

Relationship between Heart-Type Fatty Acid-Binding Protein Levels and Severity and Extent of Coronary Atherosclerosis in Patients with Acute Myocardial Infarction

Togay Evrin¹ , Aycan Fahri Erkan² , Berkay Ekici² , Selda Demirtas³ , Sule Korkmaz⁴ , Atilla Korkmaz¹ , Eylem Kuday Kaykısız⁵ , Burak Katıpoğlu¹ 

¹Department of Emergency Medicine, Ufuk University School of Medicine, Ankara, Turkey

²Department of Cardiology, Ufuk University School of Medicine, Ankara, Turkey

³Department of Medical Biochemistry, Ufuk University School of Medicine, Ankara, Turkey

⁴Department of Cardiology, VKV American Hospital, Istanbul, Turkey

⁵Department of Emergency Medicine, Bitlis State Hospital, Bitlis, Turkey

Cite this article as: Evrin T, Erkan AF, Ekici B, Demirtas S, Korkmaz S, Korkmaz A, et al. Relationship between Heart-type Fatty Acid-Binding Protein Levels and Severity and Extent of Coronary Atherosclerosis in Patients with Acute Myocardial Infarction. Eurasian J Emerg Med. DOI: 10.5152/eajem.2018.62534.

Abstract

Aim: Heart-type fatty acid-binding protein (H-FABP) is an early marker of cardiac necrosis. It is rapidly released from the myocardium as a consequence of ischemic injury. We hypothesized that more severe and extensive coronary atherosclerosis results in more pronounced myocardial injury and necrosis in patients with acute myocardial infarction (AMI). Therefore, we aimed to analyze the relationship between serum H-FABP levels and the severity and extent of coronary artery disease (CAD) assessed using the Gensini score.

Materials and Methods: Fifty patients with AMI who underwent invasive coronary angiography were divided according to their angiographic Gensini score into two groups, namely, the mild CAD group (Group 1) and the moderate-to-severe CAD group (Group 2). A point-of-care test and CardioDetect Quant device were used for detecting whether H-FABP was positive and for quantitative measurements. Data obtained from this study were evaluated using the PASW statistic program.

Results: Mean serum H-FABP levels were significantly higher in Group 2 than in Group 1. Furthermore, a strongly positive correlation was found between the Gensini score and serum H-FABP levels.

Conclusions: The findings of our study suggest that the amount of myocardial necrosis, demonstrated by serum H-FABP levels, is higher in patients with AMI with more severe and extensive CAD. H-FABP levels are also positively correlated with the Gensini score. We propose that H-FABP also provides a clue about the severity and extent of CAD, particularly in the setting of AMI.

Keywords: Myocardial infarction, coronary artery disease, Gensini score, heart-type fatty acid-binding protein

Introduction

Cardiovascular diseases have become a major cause of mortality and morbidity worldwide (1). Acute coronary syndrome (ACS), usually formed by rupture of the atherosclerotic plaque in the coronary arteries or total occlusion of the coronary artery, Subtotal thrombus clinical emergency that occur as a result of table (2-4). Early diagnosis of patients is very important for directing their treatment. Early diagnosis and timely treatment positively affect mortality and morbidity and facilitate easy control of complications that may occur during

the follow-up of the disease (5, 6). Evidence shows that inflammation plays an important role in the onset and progression of atherosclerosis; all of these suggest that inflammation markers help in predicting individual risk for cardiovascular disease (7). These risk factors may explain only half of all cases of coronary artery disease (CAD) and long-term cardiac death and complications. This inadequacy has sparked an intense interest in identification of new biomarkers that can contribute to the prediction power of classical risk factors (8). A marker of acute myocardial infarction (AMI) or AMI-induced sarco-dermal injury cardiac fatty acid-binding protein (heart-type fatty ac-

ORCID IDs of the authors: T.E. 0000-0002-8306-4303; A.F.E 0000-0002-9469-7149; B.E. 0000-0001-6135-2972; S.D. 0000-0001-9534-4612; Ş.K. 0000-0003-4354-844X; A.K. 0000-0003-0762-5559; E.K.K. 0000-0002-4699-4691; B.K. 0000-0002-7945-9273.



Corresponding Author: Eylem Kuday Kaykısız e-mail: eylemkuday@hotmail.com

Received: 27.02.2018 • **Accepted:** 16.05.2018 • **Available Online Date:** 13.11.2018

©Copyright 2018 by Emergency Physicians Association of Turkey - Available online at www.eajem.com

DOI: 10.5152/eajem.2018.62534

id-binding protein (H-FABP) begins to increase within 1-3 h, reaches the highest level within 6-8 h, and returns to normal levels within 24-36 h. These plasma kinetics, oscillation properties, and various clinical studies have shown that the performance of H-FABP is superior to myoglobin, creatine kinase (CK), creatine kinase myocardial isoband (CK-MB), and troponin in early diagnosis of AMI (9-11). Gensini score is one of the several scoring systems based on coronary angiography images that have been developed to determine the severity of CAD. There are two coronary angiography scores: vascular and stenosis scoring. These techniques were described by Gensini. According to the angiographic degree of stenosis, narrowing in the range of 0 to 25%, 25 to 50%, 50 to 75%, 75 to 90%, 90 to 99% and 100%, stenosis is scored as 1, 2, 4, 8, 16, and 32 points, respectively (12). CAD is the most common cause of death in the United States. By reviewing the literature, we considered that H-FABP, an early-stage cardiac necrosis marker, is informative in terms of severity. In this study, we aimed to investigate the relationship between H-FABP levels and Gensini scores in patients with high cardiac troponin, CK, and CK-MB levels.

Materials and Methods

This study was initiated after obtaining the necessary permission from the local ethics committee of Ufuk University School of Medicine. A retrospective study on 735 patients who underwent coronary artery bypass grafting between Dec 5, 2008, and Feb 24, 2011, in the Emergency Department of Ege University was performed according to the guideline of the American Society of Cardiology (ACC/AHA) was performed. Patients with a history of cardiopulmonary resuscitation (CPR), fibrinolytic treatment, and percutaneous coronary intervention; who had stayed in coronary artery intensive care unit, those with trauma within 3 days before admission; with unstable angina pectoris according to ACC/AHA (USAP); with chronic renal failure and serum creatinine level of 1.5 mg/dL; who had undergone coronary intensive care unit through percutaneous transluminal coronary angioplasty (PTCA) or Coronary artery bypass grefting (CABG) within 1 month; who had ST-elevation myocardial infarction (STEMI) or non-ST-elevation myocardial infarction (NSTEMI) within 1 month before admission; with pulmonary thromboembolism; and aged <18 years were not included in this study (13, 14).

According to the guidelines of ACC/AHA, patients with ACS with ST segment elevation and non-ST segment elevation were included in the study. Patient information, including biochemical parameters, ECG information, admission details until the day they are discharged from the track at the highest cardiac necrosis marker (CK-MB, troponin T and H-FABP) levels, and CAD with coronary angiography Gensini scores by examining the scores of seriousness of the form of work have been recorded (13, 14). For measurement of H-FABP levels, a test based on the rapid chromatographic immunoassay method, termed CardioDetect Med, was used (Rennesens GmbH Berlin, Germany). Coronary angiographies were interpreted with the Gensini score for assessing CAD severity (15). Patients were considered to have mild coronary atherosclerosis if they had a Gensini score of 1-19 and severe coronary atherosclerosis if they had a Gensini score of 20 (16). Patients included in the study were divided into two groups: those with Gensini scores <20 (Group 1) and those with Gensini scores ≥20 (Group 2).

For comparison, the Kolmogorov-Smirnov test, which is a normal distribution test, was performed. The normal distribution variables were evaluated by independent sample t- test. Mann-Whitney U test was used for variables without normal distribution, and chi-square test was used for categorical variables. Relationships between Gensini scores and H-FABP, CK-MB, and troponin-T levels were investigated by Spearman correlation analysis. Data obtained in this study were evaluated using PASW statistical package program. A p<0.05 was considered to be statistically significant.

Statistical analysis

For comparison, the Kolmogorov-Smirnov test, which is a normal distribution test, was performed. The normal distribution variables were evaluated by independent sample t- test. Mann-Whitney U test was used for variables without normal distribution, and chi-square test was used for categorical variables. Relationships between Gensini scores and H-FABP, CK-MB, and troponin-T levels were investigated by Spearman correlation analysis. Data obtained in this study were evaluated using PASW statistical package program. A p<0.05 was considered to be statistically significant.

Results

According to the AHA, all 50 patients included in this study were diagnosed with AMI (13, 14). In our study, 16 (32%) patients had Gensini scores <20 (Group 1) and 34 patients (68%) had scores >20 (group 2). Of the total, 38 (76%) were male and 12 (24%) were female. The mean age of the included patients was 64.2±11.498 (min: 40; max: 87) years. There was no significant difference in the distribution of age and sex between the groups in our study (p>0.05). Of the total, 36 (72%) were diagnosed with NSTEMI and 14 (28%) were diagnosed with STEMI. Plasma FABP, CK-MB, and troponin-T levels for the groups are shown in Table 1.

According to the severity of CAD, there was a statistically significant difference between the FABP levels of patients in Group 2 and those of patients in Group 1 (p<0.05). According to the severity of CAD, there was no statistically significant difference between troponin-T levels of the patients in Group 2 and those of patients in Group 1 (p>0.05). There was no statistically significant difference between CK-MB levels of patients in Group 2 and those of patients in Group 1 (p>0.05). Correlation of plasma FABP, CK-MB, and troponin-T levels and Gensini scores of patients is shown in Tables 2-4. There was a

Table 1. Plasma H-FABP, CK-MB, and troponin-T levels according to groups

	Severity of Cad	n	Mean	Min	Max	Sig. two-tailed
H-FABP	<20	16	13.0313	7	23	0.000
	≥20	34	55.1471	13	100	
CK-MB	<20	16	66.4238	5.21	332.6	0.277
	≥20	34	102.065	6,52	503	
Troponin T	<20	16	2.0112	0.04	12.61	0.172
	≥20	34	3.8253	0.11	20.81	

H-FABP: heart-type fatty acid-binding protein; CK-MB: creatine kinase heart type

Table 2. The correlation between plasma H-FABP levels and Gensini scores

Spearman's rho	Correlation	Gensini
H-FABP	r	0.926
	p	0.000
	N	50

H-FABP: heart-type fatty acid-binding protein

Table 3. The correlation between plasma CK-MB levels and Gensini scores

Spearman's rho	Correlation	Gensini
CK-MB	r	0.195
	p	0.174
	N	50

CK-MB: creatine kinase heart type

Table 4. The correlation between plasma troponin-T levels and Gensini scores

Spearman's rho	Correlation	Gensini
Troponin-T	r	0.142
	p	0.325
	N	50

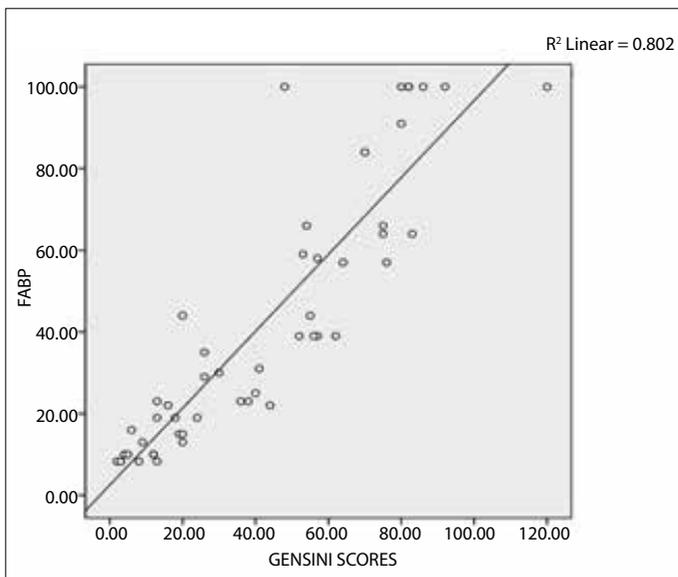


Figure 1. Correlation graph of plasma FABP levels and Gensini scores of patients

statistically significant positive correlation between FABP levels of all patients with ACS who were included in the study and their Gensini scores calculated after coronary angiography ($p < 0.005$). The correlation graph of plasma FABP levels and Gensini scores of the patients, of plasma CK-MB levels and Gensini scores of patients, and of plasma troponin-T levels and Gensini scores of patients is shown in Figure 1, Figure 2, and Figure 3, respectively.

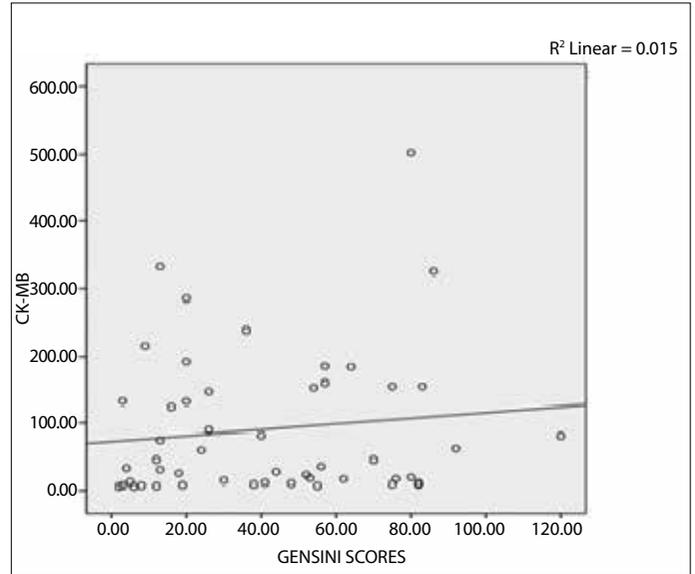


Figure 2. Correlation graph of plasma CK-MB levels and Gensini scores of patients

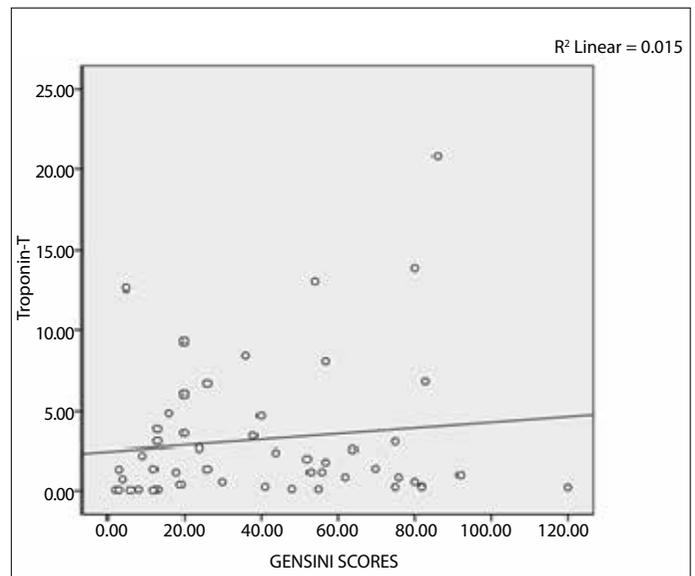


Figure 3. Correlation graph of plasma troponin-T levels and Gensini scores of patients

Discussion

Heart-type fatty acid-binding protein, an indicator of AMI-associated sarcolemmal injury, increases in 1-3 h of AMI, reaches the highest level within 6-8 h, and returns to normal levels within 24-36 h (9). Although the relationship between plasma H-FABP levels and the severity of CAD is unclear, it is known that H-FABP is an important cardiac marker for ACS with plasma kinetics and with its release characteristics. No study in the literature has yet shown a relationship between the severity of CAD and the serum H-FABP, CK-MB, and troponin-T levels in patients with ACS and positive cardiac necrosis markers. However, there are studies investigating the relationship between serum H-FABP levels and prognosis in patients with ACS (17-21). In addition, there was no study in the literature regarding the correla-

tion between serum H-FABP, CK-MB, and troponin-T levels and Gensini scores in patients with ACS and positive cardiac necrosis markers.

In a study conducted by O'Donoghue et al. (18), patients diagnosed with ACS were separated into two groups, those with serum H-FABP levels of ≥ 8 ng/dL (n=332) and those with serum H-FABP levels of < 8 ng/dL (n=1955) and monitored for 10 months. There was a statistically significant difference between these two groups in terms of development of major cardiac events (cardiac death, MI and CHF within these 10 months ($p < 0.001$) (18).

In the same study, patients diagnosed with ACS were separated in groups, i.e., those with serum H-FABP levels of > 16 ng/dL (n=166), those with serum H-FABP levels between 8 and 16 ng/dL (n=166), and those with serum H-FABP levels of < 8 ng/dl (n=1955) and monitored for 10 months. There was a statistically significant difference ($p < 0.001$) in the group with serum H-FABP levels of > 16 ng/dl in terms of developing cardiac-induced death, subsequent MI transmission, and CHF development within 10 months compared with the other groups (18).

According to the retrospective study performed by Suzuki et al. (19), 90 patients with ACS were qualitatively divided into two groups as H-FABP positive (n=56) and negative (n=34), and a statistically significant difference was found by the Cox proportional risk method for developing MI and de-compensated CHF and subsequent MI ($p < 0.005$).

According to the prospective study performed by Mc Cann et al. (20), patients admitted to the coronary intensive care unit with ischemic chest pain (n=664) were followed up for 1 year. They were separated into two groups: those who experienced one cardiac event and those who experienced no cardiac event. There was a statistically significant difference between H-FABP and troponin-T levels among these groups ($p < 0.001$ and $p < 0.001$, respectively).

According to a prospective study conducted by Viswanathan et al. (21), 955 patients with suspected ACS, who were referred to emergency services, were followed up for 48 weeks. Patients were divided into four groups according to serum H-FABP levels: serum H-FABP levels of < 3.27 ng/dL (Group I), serum H-FABP levels of 3.27-6.48 ng/dL (Group II), serum H-FABP levels of 6.49-12.77 ng/dL (Group III) and serum H-FABP levels of > 12.77 ng (Group IV). There was a statistically significant difference among Groups I, III, and IV based on the number of patients who had cardiac death and MI after 48 weeks ($p < 0.0001$, $p < 0.0001$). There was also a statistically significant difference between Group IV and the other groups based on whether patients had a history of CAD ($p < 0.001$) (21). This shows us that the CAD story of the patients is a significant risk factor for evaluating the prognosis of CAD, similar to that observed in our study.

In the same study, patients with positive troponin-T levels were excluded, and the remaining 756 patients were re-divided into four groups according to serum H-FABP levels. There was a statistically significant difference between Group III and Group I and between Group IV and Group I according to the number of patients who had cardiac death and MI at 48 weeks ($p < 0.0001$ and $p < 0.0001$, respectively) (21). In the same study, 955 patients with suspected ACS who

were admitted to emergency services were followed up for 48 weeks. In addition, patients were divided into four groups according to serum troponin-T levels: Group I, between 0.00 and 0.02 $\mu\text{g/L}$; Group II, between 0.03 and 0.08 $\mu\text{g/L}$; Group III, between 0.09 and 3.04 $\mu\text{g/L}$; and Group IV, > 3.04 $\mu\text{g/L}$. Similarly, there was a statistically significant difference between Group III and Group I and between Group IV and Group I according to the number of patients who had cardiac death and MI at 48 weeks ($p < 0.0001$ and $p < 0.0001$, respectively) (21). These studies conducted by Viswanathan et al. (21) indicate that H-FABP is a prognostic serum biomarker, independent of troponin-T, while emphasizing that serum H-FABP and troponin-T levels are important for assessing long-term mortality in CAD (21).

Ishii et al. (22) reported that patients who were admitted to the hospital with a diagnosis of ACS (n=328) were divided into two groups: Group I with H-FABP > 9.8 $\mu\text{g/L}$ and Group II with H-FABP < 9.8 $\mu\text{g/L}$. These patients were followed up for 6 months. At 6 months, there was a statistically significant difference between the group with cardiac mortality H-FABP level > 9.8 $\mu\text{g/L}$ and the other group ($p < 0.0001$) (22). In the same study, it was determined that there was a statistically significant difference in cardiac-induced mortality after 6 months ($p < 0.0001$) between patients with elevated troponin-T and H-FABP levels and those with elevated troponin-T levels alone (22).

In our study, there was a numerical difference between the mean troponin-T levels of the patient group with high CAD severity (Group 2) and of those with low CAD severity (Group 1) (Group 1=2.011 ng/mL; Group 2=3.825 ng/mL). However, there was no statistically significant difference between these two groups ($p > 0.005$). It is known that troponin-T can assess long-term mortality in patients with CAD according to literature but our study is statistically incompatible with the literature most probably related to the low number of patients in group 1.

Although H-FABP is an important cardiac marker for ACS with this plasma kinetics and oscillation feature, it is also a new cardiac marker for evaluating long-term mortality and prognosis of patients with ACS. There is a relationship between H-FABP levels and CAD severity according to data obtained from our studies and from literature.

Study limitations

The most significant limitation of our study is our small sample size. It is necessary to support our findings with larger scale, prospective, and multicenter studies.

Conclusion

There is a need for a noninvasive and easily reproducible technique that meets the clinical need for determining the severity of CAD and its early prognosis. In our study, serum H-FABP levels were significantly higher in patients with high CAD severity (Group II) than in those with low CAD severity (Group I). It was also determined that there was a significant positive correlation between Gensini score and serum H-FABP levels in all patients with positive cardiac necrosis markers. There is a relationship between H-FABP levels and CAD severity, which suggests that H-FABP can provide information about the severity of CAD even in the early period of cardiac damage. In conclusion, relevant studies that use serum H-FABP levels as a predic-

tor of cardiovascular risk require more extensive, prospective studies to diagnose patients with ACS, to determine the need for intervention, and to predict the severity of CAD.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ufuk University School of Medicine (Approval No.: 15062012-5).

Informed Consent: Informed consent was not taken from patients due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - T.E., A.F.E.; Design - B.E., S.D.; Supervision - S.K., A.T.; Resources - E.K.K., B.K.; Materials - T.E., A.F.E.; Data Collection and/or Processing - B.E., S.D.; Analysis and/or Interpretation - S.K., A.T.; Literature Search - E.K.K., B.K.; Writing Manuscript - T.E.; Critical Review - T.E., A.F.E., E.K.K., B.K.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

References

- Hennekens CH. Increasing burden of cardiovascular disease. Current knowledge and future firections for research on risc factors. *Circulation*. 1998; 97:1095-102.
- Falk E, Shah PK, Fuster V. Coronary plaque distrupction. *Circulation*. 1995; 92: 657-71.
- Mann JM, Davies MJ, Vulnerable plaque. Relation of characteristics to degree of stenosis in human coronary arteries. *Circulation*. 1996; 94: 928-31.
- Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and acute coronary syndromes. *N Engl J Med*. 1992; 326: 242-50.
- Solinas L, Raucci R, Terrazzino S, Moscariello F, Pertoldi F, Vajto S, et al. Prevalence, clinical characteristics,resource utilization and outcome of patients with acute chest pain in theemergency department. A multi-center, prospective, observational study innorth-eastern Italy. *Ital Heart J*. 2003; 4: 318-24.
- Karlson BW, Wiklund I, Bengston A, Herlitz J. Prognosis and symptoms one year after discharge from the emergency department in patients with acute chest pain. *Chest*. 1994; 105: 1442-7.
- Kelly AE, Gensini GG. Coronary arteriography and left-heart studies. *Heart Lung*. 1975; 4: 85-98.
- de Korte CL, van der Steen AF, Cepedes EI, Pasterkamp G, Carlier SG, Mastik F, et al. Characterization of plaque components and vulnerability with intravascular ultrasound elastography. *Phys Med Biol*. 2000; 45: 1465-75.
- Li-Qian Xu, Yun-Mei Yang, Hong Tong, Chang-Fu Xu. Early Diagnostic Performance of Heart-Type Fatty Acid Binding Protein in Suspected Acute-Myocardial Infarction: Evidence From a Meta-Analysis of Contemporary Studies. *Heart Lung Circ*. 2018; 27: 503-12.
- Mad P, Domanovits H, Fazelnia C, Stiassny K, Russmüller G, Cseh A, et al. Human heart-type fatty-acid-binding protein as a point-of-care test in the early diagnosis of acute myocardial infarction. *QJM*. 2007; 100: 203-10.
- Bruins Slot MH, van der Heijden GJ, Rutten FH, van der Spoel OP, Mast EG, Bredero AC, et al. Heart-type Fatty acid-binding protein in Acute Myocardial infarction Evaluation (FAME): background and design of a diagnostic study in primary care. *BMC Cardiovasc Disord*. 2008; 8: 8.
- Icli A, Gok H, Altunkeser BB, Ozdemir K, Gurbilek M, Gederet YT, et al. Evaluation of "admission index of insulin resistance (AIRI)" as an early stage risk predictor in nondiabetic acute coronary syndromes. *Anadolu Kardiyol Derg*. 2002; 2: 194-201.
- Glenn N. Levine, Eric R. Bates, James C. Blankenship, Steven R. Bailey et al. 2015 ACC/AHA/SCAI Focused Update on Primary Percutaneous Coronary Intervention for Patients With ST-Elevation Myocardial Infarction. *J Am Coll Cardiol*. 2016; 67: 1235-50.
- Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the Management of Acute Myocardial Infarction in Patients Presenting With ST-Segment Elevation: The Task Force for the Management of Acute Myocardial Infarction in Patients Presenting With ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2017; 39: 119-77.
- Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, et al. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014; 64: 139-228.
- Oishi Y, Wakatsuki T, Nishikado A, Oki T, Ito S. Circulating adhesion molecules and severity of coronary atherosclerosis. *Coron Artery Dis*. 2000; 11: 77-81.
- O'Donoghue M, de Lemos JA, Morrow DA, Murphy SA, Buros JL, Cannon CP, et al. Prognostic Utility of Heart- Type Fatty Acid Binding Protein in Patients with Acute Coronary Syndromes. *Circulation*. 2006; 114: 550-7.
- Suzuki M, Hori S, Noma S, and Kobayashi K. Prognostic Value of a Qualitative Test for Heart-Type Fatty Acid-Binding Protein in Patients with Acute Coronary SyndromeInt. *Heart J*. 2005; 46: 601-6.
- Mc Cann CJ, Glover BM, Menown IB, Moore MJ, McEneny J, Owens CG, et al. Prognostic value ofa multimarker approach for patients presenting to hospital with acute chest pain. *Am J Cardiol*. 2009; 103: 22-8.
- Viswanathan K, Kilcullen N, Morrell C, Thistlethwaite SJ, Sivananthan MU, Hassan TB, et al. Heart-Type Fatty Acid-Binding Protein Predict Long-Term Mortality and Re-Infarction in Consecutive Patients with Suspected Acute Coronary Syndrome Who Are Troponin-Negative. *J Am Coll Cardiol*. 2010; 55: 2590-8.
- Ishii J, Ozaki Y, Lu J, Kitagawa F, Kuno T, Nakano T, et al. Prognostic Value of Serum Concentration of Heart-Type Fatty Acid-Binding Protein Relative to Cardiac Troponin T on Admission in the Early Hours of Acute Coronary Syndrome. *Clin Chem*. 2005; 51: 1397-404.