ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Assessment of the Relationship Between Serum Albumin to Creatinine Ratio and Long-Term Mortality in Patients with ST-Segment Elevation Myocardial Infarction

ST-Segment Yükselmeli Miyokard İnfarktüslü Hastalarda Serum Albümin/Kreatinin Oranı ile Uzun Dönem Mortalite Arasındaki İlişkinin Değerlendirilmesi

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ABSTRACT

Aim: *In recent years, an increasing number of evidence suggests that the inflammation plays a significant role in the pathophysiology of ST-segment elevation myocardial infarction (STEMI). The association between inflammatory markers and renal functions in STEMI prognosis has been previously reported. No studies have investigated the ability of the serum albumin to creatinine ratio (sACR), defined as a prognostic score, to predict long term mortality in patients experiencing STEMI.*

Material and Method: *This retrospective study included 1133 patients experiencing STEMI. The study population was divided into two groups according to survival and analyzed whether the sACR was an independent predictor of long-term mortality.*

Results: *Out of 1133 patients, death was observed in 112 patients (9%) an average follow-up of 55 months. During the total follow-up period, patients were divided into two groups according to survival. Compared to the survival group, long-term mortality group was older, had a higher SYNTAX score and a lower sACR (p<0.05). Independent predictors of long-term mortality were found to be age, smoking, LVEF, and sACR (HR: 0.627 95% CI: 0.533–0.737; p<0.001). Receiver operating characteristic (ROC) curve comparisons for long-term mortality demonstrated that the sACR was a better predictor than both albumin and creatinine, separately.*

Conclusion: *The present study revealed that sACR is an independent predictor of long-term mortality in patients experiencing STEMI. As a marker which can be easily obtained and calculated, sACR can be an effective parameter used for prognosis estimation of STEMI.*

Key words: *serum albumin; creatinine; sACR; mortality; ST-segment elevation myocardial infarction*

ÖZET

Amaç: *Son yıllarda artan sayıda kanıtlara dayanarak enflamasyonun ST-segment yükselmeli miyokard enfarktüsünün (STEMI) patofizyolojisinde önemli bir rol oynadığını gözlenmiştir. ST-segment yükselmeli miyokard enfarktüsü prognozunda enflamatuvar belirteçler ile böbrek fonksiyonları arasındaki ilişki daha önce bildirilmiştir. Prognostik bir skor olarak tanımlanan serum albüminin kreatinin oranının (sACR) STEMI yaşayan hastalarda uzun vadeli mortaliteyi tahmin etme yeteneğini araştıran hiçbir çalışma yoktur. Bu çalışmada sACR, STEMI hastalarında prognostik önemi incelenmiştir.*

Materyal ve Metot: *Bu retrospektif tasarımlı çalışma, STEMI nedeniyle başvuran 1133 hastayı içermektedir. Çalışma popülasyonu, sağkalıma göre iki gruba ayrıldı ve sACR'nin uzun vadeli mortalitenin bağımsız bir göstergesi olup olmadığı analiz edildi.*

Bulgular: *Ortalama 55 aylık takipte, 1133 hastanın 112'sinde (%9) ölüm görüldü. Toplam takip süresi boyunca hastalar sağkalımlarına göre iki gruba ayrıldı. Sağkalım grubu ile karşılaştırıldığında, uzun dönem mortalite grubu daha yaşlıydı, SYNTAX skoru daha yüksek ve sACR daha düşüktü (p<0,05). Uzun vadeli mortalitenin bağımsız belirteçleri yaş, sigara, LVEF ve sACR olarak bulundu (HR: 0,627 %95 CI: 0,533–0,737; p<0,001). Uzun vadeli mortalite için ROC eğrisi karşılaştırmaları, sACR'nin hem albümin hem de kreatinin ayrı ayrı daha iyi bir belirleyici olduğunu gösterdi.*

Sonuç: *Bu çalışma, sACR'nin STEMI yaşayan hastalarda uzun vadeli mortalitenin bağımsız bir belirleyicisi olduğunu ortaya koydu. Kolaylıkla elde edilebilen ve hesaplanabilen bir belirteç olan sACR, STEMI'nin prognoz tahmininde kullanılan etkili bir parametre olabilir.*

Anahtar kelimeler: *serum albumin; kreatinin; sACR; mortalite; ST-segment yükselmeli miyokard enfarktüsü*

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Introduction

Ischemic heart disease is the most common cause of death worldwide and its incidence continues to increase[1]. Due to modern medical treatments and developments in reperfusion methods, in-hospital and long-term mortality rates have decreased[2,3]. Despite advances in potent medical drugs and percutaneous intervention techniques, ST-segment elevation acute myocardial infarction (STEMI) continues to be an important cause of death over the world[4].

In patients with STEMI, various biomarkers and biomarkers combinations have been investigated for the prediction of mortality. Serum albumin (SA) is a plasma protein and has an inverse association with inflammation and activation of the platelets. In addition, previous studies showed that plasma serum albumin level is a risk factor for the development of coronary artery disease[5–10]. Hypoalbuminemia, which defined as serum albumin level below 3.5 g/dl in plasma and associated with an enhanced risk of arterial and venous thrombosis, and cardiovascular and all-cause mortality in patients with acute coronary syndromes (ACS)[11–15].

There is a significant and inverse relationship between kidney functions and adverse cardiovascular events. In the literature, it has been shown that decreased renal functions is associated with increased mortality in patients with STEMI. High serum creatinine (sCr) concentration at admission is related with heightened risk of in-hospital and long-term mortality in patients with ACS. Besides, a rise in sCr levels in STEMI patients undergoing primary percutaneous coronary intervention (pPCI) during hospitalization is associated with poor myocardial blood flow and elevated risk of long-term mortality[16–19].

As a newly defined variable, serum albumin-creatinine ratio (sACR)[20] has been shown as a predictor of short-term mortality in ACS. However, the relationship between sACR and long-term mortality in patients with STEMI is unclear. We designed this study to investigate the importance of sACR in long-term mortality prediction in patients with STEMI.

Materials and Methods

Study Population

This was a retrospective study implemented between January 2015 and May 2017. A total of 1257 consecutive STEMI patients who had undergone primary percutaneous coronary intervention (pPCI) in Kafkas University Hospital were accepted to the study. Patients who were first diagnosed with STEMI and discharged healthy were included in the study population. Patients who were referred to elective or emergency coronary artery bypass graft surgery (CABG) or patients with history of CABG, chronic renal disease (hemodialysis dependent), malignancies, febrile conditions, autoimmune disorders, chronic hepatopathy or incomplete medical files or records were excluded from the study.

A total of 1133 patients met the inclusion criteria and were enrolled the study. The primary endpoint was all-cause mortality. In-hospital and post-discharge outcomes were collected from medical records, during hospital visits, or via telephone interviews.

The research protocols were as per the Declaration of Helsinki; the study was approved by the local ethical board.

Data Collection

Patients' data were obtained from hospital records and patient files. Patients' vital signs, treatment before admission, electrocardiographic and coronary angiographic features were collected at the time of admission. Information about laboratory tests and echocardiographic variables, in-hospital complications, and treatments received during hospital stay were collected before discharge from the electronic medical records at Kafkas University Hospital.

Laboratory and ECG Measurements

The STEMI diagnosis was made based on the current clinical guidelines[21]. Blood samples were collected from all patients during hospital admission and before discharge for the measurement of the values of albumin, creatinine and glucose along with other biochemical and hemogram parameters. sCr and SA levels were determined using an automatic biochemical analyzer (Roche Diagnostics Cobas 8000 c502, Indianapolis, USA). The sACR (g/mg) was calculated by dividing the serum albumin level by the creatinine level. The estimated glomerular filtration rate (eGFR) was calculated using the modification of diet in renal disease (MDRD) formula. Acute kidney injury was defined as an increase of 25% or 0.5 mg/dL in creatinine level compared to that at baseline within 48 hours.

Table 1. *Baseline clinical characteristics of sACR groups in STEMI patients*

	All-Cause of Mortality			
Variables	Long-term survivals, n: 1021	Long-term mortality, n: 112	Total patients, n: 1133	p value
Age	55±12	66±13	56±12	<0.004
Female gender, n (%)	177(17.3%)	26(23.2%)	203(17.9%)	0.124
Diabetes, n (%)	222(21.7%)	42(37.5%)	264(23.3%)	<0.004
Hipertansiyon, n (%)	397(38.8%)	64(57.1%)	461(40.7%)	0.002
Smoking, n (%)	445(43.6%)	59(52.7%)	504(44.5%)	0.066
Killip class >1, n (%)	134(13.1%)	47(42%)	181(16%)	<0.001
Systolic blood pressure, (mm/Hg)	132±29	125.6±46	132±31	<0.004
Heart rate, bpm	77±15	81±23	77±16	<0.004
Hemoglobin (g/dL)	13.7±1.7	12.9±2.2	13.8±1.8	<0.004
WBC Count (/1000)	12.1±3.5	13.9±5.5	12.8±3.8	<0.004
Glucose (mg/dL)	126(104–165)	148(116–233)	127(105–171)	<0.004
sACR	4.5±1.1	3.4±1.5	4.4±1.2	<0.001
Creatine (mg/dl)	0.88±0.21	1.19±0.49	0.91±0.27	<0.004
Serum albumin (g/dl)	3.77±0.47	3.41±0.52	3.75±0.48	<0.004
Peak Creatine Kinase MB (ng/mL)	170.5(100–298)	359(178–498)	180.5(103–321)	<0.004
Left Ventricular Ejection Fraction (%)	48±8	38±9	46±8	<0.001
Bazal syntax score	16.3±4.3	19.3±5.3	16.6±4.5	<0.001

sACR: serum albumin to creatinine ratio; WBC: white blood cell.

Statistical Analysis

The statistical analysis was performed by using Statistical Package for Social Sciences (SPSS) program version 22.0 (SPSS Inc., Chicago, IL). Kolmogorov-Smirnov test was used for the normality of the data set. Continuous variables were expressed as mean ± standard deviation or median [interquartile range] (25th–75th percentiles) in terms of data distribution and normality. T-test or Mann-Whitney U test was performed to compare variables between two groups. Continuous variables were compared between the groups using analysis of variance and the Kruskal-Wallis H-test. Fisher's exact test or chi-square test was used for comparison of Categorical variables that were presented as numbers (percentage). Multivariate Cox regression analysis was performed to identify independent predictors of long-term death using variables that showed a statistically significant association with all-cause death in univariate analysis. Multicollinearity between the serum creatinine/albumin ratio and sCr and SA levels was assessed by eigenvalues and condition indices. Linearity was tested following the logarithmic transformation of each parameter. The receiver operating characteristic (ROC) curve was utilized to derive the best cut-off values of the sACR for predicting all-cause mortality. The method proposed by DeLong et al. was then used to compare the ROC curves of creatinine, albumin, and sACR to predict all-cause mortality. P<0.05 was considered statistically significant.

Results

A total of 1133 STEMI patients with an average age of 56.4±12.3 years were included the study and the median follow-up was 55 months. During the total follow-up period, 112 patients were died. According to survival, patients were divided into two groups. Compared to the survival group, long-term mortality group was older and had a higher prevalence of diabetes, hypertension, and smoking (p<0.04). Also, they had higher systolic blood pressure, heart rate, Killip class, white blood cell (WBC) count, level of hemoglobin and creatinine, and SYNTAX score. Additionally, patients with long-term mortality had lower albumin levels, left ventricular ejection fraction (LVEF) and a lower sACR (p<0.05). The baseline demographic, clinical, and laboratory parameters are shown in Table 1.

To identify independent predictors of all-cause mortality, we performed a multivariate Cox regression analysis with a stepwise retrospective model by using variables associated with cardiac mortality in univariate analyses. Multivariate analysis showed age, smoking, LVEF, and sACR (HR: 0.627 95% CI: 0.533–0.737; p<0.001) to be independent predictors of all-cause mortality (Table 2).

In ROC curve analyses, the area under the curve (AUC) of sACR was 0.756. The cut-off value for serum creatinine/albumin ratio that indicates long-term mortality was 3.51 with 58.9% sensitivity and

Table 2. *Univariate and multivariate analysis of all-cause long-term mortality*

Variable	Univariate analysis of long-term mortality			Multivariate analysis of long-term mortality		
	Hazard ratio	95% C. I.	P value	Hazard ratio	95% C. I.	P value
Age (years)	1.070	1.054–1.087	<0.001	1.047	1.028–1.065	<0.001
Smoking	1.678	1.468–1.983	0.04	1.514	1.002–2.287	P=0.049
sACR	0.395	0.334–0.467	<0.001	0.627	0.533–0.737	<0.001
LVEF	0.862	0.841–0.883	<0.001	0.891	0.863–0.921	<0.001

sACR: serum albumin to creatinine ratio; LVEF: left ventricular ejection fraction.

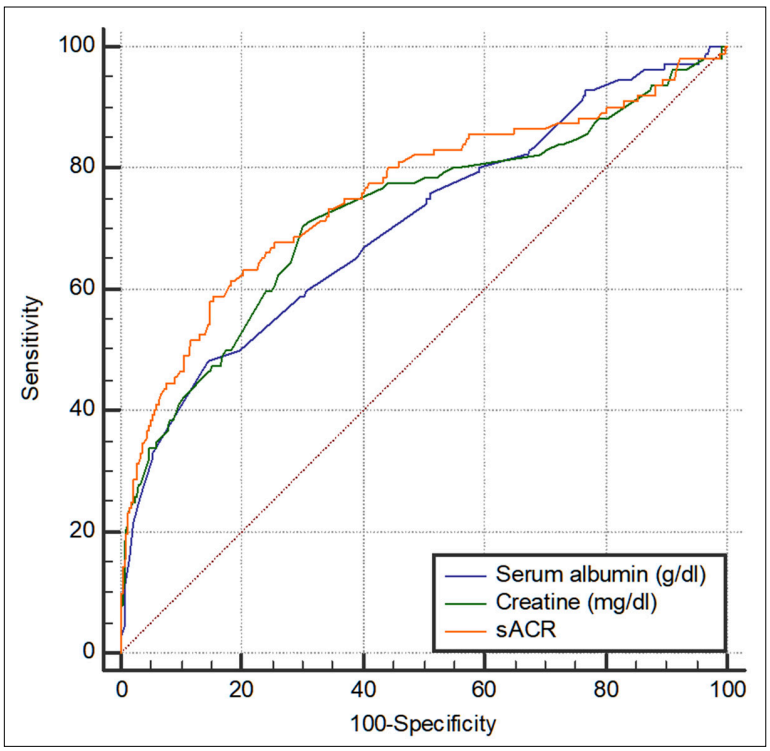

Figure 1. *Comparison of ROC curves between albumin, creatinine and sACR for predicting all-cause mortality.*

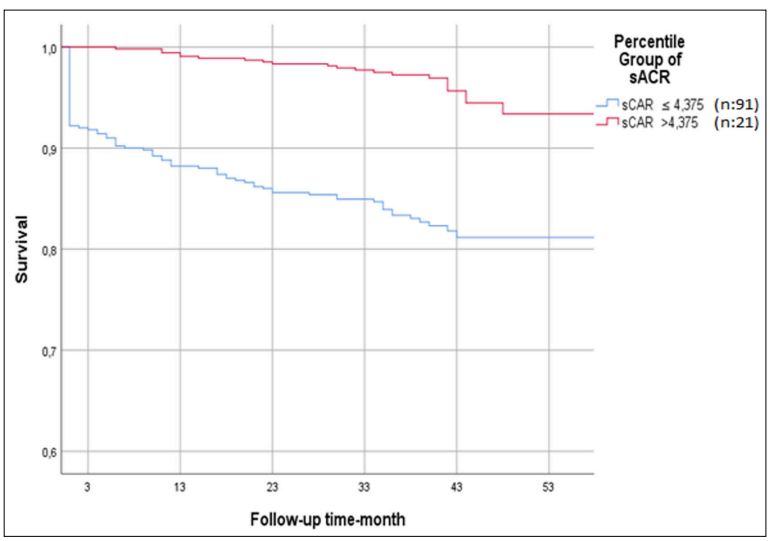

Figure 2. *Kaplan-Meier survival curves according to serum albumin to creatinine ratio (sACR).*

84.5% specificity. Receiver operating characteristic curve comparisons were performed to assess whether sACR had an additional prognostic value over creatinine and albumin levels. The AUC value of sACR was found to be significantly higher than creatinine (difference between areas: 0.03 95% CI: 0.006–0.06 p=0.01) and albumin level (difference between areas: 0.05 95% CI 0.005–0.09 p=0.02) in predicting long-term mortality (Fig. 1).

The study population were divided into two groups based on the median value (4.375) of the sACR; to assess the ability of mortality forecast: low sACR (≤4.375) and high sACR (>4.375) groups. The low sACR group was older and they had higher WBC counts and glucose levels. Moreover, the low sACR group had greater creatinine levels, peak CK-MB, and SYNTAX scores while demonstrating lower serum albumin levels and LVEF. The findings of the sACR groups are provided in Table 3. An analysis of the sACR groups demonstrated that low sACR patients (n=91) had greater all-cause mortality rather than high sACR (n=21) (P <0.001). Kaplan-Meier survival curves according to a cut-off value of sACR are shown in Fig. 2.

Discussion

In this study, we evaluated the prognostic value of sACR for predicting long-term all-cause mortality in patients with STEMI. A low sACR was associated with all-cause mortality and an independent predictor of mortality in patients with STEMI.

Table 3. *Demographic, clinical, and laboratory parameters of patients with low and high sACR*

Variables	sCAR ≤4.37 (n: 565)	sCAR >4.37 (n: 568)	P value
Age	59±12	54±12	<0.001
Female gender, n (%)	87(15.4%)	116(20.4%)	0.027
Diabetes, n (%)	139(24.6%)	125(22%)	0.302
Hypertension, n (%)	244(43.2%)	217(38.2%	0.080
Smoking, n (%)	300(53.1%)	329(57.9%)	0.102
Killip class >1 on admission (%)	117(20.7%)	64(11.3%)	<0.001
Systolic blood pressure, mm Hg	131±35	132±28	0.436
Heart rate, bpm	77±18	77±14	0.805
Hemoglobin (g/dL)	13.6±1.9	13.8±1.7	0.003
WBC Count (/1000)	12.5±4.1	12.1±3.4	0.022
Glucose (mg/dL)	130(105–178)	125(105–160	0.033
sACR	3.49±0.74	5.32±0.86	<0.001
Creatine (mg/dl)	1.07±0.29	0.75±0.11	<0.001
Serum albumin (g/dl)	3.56±0.44	3.94±0.45	<0.001
Peak Creatine Kinase MB (ng/mL)	191(113–338)	167(94–306	<0.001
Left Ventricular Ejection Fraction (%)	45±9	48±8	<0.001
Basal SYNTAX score	17.2±4.7	16.04±4.2	<0.001
Long-term Mortality, n	91	21	<0.001

sACR: serum albumin to creatinine ratio.

ST-segment elevation myocardial infarction (STEMI) is one of the primary causes of death in developed countries[21]. Recent studies have investigated and demonstrated the relation between clinical, laboratory, and hemodynamic parameters and survival in STEMI patients. In our study, 112 patients died during long-term follow-up. Consistent with the previous findings[22–24], patients with long-term mortality had higher heart rate, levels of glucose and creatinine, and SYNTAX scores and lower systolic blood pressure, levels of albumin, LVEF, and sACR ($p<0.004$) when compared to the survivors in our study.

ST-segment elevation myocardial infarction is an acute clinical condition accompanied by inflammation, platelet aggregation, and coagulation[25]. Serum albumin, which is a negative acute-phase reactant protein, has several functions such as antioxidant and anticoagulant activity, promotion of the formation of anti-inflammatory mediators, and the preservation of vascular integrity[26,27]. Previous studies states that low serum albumin levels in STEMI patients are related with poor survival and hypoalbuminemia has a prognostic value in patients with ACS. Hypoalbuminemia was also connected with multi-vessel coronary artery disease (high SYNTAX score) and no-reflow in patients with STEMI and was related to long-term all-cause cardiac mortality[28–30]. In our study we found low serum albumin levels in patients with long term mortality, similar to the literature. Serum albumin has well known anti-inflammatory, anticoagulant, and anti-platelet aggregation activity[27]. STEMI, as a clinical condition accompanied by inflammation causes a decrease in serum albumin levels. Due to low levels of albumin; increased oxidative stress, platelet activation and aggregation may lead the worsening of the clinical illness and results in elevated mortality. Similar to these findings, we observed in patients with poor long term survival has low serum albumin levels.

Impaired kidney functions were associated with an increased risk of cardiovascular disease and worse cardiovascular outcomes. Renal insufficiency was measured by corrected creatinine clearance or sCr level has already been investigated and found to be an independent predictor of mortality in patients with ACS[16–19]. Elevated sCr level has an association with coagulation, fibrinolysis, endothelial dysfunction, and anemia. Retrospective analyses demonstrated that impaired renal functions and elevated sCr concentration on admission increase the risk of death in patients with STEMI and are independent predictors of mortality[31,32]. In our study parallel with the recent findings, sCr levels were found higher in patients with long-term mortality.

sACR represents the ratio of serum albumin to creatinine level. Levels of serum albumin and creatinine were shown to be associated with poor cardiac endpoints[20]. Recent studies have shown that sACR was more significant in predicting prognosis compared to albumin or creatinine levels alone. We hypothesized that merging

these parameters may enable us to obtain a more sensitive and stable index of mortality in patients with STEMI. In line with our expectations, a low sACR was an independent predictor of poor surveillance. Also we found that sACR had a higher prognostic ability for predicting all-cause mortality compared to serum albumin (AUC: 0.706) or sCr (AUC: 0.723).

In the present study, a low sACR was associated with a high SYNTAX score, lower ejection fraction (EF) and high Killip class compared to high sACR. A low sACR related to a high SYNTAX score may reflect a high coronary atherosclerotic burden that is associated with adverse cardiac events and poor prognosis[33]. A low sACR was also associated with low EF and heart failure. The development of heart failure may be due to escalated myocardial damage and reduced myocardial reserve. The presence of heart failure with reduced LVEF is one of the most important predictors of long-term mortality in patients with STEMI[21]. Poor outcomes may have been seen in the low sACR group because of the relationship between low sACR and low LVEF.

In this study, our results demonstrate that sACR may have an additional prognostic value for the development of an individual-risk approach and surveillance of STEMI patients who underwent a pPCI. Patients with a reduced sACR may require more frequent follow-up and intense therapy. Moreover, as an easily accessible parameter, sACR is simply to calculate, and it can be standardized without additional cost, thus offering increased prognostication of these patients.

Statement of Ethics

Our institutional human research ethics committee approved this prospective study (Approval no: 80576354-050-99/85).

Conflict of Interest Statement

None to declare.

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The authors have no conflicts of interest to declare.

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