of our hospital, venous blood samples were obtained from all patients with a diagnosis of acute ischemic stroke for serum chemistry including complete blood count, serum albumin, and CRP levels. CAR was calculated by dividing the serum CRP level by the serum albumin level, while the neutrophil/lymphocyte ratio (NLR) was calculated by dividing the neutrophil count by the lymphocyte count, and the platelet/lymphocyte ratio (PLR) was calculated by dividing the platelet count by the lymphocyte count. CAR, NLR, PLR, CRP, albumin, neutrophil, lymphocyte, platelet, and erythrocyte distribution volume (RDW) levels were recorded.

The National Institutes of Health Stroke Scale Scores (NIHSS) calculated by the neurologists at the admission of the patient to the hospital, and the Acute Physiology and Chronic Health Evaluation II (APACHE II) and Simplified Acute Physiology Score II (SAPS II) calculated by the intensive care physicians at the admission to the intensive care unit were obtained from the medical records.

The patients who died within 28 days in the intensive care follow-ups were determined as the non-survival group, and the survivors were determined as the survival group.

In the study, descriptive statistics are given as mean, standard deviation, percentage, and frequency. In the study, the independent sample t-test was used to examine the measurement levels and the difference according to mortality. Chi-square analysis was performed to examine the difference in rates according to mortality groups in the study. ROC (Receiver-Operating Characteristic) analysis was performed to determine the cut-off point and to examine its consistency for SAPS II, APACHE II, CRP, Albumin, and CAR measurements, which were found to be significant according to mortality.

AUROC (Area Under The Receiver Operating Characteristic) values were calculated to compare ROC areas. Binary logistic regression analysis was applied to determine the risk factors affecting mortality on the 28th day. In logistic regression analysis, risk factors and lower and upper limit values were calculated. $p<0.05$ was considered as statistically significant. All statistical analyses were performed using the SPSS 23.00 (SPSS Inc, Chicago, USA).

Approval for the study was obtained from the Non-Interventional Ethics Committee of Kastamonu University with the decision number 2020-KAEK-143-143.

RESULTS

A total of 189 patients were included in the study, 123 people in the non-survival group and 66 people in the survival group. The mean age of the patients in both groups (Non-Survival group: 88.9±3.19 years, Survival group: 88.74±3.45 years) was similar and there was no statistically significant difference between the groups.

There was a statistically significant difference between the mean values of APACHE II, SAPS II, albumin, CRP, CAR values admitted to the intensive care unit between the two groups. (For APACHE II: p= 0.01; for SAPS II, p = 0.01; For Albumin, p = 0.02; for CRP, p = 0.03; for CAR, p= 0.03) APACHE II, SAPS II, CRP, CRP/ Albumin values were higher in the non-survival group. Albumin values were higher in the survival group. (Table1)

In the statistical analysis made according to the additional diseases of the patients; A statistically significant difference was found between the groups in the NIHSS scoring (p= 0.01). It was observed that 52.8% (n: 65) of the patients in the

Table 1: Comparison of demographic data and laboratory data

Measurement	28-day mortality		P*
	Non-Survıval Group (n:123)	Survival Group (n:66)	
	M±SD	M±SD	
Hospitalization day	9.59±7.69	40.38±27.84	**0.01****
Age	88.9±3.19	88,74±3,45	0.75
APACHE II	30.14±8.15	21.21±4.72	**0.01****
SAPS II	45.03±7.36	34.21±8.55	**0.01****
Albumin g/dL	3.20±0.65	3.43±0.64	**0.02****
CRP	7.11±8.69	6.64±5.57	**0.03****
CAR	2.32±2.68	1.95±1.44	**0.03****
LDL mg/dL	101.86±35.02	110.99±36.21	0.09
HDL mg/dL	43.15±9.36	44.17±11.08	0.50
Triglyceride, mg/dL	114.88±48.68	119.5±51.69	0.54
Total cholesterol, mg/dL	149.76±46.1	160.92±44.31	0.11
Creatinine	1.15±0.28	1.07±0.30	0.09
Glucose, mg/dL	154.63±72.49	142.5±40,41	0.21
White blood cell, /mc	9.37±2.41	9.44±2.18	0.85
Platelet, 103 /mc	200.89±76.85	221.68±71.27	0.07
Hemoglobin, g/dL	13.39±1.14	13.33±1.28	0.72
Neurophil	5.69±1.31	5.80±1.17	0.56
Lymphocyte	1.62±0.72	1.87±0.7	**0.02****
N/L	4.31±1.80	4.00±1.79	0.60
P/L	147.87±78.19	134.57±45.03	0.53
RDW	14.63±0,94	14.66±0.92	0.79

*Independent Sample T-test , **Significant difference at the 0.05 level, M: Median, SD: Standard Deviation
APACHE: Acute Physiology and Chronic Health Evaluation, SAPS: Simplified Acute Physiology Score, CRP: C-reactive protein , CAR: CRP/albumin ratio , N/L: Neutrophil Lymphocyte Ratio, P/L: Platelet Lymphocyte Ratio, RDW: Red blood cell distribution width

nonsurvival group had high values according to the NIHSS score. (Table 2)

The logistic regression model was applied to investigate the independent risk factors affecting the patients' mortality at 28 days. NHSS, APACHE II, SAPS II, albumin, CRP, CAR was found to be associated with 28-day mortality according to the logistic regression analysis. (respectively: for NIHSS; p= 0.01, for APACHE II; p= 0.02, for SAPS II; p=0.01, for Albumin; p= 0.04, for CRP; p= 0.04, for CAR; p= 0.04)

ROC analysis was performed to determine the cut off points of APACHE II, SAPS II, albumin, CRP, CAR measurements, which are open numerical measurements. Cut-off values were found to be 29 for APACHE II, 42.5 for SAPS II, 3.39 g/dl for albumin, 7.54 mg/l for CRP, and 2.47 for CAR (Table 3, Figure 1).

DISCUSSION

The ratio of Crp/albumin has been investigated in many disease groups. Based on our literature search, our study is the first to include isolated patients over 85 years of age with critical AIS. In our study, the ratio of CRP/albumin was found to be an independent risk factor for 28-day mortality in this patient group. According to the ROC curve analysis result, we determined the value of 2.47 as the cut-off value.

CRP is an acute-phase protein secreted by the liver and has been used clinically as a systematic marker of tissue damage, infection, and inflammation.[11] Albumin is a protein with important physiological functions such as maintenance of plasma colloid osmotic pressure, intravascular transport of some substances, inflammatory reactions, thrombosis, and lipid metabolism.[12] Studies have shown that high CRP and low albumin levels are poor prognostic factors for many diseases, including Covid-19 disease.[13,14]

The ratio of CRP/albumin, a new scoring system based on inflammation and nutrition; is a prognostic marker that has been used more and more in recent years. There are studies in the literature showing that this parameter has a higher sensitivity and specificity than CRP and albumin as a prognostic marker.[8] The ratio of CRP/albumin has been studied mostly in cancer patients and Covid-19 patients due to the pandemic.[15,16] It was stated in the meta-analysis of Luan *et al*., which

Table 2: Evaluation of 28-day mortality and patient characteristics

Additional diseases of the patients		28-day mortality				P*
		Non-Survival Group		Survival Group		
		n	%	n	%	
Hypertension	Yes	67	54.5%	39	59.1%	0.52
	No	56	45.5%	27	40.9%	
Diabetes mellitus	Yes	48	39.0%	21	31,8%	0.61
	No	75	61.0%	45	68.2%	
Hyperlipidemia	Yes	18	14.6%	14	21.2%	0.48
	No	105	85.4%	52	78.8%	
Heart failure	Yes	56	45.5%	21	31.8%	0.13
	No	67	54.5%	45	68.2%	
Atrial fibrillation	Yes	48	39.0%	24	36.4%	0.86
	No	75	61.0%	42	63.6%	
Coronary artery disease	Yes	45	36.6%	14	21.2%	0.22
	No	78	63.4%	52	78.8%	
NIHSS	Mild	7	5.7%	23	34.8%	**0.01****
	Moderte	51	41.5%	32	48.5%	
	High	65	52.8%	11	16.7%	

*Chi-square test was performed, **Significant difference at the 0.05 level
NIHSS: The National Institutes of Health Stroke Scale Scores

Table 3: Logistic regression analysis of risk factors affecting 28-day mortality

Variables	Wald	P	Odds Range	95 %GA	95% GA
				Lower Limit	Upper limit
NIHSS (Mild/High)	8.93	0.01*	6.70	1.63	11.65
APACHE II (>29)	2.83	0.02*	2.87	1.42	3.26
SAPS II Scor(>42,5)	7.58	0.01*	2.91	1.39	3.20
Albumin, g/dL (<3,39)	1.93	0.04*	2.35	0.60	3.95
CRP, mg/l (>7,54)	1.22	0.04*	2.22	0.62	3.12
CAR (>2,47)	0.83	0.04*	2.15	0.54	2.98
Cox & Snell R^2= 0.457; ModelX^2: 34.101; Success Rate = 93.3%					

NIHSS: The National Institutes of Health Stroke Scale Scores ,APACHE: Acute Physiology and Chronic Health Evaluation, SAPS: Simplified Acute Physiology Score, CRP: C-reactive protein , CAR: CRP/albumin ratio

included patients with head and neck cancer, that the CRP/albumin ratio is a valuable prognostic marker in classifying treatment.[17] In the study of Torun *et al*., which includes Covid-19 patients; They stated that the ratio of CRP/albumin can be used to determine the severity of the disease.[18]

There are changes in the normal values of CRP and albumin values with aging.[5,6] Studies have shown that inflammation accompanies acute ischemic stroke disease.[3] Therefore, CRP and albumin values may differ from the expected values in geriatric patients with acute ischemic stroke. As a result, the ratio of CRP/Albumin also changes. Oh *et al*. reported the relationship between CRP/albumin ratio and 30-day and 1-year mortality in their study involving postoperative

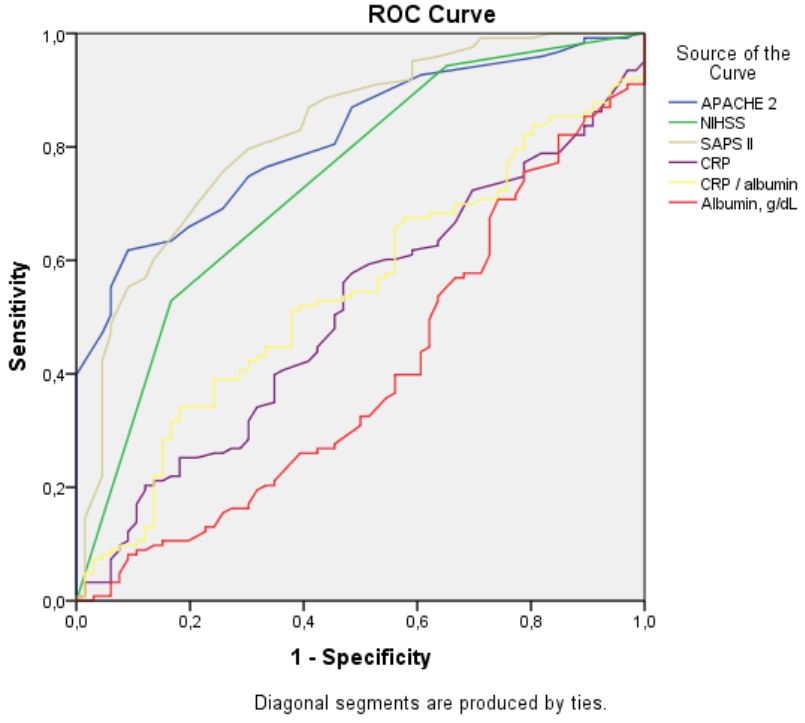

Figure 1: Roc curve analysis of APACHE II, SAPS II, CRP,albumin, CRP/Albumin measurements

intensive care patients. In this study, the cut-off value for 30-day mortality was 1.75 and the cut-off value for 1-year mortality was 1.58.[19] Ayrancı *et al*., in their study with geriatric emergency room patients, revealed the relationship between CRP/albumin ratio and in-hospital mortality and found a cut-off value of 12.3 for the CRP/albumin ratio(20). In the study of critically ill patients in the intensive care unit, Park *et al*. reported that the ratio of CRP/albumin was a predictor of mortality, and the cut-off value for the ratio of CRP/albumin was 34.3.[21] In the study of Kocatürk *et al*., which included only patients with acute ischemic stroke, they showed the relationship between CRP/albumin ratio and 90-day mortality and stated the cut-off value for the CRP/albumin ratio as 0.5.[8]

As a result of our study, we found that the CRP/albumin ratio was associated with 28-day mortality in critically ill geriatric patients over the age of 85, and the cut-off value for CRP/albumin was 2.47. In our study, similar to other studies in the literature, we found that the ratio of CRP/albumin was associated with 28-day mortality. However, we think that the cut-off value for the CRP/albumin ratio in our study was different from other studies in the literature because our study was conducted in a population of patients over 85 years of age with critical acute ischemic stroke.

In conclusion, the CRP/albumin ratio is a valuable parameter that can be used to predict 28-day mortality in critically ill very elderly patients with acute ischemic stroke. The value of 2.47 for the CRP/albumin ratio can be used as the cut-off value to predict 28-day mortality in this patient group. As far as we know, since there are no similar studies in the literature, multicenter studies with a larger patient population in this patient group will contribute to the literature.

One of the limitations of our study is the inability to generalize because it is single-centered and retrospective. Another limiting factor for our study is that we evaluate the CRP/albumin ratio at admission to the ICU and the failure to examine repetitive measurements for the CRP/albumin ratio.

DISCLOSURE

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