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Kalp Tipi Yağ Asid Bağlayıcı Proteinin Akut Koroner Sendrom Risk Skorları ile İlişkisi

The Relationship between Cardiac Fatty Acid Binding Protein and Acute Coronary Syndrome Risk Scores

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ÖZ

Amaç: Kalp tipi yağ asid bağlayıcı protein (H-FABP) düşük moleküler ağırlıklı majör sitoplazmik bir proteindir ve miyokard yaralanmasına cevap olarak hızlı bir şekilde kardiyomiyositlerden salınır. H-FABP'ın akut koroner sendrom (ACS) tanısında kullanılabilirliğini ve koroner arter hastalığının (KAH) prevalansı, şiddeti ve erken teşhisi ile olan ilişkisini araştırdık.

Materyal ve Metot: Bu prospektif gözlemsel çalışmamıza, kliniğimize Şubat 2016 ile Ocak 2017 tarihleri arasında başvuran 18 yaş ve üstü AKS tanılı 110 hasta dahil ettik.Hastaları iki gruba ayırdık: ST yükselmeli olmayan AKS (NSTE-AKS) ve ST yükselmeli AKS (STEMI).H-FABP ve kardiyak troponin I (cTnI) için hastalardan ilk hastaneye başvuru anında ve 6 saat sonra tekrar kan örnekleri alındı. Tüm hastalara koroner anjiografi yapıldı.

Bulgular: Başvuru anında, her iki grupta GRACE (Global Registry of Acute Coronary Events), SYNTAX (The synergy between percutaneous coronary intervention with taxus and cardiac surgery) ve Gensini risk skorları arasında istatistiksel olarak anlamlı bir ilişki bulunmadı (p=0,056, p=0,791, p=0,278). Altıncı saatte bakılan H-FABP düzeyi ile GRACE ve Gensini risk skorları H-FABP pozitif grupta istatistiksel olarak anlamlıydı (p=0,003, p=0,011). Ancak, SYNTAX risk skoru H-FABP pozitif grupta istatistiksel olarak anlamlı değildi (p=0,984).

Sonuç: Çalışmamızda H-FABP ile koroner arter hastalığı risk skorları arasındaki ilişkiyi ve H-FABP'ın AKS tanılı hastalarda tanısında kullanılabileceğini gösterdik.

Anahtar Sözcükler: Akut koroner sendrom, inflamasyon, ateroskleroz, kalp tipi yağ asid bağlayıcı protein, kardiyak biyobelirteç

ABSTRACT

Objective: Heart type fatty acid binding protein (H-FABP) is a low moleculer weight major cytoplasmic protein and released quickly from cardiomyocytes in response to myocardial injury. We searched functionality of H-FABP in diagnosis of acute coronary syndrome (ACS) and prevalence of coronary artery disease, relationship with its severity and early diagnosis.

Materials and Methods: This was a prospective observational study. We took in 110 patients- aged 18 and above-diagnosed ACS between the dates February 2016 and January 2017. The patient population was divided into two groups as ST segment elevation ACS (STEMI, 52 patients) and Non-ST segment elevation ACS (NSTE-ACS, 58 patients). For H-FABP and cardiac troponin I (cTnI) blood samples of the patients were taken both when they first applied to the hospital and six hours later. Coronary angiography was performed to all the patients.

Results: On admission, it wasn't found a statistically significant relationship in both groups, GRACE (Global Registry of Acute Coronary Events), SYNTAX (The synergy between percutaneous coronary intervention with taxus and cardiac surgery) and between Gensini Risk skores (p=0.056, p=0.791, p=0.278). The H-FABP level of blood samples looked over six hours later with GRACE and Gensini risk scores were statistically significant in the H-FABP positive group (p=0.003, p=0.011). However SYNTAX risk score in H-FABP positive group was not statistically significant (p=0.984).

Conclusion: In our study, we demonstrated the relationship between H-FABP and coronary artery disease risk scores and that H-FABP can be used in the diagnosis of ACS.

Keywords: Acute coronary syndrome, cardiac biomarker, heart-type fatty acid binding protein

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INTRODUCTION

Coronary artery disease (CAD) is one of the most important causes of mortality and morbidity in the world. As with all fields, with the developing technology in the field of cardiology, diagnosis and treatment modalities allow patients with Acute Coronary Syndrome (ACS) early diagnosis of diseases with increased survival and modification of risk factors.[1]

Cardiac troponins (cTn) are preferred biomarkers for the diagnosis of acute myocardial injury. Troponin is found in both skeletal muscle and cardiac muscle, but the specific versions of troponin differ between types of muscle. They are encoded by different genes and used in the diagnosis. Troponins are not used for only diagnosis; but also on risk assessment and prognosis, cTnI is the most specific.[2,3] They are more sensitive than creatin kinase isoenzyme (CKMB) in cardiac damage. Fatty acid binding proteins (FABP) were first discovered by Ockner in 1972.[4] Up to nine types are defined. H-FABP is a low molecular weight, cytosolic, soluble a protein that is not in the structure of the enzyme.[5] Due to myocardial ischemia it is released from the heart tissue and its concentration in the plasma increases. It was found that 1.5 hours after the onset of symptoms of myocardial infarction (MI), the heads peak at 6-8 hours and disappear completely within 24-36 hours.[6-8]

In calculating the risk of death and prognosis of patients with ACS, SYNTAX (The synergy between percutaneous coronary intervention with taxus and cardiac surgery), GRACE (Global Registry of Acute Coronary Events) and Gensini scores. [9]

SYNTAX score assessed for the severity of coronary lesions is the angiographic score system associated with the lesion used. In patients with CAD mortality and morbidity are determined, as well as the role of revascularization. It facilitates optimal management of revascularization by detecting high-risk patients in terms of adverse events that can occur after Percutaneous Coronary Intervention (PCI).[10] GENSINI risk scoring is graded according to angiography stenosis grade. GENSINI score is a parameter used to assess the prevalence and severity of CAD. The GRACE risk score predicts in-hospital and first 6-month mortality with using some clinical data.[11] Therefore the aim of our study is the relationship between H-FABP in patients with ACS and relation to the prevalence, severity, and early diagnosis of CAD.

MATERIALS AND METHODS

We studied 110 patients who underwent coronary angiography (General Electric, Innova, 2100) due to ACS from February 2016 to January 2017. The patient population was divided into two groups as ST segment elevation ACS (STEMI, 52 patients) and Non-ST segment elevation ACS (NSTE-ACS, 58 patients) based on diagnostic criteria of ACS. Patients were excluded if they had a history of coronary artery bypass graft surgery, normal coronary arteries, impaired renal function (serum creatinine levels of >1.5 mg/dL), chest pain lasting more than 2 h before medical contact, multi organ failure, cerebral vascular disease and missing of serum biomarker levels and under 18 years old.

The diagnosis of AMI was based on the criteria of the Joint European Society of Cardiology/ American College of Cardiology Foundation/ American Heart Association/World Heart Federation Task Force definition.

Informed consent was obtained from all patients and the study was approved by the Ethics Committee of the Çanakkale Onsekiz Mart University,Turkey. (Date: 05/08/2015, Decision no. 2015/13).

Coronary angiography and the syntax score: Selective coronary angiography was performed in all patients using the Judkins technique. Left and right coronary angiographies were performed at various projections. Assessment of coronary stenosis by coronary angiography was by 2 experienced cardiologists who used the SYNTAX score algorithm.[12]

Gensini score: Gensini score was calculated for each patient according to coronary angiography results. The score was computed by assigning a severity score to each coronary stenosis according to the degree of luminal narrowing and its geographic importance. Reduction in the lumen diameter, and the roentgenographic appearance of concentric lesions and eccentric plaques were evaluated (reductions of 25%, 50%, 75%, 90%, 99%,and complete occlusion, were given Gensini scores of 1, 2, 4, 8, 16,and 32, respectively). Each principal vascular segment was assigned a multiplier in accordance with the functional significance of the myocardial area supplied by that segment: the left main coronary artery × 5; the proximal segment of left anterior descending coronary artery (LAD) × 2.5; the proximal segment of the circumflex artery × 2.5; the mid-segment of the LAD × 1.5; the right coronary artery, the distal segment of the LAD, the posterolateral artery, and the obtuse marginal artery × 1; and others × 0.5.Stenosis reducing the intraarterial diameter of

greater than 50%was regarded as hemodynamically significant. Noncritical coronary artery disease was defined as a < 50% stenosis in coronary arteries. Single-vessel disease was defined as a ≥50% stenosis in only one major epicardial artery or an important branch of a major epicardial coronary artery. Multivessel coronary disease defined as the presence of a > 50% stenosis in two or more major epicardial arteries or left main coronary artery disease.

All patients underwent emergency, early or elective coronary angiography within 5 days of admission (mean 3 days).[13]

Grace score: GRACE consists of the following eight vari-ables at admission: age, heart rate, systolic blood pressure, plasma creatinine, Killip class, ST-segment deviation, elevated myocardial necrosis marker, and cardiac arrest at admission. In-hospital percutaneous coronary intervention (PCI), coronary artery bypass grafting surgery, and past MI history are also added to the score when calculating the discharge GRACE score. For calculating the score electrocardiographic records of the first 6 hours, the first plasma creatinine value and the troponin mea-sures for the first 12 hours were used. For each patient, GRACE score was calculated by using specific variables collected at admission. Patients were classified into 3categories low (1–108), intermediate (109–140), and high (>140), according to the GRACE score.[14]

Collection of Samples and Laboratory Analysis*:* In the first 10 minutes following the patient's admission to the triage, all participants were evaluated by using electrocardiogram (ECG) tracings, and the serum levels of H-FABP, troponin-I, lipids and the basic routine biochemical parameters.

Venous blood samples were drawn from the antecubital vein at initial presentation and 6 h later. EDTA tubes were used for the hematological test. H-FABP samples were centrifuged at 4000 rpm for 10 minutes.

The serum and the supernatant of the H-FABP samples were transferred into eppendorf tubes and stored at -80°C till further analysis. Biochemical analyses (glucose, plasma creatinine, uric acid, total cholesterol, low-density lipoprotein, low-density lipoprotein, triglyceride levels) were performed with a Beckman Coulter LH-780 device (Beckman Coulter Ireland Inc Mervue, Galway, Ireland). The analysis of H-FABP was performed by an enzyme linked immunosorbent assay (ELISA) using assay kit (Cat No: HK401, Hycult Biotechnology, The Netherlands).

The results were determined by reading on the ELX808 IU microplate reader. The cv (coefficient of variation) values for H-FABP are <10% <12.

Statistical analysis: Continuous data were expressed as mean ± standard and categorical data were expressed as number and percentage. The variables were compared using the chi-square test. The significance of relation between the H-FABP, troponin I and cardiac risk scores were evaluated by Mann-Whitney U and Kruskal-Wallis tests. A ROC (Receive Operating Curve) analysis was performed to definite the sensitivity and specificity of the measurement of the H-FABP levels to diagnose the acute coronary syndrome. Data were statistically analyzed using SPSS statistical package version 21 (SPSS Inc., Chicago, IL, USA). A p value of less than 0.05 was considered statistically significant.

RESULTS

We assessed 110 patients (mean age 60.07±10.57 years, 78.2% male) for the study. Selective coronary angiography was performed in all patients. In our study, the cut-off value for troponin I value was 0.6 ng / ml and 1700 pg / ml for H-FABP. Twenty-one patients (19.1%) had diabetes mellitus, 44 patients (40%) were hypertensive, 64 patients (58.2%) were current smokers, 52 patients (47.3%) had dyslipidemia. The time from onset of chest pain to medical contact ranged from 30 to 120 min with an average of 59.14±27.49 min. The baseline demographic/ clinical characteristics and laboratory findings of patients included in our study are summarized in Table 1 and Table 2. There were no statistically significant differences between the groups with respect to sex, body mass index (BMI), smoking status, or hemoglobin levels.

A number of patients had H-FABP positive on admission 30 patients versus 9 patients with cTnI.

At the time of admission, H-FABP had the highest sensitivity of 82.7% within the cardiac markers. The specificity was 83.3%, the positive predictive value was 97.6%, the negative predictive value was 37.0% and the test reliability was 82.7%.

For troponin I, the sensitivity was 63.3%, specificity was 100.0%, positive predictive value was 100.0%, negative predictive value was 25.0% and test reliability was 67.3% for diagnosis of ACS. We found that H-FABP within 6 h of chest pain onset had a sensitivity of 78.6%, a specificity of 100%, a positive predictive value of 100%, a negative predictive value of 36.4% for diagnosis of ACS. And we found that Troponin I within 6 h of chest pain onset had a

sensitivity of 100%, a specificity of 100%, a positive predictive value of 100%, a negative predictive value of 100% for diagnosis of ACS (Table 3).

Based on the SYNTAX risk score, 96 patients (87.3%) were in the low-risk (<22) group, 14 (12.7%) were in the intermediate-risk (22-33) group, and no patients were in the high-risk (>33) group. On admission when the patients were classified according to the positive or negative H-FABP, there was not a statistically significant relationship between the cardiac risk scores in patients with ACS. Although the GRACE risk score and GENSINI risk score were higher in the H-FABP positive group; SYNTAX risk score was higher in H-FABP negative patient group. Even though at the 6th hour in the H-FABP-positive group, we found a statistically significant relationship between the GRACE and GENSINI risk scores; there was no statistically significant correlation with SYNTAX risk score (Table 4).

A ROC curve analysis of H-FABP and Troponin in the diagnosis of the acute coronary syndrome between 0-6 hours (Figure 1). While the area under the curve (AUC) value of H-FABP was 0.86 (95% confidence interval (CI): 0.76–0.97, p<0.001), the AUC value of Tropoin I was 0.84 (95% CI: 0.76-0.97, p<0.001).

DISCUSSION AND CONCLUSION

When we evaluated the results, we showed the relationship between H-fabp and cardiac risk scores and showed that it can be used to evaluate the diagnosis and prognosis of patients with ACS. The main pathophysiological mechanism is the reduction of coronary flow due to thrombus formation on the plaque in ACS. Plaque erosion is responsible for 25% of patients.

It is a dynamic process and requires early diagnosis and urgent treatment. As a result of distal embolization of the thrombus, cardiac markers become positive and help us to make a diagnosis. It is important to determine mortality and morbidity in patients with ACS.

GRACE, SYNTAX and GENSINI scores currently used are available for this purpose. Syntax score is angiographic scoring used to determine how complex the coronary arteries are. It is helpful to determine the manner of the revascularization (CABG or PCI) according to the difficulty of coronary anatomy of the patients. The GRACE risk score provides important information for predicting mortality both in the hospital and within the first 6 months. As a result of the scoring, patients are divided into low, medium and high-risk categories and performing coronary angiopraphy in appropriate time zones is recommended accordingly.[15-18]

The GENSINI score, which is investigated by the severity of CAD lesion, is a method that shows the relationship of atherosclerotic plaque when used in conjunction with simple, catheter calibration analysis.[19,20]

The frequency of ACS is effected by factors such as region, gender and race. McManus et al.[21] and Eren et al.[22] also had male gender dominance at their studies. In our study, male gender dominance was present in STEMI and NSTE-ACS groups. The patients in the STEMI group were of older. There was no statistically significant difference in BMI category in both groups. It is important to diagnose chest pain whether it is ischemic in patients who admitted to the emergency department. Chest pain does not always lead us to the diagnosis, and neither does the ECG, hence additional assistive tests are required. Here, cardiac markers play a major role. Most studies have showed that diagnosis of ACS within the first 6 hours by troponins is superior to CKMB. However, troponin values cannot be detected at the blood level in the early hours. As a result, new cardiac markers were needed in early diagnosis.

In our study, in order to find a new cardiac marker we investigated H-FABP may associate with the prevalence and severity of the disease in the early diagnosis of ACS patients. Of the cardiac markers examined at the time of admission, Troponin I was positivity in 9 patients, but H-FABP was positivity in 30 patients. Initially H-FABP had higher sensitivity and specificity than troponin.

There was no statistically significant relationship between risk scores in both groups when we classified the patients according to whether H-FABP was positive or negative. Although Grace risk score and Gensini risk score were higher in H-FABP positive group; Syntax risk score was higher in H-FABP negative patient group. Risk scores were developed in early diagnosis and prognosis in patients. In our study, we have showed statistically significant correlations both H-FABP, Troponin I values at the 6th hour and GRACE, GENSINI risk scores. As a result of the studies in the literature, the use of GRACE risk score has become widespread.[23] Because of the inadequacy of a thick plate with axial lesions in ACS patients, as a result other stenosis scoring was needed. For example, GENSINI score was found to be associated with the major cardiac event (MKO) in

the long and short term.[24] Our study shows that H-FABP may be associated with major cardiac events. Cakar et al. showed a statistically significant relationship between the GENSINI and GRACE risk scores in ACS patients.[25] In our study, we found a significant relationship between GRACE risk score and GENSINI score (Table 4).

As a result of our study, we found the sensitivity of H-FABP as 82.7% and the specificity as 83.3% on admission. When we look at data at the 6th hour, we found the sensitivity of H-FABP as 78.6% and the specificity as 100.0%.

H-FABP was found to most sensitive cardiac marker than CKMB and cTnI at the admission to hospital. Specificity of H-FABP as 100.0% and specificity of 100.0% were found at the 6-hour, likewise Tp-I. Umut Cavus et al.[26] they found the specificity of H-FABP as 88.5% at the 4th hour. In the multicentered study of Valle et al.[27] the sensitivity and the specificity of H-FABP were found 44% and 94%, respectively. In the study of Kenji Inoue et al.[28] the sensitivity of H-FABP was 78.5% and specificity was 78.2% in patients with ACS in the emergency department. In the study conducted by Ruzgar et al.[29] the specificity of H-FABP as 95.2%, 91% and 27.3%, respectively in ACS patients. Priya Gururajan et al.[30] reported that the sensitivity and specificity of H-FABP as 87% and 93%, respectively in ACS patients. The sensitivity of H-FABP was correlated or higher than many studies. Sensitivity and specificity of H-FABP can vary according to the onset of symptoms in ACS patients as shown in the literature.

In conclusion, our study demonstrates that the H-FABP has significant value for assessment of severity, precense and early diagnosis of coronary artery disease in patients with ACS. In addition, we showed that a significant relationship between H-FABP and GRACE risk score at admission may be significant in predicting patient prognosis.

Ethics Committee Approval: Our study was approved by the Çanakkale Onsekiz Mart University Ethics Committee (Date: 05/08/2015, Decision no: 2015/13).

Conflict of Interest: No conflict of interest was declared by the authors.

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Table 1. Clinical characteristics of patients.

Baseline characteristics	All patients (n=110)	STEMI (n=52)	NSTE-ACS (n=58)	p
Male, n(%)	86 (%78.2)	44 (%84.6)	42 (%72.4)	0.122
Female, n(%)	24 (%21.8)	8 (%15.4)	16 (%27.6)	
DM Presence, n(%)	21 (%19.1)	4 (%7.7)	17 (%29.3)	0.004
HT Presence, n(%)	44 (%40)	14 (%26.9)	30 (%51.7)	0.008
Tobacco use, n(%)	64 (%58.2)	32 (%61.5)	32 (%55.2)	0.499
Hyperlipidemia Presence, n(%)	52 (%47.3)	27 (%48.1)	25 (%46.6)	1.0
Family history, n(%)	29 (%26.4)	18 (%34.6)	11 (%19)	0.063
Body mass index, kg/m2, n(%)	30 (%27.3)	16 (%30.8)	14 (%24.1)	0.436

All values are presented number (%). Abbreviations: HT: hypertension; DM: diabetes mellitus

Table 2. Laboratory findings of patients.

	All patients	STEMI	NSTE-ACS	
	Mean± SD	**Mean± SD**	**Mean± SD**	**p**
Glucose mmol/L	154.02±74.28	149.98±74.59	157.64±74.46	0.886
Urea mmol/L	34.00±9.78	34.08±8.26	33.92±11.05	0.933
Creatinine mmol/L	0.83±0.17	0.83±0.16	0.83±0.18	1.0
Sodium	139.49±3.17	140.12±3.21	138.93±3.06	0.132
Potassium	4.26±0.51	4.20±0.58	4.32±0.44	0.21
Wbc x 10^9/mL	14.90±22.03	15.52±18.76	14.35±24.75	0.005
Hgb g/dL	14.28±1.79	14.59±1.66	14.01±1.88	0.108
Plt	239.46±66.29	243.36±58.99	235.97±72.54	0.56
Ldl mmol/L	132.79±35.23	133.90±37.44	131.73±33.34	0.756
Hdl mmol/L	44.05±11.88	44.53±11.72	43.60±12.13	0.695
Total-cholesterol mmol/L	190.84±41.98	194.00±39.09	187.93±44.65	0.468
Triglyceride mmol/L	159.35±98.43	149.98±90.27	168.17±105.66	0.272
Grace	109.10±23.32	109.96±22.41	108.32±24.28	0.551
Syntax	13.7±6.31	12.57±5.50	14.72±6.84	0.981
H-fabp	6166.46±5858.75	8822.16±6660.81	3783.59±3705.52	0.004
Gensini	51.99±30.40	56.74±30.69	47.74±29.77	0.024
TnI	1.6±1.9	1.11±1.47	2.03±2.27	0.008

All values are presented mean±standard deviation (SD). Abbreviations: HDL: high density lipoprotein; LDL: low density lipoprotein; Hb: Hemoglobin; Wbc: white blood cell; Plt: Platelets; Grace: Global Registry of Acute Coronary Events; Syntax: The synergy between percutaneous coronary intervention with taxus and cardiac surgery; H-fabp: Heart type fatty acid binding protein; TnI: Troponin I

Table 3. The sensitivity and specificity of the cardiac markers at the time of admission and 6th hour.

Admission time	Sensitivity	Specificity	PPV	NPV
TnI	%63.3	%100.0	%100.0	%25.0
H-FABP	%82.7	%83.3	%97.6	%37.0
6th hour				
TnI	%100.0	%100.0	%100.0	%100.0
H-FABP	%78.6	%100.0	%100.0	%36.4

Abbreviations: TnI: Troponin I; H-FABP: Heart type fatty acid binding protein; PPV: Positive Predictive Value; NPV: Negative Predictive Value

Table 4. The relationship between cardiac risk scores and H-FABP on admission and 6th hour.

Admission time	H-FABP +	H-FABP -	p
Grace risk score in hospital	199.66±33.91	183.89±43.96	0.056
Grace risk score 6 months term	160.86±29.62	154.00±29.68	0.199
Syntax score	13.61±6.31	14.02± 6.41	0.791
Gensini score	53.34±29.54	47.87±33.19	0.278
6th hour			
Grace risk score in hospital	203.74±32.85	177.24±40.08	0.003
Grace risk score 6 months term	164.27±29.48	147.27±26.84	0.009
Syntax score	13.66±6.09	13.83±6.90	0.984
Gensini score	57.0±131.48	40.29±24.36	0.011

Abbreviations: H-FABP: Heart type fatty acid binding protein

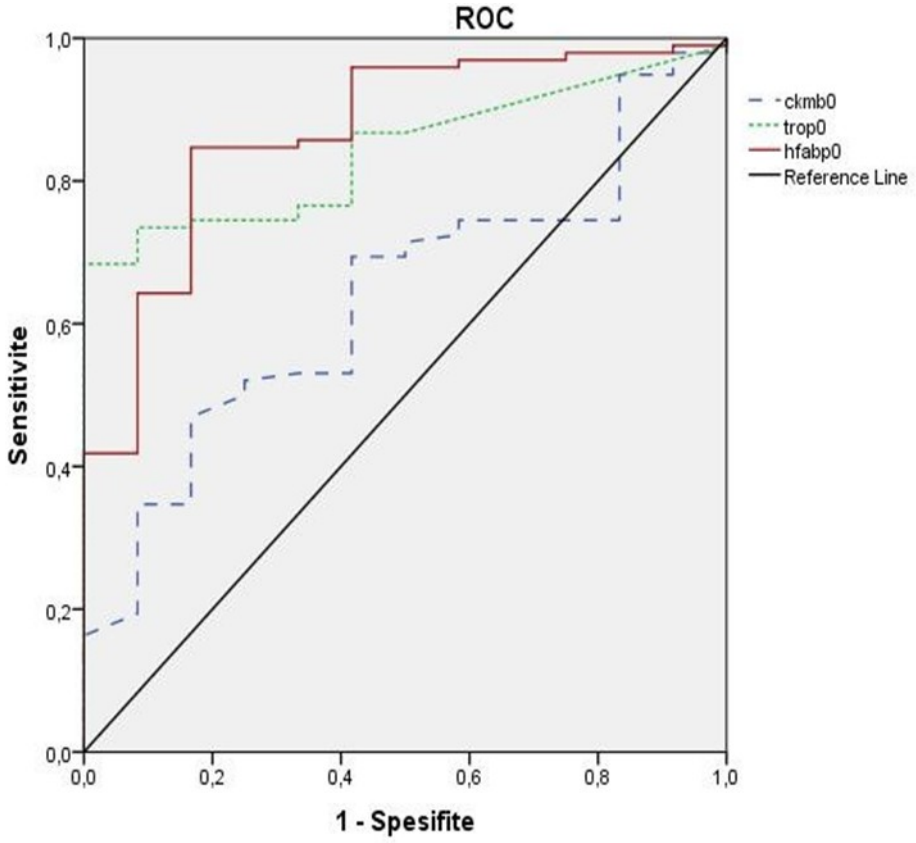

Figure 1. ROC curve analysis of H-FABP and troponin in the diagnosis of the acute coronary syndrome between 0-6 hours.