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The utility of the serum albumin levels on admission for predicting angiographic no reflow after primary percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction

ST-Segment yükselmesi miyokard infarktüsülü hastalarda primer perkütan koroner girişim sonrası anjiyografik akışsızlık fenomenini öngürmede başvuru serum albümin düzeylerinin yararı

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Özet

Amaç: Düşük serum albümin (SA) düzeyleri artmış kardiyovasküler mortalite ile ilişkilidir. Bazal SA seviyelerinin primer perkütan koroner girişim (p-PKG) yapılan hastalarda akışsızlık fenomeni ile ilgili olup olmadığını araştırdık.

Yöntem: Geriye dönük olarak p-PKG ile tedavi edilen ST yükselmeli myokard infarktüsü (STYMI)'lı 358 hasta alındı. Hasta takibi hastaneiçi dönemde yapıldı. Önceki çalışmalara uygun olarak, TIMI akım derecesi ≤2, TIMI akım derecesi >3 olanlarda ise MBG <2 olanlar akışsızlık fenomeni olarak değerlendirildi. Hastalar başvuru SA düzeylerine göre iki gruba ayrıldı. SA <3,5 g/dl olanlar hipoalbüminemik grup ve SA düzey > 3,5 g/dl yüksek albüminemik grup olarak değerlendirildi.

Bulgular: PKG yapılan toplam 358 (yaş 62±14 yaş, % 72 erkek) hasta alındı. Başvuru SA düzeyleri akışsızlık fenomeni olan grupta normal akım olan gruba göre anlamlı bir şekilde daha düşüktü (p=0,021).

Sonuç: Başvuru SA seviyeleri akut STYMI hastalarda p-PKG sonrası-akışsızlık fenomeninin gelişimini tahmin edebilir. Başvuru hipoalbüminemili hastalar kötü klinik ve anjiyografik sonuçları ile ilgilidir ve STYMI p-PKG ile tedavi edilen hastalarda hastane içi mortalite ve pulmoner ödem ve kardiyojenik şok gelişimi tahmin edilebilmektedir.

Anahtar Kelimeler: Serum albumin düzeyi, Akışsızlık fenomeni, Perkütan koroner girişim, Akut myokard infarktüsü.

Abstract

Objective: Low serum albumin (SA) levels are associated with increased cardiovascular mortality. We investigated whether baseline SA levels are associated with no-reflow in patients undergoing primary percutaneous coronary intervention (p-PCI).

Method: STEMI patients treated by p-PCI were included in the study. The patients were followed during in hospital period. We defined angiographic no-reflow phenomenon as a coronary TIMI flow grade ≤2 after vessel re-canalized or TIMI flow grade 3 together with a final MBG < 2, in the same manner as was adopted in previous studies. The patients were divided into two groups according to the SA levels on admission, that is hypoalbuminemia group was SA<3.5 g/dl and high albuminemia group SA level was >3.5 g/dl.

Results: A total of 358 patients (aged 62+14 years; 72% men) who underwent p-PCI were enrolled in the study. Admission SA levels were significantly lower in the no-reflow group than in the normal-reflow group (p=0.021)

Conclusion: Admission SA levels may predict the development of no-reflow phenomenon after p-PCI in patients with acute STEMI. Hypoalbuminemia on admission is related to worse clinical and angiographic outcomes and predicts inhospital mortality and development of advanced pulmonary edema and cardiogenic shock (higher Killip class) in patients treated with p-PCI for STEMI.

Keywords: Serum albumin level, no-reflow phenomenon, primary percutaneous coronary intervention, acute myocardial infarction.

Introduction

Primary percutaneous coronary intervention (p-PCI) significantly improves the survival of patients with ST-segment elevation myocardial infarction (STEMI) (1). Postintervention microvascular obstruction, the so-called no-reflow phenomenon, despite the presence of normal epicardial coronary artery patency, remains an important limitation of the procedure which is related to larger infarct size, worse functional recovery, higher incidence of complications, and short-and long-term morbidity and mortality in the setting of STEMI (2,3). The mechanisms of no-reflow phenomenon are complex and multifactorial. The most probably causes include a combination of platelet aggregation, distal embolization, microvascular vasoconstriction, neutrophil plugging, and tissue edema (4). Noninvasive markers of no-reflow phenomenon may thus provide important prognostic information.

Albumin is the major protein in human serum and the most significant protein found in the extracellular fluid compartment (5).

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In epidemiologic studies, a relationship has been found between hypoalbuminemia and the development of coronary artery disease (CAD). Moreover, hypoalbuminemia has been found to be a risk factor for the development of a new myocardial infarction in patients with CAD (6). Besides, serum albumin (SA) is an important inhibitor of platelet aggregation and increases the production of the antiaggregatory prostaglandin D2 (PGD2) from cyclic endoperoxides (7,8). Furthermore, hypoalbuminemia may increase blood viscosity and disrupt endothelial function on account of increased concentrations of free lysophosphatidylcholine (9). Several studies have showed a relation between low SA levels and increased cardiovascular morbidity and mortality (10,11). The SA might also have important roles in the acute phase of CAD, such as acute STEMI. SA level on admission and postintervention coronary blood flow in patients with STEMI is unclear. Due to the potential role of platelets in induction and maintenance of no-reflow, mediators affecting platelet activation, such as SA, might be involved in the no-reflow phenomenon. As SA is an important inhibitor of platelet activation and aggregation, and an important mediator of platelet-induced coronary artery constriction (7,8), we investigated whether preintervention SA levels are related to coronary noreflow in patients with STEMI who underwent p-PCI.

Patients and Methods

Study population

We retrospectively reviewed 1018 patients with acute STEMIs who were admitted to the Dicle University Faculty of Medicine and underwent p-PCI within 12 hour of symptom onset between January 2012 and September 2014. Of these, 358 patients whose SA levels were measured within the first 24 h of admission comprised the study population. STEMI was defined based on the criteria formulated by the American College of Cardiology and the European Society of Cardiology (12) as: an increase in troponin I >1 ng/mL with a new ST elevation was measured from the J point in ≥2 contiguous leads with at least 0.2 mV in leads V1, V2 and V3 or at least 0.1 mV in the remaining leads during the first 12 hour after the onset of symptoms. The patients were divided into two groups according to the SA levels on admission, that is hypoalbuminemia group with SA<3.5 g/dl and high albuminimia group with SA level >3.5 g/dl. Patients with severe liver disease, autoimmune disease, known malignancy, hematological disorders, severe valvular disease, known cases of hypothyroidism, inflammatory or infectious diseases, a history of bleeding diathesis, patient who was not given a PCI consent, missing or unavailable SA values and follow-up was not documented before p-PCI, patients who were treated with thrombolytic therapy or the use of glycoprotein IIb/ IIIa inhibitors, and patients who presented > 12 h from the onset of symptoms were excluded from the study. After accounting for all of these exclusion criteria, a total of 358 patients remained in study sample.

All patients underwent a complete physical examination, coronary risk factors, and their medical histories and clinical features were recorded. İn hospital mortality during in-hospital follow up period. İn-hospital mortality had to be verified as death due to myocardial infarction, cardiac arrest or other cardiac causes. Cardiogenic shock was defined as marked and persistent (>30 minutes) hypotension with systolic arterial pressure <80 mm Hg and signs of hypoperfusion due to left ventricular dysfunction, right ventricular infarction, or mechanical complications. Serious ventricular arrhythmia was defined on admission as advanced ventricular fibrillation-tachycardia or asystole 48 hours later. Patients were also evaluated according to Killip clinical examination classification (13). The study protocol was in accordance with the Declaration of Helsinki and was approved by the local Ethics Committee.

Blood samples and echocardiography

Venous blood samples were drawn when the patient initially presented to the emergency room or the intensive coronary care unit (ICCU) before p-PCI. Hematologic indexes counts were measured by an automated hematology analyzer (Abbott Cell-Dyn 3700; Abbott Laboratory, Abbott Park, Illinois). SA and other biochem-

ical parameters were measured using the Abbott Architect C16000 auto analyzer (Abbott Laboratory).

Coronary angiography (TIMI and MBG Flow)

All patients underwent selective coronary angiography using the Judkins technique. PCI procedures were performed with standard femoral approach using a 7 Fr guiding catheter. Coronary blood flow patterns before p-PCI were subjected to a thorough evaluation on the basis of thrombosis in myocardial infarction (TIMI) flow grade, using grades 0, 1, 2, and 3 (14). The final TIMI flow grade and myocardial blush grade (MBG) were assessed using standard methods. Two cardiologists who were blinded to patients clinical situation assessed the pre-and postprocedural TIMI flow grade of the infarct related artery (IRA). We defined angiographic no-reflow phenomenon as a coronary TIMI flow grade ≤2 after vessel recanalized or TIMI flow grade 3 together with a final MBG < 2, in the same manner as was adopted in previous studies (15,16). For all study participants, only one artery was identified as the IRA. Coronary artery disease was defined as a greater than 50% stenosis in one of the major coronary arteries.

Statistical analysis

All analyses were performed using SPSS for Windows version 18.0 (SPSS Inc. Chicago, Illinois, USA). Continuous variables were expressed as mean±standard deviation and categorical variables were expressed as percentages. Distribution of continuous variables was assessed with a two sample Kolmogorov-Smirnov test. Comparisons of categorical and continuous variables between the two groups (high and low SA level) were performed using the $\chi 2$ or Fischer's exact test and independent samples t or Mann-Whitney U test, respectively. Statistical significance was defined as $p < 0.05$. The cut-off values for SA for predicting no-reflow and in-hospital death with corresponding sensitivity and specificity was estimated by receiver operator characteristic (ROC) curve analysis.

Results

A total of 358 patients were included in the data analysis. Among our patients (mean age 61.8±13.6, 72% men), admission hypoalbuminemia was present in 133 cases (37%), and the remaining 225 (63%) were stratified into the high albuminemia group. Admission SBP was higher in high albuminemia group patients (p=0.021). Other baseline characteristics are shown in Table 1. Admission laboratory findings were compared according to albumin levels (Table 2). Hemoglobin (p<0.001), red blood cell counts (p<0.001), total cholesterol (p<0.001), low-density lipoprotein (p=0.003), high-density lipoprotein (p<0.001) values of the high albuminemia group were significantly greater than that of the hypoalbuminemia group, whereas baseline C-reactive protein (CRP) levels of high albuminemia group was significantly lower (p<0.001). Angiographic characteristics are listed in Table 3. The final TIMI grade 3 flow (p=0.026) and MBG 2/3 (p=0.012) were significantly less frequent in the hypoalbuminemia group. In-hospital adverse outcomes are presented in Table 4. The in-hospital mortality rate was greater in the hypoalbuminemia group than in the other group (19.5 % vs 4.9%, p<0.001). Similarly, cardiogenic shock (p=0.036), advanced pulmonary edema (p=0.032) and cardiopulmonary resuscitations (p<0.001), were higher in the hypoalbuminemia group. A cut-off level of 3.51mg/dL for SA predicted impaired IRA flow after p-PCI with a sensitivity of 59.6 % and a specificity of 61.2 % (ROC area under the curve (AUC) 0.642, 95% CI 0.577-0.706, p<0.001). A cut-off level of 3.51 mg/dL for SA predicted in-hospital mortality with a sensitivity of 56.7 % and a specificity of 72.0 % (AUC 0.713, 95% CI 0.613-0.813, p<0.001).

Table 1. Baseline demographic characteristics of patients

Variables	Serum Albumin <3.5 mg/dl	Serum Albumin ≥3.5 mg/dl	P Value
Age, years	65.6±13.2	59.6±13.4	<0.001*
Sex, male, n (%)	89(66.9)	170(75.6)	0.077
Previous history			
Hypertension , n (%)	46(34.6)	84(37.3)	0.602
Diabetes mellitus, n (%)	36(27.1)	50(22.2)	0.300
Smoking, n (%)	63(47.4)	131(58.2)	0.046
Hyperlipidemia, n (%)	4(3.0)	17(7.6)	0.077
Family history, n (%)	20(15.0)	48(21.3)	0.142
Previous MI or CAD, n (%)	8(6.0)	8(3.6)	0.496
Previous PCI , n (%)	6(4.5)	14(6.2)	0.373
Prehospital medication			
Aspirin use, n (%)	97(75.2)	164(77.7)	0.592
Clopidogrel, n (%)	67(51.9)	107(50.7)	0.826
Beta blocker, n (%)	11(8.3)	24(10.7)	0.453
ACE inhibitors, n (%)	10(7.5)	26(11.6)	0.220
Statin, n (%)	13(9.8)	11(4.9)	0.074
Enoxaparine, n (%)	118(88.7)	212(94.2)	0.061
Killip class on presentation, n (%)			
I-II	118(88.7)	204(90.7)	0.061
III-IV	15(11.3)	13(5.8)	
Admission SBP (mmHg),	122.6±25.9	128.8±23.0	**0.021**
Admission heart rate (bpm)	81.7±18.1	85.0±15.7	0.064
Type of infarction			
Anterior, n (%)	48(37.26)	106(50.2)	**0.038**
İnferior, n (%)	74(57.4)	91(43.1)	
Other, n%	7(5.4)	14(6.6)	
Duration of chest pain (hour)	5.8±3.6	5.6±4.3	0.648

Values are mean ±SD or n (%),*Mann – Whitney U test; Other Statics Student's t -test; χ 2 test

Table 2. Laboratory findings of patients

Initial laboratory findings	Serum Albumin <3.5 mg/dl	Serum Albumin ≥3.5 mg/dl	P Value
White blood cell count, $10^3/mm^3$	14.4±6.9	13.4±4.4	0.137
Red blood cell, $10^3/mm^3$	4.6±0.6	5.0±0.5	**<0.001***
Hemoglobin, g/dL	13.2±1.5	14.3±1.7	**<0.001***
RDW, %	16.2±1.5	15.9±1.5	**0.007**
PDW, NULL	17.9±1.1	17.9±1.3	0.726
Platelet count, $10^3/mm^3$	251.8±71.9	252.7±60.2	0.910
Lymphocyte count, $10^3/mm^3$	2.0±1.5	1.9±1.0	0.478
Monocyte count, $10^3/mm^3$	0.7±0.3	06.±0.3	0.755
Neutrophil count, $10^3/mm^3$	11.5±6.3	10.6±4.3	0.181
Platelet to lymphocyte ratio	184.2±135.2	164.6±89.0	0.145
Neutrophil/to lymphocyte ratio	8.5±7.1	7.0±4.4	**0.039**
Glucose on admission, mg/dL	184.4±108.2	173.6±84.9	0.341
Creatinin on admission, mg/dL	0.9±0.6	0.9±0.4	0.346
Total cholesterol, mg/dL	170.5±46.9	185.5±38.5	**<0.001***
Low-density lipoprotein, mg/dL	108.5±28.4	119.6±31.5	**0.003***
High-density lipoprotein, mg/dL	32.0±8.3	37.3±10.2	**<0.001***
Triglycerides, mg/dL	141.7±84.6	153.7±97.9	0.244
Uric acid, mg/dL	6.9±2.9	6.7±2.5	0.486
Total protein	6.2±0.9	7.4±4.1	**<0.001***
Serum albumine	3.0±0.4	3.8±0.2	**<0.001***
Baseline CRP	2.5±4.9	0.9±2.0	**<0.001***

Values are mean ±SD or n (%),*Mann–Whitney U test; Other statics Student's t –test.

Table 3. Angiographic characteristics of patients

		Serum Albumin <3.5 mg/dl	Serum Albumin ≥3.5 mg/dl	P Value
Culprit lesion				
Left descendan coronary artery, n %		51(38.3)	117(52.0)	0.024
Right coronary artery, n %		62(46.6)	74(32.9)	
Circumflex coronary artery, n %		20(15.0)	34(15.1)	
Severity of coronary artery disease				
Single-vessel disease, n %		53(39.8)	99(44.2)	0.422
Multi-vessel disease n, %		80(60.2)	125(55.7)	
Preprocedural TIMI Flow	3	33(25.0)	33(25.0)	0.253
	0/1/2	99(75.0)	99(75.0)	
Final TIMI Flow	3	101(75.9)	101(75.9)	**0.026**
	0/1/2	32(24.1)	32(24.1)	
Final MBG	2/3	110(82.7)	110(82.7)	**0.012**
	0/1	23(17.3)	23(17.3)	

LVEF, left ventricular ejection fraction; TIMI, Thrombolysis in Myocardial Infarction; MBG, Myocardial blush grade.

Table 4. In-hospital adverse outcomes of patients

	Serum Albumin <3.5 mg/dl	Serum Albumin ≥3.5 mg/dl	P Value
Advanced pulmonary edema, n %	10(7.5)	6(2.7)	**0.032**
Cardiogenic shock, n %	16(12.0)	13(5.8)	**0.036**
Complete atrioventricular block requiring transient pacemaker, n %	8(6.0)	9(4.0)	0.386
Serious ventricular arrhythmia n %	18(13.5)	15(6.7)	**0.030**
Cardiopulmonary resusitation, n %	29(21.8)	12(5.3)	**<0.001**
Hospitalization duration (days)	6.1±6.7	4.9±3.5	0.066
In-hospital mortality, n %	26(19.5)	11(4.9)	**<0.001**

Discussion

This retrospective study demonstrated that admission SA level has an important prognostic value in patients with STEMI. Hypoalbuminemia was related to poorer postprocedural myocardial reperfusion and inhospital outcomes (mortality, cardiogenic shock, pulmonary edema, severe arrhythmia) during in-hospital period. We found that decreased SA levels on admission are signifficantly related to angiographic no-reflow phenomenon and higher Killip class after p-PCI in patients with acute STEMI.

Rapid restoration of coronary flow to the jeopardized myocardium has become an essential part of therapy after STEMI and p-PCI significantly improves the survival of these patients (1). Despite an open IRA, breakdown of obstruction to coronary microvasculature can markedly decrease blood flow to the infarct zone. This effect is known as the no-reflow phenomenon (17,18). This phenomenon is strongly correlated with short and long-term morbidity and mortality in the settings of STEMI. (19). For these reasons, various pharmacologic interventions and catheter-based devices have been applied to prevent this phenomenon (17,18). The pathophysiology of noreflow phenomenon has not been fully clarified and its etiology appears to be multifactorial. Several mechanisms may be responsible. First, an increased inflammatory activity in the setting of STEMI may be one of the underlying mechanism. In fact, an elevated

leukocyte–platelet interaction at the site of the plaque rupture may play an negative role in distal myocardial reperfusion by activating further inflammation. A previous study also demonstated increased levels of soluble CD40 ligand, interleukin 6, serotonin, tissue factor, and factor VII in the IRA than those in peripheral blood (20). Botto et al (21) have showed an increased leukocyte–platelet functional interaction in STEMI at the site of plaque rupture relative to the systemic circulation, which may be one of the pathogenetic mechanisms liable for no-reflow phenomenon. Thus, both locally increased inflammatory markers and leukocyte–platelet coaggregates at the site of the plaque rupture may be pathogenic mechanisms responsible for angiographic no-reflow phenomenon after p-PCI in STEMI. Physiological concentrations of SA selectively inhibit tumor necrosis factor a-induced vascular cell adhesion molecule 1 expression, monocyte adhesion, and nuclear factor-k B activation in human aortic endothelial cells, suggesting the role of albumin as an anti-inflammatory and antiatherogenic marker (22). Hypoalbuminemia has been ascribe to the existence of inflammatory cytokines. Lower SA levels are related to increased inflammatory burden in the body (23). Inflammation has been related to decreasing albumin synthesis rate and increasing catabolism (23,24). For these reasons, SA may be considered as a surrogate marker of what which is an important inhibitor of platelet aggregation and increases the production of the antiaggregatory PGD2 from cyclic endoperoxides as well (7). According to our findings, decreased SA level may induce no-reflow phenomenon because of increased platelet activity and aggregation. The other explanation for this inverse relationship between SA levels and no-reflow may be associated with endothelial dysfunction. As indicated in animal models of coronary artery occlusion and reperfusion, localized swelling and protrusions are mainly confined to the capillary bed, demonstrating that endothelial dysfunction plays an important role in tissue perfusion. (25). On the other hand, hypoalbuminemia may increase blood viscosity and disrupt endothelial function because of increased concentrations of free lysophosphatidylcholine (9). Hypoalbuminemia may cause aggravated ischemia and reperfusion injuries (26) and may aggravate interstitial edema. Furthermore, SA has antioxidant and anti-inflammatory properties (27,28). Hypoalbuminemia may lead to exacerbation in oxidative damage and inflammation. Hypoalbuminemia is related to reduced colloid oncotic pressure, which can lead to the development of pulmonary edema even in the presence of low capillary wedge pressures (29). We found that the incidence of advanced pulmonary edema and cardiogenic shock during inhospital period was higher in patients with hypoalbuminemia. SA is the main determinant of plasma oncotic pressure and transports numerous substances and participates in both acute and chronic inflammatory responses (30,31). Malnutrition, malabsorption, decreased hepatic synthesis, increased capillary loss, inflammation, and increased plasma volume may all cause hypoalbuminemia (30,31). This study found that there is a significant relationship between hypoalbuminemia and poor survival in patients with STEMI. This may be related to the fact that as a negative acute phase reactant, the SA level decreases in correlation with the severity of inflammation (30-33). Acute coronary syndrome (ACS) is an inflammatory state (34) and during this period, the SA level undergoes dynamic changes. In react to an inflammatory state, SA levels will decrease. (35). The inflammatory response in acute myocardial infarction is serious and, as a marker of inflammation, elevated CRP has been found to be related to high mortality in the course of STEMI (36). Hartopo et al (37) have demonstrate that low SA level is related to in-hospital adverse outcomes in ACS. Oduncu et al (11) have shown that hypoalbuminemia on admission was a strong independent predictor of long-term mortality and development of advanced heart failure in patients with STEMI undergoing p-PCI. Polat et al (38) demonstrate that hypoalbuminemia on admission was a strong independent predictor of long-term mortality in patients with acute decompensated systolic heart failure. In this study, we demonstrated that SA level on admission was related to in-hospital outcomes

(mortality, cardiogenic shock, pulmonary edema, severe arrhythmia). and SA level is positively correlated with hemoglobin and total cholesterol levels hypoalbuminemia apperars to be associated with the nutritional status. Similarly, there was a negative correlation between SA level and baseline CRP level.

We found that hypoalbuminemia was related to poor epicardial and tissue-level reperfusion after p-PCI. This may be because of its relation to the severity of atherosclerosis (39). In summary, in the present study, we showed that decreased preprocedural SA levels display a significant relationship with no-reflow. From this perspective, we suggest that increased preprocedural inflammatory activity and increased platelet aggregation represented by SA levels may be an important factor contributing to poor postprocedural coronary blood flow in patients with STEMI. Lower levels of SA in patients with no-reflow may be the result of increased inflammatory activity, disrupted endothelial function, and elevated platelet activity or aggregation.

Study Limitations

The present study has several limitations. The present study has the well-known limitation of retrospective design and a single-center study. We measured only baseline SA levels. The changes that will be observed by serial measurements may have an additional prognostic value. The baseline CRP level was present only in 47% of the patients; thus, the value of this marker is limited compared with the baseline CRP in our study. Finally, we assess the association between final TIMI flow and other angiographic surrogate markers of myocardial perfusion (eg, myocardial blush). Future prospective studies are warranted to clarify whether SA is just a biomarker or plays a pathophysiologic role in the course of STEMI.

Conclusions

Admission SA levels may predict the development of no-reflow phenomenon after p-PCI in patients with acute STEMI.

Hypoalbuminemia on admission is associated with worse clinical and angiographic outcomes and predicts higher Killip class and in-hospital mortality in patients treated with p-PCI for STEMI

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