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Fibrinogen to Albumin Ratio Predicts Burden of Coronary Artery Disease in Patients with NSTEMI

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Abstract

Objective: Fibrinogen plasma level rises in the event of inflammatory cases. It is known that there is a powerful intercourse between fibrinogen level and plasma viscosity. Albumin plasma level dropes during the inflammatory cases. The aim of this work determine significance of fibrinogen albumin ratio (FAR) as a indicator emphases the burden of atherosclerosis.

Method: The study included 83 patients diagnosed with non-ST-segment elevation myocardial infarction (NSTEMI) between January and September 2015. The definition of NSTEMI was made according to "Definition of Third Universal Myocardial Infarction" guidelines published on 2013 by European Society of Cardiology. Burden of atherosclerosis was evaluated by Syntax score (SS) and Gensini Score. Patients were seperated two groups as medium-high SS (n=23) and low SS (n=60). FAR levels were compared.

Results: FAR was 80.71 ± 30.3 in low SS group and 120 ± 49.72 in the mid-high SS group respectively (p <0.001). In correlation evaluation, FAR and SS showed a poor positive correlation (r = 0.496, p <0.001). In multivariate logistic regression assesment of elements impacting the SS, prominent variable was found to be FAR [p = 0.01, 95% CI (1005-1042)]. In ROC evaluation FAR values of 85 and over demonstrated 83% sensitivity and 68% specificity in determining the burden of coronary artery disease (CAD).

Conclusions: In moderate-high SS group FAR value is considerably higher than those with a low SS group. FAR value may be usefull indicator in clinical practice to determine the burden of coronary artery disease.

Keywords: Fibrinogen, albumin, syntax score

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ST-Segment Elevasyonsuz Miyokart Enfarktüsü Hastalarında Fibrinojen Albümin Oranı Koroner Arter Hastalığının Yükünü Öngördürür

Öz

Amaç: İnflamatuar süreçler fibrinojenin plazma düzeyini yükseltir. Fibrinojenin plazma düzeyi ile viskozite arasında güçlü bir ilişki mevcuttur. İnflamatuar süreçlerde plazmada albümin düzeyi düşer. Bu çalışmanın hedefi, ateroskleroz yükünü vurgulayan bir gösterge olarak fibrinojen albümin oranının (FAO) klinik açıdan önemini göstermektir.

Yöntemler: Ocak 2015 ile Eylül 2015 tarihleri arasında 40-93 yaş sınırında "Avrupa Kardiyoloji Derneği" 2013 ST yükselmesi olmayan miyokart enfarktüsü rehberine göre akut koroner sendrom tanılı 83 hasta dahil edilmiştir. Aterosklerozun yükü Syntax ve Gensini skoru ile değerlendirildi. Hastalar Syntax Skoru (SS); düşük SS (n:60) ve orta-yüksek SS (n:23) olmak üzere iki grup şeklinde analiz edildi. Fibrinojen/albümin oranı (FAO) gruplar arasında değerlendirildi.

Bulgular: Düşük SS grubunda FAO 80.71±30.3, orta-yüksek SS grubunda 120±49.72 (p<0.001) bulundu. FAO ile SS pozitif korelasyon gösterdi (r=0.496,p<0.001). SS'nu etkileyen değişkenleri tespit etmek için multivariate logistik regresyon analizinde en önemli faktörün FAO olduğu gösterildi [p=0.01,%95 CI(1.005-1.042)]. ROC değerlendirmesinde FAO 85 ve üstündeki değerler %83 sensitivite, %68 spesifite ile koroner arter hastalığının yaygınlığını gösterir.

Sonuç: FAO, SS orta-yüksek grupta SS düşük olan gruba göre anlamlı olarak daha yüksektir. FAO klinik pratikte koroner arter hastalığının yükünü göstermek için kullanışlı bir indikatör olarak kullanılabilir.

Anahtar kelimeler: Fibrinojen, albümin, syntax skoru.

INTRODUCTION

Atherosclerosis is a sophisticated inflammatory disease[1]. Inflammation is a crucial point in the development of atherosclerosis[2]. Atherosclerosis and its most serious complication, acute myocardial infarction (AMI), are foremost cause of death in women and men in many countries and significantly restricts life[3]. Atherosclerosis is the basic cause of non-ST-segment elevation myocardial infarction (NSTEMI) and affects the heart vessels to different degrees. Therefore, clinicians have focused on studies that classify risk to assess the burden of CAD in patients with ACS. Many laboratory parameters and scoring systems were used to make this classification. Syntax Score(SS) is the scoring systems used to assess burden of CAD[4-7].

Elevated fibrinogen boost tendency to atherosclerosis both fibrinogen degradation by products and raised plasma viscosity[8]. Albumin is a negative acute phase reactant which reduces plasma concentration in inflammatory cases. Albumin increases fibrinolysis and inhibits red blood cell aggregation. It neutralizes the binding of fibrinogen to the endothelial cell[9]. Thus, albumin antagonizes many prothrombotic effects of fibrinogen. Albumin prevents vascular endothelial damage due to free radicals. Albumin also modulates antioxidant activity in diabetic patients[10]. Epidemiological works have demonstrated an intercourse between plasma albumin concentration and cardiovascular mortality[11,12]. A lot of study have shown an intercourse between high fibrinogen, low albumin concentrations and CAD[13-16]. To our knowledge, there is no study that uses the relationship between the fibronogen to albumin ratio (FAR) and SS to determine the burden of CAD in patients NSTEMI.

Purpose of this work is evaluate whether high FAR is associated with the extent and burden of CAD in patients with NSTEMI.

METHOD

Study Population

A single-center, observational study included 83 patients between the ages of 40-93 between January 2015 to September 2015 with the diagnosis of NSTEMI as per the "Third Universal Myocardial Infarction Description" guideline of the European Society of Cardiology. Hemogram, biochemistry, D-dimer, fibrinogen, troponin I, CK-MB and electrocardiogram were studied for the diagnosis of NSTEMI. The extent and burden of CAD were evaluated with SS after standard femoral coronary angiography. Patients were divided into two groups according to SS as low (n: 60) and medium-high (n: 23). Patients with pulmonary embolism, chronic liver disease, chronic renal failure, chronic lung disease, connective tissue disease, malignancy, acute or chronic infection, previous cerebrovascular disease and prosthetic heart valve diseases were excluded. Patients who refused to attend in the study were removed. Each patient was informed about the scope of the study and a signed consent form was obtained for participation. The study endorsement was taken from the Ethics Committee of Dicle University Faculty of Medicine (Date of approval: 23/10/2015 and number: 140).

Clinical Variables and Cardiovascular Risk Factors

To obtain demographic and clinical data of all patients: Age, sex, body mass index [body weight/square of lenght (kg / m2)], smoking, hypertension (antihypertensive drugs treated with known hypertension or twice blood pressure above 140/90 mmHg), diabetes mellitus (treated with diet or medications known diabetes or fasting serum glucose levels above 126 mg / dl), dyslipidemia (according to ACC / AHA 2013 current guidelines) were questioned.

Biochemical and Hematological Parameters and Calculation of Syntax Score

Blood samples was collected from all patients in the supine position, without applying bandage to the forearm. Hemogram; Wbc (white blood cell), neutrophil, lymphocyte, MPV (mean platelet volume), biochemical parameters; fasting blood glucose (glucose), urea, creatinine, ALT (alanine aminotransferase), AST (aspartate aminotransferase), total protein, albumin, cardiac enzymes; troponin I, CK-MB, coagulation parameters; D-dimer and fibrinogen were studied. The hemograms of the patients were stored in a K3 ETDA tube for 2 hours at room temperature and the Sysmex SE 9000 analyzer (Roche Diagnostics, Germany) was used. Plasma fibrinogen level was measured by Claus Clotting method in Symex CA 1500 and D-dimer level was measured in AQT90 Flex device. Biochemistry parameters were routinely measured in hospital central biochemistry laboratory.

The Syntax score is calculated by a series of sequential, interactive questions using a computer program. It includes 12 basic questions. The first three question include dominance, the total number of lesions, and the vessel segment where the lesions are located. The segment with each lesion is numbered from 1 to 16. The total number of lesions allowed is limited to 12. Lesions are calculated from the third question. Each lesion may involve one or more vascular segments. In this case, each segment will contribute to the score. The last nine question queries the characteristics of each lesion individually. Here, it is first mentioned whether the vessel is total or not. If it is specified as total, a few more detailed questions will be asked afterwards. These questions are about whether there is a side branch or not, and if so, what is the width of the vessel diameter. If there is no side branch or if the vessel diameter is <1.5 mm, it will automatically go to the next step and ask if there is a trifurcation or bifurcation lesion. If the lateral branch vessel diameter is >1.5 mm, questions will be asked according to the algorithm for total occluded and bifurcation lesions. All remaining questions will be

answered yes or no, except for bifurcation or trifurcation lesions. The last question concerns whether there is diffuse disease in the vessel. If yes, segments with diffuse disease will be re-marked. An important feature of the Syntax score is that it is lesion-based. A score is calculated for each lesion separately. The total score obtained from each lesion is calculated as the Syntax score. The characteristic of each lesion is reported after the algorithm is completed. A syntax score of 0-22 is considered low, 23-32 is considered moderate, and 33 and above is high.

Statistical Analysis

Statistical Package for Social Sciences (SPSS) for Windows 18 program was applied for data process. The distributions of continuous variables were determined by Kolmogorov-Simirnov and Shapiro-Wilk tests. Descriptive statistics were explained as mean ± standard deviation for continuous variables, and nominal variables were expressed as the number of cases and (%). Student's t-test was utilized for continuous variables with normal distribution, and Mann Whitney-U test was used for continuous variables without normal distribution. Chi-square test or Fischer Exact test was utilized to compare categorical variables. Pearson correlation test was utilized to evaluate the relationship between normally distributed parameters, and Spearman's rho correlation test was utilized to examine the relationship between non-normally distributed parameters. In Pearson correlation analyzes, correlation coefficient (r) was calculated. Correlation coefficient defined as (0-0.25) very weak, (0.25-0.50) weak, (0.50-0.69) moderate, (0.70-0.89) high and (0.90-1) very high. In addition, p-values, also known as the degree of significance, were given to the correlations.

"P" value <0.05 was accepted statistically meaningful. The cutoff points for sensitivity and specificity of FAR in predicting SS were calculated by applying a receiver operator characteristic(ROC) curve evaluation. Multivariate logistic regression evaluation was applied to find the variable conditions affecting the SS.

RESULTS

83 patients were included in the study. Of these, 60 had low SS and 23 had moderate-high SS. Of the participants, 51 (61.44%) were male and 32 (38.55%) were female. The mean age was 67.01 ± 12.24 years in the low SS group and 70.65 ± 10.14 years in the moderate-high SS group. There was no statistically important variety between the groups in point of age (p = 0.20). Laboratory findings between groups were compared separately with SS. According to SS, other parameters were found statistically significant except MPV and lymphocyte. Fibrinogen was 282.78 ± 93.6 mg / dl in the low SS group and 360.9 ± 136.9 mg / dl in the moderate-high SS (p = 0.004). Albumin was 3.57 ± 0.41 g / dl in the low SS group and 3.09 ± 0.42 g / dl in the moderate-high SS group (p <0.001). FAR was 80.71 ± 30.3 in the low SS group and 120 ± 49.72 in the moderate-high SS (p <0.001). The comparison of the main characteristics of the groups is given in Table 1. As shown in Table 2, there is a poor positive correlation between fibrinogen and SS, and it is statistically significant (r = 0.364, p = 0.001). There is a moderate negative correlation between albumin and SS and which is statistically significant (r = -0.504, p <0.001). As shown in Figure 1 and Table 2, there is a poor positive correlation between FAR and SS, which is statistically marked (r = 0.496, p <0.001). Multivariate logistic regression evaluation was performed to find variable factors affecting the SS. The most significant variable was FAR (OR: 1.02, 95% CI: 1.005-1.042, p = 0.01). (Table 3). At a cutoff value of 85.38, FAR predicted the burden of CAD with a sensitivity of 83% and a specificity of 68% (ROC area under curve [AUC]: 0.76, p <0,001, Figure 2).

Table I: Comparison of demographic characteristics and initial laboratory values of patients in SS groupsa

Variables	SS low (<22) n: 60	SS moderate-high (≥22) n: 23	P value
Male n(%)	38(45.7)	13(15.6)	
Sex			0.750
Female, n(%)	22(26.5)	10(12)	
Hypertension, n(%)	33(55)	13(56.5)	0.900
Diabetes mellitus, n(%)	17(28.3)	11(47.8)	0.155
Dislipidemia, n(%)	30(50)	13(56.5)	0.774
Smoking, n(%)	21(35)	8(34.7)	0.985
Age, year	67.01±12.24	70.65±10.14	0.200
BMI (kg/m^2)	26.83±4.5	26.28±5.1	0.620
WBC x10^3 /μL	9.15±2.78	13.17±4.99	**<0.001**
MPV fL	7.93±1.44	8.04±1.56	0.750
Neutrophil count x10^3 /μL	6.06±2.52	10.13±4.2	**<0.001**
Lymphocyte, x10^3 /μL	2.08±0.89	1.66±0.55	0.420
NLR	3.68±3.1	7.04±4.27	**<0.001**
Fibrinogen (mg/dl)	282.78±93.6	360.9±136.9	**0.004**
Albumin (g/dl)	3.57±0.41	3.09±0.42	**0.001**
FAR	80.71±30.32	120±49.72	**0.001**
D-dimer(mg/dl)	0.63±0.87	1.49±1.18	**0.001**

Abbreviations: BMI, body mass index; WBC, White blood cell; MPV, mean platelet volume; NLR, neutrophil to lymphocyte ratio; FAR, fibrinogen to albümin ratio; SD, standart deviation a Values are mean + SD or n (%).

Table II: Correlation of fibrinogen, albumin, FAR parameters with Syntax Score

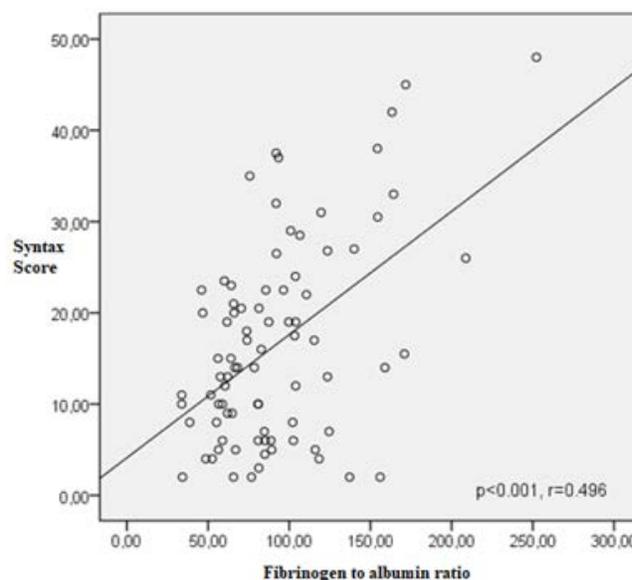|	Fibrinogen	Albumin	FAR
Syntax Score			
Pearson correlation (r)	0.364	-0.504	0.496
P value	0.001	<0.001	<0.001

Figure 1. Correlation between fibrinogen to albumin ratio and Syntax score

Table III: Multivariate logistic regression analysis

Parameter	OR	%95 CI	P value
Age	0.98	0.92-1.04	0.59
Sex	1.39	0.35-5.4	0.63
BMI	0.96	0.82-1.13	0.66
Dislipidemia	0.45	0.22-11.7	0.25
Smoking	1.62	0.36-7.2	0.52
Hypertension	1.72	0.41-7.2	0.45
Diabetes mellitus	0.39	0.08-1.7	0.22
NLR	1.18	0.97-1.4	0.08
FAR	1.02	1.005-1.042	**0.01**
D-dimer	1.75	0.86-3.55	0.12

BMI, body mass index; NLR, neutrophil to lymphocyte ratio; FAR, fibrinogen to albumin ratio
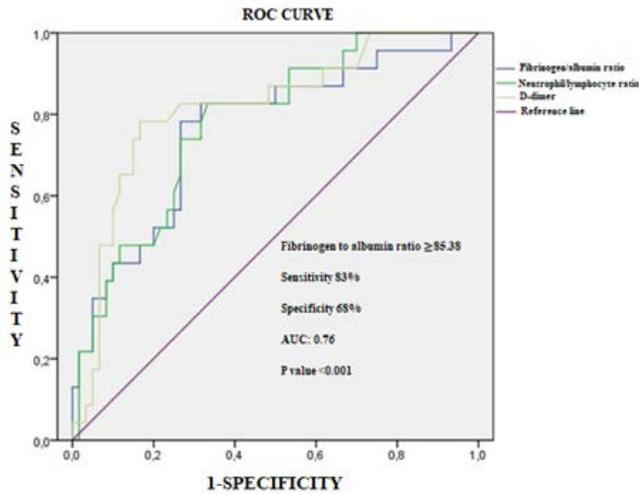
Figure 2. Receiver operator characteristic curve analysis of fibrinogen to albumin ratio predicting in Syntax Score

DISCUSSION

The scope of this study was to predict the burden of CAD using well-known cardiovascular risk factors as well as fibrinogen and albumin, which increased and decreased respectively as an acute phase response. In this study, the plasma FAR was clearly higher in the patient group with a high level SS compared to the group with a low-level SS.

As it is known, there are many scoring systems showing the burden of CAD. However, in a study by Sullivan et al.[17] angiographic scores were similar. But, in the Syntax scoring system, coronary lesions were evaluated in many respects such as lesion characteristics, bifurcation or trifurcation characteristics, anatomic location, thrombus burden, collateral circulation feature compared to other scoring systems. Elevated fibrinogen boost incline to atherosclerosis both products after degradation of fibrinogen and elevated plasma viscosity[18]. This has been demonstrated in stable and unstable CAD, peripheral occlusive artery disease, and cerebrovascular diseases[19]. In a study by Tataru et al[20], it was observed that increased plasma fibrinogen level was associated with extent and burden of CAD. In a study by Koichi Honda et al[21], the interrelation between fibrinogen level and burden of CAD was shown using the gensini score.

Generally in the literature, the burden of CAD with microalbuminuria has been investigated, and limited number of studies have investigated the burden of CAD by direct plasma albumin concentration. In our study, FAR parameter was used to evaluate the burden of atherosclerosis.

There are many studies in the literature on changes in plasma proteins that occur during AMI. In these studies, it was observed that plasma protein values droped during acute myocardial infarction[22]. In patients with acute myocardial infarction, this significant reduction in blood proteins may be due to increased urinary excretion of albumin and globulin, as well as to changes in plasma proteins during the acute phase reaction in the body. Because albumin and prealbumin are known as negative acute phase reactants.

Epidemiological works have demonstrated a relationship plasma albümin concentration and cardiovascular mortality[11-12]. In a retrospective study by Narang et al[23], a negative correlation was found between serum plasma albumin level and the burden of CAD (p = 0.004) in a population with stable CAD.

In a study by Joki et al[24], plasma albumin levels and burden of CAD were investigated in end-stage renal disease patients with recommended hemodialysis. At this work, a statistically prominent intercourse was found between age and low plasma albumin level, and multi-vessel disease and Gensini score. Lekatsas et al[25] investigated the burden and extent of CAD with the Gensini score and Hamsten score in 87 normoalbuminuric, 47 microalbuminuric patients without diabetes. Gensini and Hamsten scores were significantly higher in patients with microalbuminuria. The study by Parvizi et al[26] showed a strong relationship between urine albumin / creatinine ratio and the burden of atherosclerosis. In a study by Karahan et al[27], it

was found that there was a statistically significant relationship between FAR value and the prevalence of CAD in the STEMI patient group who applied to the emergency department.

Study Limitations

Being a single center and cross-sectional study and the number of patients with small sample volume are the most important limitations of this study. In this study, it would be more valuable if we could show the extent and burden of CAD with coronary intravascular ultrasound and coronary computed tomography in addition to coronary angiography. However, these tests are not routinely performed in case of ACS.

CONCLUSION

Plasma FAR was significantly higher in the patient group whose SS was moderate-high compared to the group with low SS. In conclusion, burden of CAD assessed by the FAR is preferable with regards to the detection of severity of CAD in patients with NSTEMI. However, larger studies are warranted to investigate if our preliminary findings translate into burden of CAD in patients with NSTEMI.

Acknowledgements

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