

Oxidant and antioxidant levels in patients diagnosed with acute coronary syndrome at the emergency department

 Selma Tekkanat¹,  Nalan Kozaci²,  Mustafa Avci³,  Fatih Selvi³,  Yavuz Yilmaz⁴,  Hamit Yasar Ellidag⁵

¹Department of Emergency Medicine, Yuksekova State Hospital, Hakkari, Turkey

²Department of Emergency Medicine, Alanya Education and Research Hospital, Alanya Alaaddin Keykubat University, Antalya, Turkey

³Department of Emergency Medicine, Antalya Education and Research Hospital, University of Health Sciences, Antalya, Turkey

⁴Department of Emergency Medicine, Basaksehir City Hospital, Istanbul Turkey

⁵Department of Medical Biochemistry, Antalya Education and Research Hospital, University of Health Sciences, Antalya Turkey

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Abstract

Aim: The aim of this study is to compare high sensitive Troponin T (hs-TnT), total antioxidant capacity (TAC), total oxidant capacity (TOC), oxidative stress index (OSI), ischemia-modified albumin (IMA) levels and IMA/albumin ratios (IMAR) with the results of coronary angiography (CAG) in patients diagnosed with ACS at the emergency department.

Materials and Methods: Over a period of nine months, patients that were diagnosed with ACS at the emergency department, admitted to the cardiac intensive care unit, subjected to percutaneous CAG and over the age of 18 were included in the study.

Results: One hundred twenty five patients with suspected ACS and 52 healthy volunteers were included in the study. When the patients were evaluated with regards to the length of time between symptoms and arrival, TAC levels were found to decrease especially after the 6th hour. There was no significant difference between TOC, OSI, IMA and IMAR values in this regard.

Conclusion: In early-phase ACS, levels of TOC, OSI, IMA and IMAR rise from the 0th hour onwards. TAC levels gradually decrease after the early phase of ischemia. Therefore, oxidants and antioxidants can be used for early diagnosis of ischemia in ACS, as well as for estimating time of ischemia onset.

Keywords: Acute coronary syndrome; coronary angiography; myocardial infarction; total antioxidant capacity; total oxidant capacity

INTRODUCTION

Acute coronary syndrome (ACS) includes a spectrum of disease ranging from Unstable Angina (UA) to ST-Elevated Myocardial Infarction (STEMI) (1,2). Ischemic heart disease is the most common cause of death globally and the annual mortality rate is reported to be approximately 1.8 million (3).

Symptoms of myocardial infarction (MI) are varied, including chest pain, epigastric distress, shortness of breath, nausea, vomiting, sweating, syncope, etc (4,5). However, these symptoms are nonspecific and may not be associated with MI (1). There is no diagnostic physical examination finding for ACS and physical examination is generally normal. The aim of physical examination is to differentiate between pathologies such as pulmonary embolism, aortic dissection, pericarditis, pneumonia, pneumothorax and pleural effusion, which cause similar symptoms. Patients who had suspected ACS should be evaluated quickly in the emergency department.

The patient's targeted anamnesis is questioned, the patient is monitored and electrocardiography (ECG) is obtained within the first 10 minutes (6).

Assessment of cardiac biomarker levels (myoglobin, creatine kinase myocardial band [CK-MB] and troponins) is one of the most fundamental and effective methods of determining myocardial damage. Recent conventional cardiac biomarkers CK-MB, troponin I and troponin T are sensitive markers for detecting myocardial necrosis. However, all these biomarkers exhibit substantial increase approximately 3-6 hours after initial myocardial cell damage (2,6,7). Two-dimensional echocardiography (ECHO) has been shown to have high sensitivity and specificity in the diagnosis of ACS (8). However, other diagnostic tools such as ECHO and stress testing are not routinely available in emergency department conditions.

Reactive oxygen species (ROS), reactive nitrogen species (NOS) and sulfur-centered radicals are classified as oxidants. Recent research has shown that ROS play a

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Corresponding Author: Mustafa Avci, Department of Emergency Medicine, Antalya Education and Research Hospital, University of Health Sciences, Antalya, Turkey E-mail: dravcimustafa@gmail.com

major role in pathogenesis of cardiovascular diseases and myocardial damage. ROS are capable of reacting with biological molecules such as proteins, lipids and DNA. Rise in ROS levels disturbs cellular functions by damaging lipid membranes, enzymes and nucleic acids (8-12).

Total antioxidant capacity (TAC), total oxidant capacity (TOC) and oxidative stress index (OSI) reflect the balance between oxidation and antioxidation. Measurement of TAC provides more valuable information compared to separate measurements of different antioxidants. In addition, TOC of the plasma reflects the interaction between different antioxidants. Therefore, TAC measurement is becoming widespread in determining the antioxidant level of the blood (13-16).

The aim of this study is to compare high sensitive Troponin T (hs-TnT), TAC, TOC, OSI, ischemia-modified albumin (IMA) levels and IMA/albumin ratios (IMAR) with the results of coronary angiography (CAG) in patients diagnosed with ACS at the emergency department.

MATERIALS and METHODS

This prospective study was approved by the Clinical Research Ethics Committee of Antalya Research and Training Hospital on 24.01.2019 with the registration number of 2/014. Financial support for this study was approved by the Medical Specialty Training Board on 11.09.2018.

Over a period of nine months, patients that were diagnosed with ACS at the emergency department, admitted to the cardiac intensive care unit, subjected to percutaneous CAG and over the age of 18 were included in the study. Patients that had their cardiac biomarkers assayed before visiting the emergency department carrying out the study, were below 18, had prior coronary artery bypass surgery, had comorbidities that may affect oxidant and antioxidant levels (chronic lung disease, kidney failure, liver failure, stroke), were taking vitamin C and E, were pregnant, and were unsuitable for CAG were excluded from the study.

Study patients were firstly evaluated by emergency physicians at the emergency department. ECG was performed within the first 10 minutes. Concurrently, vascular access was established and blood samples were taken for laboratory analysis. Patients were divided into three groups, STEMI, non-STEMI (NSTEMI) and UA, depending on their ECG and laboratory results.

Patients that felt chest pain or distress, together with ECG results showing ST-segment elevations on two or more contiguous leads or new left bundle branch blocks were regarded as STEMI. Threshold values for ST-segment elevation were as follows: For men over 40, 0.2 mV (2 mm) from the J-point in V2 and V3 leads, and 0.1 mV (1 mm) elevation in other leads; for men under 40, 0.25 mV (2.5 mm) from the J-point in V2 and V3 leads, and 0.1 mV (1 mm) elevation in other leads; for women, 0.15 mV (1.5 mm) from the J-point in V2 and V3 leads, and 0.1 mV (1 mm) elevation in other leads (3).

Patients that felt chest pain or distress, together with ECG results showing ischemic ST-segment depressions >0.05 mV (0.5 mm) or dynamic T-wave inversions were regarded as NSTEMI/UA (17). Threshold values for ST-segment depression concordant with ischemia were as follows: for both genders, <0.05 mV (0.5 mm) depression from the J-point in V2 and V3 leads, and <0.1 mV (1 mm) depression in other leads (4). Among these patients, those with high-sensitive troponin-T (hs-cTnT) levels over 50 ng/L were considered as NSTEMI, while those with hs-cTnT levels in the range of 0-50 ng/L were considered as UA.

As a control group, healthy volunteers that had no previously diagnosed diseases, were not taking any drugs or vitamins, and gave consent were enrolled in the study.

Before the start of the study, a standardized data collection form was prepared, on which demographic information (name, age, gender, etc.), ECG findings and routine test results (hs-cTnT) of patients were recorded. In addition to routine tests, plasma TAC, TOC, IMA and albumin levels of the study patients were assayed. Only plasma TAC, TOC, IMA and albumin levels of healthy volunteers were examined.

All patients enrolled in the study were evaluated according to the ACS guidelines. Informed consent was obtained from all patients and their relatives. CAG and echocardiography results were gathered from the hospital automation system. Blood samples were examined by medical biochemistry specialists at the hospital laboratory.

Blood Samples and Laboratory Analysis

Blood samples of the patients were drawn at the time of entry into vacuum-capped biochemistry tubes containing separation gel. Within half an hour, blood samples taken from study and control groups were spun at 4,000 rpm for 10 minutes in a non-cooled centrifuge to separate plasma. The plasma samples were then transferred into plastic-cap Eppendorf tubes and stored at -80°C until the time of analysis. These stored plasma samples were used for analyses of TAS, TOS, IMA and albumin levels.

TOC analysis: Measurements were made with an Abbott Architect® c16000 (Abbott Diagnostic, USA) autoanalyzer using full automatic RL0031 RelAssay® (Gaziantep, Turkey) commercial kits. Results were reported in $\mu\text{mol H}_2\text{O}_2$ equivalent/L (10,18).

TAC Analysis: Measurements were made with an Abbott Architect® c16000 autoanalyzer using full automatic RL0031 RelAssay® commercial kits. Results were reported in $\mu\text{mol trolox}$ equivalent/L (10,18).

Albumin Analysis: Measurements were made with an Abbott Architect® c16000 autoanalyzer using the bromocresol green method.

IMA Analysis: Measurements were made according to the albumin cobalt binding test described by Jonathan et al. (18). Results were reported in absorbance units (ABSU).

All analyses were performed by two operators simultaneously. All reactions were carried out in glass vials. All measurements were made within two days.

Calculation of OSI: OSI was calculated by dividing the TOC level by the TAC level, as given below:

$$\text{OSI} = [\text{TOC} (\mu\text{mol H}_2\text{O}_2 \text{ equivalent/L}) / \text{TAC} (\mu\text{mol trolox equivalent/L})]$$

Calculation of IMAR: IMAR was calculated by dividing the ischemia-modified albumin level by the albumin level, as given below:

$$\text{IMAR} = [\text{IMA (ABSU)} / \text{albumin (g/dL)}]$$

Hs-cTnT Analysis: Measurements were made using the chemiluminescence method on the day of blood sampling at the emergency department laboratory. The reference range was set as 0-50 ng/L.

The approximate duration of centrifugation was 10 minutes in the laboratory study. Measurement of plasma level took 15 minutes for IMA, 7 minutes for TAS and TOS, and 5 minutes for albumin. IMAR and OSI were recalculated parameters. Analysis of hs-cTnT levels were performed in approximately 45 minutes.

Statistical Analysis

IBM SPSS Statistics version 21.0 software package was used for statistical analysis of the demographic data by utilizing frequency distribution and the Chi-squared test. The Shapiro-Wilk test was used for determining distribution of the groups. When comparing paired groups with parametric distribution, Student's t-test was applied, whereas the Mann-Whitney U test was used in cases of non-parametric distribution. For comparisons of multiple groups, the one-way analysis of variance test or the Kruskal-Wallis H test was applied if there was parametric or non-parametric distribution, respectively. A $P < 0.05$ value was regarded statistically significant.

Statistical analysis was initiated by comparing TAC, TOC, OSI, IMA and IMAR values of the patients and healthy controls. Receiver operating characteristic (ROC) analysis was then performed in order to identify the marker that showed the highest difference. Secondly, TAC, TOC, OSI, IMA and IMAR values were inspected in relation to the length of time between onset of symptoms and hospital arrival. The third comparison involved TAC, TOC, OSI, IMA and IMAR values of patients diagnosed with STEMI, NSTEMI or UA. Results of CAG reports were used for the fourth comparison, in which stenosis of more than 50% in any of the coronary arteries was regarded as a pathological finding indicating ACS (17). Accordingly, the patients were divided into two groups: those with $\geq 50\%$ stenosis and $< 50\%$ stenosis. TAC, TOC, OSI, IMA and IMAR values of these two groups were compared.

RESULTS

One hundred twenty five patients with suspected ACS and 52 healthy volunteers were included in the study. Of the patients, 94 (75%) were male and 31 (25%) were female,

whereas 32 (62%) of the healthy volunteers were male and 20 (38%) were female ($P = 0.072$). The mean ages were 55 ± 8 and 52 ± 11 years in the patient and control groups, respectively ($P = 0.116$). There was no significant difference between patients and healthy volunteers in terms of past medical history (Table 1).

Table 1. Chronic Diseases of Patients and Healthy Volunteers

Disease	Patients, N (%)	Healthy volunteers, N (%)	P
Diabetes Mellitus	44 (%35)	21(40%)	0.379
Hypertension	64(%51)	11(21%)	0.248
Hyperlipidemia	37(%30)	12(23%)	0.462
Smoking	58(%46)	23(44%)	0.869
Family history	36(%29)	9(17%)	0.131

When the oxidant and antioxidant levels of the patients and healthy volunteers were compared, it was found that the TAC level decreased and the TOC, OSI, IMA and IMAR levels increased in the patients (Table 2). ROC analysis of TAC, TOC, OSI, IMA and IMAR values revealed that the area under the curve of IMA was the largest, while that of TAC was the smallest (Figure 1, Table 3).

Table 2. Comparison of laboratory results of patients and healthy volunteers

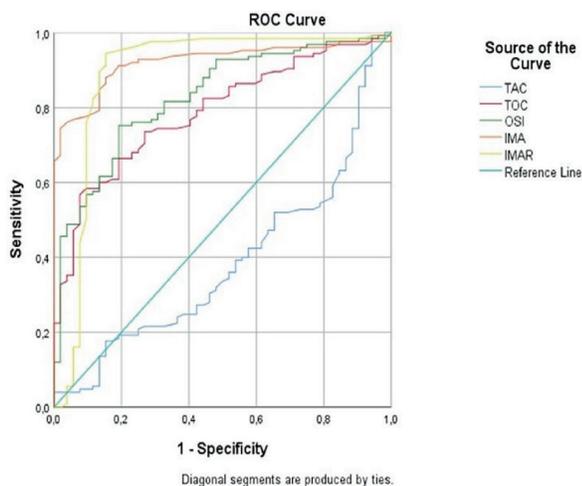
Oxidant/antioxidant Values	Patients Median (min-max)	Healthy volunteers Median (min-max)	P
TAC	1.7 \pm (1.2-3.0)	1.8 (1.2-2.3)	0.017
TOC	5.34 (2.06-23.08)	3.45 (2.10-7.26)	0.001
OSI	3.07 (0.98-9.49)	1.80 (1.17-4.76)	0.001
IMA	0.59 (0.42-0.74)	0.55 (0.52-0.58)	0.001
IMAR	0.15 (0.09-0.21)	0.13(0.11-0.26)	0.001

TAC: Total Antioxidant Capacity, TOC: Total Oxidant Capacity, OSI: Oxidative Stress Index, IMA: Ischemic Modified Albumin, IMAR: Ischemic Modified Albumin/Albumin Ratio

Table 3. ROC analysis for TAC, TOC, OSI, IMA and IMAR

Variable(s)	Area	Asymptotic 95% Confidence Interval	
		Lower Bound	Upper Bound
TAC	0.386	0.297	0.474
TOC	0.788	0.720	0.856
OSI	0.828	0.765	0.892
IMA	0.921	0.881	0.961
IMAR	0.891	0.819	0.963

TAC: Total Antioxidant Capacity, TOC: Total Oxidant Capacity, OSI: Oxidative Stress Index, IMA: Ischemic Modified Albumin, IMAR: Ischemic Modified Albumin/Albumin Ratio



TAC: Total Antioxidant Capacity, TOC: Total Oxidant Capacity, OSI: Oxidative Stress Index, IMA: Ischemic Modified Albumin, IMAR: Ischemic Modified Albumin/Albumin Ratio

Figure 1. ROC analysis for TAC, TOC, OSI, IMA and IMAR

Table 4. Comparison of patients according to the time from the onset of symptoms to the emergency department admission					
	Hour	Median	Minimum	Maximum	P
hs-cTnT	0-3.0	43	4	927	0.141
	3.1-6.0	84	3	831	
	6.1-24	74	3	887	
TAC	0-3.0	1.75	1.36	2.74	0.009
	3.1-6.0	1.74	1.22	3.00	
	6.1-24	1.62	1.38	2.18	
TOC	0-3.0	5.78	2.06	10.22	0.387
	3.1-6.0	4.98	2.26	23.08	
	6.1-24	5.24	2.12	11.44	
OSI	0-3.0	3.20	0.99	6.08	0.914
	3.1-6.0	2.91	1.21	9.49	
	6.1-24	3.05	1.38	6.34	
IMA	0-3.0	0.59	0.42	0.66	0.409
	3.1-6.0	0.59	0.54	0.74	
	6.1-24	0.59	0.50	0.68	
IMAR	0-3.0	0.15	0.09	0.21	0.517
	3.1-6.0	0.15	0.13	0.19	
	6.1-24	0.15	0.13	0.20	

TAC: Total Antioxidant Capacity, TOC: Total Oxidant Capacity, OSI: Oxidative Stress Index, IMA: Ischemic Modified Albumin, IMAR: Ischemic Modified Albumin/Albumin Ratio

The mean length of time between onset of symptoms and patient arrival at the emergency department was 6.5±6.1 hours. 49 (39%) of the patients arrived within the first three hours, 39 (31%) between 3.1 and 6 hours, and 37 (30%) between 6.1 and 24 hours. hs-cTnT levels were within the reference range in 25 (51%) patients that arrived in the

first three hours of symptom onset, 11 (28%) patients that arrived in 3.1-6 hours and 13 (35%) patients that arrived in 6.1-24 hours. When these patients were evaluated with regards to the length of time between symptoms and arrival, TAC levels were found to decrease especially after the 6th hour. There was no significant difference between TOC, OSI, IMA and IMAR values in this regard (Table 4).

Forty-two (34%), 60 (48%) and 23 (18%) of the patients were admitted to the cardiac intensive care unit with diagnoses of STEMI, NSTEMI and UA, respectively. In 19 (45%) of STEMI patients, 7 (12%) of NSTEMI patients and 23 (100%) of UA patients, hs-cTnT levels were within the reference range. Comparison of laboratory results in these patients revealed no significant difference in TOC, OSI, IMA and IMAR values. Nonetheless, TAC levels were highest in STEMI patients while hs-cTnT levels were highest in NSTEMI (Table 5).

Table 5. Comparison of laboratory results of ACS patients					
Laboratory Results		Median	Minimum	Maximum	P
hs-TnT	UA	9	3	41	0.001
	STEMI	46.5	4	927	
	NSTEMI	111	21	887	
TAC	UA	1.66	1.22	3.00	0.043
	STEMI	1.77	1.37	2.74	
	NSTEMI	1.66	1.40	2.31	
TOC	UA	4.62	2.20	23.08	0.437
	STEMI	5.69	2.70	10.22	
	NSTEMI	5.09	2.06	18.16	
OSI	UA	2.83	1.61	7.67	0.979
	STEMI	3.14	1.62	6.08	
	NSTEMI	3.12	0.99	9.50	
IMA	UA	0.59	0.50	0.74	0.383
	STEMI	0.59	0.42	0.66	
	NSTEMI	0.59	0.50	0.68	
IMAR	UA	0.15	0.11	0.21	0.110
	STEMI	0.15	0.09	0.19	
	NSTEMI	0.15	0.13	0.20	

ACS: Acute Coronary Syndrome, TAC: Total Antioxidant Capacity, TOC: Total Oxidant Capacity, OSI: Oxidative Stress Index, IMA: Ischemic Modified Albumin, IMAR: Ischemic Modified Albumin/Albumin Ratio, UA: Unstable Angina, STEMI: ST Elevation Myocardial Infarction, NSTEMI: Non ST Elevation Myocardial Infarction

According to CAG results, 34 (27%) of the patients had stenosis below 50%, while 91 (73%) had 50% or more stenosis. No significant difference was observed in TAC, TOC, OSI, IMA and IMAR values between patients with <50% and ≥50% stenosis. While hs-cTnT levels were lower in patients with <50% stenosis, they were still higher than the reference range (>50 ng/L) (Table 6).

Table 6. Comparison of laboratory results of patients with coronary artery stenosis of $\geq 50\%$ and $< 50\%$

Laboratory Values	The patients with stenosis of $< 50\%$ Median (min-max)	The patients with stenosis of $\geq 50\%$ Median (min-max)	P
hs-TnT	55 (3-927)	93 (5-887)	0.020
TAC	1.74 (1.38-3.00)	1.66 (1.22-2.08)	0.075
TOC	5.44 (2.06-23.08)	5.14 (2.20-18.16)	0.303
OSI	3.20 (0.98-7.67)	2.94 (1.61-9.49)	0.585
IMA	0.59 (0.50-0.74)	0.59 (0.50-0.66)	0.732
IMAR	0.15 (0.11-0.20)	0.15 (0.13-0.21)	0.349

hs-TnT: High Sensitive Troponin T, TAC: Total Antioxidant Capacity, TOC: Total Oxidant Capacity, OSI: Oxidative Stress Index, IMA: Ischemic Modified Albumin, IMAR: Ischemic Modified Albumin/Albumin Ratio

Among the patients that exhibited $\geq 50\%$ stenosis on their CAG, 3 (3.3%) lost their lives, 71 (78%) had coronary angioplasty, 12 (13.2%) were elected for coronary artery bypass graft surgery and 5 (5.5%) received medical treatment plans. Medical treatment was planned for all patients that showed $< 50\%$ stenosis on their CAG.

DISCUSSION

Acute coronary syndrome is amongst the leading causes of death globally. As such, early and accurate diagnosis is crucial for reducing morbidity and mortality. Biochemical markers that indicate necrosis due to myocardial ischemia are used for diagnosis of ACS (7).

It is presently known that oxidative stress plays a major role in pathogenesis of heart diseases via lipid peroxidation and production of free radicals (19,20). Accordingly, plasma oxidant and antioxidant levels of ACS patients have been subjects to numerous studies as biochemical biomarkers. In such studies, increase in oxidant levels and decrease in antioxidant levels have been reported in patients diagnosed with ACS compared to control groups (19,21,22). Furthermore, the extent of alteration in oxidant and antioxidant levels has been shown to be more prominent in acute cases compared to chronic patients (22). Additionally, it has been found that oxidant and antioxidant levels change depending on the severity of the disease. To elaborate, total oxidant parameters gradually increase, while antioxidant parameters gradually decrease in the order of UA, NSTEMI and STEMI (23,24).

In this study where we investigated the changes in TAC, TOC, OSI, IMA and IMAR levels in patients diagnosed with ACS, we found that TOC, OSI, IMA and IMAR values of the patients were higher than those of healthy volunteers. On the other hand, TAC levels were measured lower than healthy volunteers. When patients were evaluated with respect to the length of time spent before arrival, we observed that TAC levels decreased after the 6th hour, whereas TOC, OSI, IMA and IMAR values increased from the 0th hour onwards. In addition to these results, TAC levels were found to be higher in STEMI patients compared to

NSTEMI and UA patients. Higher TAC levels in STEMI were considered to be associated with these patients' early arrival at the emergency department and early diagnosis. Conversely, there was no significant difference between oxidant levels of STEMI, NSTEMI and UA patients. These results indicate that the rise in oxidant levels in ACS is subsequent to onset of ischemia. Furthermore, our hs-cTnT analysis revealed that hs-cTnT levels were within the reference range at the time of arrival in 100%, 45% and 12% of UA, STEMI and NSTEMI patients, respectively. Characteristic ECG findings of STEMI patients facilitate early diagnosis and early intervention. On the other hand, laboratory tests may be required for UA and NSTEMI patients. The facts that laboratory analyses of oxidant and antioxidant levels take as short as 15 minutes on average and that oxidants start to increase at the early phase of ischemia onset make these markers advantageous. As hs-cTnT levels do not increase in UA patients and may increase late in NSTEMI patients, oxidants can be used as biomarkers for ACS. Based on this interpretation, our ROC analyses of TAC, TOC, OSI, IMA and IMAR values showed that the area under the curve of IMA was the largest, while that of IMAR, OSI and TOC were large as well. We therefore deduced that IMA, IMAR, OSI and TOC could be useful markers for early diagnosis of NSTEMI and UA. Even though TAC is not used for early diagnosis, it may be utilized for predicting how much time has passed since the onset of ischemia, because TAC levels decrease after six hours.

CAG is traditionally the gold standard for diagnosis of coronary atherosclerosis. In a study that compared the severity of coronary artery disease with oxidant and antioxidant levels, a high level of correlation was found between the SYNTAX (Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery Study) score and levels of OSI and TOC (25). When we compared patients that showed below 50% stenosis on their CAG with those that had 50% or more stenosis, no significant difference was observed between TAC, TOC, OSI, IMA and IMAR values. In Patients who had 50% or more stenosis, hs-cTnT levels were higher. However, the hs-cTnT levels were above the reference range in patients who had stenosis below 50%. These results suggest that the extent of stenosis determined with CAG is not the only parameter for ischemia development. Our results indicate that the oxidant/antioxidant balance is independent of the severity of stenosis and is rather associated with the burden of emerging myocardial necrosis.

LIMITATIONS

The limitation of our study is that our study population was relatively small because of our budget was low. Therefore, TAC, TOC, IMA and albumin levels of the patients were measured only once. Periodically repeated measurements of oxidant and antioxidant levels like other cardiac markers may cause different results. In addition, the effect of oxidative stress on prognosis could not be evaluated because the patients were not followed up.

CONCLUSION

To conclude, in early-phase ACS, levels of TOC, OSI, IMA and IMAR rise from the 0th hour onwards. Moreover, TAC levels gradually decrease after the early phase of ischemia. Therefore, oxidants and antioxidants can be used for early diagnosis of ischemia in ACS, as well as for estimating time of ischemia onset. Nonetheless, further larger-scale research building on these results is needed.

Competing interests: The authors declare that they have no competing interest.

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Ethical approval: The study was approved by the Clinical Research Ethics Committee of Antalya Research and Training Hospital on 24.01.2019 with the registration number of 2/014.

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