Cardiovascular Topics

Correlation of osteopontin hormone with TIMI score and cardiac markers in patients with acute coronary syndrome presenting with chest pain

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Abstract

Aim: Rapid evaluation of patients with acute coronary syndrome (ACS) attending the emergency service under emergency room conditions and using appropriate risk scoring would improve treatment success. Calcium levels accumulate in the tissue in people with coronary artery disease and this has been found to correlate with osteopontin levels in some studies. It is predicted that osteopontin level could be used as a biomarker to detect coronary artery calcification. In this study, we aimed to evaluate the use of osteopontin levels in the differential diagnosis of ACS in conjunction with cardiac troponin I (cTnI) levels, and HEART (history, ECG, age, risk factors, troponin) and thrombolysis in myocardial infarction (TIMI) scores in patients with chest pain who attended the emergency service.

Methods: This study was conducted as a prospective observational clinical study in the Department of Emergency Medicine, Faculty of Medicine, Ataturk University. There was a total of 90 participants, including 60 patients and 30 healthy individuals in the control group. All participants' demographic information, electrocardiography (ECG) findings, cTnI level, TIMI and HEART score, and osteopontin level were evaluated.

Results: The patients' mean age was 51.61 ± 17.56 years and 63.3% (n = 57) were male. The body mass index (BMI) of the patients was 25.63 ± 4.67 kg/m^2. Patients with chest pain [CP(+)] and high cardiac troponin I levels [cTnI(+)] were found to be older and to have higher HEART and TIMI scores than individuals with CP(+) and normal cardiac troponin I levels [cTnI(–)] and the healthy control group (p < 0.001). While the HEART score was zero in 22 (24.4%) of the patients, the TIMI score was zero in 42 (46.7%). In terms of gender distribution, vital signs and serum osteopontin levels, there was no significant difference between the patient groups (p > 0.05).

It was found that patients with CP(+) and cTnI(+) had a higher rate of ECG abnormalities than the CP(+) and cTnI (–) group and the healthy control group (p = 0.13 and p < 0.001, respectively). In 65 (72.2%) of the patients, the ECG results were normal. ST-segment elevation was detected in 13 (14.4%) patients. In our study, cTnI levels were found to be positively correlated with age (r = 0.624), BMI (r = 0.291), HEART score (r = 0.794) and TIMI score (r = 0.805) (p = 0.001, p = 0.005, p = 0.001 and p = 0.001, respectively). In our study, we discovered that osteopontin levels could not reach the differential diagnostic level for ST-elevation myocardial infarction or non-ST-elevation myocardial infarction. No statistically significant difference was found in osteopontin levels between the groups (p > 0.05).

Conclusion: While very positive results were obtained in this approach to the ACS diagnosis using HEART and TIMI scores in patients with chest pain who attended the emergency service and were diagnosed with ACS, no significant results could be obtained regarding the use of osteopontin levels as a biomarker. More comprehensive, multicentre studies involving a large number of appropriately selected patients are considered to be necessary.

Keywords: acute coronary syndrome, cTnI, HEART, NSTEMI, osteopontin, STEMI, TIMI

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Cardiovascular disease (CVD) is one of the leading causes of morbidity and mortality worldwide.[1] Despite the rapidly developing treatment modalities and improved early revascularisation options, hospital re-admission, heart failure and death rates in patients with acute coronary syndrome (ACS) remain high.[2] The use of preventative and reducing treatment strategies in the early stages of ACS-related negative outcomes plays an important role in the prognosis of the disease.

Rapid evaluation of patients with ACS attending the emergency service under emergency room conditions using appropriate risk scoring would improve treatment success. Scores are used to exclude the diagnosis of ACS in patients with chest pain who attend the emergency service, as well as to aid in rapid triage.[3]

One of the scores used for this purpose is the thrombolysis in myocardial infarction (TIMI) score, which is a scheme that provides guidance for therapeutic decisions by categorising ischaemic events and risk of death in patients with unstable angina pectoris (USAP) and non-ST-segment elevation myocardial infarction (NSTEMI).[4] The HEART score (history, ECG, age, risk factors, troponin) has a wider range than other scores. The degree of risk is better classified using the HEART score during the initial evaluation in the emergency service, and clinical severity is determined.[5]

However, there are some limitations to both the applicability and reproducibility of risk-scoring applications in the emergency service. It is clear that sensitive new biomarkers are required, particularly for the early triage of patients who present to the emergency service with atypical chest pain but whose cardiac troponin I (cTnI) levels are normal at the time of admission.

Osteopontin is an extracellular matrix glycoprotein produced by osteoblasts and found in abundance in bone tissue. It was discovered in 1986 in osteoblasts and osteoclasts, and later, in many other cell types. Its biological functions are still being researched.

Osteopontin has important activations, particularly in diseases such as CVD, cancer, diabetes and urolithiasis, and in processes such as wound healing. Osteopontin levels in the healthy myocardium are quite low. Increased osteopontin levels in the myocardium, plasma, or both, were found in patients with atherosclerosis, valvular stenosis, ventricular hypertrophy, myocardial infarction, and both ischaemic and non-ischaemic heart failure.[6]

Osteopontin is strongly present in the atherosclerotic plaques that constitute the ACS pathogenesis. Furthermore, osteopontin interacts with integrins, which are involved in pathological processes such as macrophage chemotaxis and inflammation. In some studies, accumulated calcium levels in the tissue of people with coronary artery disease (CAD) have been found to correlate with osteopontin levels, and it is predicted that osteopontin can be used as a biomarker to detect coronary artery calcification.[7]

The role of osteopontin levels in risk-determination strategies for ACS patients has yet to be determined. Based on this, in this study, we aimed to evaluate the use of osteopontin levels in the differential diagnosis of ACS in conjunction with cTnI level, and HEART and TIMI scores in patients with chest pain who attended the emergency service.

Methods

This study was carried out as a prospective, observational, clinical study in the adult emergency department, Department of Emergency Medicine, Faculty of Medicine, Ataturk University. The study spanned six months, between 1 August 2020 and 31 January 2021. The study was approved by the Ataturk University Faculty of Medicine ethics committee (decision no: 41, date: 27.02.2020).

All patients with chest pain who attended the adult emergency service were informed about the study and if they agreed to participate, their consent was obtained. Patients with chronic renal failure (glomerular filtration rate < 30 ml/min), congenital heart disease and cardiogenic shock, known CAD, moderate-to-severe valve disease, cancer, atrial fibrillation, active infection, and those whose consent for the study could not be obtained were excluded from the study.

Our study included 30 people, in a healthy control group, with similar age and gender characteristics to the patient group. In the analysis, the clinical and laboratory findings of the patient and control groups were recorded and evaluated together.

Patients with chest pain who presented to the adult emergency service and were included in our study had their complaints evaluated by a paramedic working under the supervision of the emergency service's senior doctor. Their vital signs were checked and an electrocardiography (ECG) was performed within the first 10 minutes. The patients were taken to the appropriate examination area after the initial evaluation. The responsible doctor here requested a physical examination and the necessary tests, and treatment was initiated. Control ECGs were analysed, and risk scores for each patient were calculated. The HEART and TIMI scores of all patients included in the study, as well as the healthy control group, were calculated and recorded within the first few hours of their admission to the emergency service.

The following biochemical analyses were performed: complete blood count, fasting blood glucose, blood urea nitrogen (BUN), creatinine, serum sodium and potassium levels, high- and low-density lipoprotein cholesterol, total cholesterol and triglyceride levels, creatinine kinase isoenzyme MB and cTnI. All patients' estimated glomerular filtration rate was calculated using their age, gender, and BUN and creatinine values. The patients' 12-lead ECGs and telecardiograms were performed. In the case of abnormal findings, further examination and treatment was performed.

The HEART and TIMI scores were calculated using only the data collected at admission (Table 1). The TIMI score is a scoring table created by defining independent prognostic options with multivariate parameters and adding the number of available parameters, assigning one point when a factor exists and zero when no factor exists[8] (Table 2). In terms of risk classification, the HEART score had the following thresholds: for major

Table 1. HEART score

Elements	*Points*
History (anamnesis)	
Highly suspicious	2
Moderately suspicious	1
Slightly suspicious	0
ECG	
Significant ST-segment deviation	2
Non-specific repolarisation disturbance/LBBB/PM	1
Normal	0
Age (years)	
≥ 65	2
45–65	1
≤ 45	0
Risk factors*	
≥ 3 risk factors *or* history of atherosclerotic disease	2
1 or 2 risk factors	1
No risk factors known	0
Troponin	
≥ 3× normal limit	2
1–3× normal limit	1
≤ normal limit	0
Total	

*Risk factors for atherosclerotic disease: hypercholesterolemia, hypertension, diabetes mellitus, cigarette smoking, positive family history, obesity (BMI > 30 kg/m^2).
BBB: left bundle branch block; PM: pacemaker.

Table 2. TIMI score

Risk indicator	*Points*
History	
Age 75 years	3
Age 65–75 years	2
History of DM, HTN or angina	1
Examination	
SBP < 100 mmHg	3
Heart rate > 100 bpm	2
Killip class > 1	2
Weight < 67 kg	1
Presentation	
Anterior ST-segment elevation or LBBB	1
Time to reperfusion, therapy > 4 h	1
Total possible points	14

DM: diabetes mellitus, HTN: hypertansion; SBP: systolic blood pressure; LBBB: left bundle branch block.

adverse cardiac events (MACE), 0–3 points equalled low risk, 4–6 points equalled medium risk and 7–10 points equalled high risk. The TIMI score threshold was as follows: a TIMI score of zero was considered low risk. No further risk classification was performed in TIMI groups 1–7.

The human osteopontin ELISA kit was used to measure the concentration of osteopontin in serum samples (cat no: E1435Hu, BT lab). The experimental protocol was created in accordance with the manufacturer's instructions, using the reactive solutions provided in the kit and following the instructions and explanations in the measurement procedure booklet.

Statistical analysis

In the analysis of the variables, the SPSS 25.0 (IBM Corporation, Armonk, New York, United States) program was used. The conformity of the data for normal distribution was evaluated with the Shapiro–Wilk–Francia test, while the homogeneity of variance was evaluated with the Levene test. In order to compare groups based on age, one of the parametric tests, the one-way ANOVA test (robust test: Brown–Forsythe) was used, while the Tukey HSD test was used for *post hoc* analysis. One of the non-parametric methods, the Kruskal–Wallis *H*-test, was used in conjunction with the Monte Carlo results to compare other quantitative variables according to groups, and Dunn's test was used for *post hoc* analyses.

The Spearman correlation test was used to examine the correlation between troponin and osteopontin variables, and other variables. While Pearson's chi-squared test was used to compare the groups based on gender, the ECG findings were compared using Fisher–Freeman–Halton tests and the Monte Carlo simulation technique. The column ratios were compared using Benjamini–Hochberg corrected *p*-value results.

In order to find and estimate the variable with the highest significance in the groups, supervised machine learning methods [logistic regression, discriminant analysis, support vector machine, random forest, K-nearest neighbour algorithm, simple (native) Bayes classification, C5 algorithm from decision trees, and neural network (multilayer perceptron-radial basis)] were used. The results of neural network (multilayer perceptron) analysis, which was the most successful model, were used.

Gradient descent was used for the optimisation algorithm, sigmoid as the hidden layer activation function, and identity as the output layer activation function. The mini-batch method was used to select training data. The setting was 70% training and 30% testing. In the tables, quantitative variables are represented as mean (standard deviation) (minimum–maximum) and median (minimum–maximum), while categorical variables are represented as *n* (%). The variables were analysed at a 95% confidence level and a *p*-value less than 0.05 was considered significant.

Results

Our study was conducted over six months between August 2020 and January 2021. Between these dates, 61 849 patients attended the emergency department of Ataturk University. Of these patients, 5 432 (8.78%) had chest pain. A total of 3 241 patients who attended did not agree to participate in the study. The vital signs of 507 of the patients were unstable. Following the application of the exclusion criteria, 90 subjects were evaluated,

Table 3. Demographics and laboratory results

	Total (n = *90*)	*CP(+), cTnI(+) = I* (n = *30*)	*CP(+), cTnI(−) = II* (n = *30*)	*CP(−), cTnI(−) = III* (n = *30*)	p-*value*	*Pairwise comparison*		
						I vs II	*I vs III*	*II vs III*
Gender, *n* (%)					0.606 *	ns	ns	ns
Female	33 (36.7)	9 (30.0)	11 (36.7)	13 (43.3)				
Male	57 (63.3)	21 (70.0)	19 (63.3)	17 (56.7)				
Age, mean (SD) (min–max)	51.61 (17.56) (20–90)	66.83 (12.47) (40–90)	50.57 (15.46) (23–81)	37.43 (10.16) (20–61)	< 0.001#	< 0.001	< 0.001	< 0.001
Height (m), median (min–max)	1.65 (1.5–1.9)	1.665 (1.5–1.85)	1.65 (1.5–1.83)	1.7 (1.5–1.9)	0.236†	ns	ns	ns
Weight (kg), median (min–max)	70 (50–110)	80 (60–90)	70 (50–110)	70 (50–90)	0.041†	0.396	0.042	0.999
BMI (kg/m^2), median (min–max)	24.89 (18.29–42.97)	26.67 (21.97–35.16)	24.83 (18.37–42.97)	22.35 (18.29–31.25)	0.001†	0.440	< 0.001	0.059
SBP (mmHg), median (min–max)	128 (77–194)	136 (90–194)	125.5 (98–182)	128 (77–187)	0.081†	ns	ns	ns
DBP (mmHg), median (min–max)	83 (34–120)	84 (50–120)	83.5 (55–98)	82 (34–117)	0.285†	ns	ns	ns
Heart rate (bpm), median (min–max)	74 (52–99)	74 (52–98)	74 (68–99)	74.5 (61–92)	0.836†	ns	ns	ns
Fever (°C), median (min–max)	36.6 (35.9–37.2)	36.6 (35.9–37.2)	36.4 (35.9–37.2)	36.7 (35.9–37.2)	0.180†	ns	ns	ns
cTnI (ng/ml), median (min–max)	6.05 (0.01–25271.2)	443.25 (12.1–25271.2)	4.6 (0.01–202.5)	2.25 (0.01–8.3)	< 0.001†	< 0.001	< 0.001	0.078
Osteopontin (ng/l), median (min–max)	5.31 (0.58–21.12)	5.355 (0.58–10)	5.325 (0.6–20.71)	5.215 (4.2–21.12)	0.839†	ns	ns	ns
Heart score, median (min–max)	3.5 (0–10)	7 (5–10)	3 (0–8)	0 (0–4)	< 0.001†	< 0.001	< 0.001	< 0.001
TIMI score, median (min–max)	1 (0–7)	3 (2–7)	1 (0–4)	0 (0–1)	< 0.001†	< 0.001	< 0.001	0.029

*Pearson's chi-squared test (Monte Carlo, exact), ‡Fisher–Freeman–Halton (Monte Carlo); *post hoc* test: Benjamini–Hochberg correction.
#One-way ANOVA (Robuts statistic: Brown–Forsythe); *post hoc* test: Tukey HSD. †Kruskal–Wallis test (Monte Carlo); *post hoc* test: Dunn's test.
SD: standard deviation, min: minimum, max: maximum, CP: chest pain, cTnI: cardiac troponin I, SBP: systolic blood pressure, DBP: diastolic blood pressure.

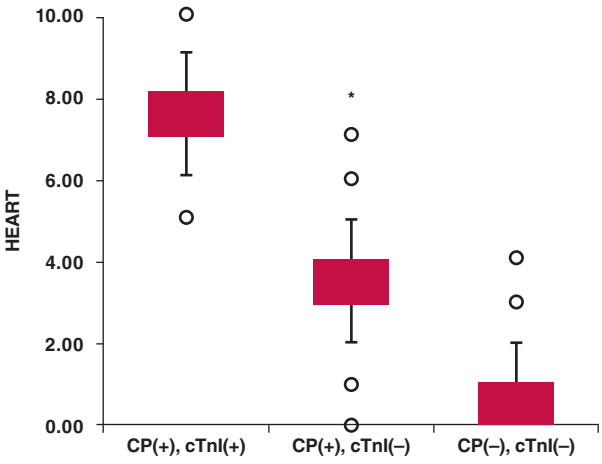

Fig. 1. HEART score results.

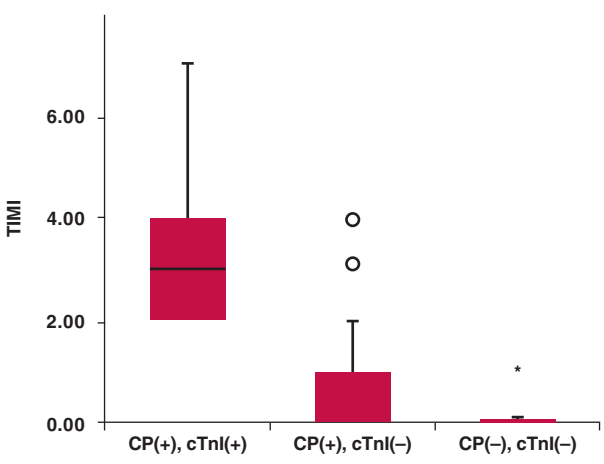

Fig. 2. TIMI score results.

including 60 patients and 30 healthy individuals in the control group.

The patients were divided into three groups. The first group consisted of patients positive for chest pain [CP(+)] and with high cTnI levels [cTnI(+)] (n = 30). The second group consisted of patients who were CP(+) and had normal cTnI levels (cTnI–) (n = 30). The third group was the healthy control group (n = 30) who were CP(–) and cTnI(–) (Table 3).

The patients' mean age was 51.61 ± 17.56 years and 63.3% (n = 57) were male. The body mass index (BMI) of the patients was 25.63 ± 4.67 kg/m^2. It was found that the CP(+) and cTnI(+) patients were older than the CP(+) and cTnI(–) patients and the healthy control group, and had higher HEART and TIMI scores (Table 3). The average values measured at the time of admission of the patients were calculated as follows: systolic blood pressure: 132.74 ± 22.73 mmHg, diastolic blood pressure: 83.52 ± 15.05 mmHg, heart rate: 77.4 ± 7.91 beats/min and body temperature 36.57 ± 0.4°C.

The distribution of patients enrolled in the study is shown based on the risk score they received during their first visit to the emergency service, from the five sub-parameters that comprise the HEART score (Fig. 1). Furthermore, the risk assessments of the patients based on the total score obtained from the seven sub-parameters that comprise the TIMI score are summarised in Table 3 and Fig. 2. While the HEART score was zero in 22 (24.4%) patients, the TIMI score was zero in 42 (46.7%) (Table 3).

In terms of gender distribution, vital signs and serum osteopontin levels, there was no significant difference between the patient groups (Table 3). It was found that the Cp(+) and cTnI(+) patients had higher BMI values than the individuals in the healthy control group. No significant difference was found between the CP(+) and cTnI(+) patients and the CP(+) and cTnI(–) patients in terms of BMI (Table 3).

It was found that the CP(+) and cTnI(+) patients had a higher rate of ECG abnormalities than the CP(+) and cTnI(–) group and the healthy control group (p = 0.13 and p < 0.001, respectively). In 65 (72.2%) of the patients, the ECG results were normal. ST-segment elevation was detected in 13 (14.4%) patients (Table 4). Although the incidence of ST-segment elevation was similar in the CP(+) and cTnI(+) and CP(+) and cTnI(–) groups, no ST-segment elevation was observed in the healthy control group (Table 4).

Table 4. ECG findings

	Total (n = *90*)	*CP(+), cTnI(+) = I* (n = *30*)	*CP(+), cTnI(–) = II* (n = *30*)	*CP(–), cTnI(–) = III* (n = *30*)		*Pairwise comparison*		
	n *(%)*	n *(%)*	n *(%)*	n *(%)*	p-*value*	*I vs II*	*I vs III*	*II vs III*
ECG finding					< 0.001‡			
Normal	65 (72.2)	13 (43.3)	23 (76.7)	29 (96.7)		0.013	< 0.001	0.023
Abnormal	25 (27.8)	17 (56.7)	7 (23.3)	1 (3.3)		0.013	< 0.001	0.023
ECG finding					< 0.001‡			
Normal	65 (72.2)	13 (43.3)	23 (76.7)	29 (96.7)		0.013	< 0.001	0.023
ST-segment elevation	13 (14.4)	8 (26.7)	5 (16.7)	0 (0.0)		ns	ns	< 0.001
ST-segment depression	1 (1.1)	1 (3.3)	0 (0.0)	0 (0.0)		ns	ns	ns
Bradycardia	2 (2.2)	1 (3.3)	0 (0.0)	1 (3.3)		ns	ns	ns
LBBB	5 (5.6)	4 (13.3)	1 (3.3)	0 (0.0)		ns	ns	ns
Atrial fibrillation	2 (2.2)	1 (3.3)	1 (3.3)	0 (0.0)		ns	ns	ns
T negative	1 (1.1)	1 (3.3)	0 (0.0)	0 (0.0)		ns	ns	ns
Tachycardia	1 (1.1)	1 (3.3)	0 (0.0)	0 (0.0)		ns	ns	ns

*Pearson's chi-squared test (Monte Carlo, exact). ‡Fisher–Freeman–Halton (Monte Carlo); *post hoc* test: Benjamini–Hochberg correction.
¶One-way ANOVA (Robuts statistic: Brown–Forsythe); *post hoc* test: Tukey HSD. †Kruskal–Wallis test (Monte Carlo); *post hoc* test: Dunn's test.
SD: standard deviation, min: minimum, max: maximum, CP: chest pain, LBBB: left bundle branch block, ns: not significant.

Table 4 summarises the correlation of patients' cTnI and osteopontin levels with the demographic data and vital signs. In our study, it was found that cTnl levels were positively correlated with age ($r = 0.624$), BMI ($r = 0.291$), HEART score ($r = 0.794$) and TIMI score ($r = 0.805$) (respectively, $p < 0.001$, $p = 0.005$, $p < 0.001$ and $p < 0.001$) (Table 5).

When the supervised machine learning method was applied to find and predict the variable with the highest significance among the risk markers used in our study, the scores with the highest predictive power for the diagnosis of ACS were found to be TIMI (100%) and HEART scores (96.3%). In our study, we discovered that osteopontin levels could not reach the diagnostic level for ST-segment elevation myocardial infarction (STEMI) or NSTEMI diagnoses ($p < 0.001$) (Table 6).

Discussion

ACS accounts for less than 15% of all patients presenting with chest pain.[9] Patients describe their pain as a sharp pain that spreads to the left arm, back, neck and jaw, lasts more than 20 minutes, and is not relieved by rest or nitroglycerin.[10] The presence or absence of ST-segment elevation on the ECG is used to classify ACS.[11] USAP and NSTEMI are fairly common, and in addition to a 12-lead ECG, risk scoring and cardiac biomarker troponin values are used for a diagnosis. The absence of data on myocardial damage is the most important feature that distinguishes USAP from NSTEMI. In other words, the patient's ECG and the cTnI value should be normal. The clinician's comments and the patient's history are used for USAP diagnosis.[12]

Some risk scorings are used to diagnose USAP and NSTEMI in the early stages. Among these, the scoring systems that are easy to apply under emergency room conditions are the HEART and TIMI risk scores. Despite cardiac biomarkers and ACS risk score calculation (TIMI and HEART) for the evaluation of patients with chest pain who attend the emergency service and are suspected of having ACS, a diagnosis can be missed at a rate of 2–4%.[13]

Studies on chest pain and ACS revealed disparities in age and gender distribution. The mean age of the patients in our study was 51.61 ± 17.56 years and 63.3% ($n = 57$) were male. The BMI of the patients was 25.63 ± 4.67 kg/m^2. We found that CP(+) and cTnl(+) patients were older than CP(+) and cTnl(–) patients and healthy controls, and they had higher HEART and TIMI scores.

The median systolic (128 mmHg) and diastolic blood pressure values (83 mmHg) of patients with ACS were found to be within the normal range in our study. This was considered to be due to the exclusion of patients with unstable vital signs from our study.

Patients who had a normal ECG pattern at the time of hospitalisation had a better prognosis than those who had active ECG changes. Persistent (> 20 min) ST-segment elevation at the time of admission of a patient with chest pain is defined as STEMI and requires immediate reperfusion therapy. Early mortality in these patients is more common than in NSTEMI patients and is caused by ventricular fibrillation.[14]

Patients with ST-segment depression have a poor prognosis, depending on the degree and extent of ECG changes.[15] The presence of depressions exceeding 0.2 mV in the ST segment increases the risk of mortality approximately six times. Patients with transient ST-segment elevation and ST-segment depression have poor prognoses and are frequently associated with coronary artery thrombosis. Furthermore, ST-segment elevation (> 0.1 mV) in lead aVR most likely indicates the left main coronary artery or three-vessel disease, which has a worse prognosis.

Fanaroff *et al*. discovered in their study of 29 973 NSTEMI patients, the mean heart rate was 94 beats/min in patients with complications and 84 beats/min in those without complications.[16] In their study of 884 patients with ACS, Ma *et al*. demonstrated that 31% of the patients had a heart rate greater than 75 beats/min.[17]

Diaz *et al*. discovered a high mortality and hospitalisation rate in patients with a heart rate of 77 beats/min or higher at the time of admission to their study investigating the effect of CAD heart rates on the prognosis. They also discovered that resting heart rate values were associated with CAD.[18] In their study of 1 807 patients with myocardial infarction (MI), Hjalmarson *et al*. discovered that patients with a heart rate of 50–60 beats/min had a mortality rate of 15%, while patients with a heart rate of more than 90 beats/min had a mortality rate of more than 40%.[19] In our study, the median heart rate of patients with ACS was 74 (52–99) beats/min. We believe that counting vital instability as an exclusion criterion may explain this difference.

The TIMI score was validated by the TACTICS-TIMI study[20] and the PRISM-PLUS study.[21] The TIMI risk score also includes clinical features, ECG changes and predictive factors of cardiac

Table 5. Correlations analysis

	Troponin		*Osteopontin*	
	r	p-*value*	r	p-*value*
cTnI	–	–	0.064	0.551
Osteopontin	0.064	0.551	–	–
Age	0.624	< 0.001	0.005	0.961
Height	–0.009	0.935	0.061	0.566
Weight	0.276	0.008	0.014	0.893
BMI	0.291	0.005	–0.069	0.516
SBP	0.175	0.100	–0.111	0.296
DBP	0.068	0.524	–0.046	0.666
Heart rate	0.047	0.657	–0.106	0.318
Fever	0.026	0.811	0.008	0.940
Heart	0.794	< 0.001	–0.064	0.546
TIMI	0.805	< 0.001	0.051	0.635

Spearman's rho test, *r*: correlation coefficient.
cTnI: cardiac troponin I, SBP: systolic blood pressure, DBP, diastolic blood pressure.

Table 6. Supervised machine learning analysis

Independent variable	*Normalised importance (%)*	*Sample (holdout)*	*Predicted*			
			CP(+), cTnI(+)	*CP(+), cTnI(–)*	*CP(–), cTnI(–)*	*Percentage correct*
		Training				
ECG finding	8.0	CP(+), cTnI(+)	17	0	0	100.0
		CP(+), cTnI(–)	2	16	1	84.2
Age	17.5	CP(–), cTnI(–)	0	3	16	84.2
		Overall percentage	34.5	34.5	30.9	89.1
BMI	23.8	Testing				
		CP(+), cTnI(+)	13	0	0	100.0
HEART	96.3	CP(+), cTnI(–)	1	8	2	72.7
		CP(–), cTnI(–)	0	1	10	90.9
TIMI	100.0	Overall percentage	40.0	25.7	34.3	88.6

Neural network (multilayer perceptron), hidden layer activation function: sigmoid, output layer activation function: identity.
CP: chest pain, cTnI: cardiac troponin I.

biomarkers for risk assessment, based on the ESSENCE study and the TIMI IIB study.[4] This score also identifies high-risk patients and determines whether they would benefit from an immediate invasive strategy.

Although the basic guideline states that 'chest pain is the leading symptom that initiates the diagnosis and therapeutic decision-making process,' the TIMI score does not classify the patient's history (anamnesis).[22] The importance of the history decreases once the diagnosis of ACS is made. The TIMI score has been evaluated for risk classification for patients with chest pain in the emergency service and is generally ineffective in determining patient propensity.[23] In our study, the HEART score was zero in 22 (24.4%) patients and the TIMI score was zero in 42 (46.7%).

In our study, the median body temperature of the patients was found to be 36.6°C (35.9–37.2°C). Our body temperature findings were consistent with the majority of previous studies. In previous similar studies, body temperature measurements were conducted within an average of four to eight hours after the diagnosis and another difference was the conduction of body temperature measurements after 24 to 48 hours in intensive care units. The body temperatures of the patients were measured at the time of admission in our study, and the measurements were conducted in the emergency service. This may explain the differences between the studies.

The HEART score provides a reliable predictor of outcomes for patients with chest pain who attend the emergency service, without requiring complex calculations. Once the troponin test results are available, they can usually be evaluated within one hour of the patient's arrival.[24,25] The HEART score is a strong diagnostic score in identifying low-risk patients. The extent to which a missed diagnosis is acceptable in the case of suspected ACS is still a matter of clinical debate.[26,27]

Several systematic reviews and meta-analyses have shown that the TIMI, HEART and GRACE scoring systems are predictive of MACE in ACP patients.[28,29] Hess *et al.* included eight prospective studies in their analysis and discovered that the TIMI score provided effective risk classification in predicting MACE in potential ACS patients, but it should not be used as the sole tool for determining patient propensity.[28] Van Den Berg *et al*. included two prospective and 10 retrospective cohort studies in their analysis and suggested that the HEART score could be used to identify MACE in patients with a suspected ACS diagnosis.[30] In their study, Mahler *et al.*[31] demonstrated that patients randomised for HEART (a combination of the HEART score and serial troponins) had lower objective cardiac testing rates and a shorter length of hospital stay than patients randomised for the usual evaluation group.

In our study, cTnl levels were found to be positively correlated with age ($r = 0.624$), BMI ($r = 0.291$), HEART score ($r = 0.794$) and TIMI score ($r = 0.805$) ($p < 0.001$, $p = 0.005$, $p < 0.001$ and $p < 0.001$).

When the supervised machine learning method was applied to find and predict the variable with the highest significance among the risk markers used in our study, the scores with the highest predictive power for the diagnosis of ACS were found to be TIMI (100%) and HEART (96.3%). In our study, we discovered that osteopontin levels could not reach the differential diagnostic level for STEMI or NSTEMI.

Patients with chest pain who arrive at the emergency service are triaged based on their clinical conditions or ECGs obtained within the first 10 minutes.[32] In the study of Hedges *et al*., among 261 patients over the age of 30 years who were admitted to follow up with chest pain, they performed serial ECG recordings in patients who did not demonstrate ST-segment elevation in their first ECG. Of these patients, 11% were diagnosed with MI. They discovered that 15% of the patients had changes in their serial ECGs and 39% of patients with MI had changes in their serial ECGs.

In our study, 33.3% of the patients (30 patients) did not experience chest pain. The remaining patients presented with chest pain to the emergency service and were diagnosed with ACS. The 12-lead ECGs of the patients in our study were obtained during the initial admission. In the ECGs taken, the sinus rhythm was found to be normal in 72.2% of the patients. ST-segment elevation was detected in 14.4% of the patients. When all patients with chest pain were evaluated, ECG changes were observed in 27.8% of the patients. The difference between our study and data in the literature, we believe, is due to the exclusion of individuals with vital instability.

Osteopontin levels may be an important marker in ACS patients, according to the study by Yu *et al.* with 210 ACS patients and 210 individuals who served as the control group.[7] In their study with 9 326 ACS patients, Kwee *et al.* showed that osteopontin levels can be effective in predicting the poor prognosis associated with ACS.[33] In a study of 110 patients, Zheng *et al*. discovered that the osteopontin marker was elevated in patients with ACS.[34] Coşkun *et al*. found that osteopontin levels were significantly higher in patients with NSTEMI compared to other groups in a study of 108 people, including 65 patients with NSTEMI,[25] with stable angina, and 18 healthy individuals in the control group.[35] Hosbond *et al.* examined osteopontin marker levels in ACS patients and discovered that they were associated with ACS in 120 people.[36] Mazzone *et al*., on the other hand, examined the osteopontin marker level in 77 patients with CAD and discovered that the osteopontin marker was a good prognostic marker.[37]

The mean and median values of osteopontin marker levels of the patients participating in our study were 5.97 ng/l (± 2.89) and 5.31 ng/l, respectively. We found that there was no correlation between the patients' troponin level, HEART and TIMI scores and their osteopontin levels.

Due to the design of our study, there are some inevitable limitations. Since the early and late mortality and morbidity outcomes of patients with chest pain who presented to the emergency service and were diagnosed with ACS were not evaluated, it was not possible to assess the predictive power of osteopontin levels for MACE outcomes. In addition, since it is not technically possible to measure osteopontin levels in a similar way to cTnI serial measurements, its usability in early clinical follow up could not be evaluated. However, we believe that the fact that we obtained important results in terms of comparing osteopontin levels with clinical risk criteria during emergency service admission is important.

Conclusion

As a result of the high fatality rate of ACS among patients, physicians must exercise extreme caution in their diagnosis. In the diagnosis of ACS, ECG and practical clinical risk criteria should be used. Few studies have been conducted to investigate

the role of the osteopontin biomarkers in patients diagnosed with ACS in the emergency services. Therefore, it is believed that multicentre studies with more appropriately selected patients are required.

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