Is There a Relationship Between Acute Coronary Syndrome and Prostate Specific Antigen Level?

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Purpose: Interestingly, prostate-specific antigen (PSA), which is used to monitor prostate disorders, has been suggested to be beneficial in estimating prognosis associated with coronary artery disease (CAD). The aim of the present study was to investigate the relationship of serum levels of PSA and free PSA (fPSA) with prognosis of acute coronary syndromes (ACS), extent of CAD and major adverse cardiac events in patients with acute coronary syndromes.

Materials and Methods: Sixty-seven male patients who were diagnosed with acute coronary syndromes were included. All patients were assessed according to the Thrombolysis in Myocardial Infarction (TIMI) classification [ST elevation myocardial infarction (STEMI) and non-ST elevation (NSTE)-ACS groups, separately], the Global Registry of Acute Cardiac Events (GRACE) (difference between PSA and fPSA) risk score and the Killip classification. All patients underwent angiography. The degree of stenosis was scored using the Gensini score to assess the extent of CAD.

Results: Serum PSA, fPSA, fPSA/PSA levels, and alpha 1-antichymotrypsin-PSA (ACT-PSA) (difference between PSA and fPSA) results were found to be moderately correlated with the TIMI and GRACE risk scores, which are predictors of short- and mid-term prognosis. While there was no correlation between the Gensini score and PSA and ACT-PSA, the Gensini score was moderately correlated with fPSA and fPSA/PSA. There were no significant differences between patients with major adverse cardiovascular events (MACEs) and those without MACEs at the 6-month follow-up in terms of PSA, fPSA, fPSA/PSA, and ACT-PSA results.

Conclusion: There may be a relationship between serum PSA and fPSA levels and prognosis of ACS and extent of CAD. It should be kept in mind that additional biomarkers could be used together with current scoring systems in risk classification in cases for which clinical decision-making is challenging. Moreover, PSA and fPSA results should be approached with caution in patients to be screened for prostate cancer as their serum levels may be influenced from several factors (ACS, infection, etc.).

Keywords: acute coronary syndrome; predictive value of tests; male; prostate-specific antigen; blood.

INTRODUCTION

Ischemic heart disease is the leading cause of mortality and morbidity in adults worldwide. Although coronary atherosclerosis mostly results in chronic coronary artery disease (CAD), obstructive lesions in the coronary vessels, plaque erosion and rupture, and atherosclerotic plaques may also lead to acute myocardial ischemia. Rapidly progressing ischemic lesions threatening myocardial tissue are currently defined as acute coronary syndrome (ACS). ACS is mainly classified in the following three groups: 1) ST elevation myocardial infarction (STEMI), troponin-positive, 2) non-ST elevation myocardial infarction (NSTEMI), troponin-positive, 3) unstable angina pectoris (UAP), non-ST elevation, troponin-negative; the latter two being also named as NSTE-ACS. Every year, more than one million people suffer from acute myocardial infarction (MI) in the USA. Registry data consistently show that NSTE-ACS is more frequent than STE-ACS. The annual incidence is 3 per 1000 inhabitants, but varies between countries.[1] Although there has been a reduction in mortality due to the increase in the number of coronary intensive care units and advances in fibrinolytic and catheter-based reperfusion treatments, overall mortality rate associated with acute MI including deaths before admission to hospital is greater than 30%.[2]

Although several markers have been identified in order to predict mortality, determine prognosis, and demonstrate the extent of CAD in ACS, novel markers are still being investigated. Recent case reports have suggested that there might be an association between prostate-specific antigen (PSA) and CAD and that this marker may be helpful in predicting prognosis. Being responsible for the liquefaction of semen, PSA is a 33000 Da single chain glycoprotein comprised of 237 amino acids and 4 carbohydrate side chains. The gene encoding the PSA molecule is located on the 19th chromosome. Based on gene location, and amino acid composition and function, PSA is identified as a member of the human kallikrein (hK3) family of the serine proteases.[3] Inactive form of PSA, pro-PSA, is rapidly converted to active PSA by hK2; hK2 also activates single-chain urokinase-type plasminogen activator and plasminogen activator inhibitor-1 (PAI-1).

PSA induces apoptosis and inhibits negative growth factor and angiogenesis. PSA increases the release of insulin like growth factor-1 (IGF-1), which has been shown to increase all-cause mortality and risk of development of heart failure, by binding to insulin-like growth factor binding protein-3. It has been determined that PSA exhibits antiangiogenic activity through inhibition of endothelial cell proliferation induced by fibroblast growth factor–2 and vascular endothelial growth factor.[4] It has also been shown that PSA levels are reduced by statin treatment and PSA production is regulated by angiotensin receptor blockers through a peroxisome proliferator-activated receptor gamma like effect.[5] PSA levels have been demonstrated to be increased in cases of cardiogenic shock due to prolonged cardiopulmonary resuscitation, cardiac surgery, on-pump bypass, and acute MI.[6,7] In a controlled study, serum PSA and fPSA levels was found to be higher in patients after elective stent implantation compared to those who were not treated with stent implantation, whereas no significant difference was found between these groups in terms of fPSA/PSA ratio.[8] In a study comparing NSTE-ACS and control groups, no significant difference was found between these two groups in terms of PSA level. PSA was determined to be correlated with high-sensitivity C-reactive protein (hsCRP) and increased in heart failure in 14 days of follow-up. Although there have been no large randomized studies, it has been observed in several case reports that coronary lesions is more common, extensive and severe and that major adverse cardiac events (MACEs) is more frequent within the initial 8 days after acute MI in cases with elevated PSA. These reports have suggested that large randomized studies were needed to confirm this association.[9-11]

The aim of the present study is to investigate the relationship of serum PSA, fPSA, complex PSA (ACT-PSA; difference between PSA and fPSA) levels and fPSA/PSA ratio with prognosis of ACS, extent of CAD, development of arrhythmias, troponin and hsCRP levels, and MACEs (death, MI, reinfarction, re-revascularization, hospitalization, stroke).

MATERIALS AND METHODS

Sixty-seven male patients who were hospitalized in the Coronary Intensive Care Unit with the diagnosis of ACS between November 2009 and April 2010 were included in this prospective study. Patients with a history of Lower Urinary Tract Symptoms (LUTS), prostate cancer and benign prostatic hy-

Table 1. Baseline clinical, laboratory, and procedural characteristics of the patients.

Characteristics	Study Patients (n=67)
Age (years)	58.4 ± 11.4
BMI (kg/m2)	27.34 ± 2.7
Time before hospital admission (hours)	6.4 ± 5.1
DM (%)	16.4
HT (%)	41.8
Smoking (%)	67.2
Family history (%)	9
Functional capacity (NYHA class) (%)	
I	68.6
II	23.9
III	7.5
IV	0
STEMI (%)	47.7
NSTEMI (%)	46.3
UAP (%)	6
LVEF (%)	47.8 ± 11.2
Heart rate (beats/min)	77.9 ± 18
Systolic BP (mmHg)	129.25 ± 22.6
Diastolic BP (mmHg)	77.08 ± 12.4
Total cholesterol (mg/dL)	190.08 ± 35.94
Triglyceride (mg/dL)	179.08 ± 122.45
LDL (mg/dL)	117.9 ± 36.01
HDL (mg/dL)	36.18 ± 9.33
Peak troponin I (ng/mL)	2.16 ± 27.9
Peak CK-MB (ng/mL)	71.59 ± 100.9
hsCRP (mg/L)	6.6 ± 7.1
TIMI Risk Score	3.3 ± 1.9
GRACE Risk Score (inhospital)	119 ± 26.2
GRACE Risk Score (6 months)	100 ± 29.1
Gensini score	61.2 ± 46.4
PSA (0-4 ng/mL)	1.1 ± 0.9
fPSA (0-3.7 ng/mL)	0.49 ± 0.55
PSA- fPSA	0.61±0.65
fPSA/PSA ratio	0.46 ± 0.23
Percutaneous coronary intervention (%)	67.16
Fibrinolytic treatment (%)	17.9
Infarction releated artery (%)	
LAD	37.3
RCA	38.8
LCx	23.9

key: BMI, body mass index; DM, diabetes mellitus, HT, hypertension, NYHA, New York Heart Association; STEMI, ST elevation myocardial infarction; NSTEMI, Non-ST elevation myocardial infarction; UAP, unstable angina pektoris; LVEF, left ventricular ejection fraction; BP, blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CK, creatinine kinase; hsCRP, high sensitivity C-reactive protein; TIMI, Thrombolysis in Myocardial Infarction; PSA, prostate-specific antigen; fPSA, free prostate-specific antigen; LAD, left anterior descending artery; RCA, right coronary artery, LCx, circumflex coronary artery.

Table 2. PSA, fPSA, fPSA/PSA and PSA- fPSA results and their correlation with the TIMI and GRACE risk scores.

	TIMI risk score		GRACE Score inhospital period		GRACE score at 6-month follow-up	
	r	*p*	*r*	*P*	*r*	*p*
PSA	0.30	.01	0.08	.50	0.17	.15
fPSA	0.41	.001	0.23	.05	0.31	.01
fPSA/PSA	-0.25	.04	-0.23	.05	-0.26	.03
PSA-fPSA	0.08	.48	0.09	.46	0.04	.74

Key: TIMI, Thrombolysis in Myocardial Infarction; GRACE, Global Registry of Acute Cardiac Events; PSA, prostate-specific antigen; fPSA, free prostate-specific antigen.

perplasia (BPH), those who underwent urinary catheterization, those with a recent history of prostate biopsy, prostatitis or urinary tract infection, those who had a survival expectancy of less than one year due to non-cardiac pathologies, and those who did not provide informed consent were excluded. These were 30 patients.

Routine follow-up and treatment were performed on study patients in accordance with the recommendations in the current guidelines. Blood samples were obtained from all patients diagnosed with acute coronary syndromes on admission for routine laboratory investigations, creatinine kinase (CK)-MB, troponin I, and hsCRP levels in addition to serum PSA and fPSA levels. fPSA/PSA ratio and ACT-PSA levels were calculated. Information regarding risk factors including age, gender, type II diabetes mellitus, hypertension, hyperlipidemia, and smoking were recorded. All patients were assessed according to the Thrombolysis in Myocardial Infarction (TIMI) classification (STEMI and NSTE-ACS groups, separately), the Global Registry of Acute Cardiac Events (GRACE) risk score (during inpatient period and 6 months after discharge), and the Killip classification. Left ventricular ejection fraction (LVEF) was measured by transthoracic echocardiography (Vivid 3 pro, GE Vingmed, Milwaukee, WI, USA) using the modified biplane Simpson's method. ST-segment resolution (STR) was assessed by electrocardiography that was performed 60 min after the procedure; a STR of > 70% was defined as successful reperfusion. All patients underwent angiography. Coronary angiographies were performed by experienced cardiologists via femoral arterial route using standard techniques. Lesions were assessed from at least two angles and at end-diastolic phase. According to the recommendations of current guidelines, primary percutaneous coronary intervention (PCI), early invasive intervention, medical treatment, and bypass treatments were performed. Following the procedure, coronary angiographies of all patients were evaluated in order to assess the extent of CAD, and stenosis was scored using the Gensini score. [12] The degree of angiographic stenosis was scored between 1 and 32, this score was then multiplied by a factor defined for each main coronary artery and each segment, and finally summed up. MACEs (death, MI, re-revascularization, stroke) during inpatient period, one month and 6 months after discharge were recorded for all patients. Informed consent was obtained from all patients at the time of admission, and the study was approved by the Hospital Local Ethics Committee.

Measurement of Prostate-Specific Antigen

Blood samples for PSA and fPSA measurements were obtained from the antecubital veins of all patients in a single puncture before the procedure. Samples were immediately frozen in citrate tubes at -20°C, and measurements were performed by electrochemiluminescence immunoassay (ECLIA) method using Cobas 6000 device (Roche Diagnostic). fPSA/PSA ratio and ACT-PSA were calculated for all samples.

Statistical Analysis

The statistical package for the social science (SPSS Inc, Chicago, Illinois, USA) version 14.0. Numerical variables were expressed as mean ± standard deviation (SD), whereas categorical variables were expressed as percentage. Groups were compared using the Student's *t* test for normally distrib-

uted variables and using the Mann-Whitney *U* test for non-normally distributed variables. The Pearson correlation test was used for normally distributed variables, and the Spearman correlation test was used for non-normally distributed variables. A *P* value of < .05 was considered statistically significant.

RESULTS

Sixty-seven male patients with ACS were included in the present study. Their mean age was 58.4 ± 11.4 years (range, 29-86 years). Thirty-two patients had STEMI, 31 patients had NSTEMI, and four patients had UAP. Fibrinolytic treatment was administered in 18% of STEMI patients, and successful reperfusion was observed in half of these cases. Coronary angiography was performed in all patients, and revascularization through PCI was performed in 67% of the patients. Coronary arteries were noted to be normal in two patients. General features of the study patients are presented in (Table 1).

No significant difference was found between STEMI and NSTE-ACS groups in terms of PSA and fPSA levels, fPSA/PSA ratio and ACT-PSA (*P* = .58). Correlation analysis of PSA, fPSA, fPSA/PSA, and ACT-PSA with other laboratory and clinical variables revealed no significant correlation with LVEF, Killip class, peak CK-MB, peak troponin I, and hsCRP levels. However, moderate correlation was noted with the TIMI and GRACE risk scores, which are predictors of short- and mid-term prognosis (Table 2).

Correlation analysis between the Gensini score, which is an indicator of the extent of CAD, and PSA, fPSA, fPSA/PSA, and ACT-PSA revealed no significant correlation with PSA and ACT-PSA, whereas a moderate correlation was noted with fPSA and fPSA/PSA ratio (Table 3). Multivariate regression analysis between the Gensini score, which is an indicator of the extent of CAD, and PSA, fPSA, fPSA/PSA, and ACT-PSA revealed significant correlation with fPSA, fPSA/PSA (Table 4). During inpatient follow-up, atrial fibrillation was noted in 3%, atrioventricular complete block was noted in 1.5%, ventricular tachycardia in 4.5%, and MACEs (death in 2 patients, re-revascularization in 1 patient) was noted in 4.5% of the patients. At the 1-month follow-up, MI was noted in 4 (6%) patients and death was noted in 3 (4.5%) patients, which did not reach statistical significance. MACEs were noted in 23.5% of the patients at the 6-month follow-up. There were no significant differences between patients with MACEs and those without MACEs at the 6-month follow-up in terms of PSA, fPSA, fPSA/PSA, and ACT-PSA results (*P* = .60).

DISCUSSION

The relationship of serum PSA, fPSA, fPSA/PSA levels and ACT-PSA on admission and prognosis of ACS, extent of CAD, and other biomarkers in patients diagnosed with ACS was investigated in the present study. A significant moderate correlation was found with the TIMI and GRACE risk scores and the Gensini score was not found to be correlated with PSA and ACT-PSA; however, it was found to be significantly moderately correlated with fPSA and fPSA/PSA. Gensini score was found to be correlated with fPSA and fPSA/PSA by multivariate regression analysis. No significant difference was found between STEMI and NSTE-ACS groups in terms of PSA and fPSA levels, fPSA/PSA ratio and ACT-PSA.

Table 3. Correlation of PSA, fPSA, fPSA/PSA, and PSA-fPSA results with Gensini score.

	Gensini score	
Variables	***r***	***p***
PSA	0.10	.42
fPSA	0.35	.003
fPSA/PSA	-0.42	.001
PSA-fPSA	-0.18	.13

Key: PSA, prostate-specific antigen; fPSA, free prostate-specific antigen.

Table 4. Multivariate regression analysis for GENSINI score; including age, PSA, ACT-PSA, fPSA, fPSA/PSA.*

	Gensini Score	
Variables	**Coefficient β**	***p***
Age	0.051	> .05
PSA	0.082	> .05
ACT-PSA	0.056	> .05
fPSA	0.418	< .001
PSA/fPSA	0.483	< .001

* A *P* value < .05 was considered to be significant. F ratio = 41.2, r_2 = 0.776.

Key: PSA, prostate-specific antigen; fPSA, free prostate-specific antigen; ACT-PSA, alpha 1-antichymotrypsin-PSA.

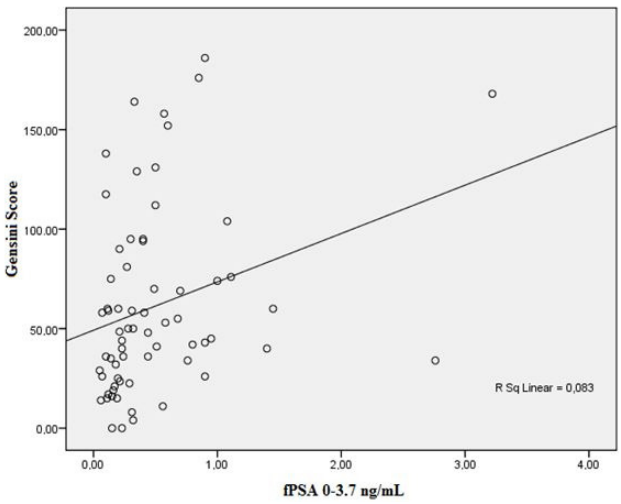

Figure 1. Correlation between Gensini score and free prostate-specific antigen (fPSA) ($r = 0.35$, $P = .003$).

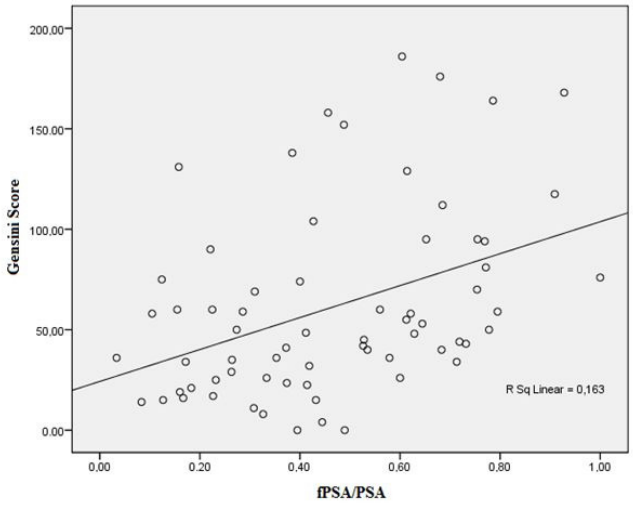

Figure 2. Correlation between Gensini score and fPSA/PSA ratio ($r = -0.42$, $P = .001$). PSA, prostate-specific antigen, fPSA, free prostate-specific antigen.

There were no significant differences between patients with MACEs and those without MACEs at the 6-month follow-up in terms of PSA, fPSA, fPSA/PSA, and ACT-PSA results.

Atherosclerosis and acute MI as its complication are still the leading cause of mortality and morbidity worldwide. Similar to atherosclerosis, prevalence of prostate cancer increases with age, and it is one of the most common cancers in males. Biochemical markers indicating myocardial damage in acute coronary syndromes patients play a vital role both in establishing diagnosis and in making treatment decisions. Cardiac troponins that are markers for myocardial necrosis are found to be elevated only in 1/3 of acute coronary syndromes patients and are associated with increased short-term mortality and nonfatal MI risk in these patients.[13] Although this risk is significantly lower in troponin-negative patients as compared to troponin-positive ones, a relatively high number of troponin-negative acute coronary syndromes makes risk assessment and treatment selection rather challenging. Thus, simultaneous measurement of several biomarkers defining different stages of acute coronary syndromes pathophysiology may enable a better risk assessment in patients with negative myocardial necrosis markers.[14] A sensitive and specific biomarker, which can indicate plaque instability and can be measured in systemic circulation independent from myocardial necrosis, can provide improvement in diagnosis and treatment decision-making. In this context, several novel biomarkers such as hsCRP, fibrinogen, PAI-1, pregnancy-associated plasma protein A (PAPP-A), and myeloperoxidase have been introduced, and some have indeed been implemented into clinical practice, whereas others remain at an experimental level.[15-17] Detection of unstable or potentially unstable coronary lesions, in which particularly early interventional and medical treatments provide considerable benefit, is an important clinical goal. It is clear that inflammatory markers have a significant role in the detection of these unstable lesions. It has been increasingly emphasized in recent years that inflammation, which is one of the most significant steps in the pathogenesis of atherosclerosis, has an important role in clinical diagnosis and treatment. The role of PSA also appears in this context. It has been suggested that PSA may assist in the diagnosis and treatment of acute coronary syndromes as acute phase reactants, which are markers of inflammation.

PSA is secreted into the lumen of the prostatic duct by exocytosis and transferred into the seminal fluid. The concentration of PSA is 0.5-2.0 g/L in semen.[18] Its concentration in the semen is approximately a million times of its concentration in the serum (0.1-4 ng/mL). PSA in serum is found predominantly in three distinct molecular forms: 1) free PSA (fPSA, molecular weight of 30 kDa), 2) alpha-2 macroglob-

ulin-bound PSA (A2M-PSA; molecular weight of 780 kDa) and 3) alpha 1-antichymotrypsin-PSA (ACT-PSA); molecular weight of 90 kDa). Malignant tissues such as adrenal neoplasms (neuroblastoma), renal cell carcinoma, and breast cancer can also synthesize PSA in low concentrations.[19,20] The mean half-life of total PSA (free + bound forms) is 2.6 days.[21] As fPSA has a relatively lower molecular weight, it can be eliminated through renal clearance. Having a half-life of 1.5 hours, fPSA constitutes 5% of serum PSA, and fPSA/PSA ratio reduces in patients with prostate cancer. Measurement of fPSA is used to increase sensitivity during screening for cancer in patients with normal total PSA levels and to increase specificity and reduce the number of unnecessary prostate biopsies in patients with high total PSA levels (> 4-10 ng/mL). Prostate manipulations (firm rectal examination), prostate biopsy, and urethral instrumentations lead to increase in fPSA component of total PSA. Therefore, any kind of manipulations should be avoided 48-72 hours before fPSA measurement. Impairment of normal structure of prostate, which enables the diffusion of PSA into the prostate tissue, leads to the elevation of serum PSA levels. Major causes of elevated PSA include BPH, prostate cancer, prostate inflammation or infection, and trauma to the prostatic or perineal region. Serum PSA level increases with age and accompanying increase in prostate volume. This is due to PSA-producing BPH tissue.[22] Significant portion of serum PSA is found as a complex with ACT. In patients with prostate cancer, ACT-PSA or complex PSA levels increases more than that in patients with BPH. ACT-PSA is directly associated with total PSA and calculated by subtracting fPSA from total PSA.[22-24]

Although it was shown in a study that PSA is correlated with hsCRP during a 14-day of follow-up and increased in heart failure,[25] in the present study, PSA, fPSA, ACT-PSA levels, and fPSA/PSA ratio was not found to be correlated with LVEF, Killip class, peak CK-MB, peak troponin I, and hsCRP levels. However, a significant moderate correlation was found with the TIMI and GRACE risk scores, which are predictors of short- and mid-term prognosis. In certain case reports, coronary lesions were reported to be more severe and extensive in cases with elevated PSA.[11,26] In the present study, the Gensini score, which is calculated from coronary angiography findings and is an indicator of the extent of CAD, was not found to be correlated with PSA and ACT-PSA; however, it was found to be significantly moderately correlated with fPSA and fPSA/PSA. Also Gensini score was found to be correlated with fPSA and fPSA/PSA by multivariate regression analysis with there was no difference in age. Due to low number of arrhythmias and MACEs occuring during hospitalization and one month after discharge, statistical analysis could not be performed. Furthermore, there were no significant differences between patients with MACEs and those without MACEs at the 6-month follow-up in terms of PSA, fPSA, fPSA/PSA, and ACT-PSA results.

Recent studies have suggested that there might be a relationship between cardiovascular disorders and PSA levels.[27] PSA levels have been demonstrated to be increased in cases of cardiogenic shock due to prolonged cardiopulmonary resuscitation, cardiac surgery, on-pump bypass, and acute MI.[7,27-30] Although the precise mechanism of increase in PSA levels in such conditions is unclear, it has been suggested that it might be caused by pelvic ischemia due to aortic clamp or cardiogenic shock. Therefore, PSA results should be interpreted with caution when screening for prostate cancer in patients who have sustained such events within previous weeks. Moreover, to our knowledge, there have been no previous randomized studies investigating the relationship between PSA and prognosis and the extent of CAD following acute coronary syndromes. Recently, several case reports suggested that coronary lesions was more common and extensive, presenting with more severe clinical manifestations and that number of MACEs within the 8 days following acute MI was higher in cases with elevated PSA.[10,26] However, it was also reported in these case reports that PSA level was low on the 1st and 3rd days, while it was high on the 2nd day. In the present study, we measured the PSA levels of the patients on admission. Monitorization of PSA levels with 12-hour intervals may be more valuable in detecting the significance of PSA in acute coronary syndromes. In another case report, a low PSA level was emphasized in a case of coronary spasm without a significant coronary stenosis.[28] In a controlled study, PSA and fPSA levels was found to be higher in patients following elective stent implantation compared to those who were not treated with stent implantation, while no significant differ-

ence was reported between these groups in terms of fPSA/PSA ratio.[8] In another controlled study comparing NSTE-ACS and control groups, no significant difference was found between PSA levels of these two groups.[31] Supporting some of the previous studies, we also found a significant moderate correlation of PSA and fPSA with acute coronary syndromes. Large, randomized controlled studies are needed to confirm this relationship.

CONCLUSION

In conclusion, PSA, fPSA and fPSA/PSA were found to be correlated with the TIMI and GRACE risk scores, which are prognosis markers in acute coronary syndromes, and the Gensini scores, which are markers for the extent of CAD, in the present study. Moreover, PSA and fPSA results should be approached with caution in patients to be screened for prostate cancer as their serum levels may be influenced from various other cardiovascular disorders commonly seen in the elderly population.

CONFLICT OF INTEREST

None declared.

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