Research Article

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Evaluation of oxidative stress biomarkers together with myeloperoxidase/paraoxonase-1 and myeloperoxidase/high density lipoprotein cholesterol in ST-elevation myocardial infarction

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Abstract

Objectives: Oxidative stress is closely associated with atherosclerosis and acute coronary syndromes. The purpose of this study was to evaluate well-known and proportional oxidative stress biomarkers in ST-Elevation Myocardial Infarction (STEMI) patients.

Methods: In this single center, prospective and cross-sectional study, 107 individuals (63 patients) were studied. Total oxidative status (TOS), total antioxidant status (TAS), oxidative stress index (OSI), ischemia modified albumin (IMA), myeloperoxidase (MPO), paraoxonase-1 (PON-1) and arylesterase (AREase) enzyme activities as well as MPO/PON-1, MPO/AREase and MPO/HDL-C ratios were studied. As short-term in-hospital prognosis biomarkers; in-hospital mortality, early systolic dysfunction and spontaneous complete revascularization were investigated.

Results: Our results indicated that TOS, OSI, IMA, MPO, MPO/PON-1 and MPO/HDL ratios were significantly higher, PON-1 and AREase were significantly lower in STEMI patients compared to the control group. However, in the regression analysis performed by adjusting the differences between the groups, only IMA was found as an independent risk factor (OR=2.711, 95 % CI=1.094–6.719, p=0.031). In terms of in-hospital short-term prognostic biomarkers, a significant relationship was found only between OSI and spontaneous complete revascularization. The OSI value was higher in the group with TIMI grade 3 flow than in the group with TIMI grade 0–2 flow (2.42 [0.81–4.49] vs. 1.63 [0.33–6.07], p=0.016).

Conclusions: In STEMI patients, both the well-known (TOS, OSI, and MPO) and proportional (MPO/PON-1 and MPO/HDL cholesterol ratios) oxidative stress markers were elevated and can be considered as having a role in the pathogenesis of STEMI.

Keywords: coronary artery disease; myeloperoxidase; oxidative stress; ST-elevation myocardial infarction

Introduction

Cardiovascular diseases are still the most important causes of death and the mortality rates continue to rise every year [1]. Atherosclerosis related complications such as heart attack, stroke and myocardial infarction cause the majority of cardiovascular diseases. Atherosclerosis is known to be caused by several reasons, but the oxidative stress (OS) hypothesis takes the lead [2]. According to this hypothesis, there are free radicals within the body which have unpaired electrons and are therefore, extremely reactive molecules. They can attack every component of the cell such as lipids, proteins, carbohydrates and nucleic acids and as a result of consequent oxidative reactions, tissue damage occurs. Several factors such as smoking, ageing, irradiation induce the formation of free radicals. On the other hand, there is an antioxidant defence system within the body which scavenges the free radicals. In good health, the system works well. However, under the condition of several diseases,
including cardiovascular diseases, an imbalance between free radicals and antioxidants occurs and this leads to OS [3]. It has been reported that OS triggers the oxidation of lipids [4]. Macrophages can recognize oxidized low density lipoprotein (ox-LDL) and transform into foam cells [5]. Early atherosclerotic lesions occur after the emergence of these foam cells [6].

The large part of the acute coronary syndrome (ACSs) are associated with the rupture of the atherosclerotic plaque [7]. Together with the thrombosis formation on the ruptured atherosclerosis plaque, ischemia develops. This is caused by the insufficient amount of blood and oxygen transport in the myocardium fed by the coronary artery. Following ischemic injury, both the OS and the platelet activity increases [8].

OS of an individual can be measured by using several methods and by investigating various OS parameters. In our study, we evaluated well-known OS biomarkers such as total oxidative status (TOS), total antioxidant status (TAS), OS index (OSI), ischemia modified albumin (IMA), myeloperoxidase (MPO), paraoxonase-1 (PON-1) and arylesterase (AREase) enzyme activities in ST-elevation myocardial infarction (STEMI) patients and compared the findings with the control group. The individuals in the control group had no significant stenosis in the epicardial coronary arteries. We also examined the differences between both groups in terms of the ratios of some inversely related parameters. MPO/PON-1, MPO/AREase and MPO/high density lipoprotein (MPO/HDL) cholesterol ratios are the proportional OS parameters. According to our knowledge, these proportional OS parameters were not studied in STEMI patients. Our aim in conducting this study was to examine both the well-known OS biomarkers and the proportional OS parameters in patients with STEMI and to investigate their effects on in-hospital short-term prognosis.

Materials and methods

This is a single centre, prospective and cross-sectional study. Between October 2019 and January 2020, a total of 107 patients who met the study criteria were included in the study. Sixty-three patients who were diagnosed with acute STEMI and underwent urgent coronary angiography formed our patient group. Forty-four patients whose epicardial coronary arteries were found to be normal or near normal in coronary angiography formed our control group. Breastfeeding mothers, individuals under the age of 18, as well as individuals with systolic heart failure, acute or chronic infection, malignancy, autoimmune disease, and pregnancy were excluded.

STEMI was defined as chest pain together with the detection of new or presumed as new ST segment elevation in two or more adjacent leads in 12-lead electrocardiography. Emergency coronary angiography was performed to all patients in this group, and as a standard, acetylsalicylic acid, clopidogrel or ticagrelor and heparin were administered before angiography. Also, if not contraindicated, beta-blockers, angiotensin-converting enzyme inhibitors, and statins were prescribed during hospitalization.

This study was initiated in accordance with the principles stated in the Helsinki Declaration and after the approval of the local Ethics Committee (date: October 16, 2019, decision no: 2019-175-16/10). Written informed consent forms were read and signed by all patients participating in the study.

Demographic information, heart rate, systolic blood pressure, body mass index, hypertension, diabetes, smoking, presence of hyperlipidaemia and the drugs used were recorded for all patients included in the study. Hypertension was defined if an individual had systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg in more than two measurements in the hospital, previously diagnosed as hypertensive or if an individual was under the usage of any antihypertensive medications. Hyperlipidaemia was defined if an individual had serum triglyceride levels ≥200 mg/dL, low-density lipoprotein cholesterol levels ≥130 mg/dL, serum total cholesterol levels ≥240 mg/dL, previously diagnosed with hyperlipidaemia, or if an individual was under the prescription of lipid-lowering medication. Diabetes mellitus was defined as having fasting plasma glucose levels more than 126 mg/dL in multiple measurements or if an individual was already diagnosed as diabetic, or if a person was under the usage of antidiabetic medications. Both the active smokers and ex-smokers were included in the study as smokers.

We identified spontaneous complete recanalization, early left ventricular systolic dysfunction and in-hospital mortality as short-term prognosticators for the patient group. Detection of infarct related artery (IRA) as spontaneous complete recanalized in coronary angiography performed before primary percutaneous coronary intervention (PCI) in patients with STEMI was defined as Thrombolysis in Myocardial Infarction (TIMI) flow grade 3. Absence of complete coronary flow in IRA was also defined as TIMI 0–2.

Transthoracic echocardiography was performed to the patients in the patient group within 24–48 h after admission to the hospital, and to the patients in the control group at the outpatient clinic after the admission. Left ventricular ejection fraction (LVEF) was measured and recorded with biplane images, and patients with LVEF <50 % was accepted as early left ventricular systolic dysfunction, reduced LVEF. In-hospital mortality was also recorded in the patient group.

Blood samples of the study patients were taken from the antecubital veins during the preparation of the patient for coronary angiography and put into biochemistry tubes containing K₂EDTA. Lipid parameters and routine biochemistry parameters were immediately measured with the ADVIA 2,400 (Siemens, NY, USA) device. The blood samples were centrifuged at 1,500 × g for 10 min and the plasma were separated. Separated plasma were stored in Eppendorf tubes at –80 °C until the measurement of OS parameters.

Measurement of total antioxidant status (TAS)

TAS levels were measured colorimetrically. The method is based on reducing the oxidized ABTS (2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid)) in the presence of antioxidants. The antioxidant content
Measurement of total oxidant status (TOS)

The method of Erel O. was used to determine plasma TOS levels colorimetrically. The principle of the assay depends on the oxidization of Fe²⁺ to Fe³⁺ by the oxidants in the sample. Fe³⁺ then binds with xylenol orange to produce a blue-purple complex. At pH values between 2 and 3 and 390 nm wavelength, the color depth is proportional to the amount of oxidants within the sample. The data were expressed as “micromole hydrogen peroxide equivalent per litre” due to the calibration of the assay with hydrogen peroxide.

Calculation of oxidative stress index (OSI)

TOS (micromole H₂O₂ equivalent/L) to TAS (micromole Trolox equivalent/L) ratio × 100 was used to calculate OSI in Arbitrary Units (AU) [10].

Determination of paraoxonase-1 (PON-1) and arylesterase (AREase) activities

PON-1 and AREase activities were determined colorimetrically (Relassay, Turkey). The principle of PON-1 assay is based on the measurement of the linear increase of the absorbance of p-nitrophenol produced from paraoxon in the presence of PON-1 and calcium (cofactor). PON-1 activity was measured spectrophotometrically at 37 °C and 412 nm. PON-1 activity was expressed as international units per 1 L of plasma (U/L).

The principle of AREase activity is based on the measurement of the absorbance of phenol as a product of phenylacetate. One unit of AREase activity is equal to 1 mmol of phenylacetate hydrolysed per liter per minute at 37 °C [11, 12].

Measurement of plasma ischemia modified albumin (IMA)

The principle of the assay is based on the determination of the unbound cobalt remained after the binding of albumin in plasma with the cobalt of the cobalt chloride solution. Dithiothreitol was the colorizing agent and the absorbance values were recorded at 470 nm [13]. Human IMA kits belonging to Relassay, Turkey were used and the kit usage protocols were followed.

Measurement of myeloperoxidase (MPO)

MPO activity was measured according to Kruidnenier et al. [14]. MPO kits (Relassay, Turkey) were used and the kit usage protocols were followed. The principle of the assay depends on the measurement of the yellowish-orange colored complex formed by 0.5 % hexadecyl trimethylammonium bromide (pH 3.5) and 0.026 % ortho-dianisidinedihydrochloride plus 0.018 % H₂O₂ at 460 nm. The MPO activity values were expressed as units per litre of plasma.

Statistical analysis

Statistical analysis were performed by using SPSS 19.0 software. Distribution of data was determined by Shapiro–Wilk test. Continuous variables were expressed as mean ± standard deviation or median (minimum–maximum) and categorical variables as frequency and percentage. Categorical variables were compared by using Pearson Chi-square test. Continuous variables were compared by using independent sample t test or the Mann–Whitney U test for two groups. Binary logistic regression analysis with backward stepwise LR method was used to determine of independent risk factors between the groups and to predict the relationship between OSI value and TIMI score groups. Spearman’s correlation analysis was performed to determine the relationship between continuous variables. MedCalc 19.6.4 was used to calculate receiver operating characteristic (ROC) analyses, to determine the optimal cut-off value of OSI to identify the TIMI score group. p-Value of less than 0.05 was considered as statistically significant for all tests.

Results

Our study consisted of 63 patients and 44 controls. A total of 78 % of 107 patients included in the study were male and the mean age was 58 ± 11. Demographic and clinical characteristics are shown in Table 1.

The comparisons of routine biochemical values, lipid profiles and OS parameters, between patient and control groups are shown in Table 2. Among the lipid parameters, HDL-cholesterol was found to be significantly lower in STEMI patients compared to the control group (p=0.010). TAS values were statistically similar in both groups (p=0.062). TOS and OSI values were found as significantly high in the patient group (p<0.001, p=0.007, respectively).

MPO and IMA values were found to be higher in the patient group than the control group (p=0.002, p<0.001, respectively). PON-1 and AREase values were found to be lower in the patient group and these differences were found to be statistically significant (p=0.003, p=0.026, respectively). MPO/PON-1, MPO/HDL cholesterol and MPO/AREase ratios were also compared between the patient and control groups, and it was found that as HDL cholesterol and HDL cholesterol-related enzymes, PON-1 and AREase decreased, while MPO increased in the patient group. MPO/PON-1 was found to be statistically significantly high in the patient group and is shown in Figure 1 (p=0.004). MPO/HDL cholesterol ratio was also found to be high in the patient group and is shown
in Figure 2 (p=0.029). Although MPO/AREase ratio was high in the patient group, this difference was not statistically significant (p=0.097).

The relationship between these proportional OS parameters, MPO/PON-1 and MPO/HDL cholesterol, which were found to be significantly higher in STEMI patients, and the other OS parameters as well as lipid profile was examined by correlation analysis and was shown in Table 3. When we considered the lipid profile, we found a moderately positive statistically significant correlation between triglyceride values and both MPO/PON-1 and MPO/HDL cholesterol ratios (r=0.432, r=0.472, respectively). A weak negative correlation was also detected between HDL cholesterol and MPO/PON-1 (r=-0.296, p=0.002). However, in a multivariate regression analysis, when proportional OS parameters were considered, only IMA level was found to be an independent risk factor in determining the patient and the control group, when adjusted for hypertension, hyperlipidaemia, smoking and HDL cholesterol, as (OR=2.711, 95% CI=1.094–6.719, p=0.031). In our study, between OS parameters examined and in hospital short term prognostic factors, there was only a statistically significant relationship between OSI and TIMI score groups. In the patient group, 17 patients had TIMI score 3 flow and 46 patients had TIMI score 0–2 flow. The OSI values were significantly higher in the patients with TIMI score 3 flow than in patients with TIMI score 0–2 flow (2.42 [0.81–4.49] vs. 1.63 [0.33–6.07], p=0.016) as shown in Figure 3. In ROC analysis, it was concluded that OSI≤2.17 AU values predicts TIMI 0–2 with 80.4% sensitivity and 64.7% specificity (AUC=0.698, 95% CI 0.570–0.808, p=0.012).

Discussion
In this study, TOS, OSI, IMA, MPO, MPO/PON-1 and MPO/HDL cholesterol ratios were found to be significantly elevated, whereas, PON-1 and AREase levels were significantly reduced in STEMI patients compared to the control group. However, we found that only IMA level was an independent risk factor between groups when adjusted according to baseline characteristics and laboratory values. When the relationship between these parameters and in-hospital
short-term prognosis were considered, OSI value was found high in patients with complete spontaneous reperfusion. We did not find any relationship between the proportional OS parameters and in-hospital mortality and early systolic dysfunction.

The relationship between OS and atherosclerotic processes has been on the front burner of scientists for the last 30 years. It has been shown that ROS generated by NADH/NADPH oxidase cause oxidative modification of LDL-cholesterol in individuals with atherosclerotic coronary artery disease [15]. Bhat et al. reported that serum TAS, TOS and malondialdehyde values were increased in peripheral blood leukocytes, indicating more oxidative DNA damage and OS, in people with coronary artery disease [16]. OS parameters have also been studied in ACSs. In a study comparing non-ST elevation myocardial infarction (NSTEMI) and unstable angina pectoris (USAP) patients, TOS and OSI were found to be higher in the NSTEMI group than the USAP group. This suggested the role of OS in the pathogenesis of acute NSTEMI [17]. In another study, TAS and OSI values were found to be higher in patients with myocardial infarction than the normal population, and TAS and OSI values were found to be correlated with age and a prognostic score, known as GRACE score. Therefore, these authors suggested that OSI could be a predictor of the risk and severity in myocardial infarction patients [18].

Spontaneous recovery of the total occlusion of the infarct-related coronary artery (IRA) in STEMI allows rapid restoration of blood flow and improves survival [19]. Complete recovery of distal flow, in other words TIMI score 3 flow, in IRA before primary percutaneous intervention, is in association with improved prognosis [20]. Borekci et al. examined the relationship between TAS, TOS and OSI in STEMI patients, and spontaneous complete reperfusion in IRA, and found a significant relationship between these parameters and TIMI score 3 flow Patients with TIMI score 3 flow were considered as spontaneous reperfusion group, and patients with TIMI score 0–2 flow were considered as non-spontaneous reperfusion group. In this study, in the

### Table 2: Laboratory findings and the studied oxidative stress markers.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Patient group (n=63)</th>
<th>Control group (n=44)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea, mg/dL</td>
<td>35 [12–87]</td>
<td>30 [15–47]</td>
<td>0.319</td>
</tr>
<tr>
<td>Creatinin, mg/dL</td>
<td>0.9 [0.5–4.6]</td>
<td>0.8 [0.5–1.3]</td>
<td>0.699</td>
</tr>
<tr>
<td>TC, mg/dL</td>
<td>188 ± 74</td>
<td>193 ± 45</td>
<td>0.643</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>120 ± 38</td>
<td>115 ± 35</td>
<td>0.242</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>40 [26–57]</td>
<td>47 [25–102]</td>
<td>0.010</td>
</tr>
<tr>
<td>Triglyceride, mg/dL</td>
<td>139 [52–465]</td>
<td>131 [36–434]</td>
<td>0.505</td>
</tr>
<tr>
<td>TAS, mmol/L</td>
<td>1.25 [0.73–2.76]</td>
<td>1.17 [0.72–2.75]</td>
<td>0.062</td>
</tr>
<tr>
<td>TOS, μmol/L</td>
<td>20.95 [6.53–70.89]</td>
<td>18.63 [9.46–33.12]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OSI, AU</td>
<td>1.65 [0.33–6.07]</td>
<td>1.61 [0.67–3.00]</td>
<td>0.007</td>
</tr>
<tr>
<td>IMA, AU</td>
<td>1.24 ± 0.44</td>
<td>0.95 ± 0.67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PON-1, U/L</td>
<td>106 [30–405]</td>
<td>152 [46–752]</td>
<td>0.003</td>
</tr>
<tr>
<td>ARES, U/L</td>
<td>867 [252–1007]</td>
<td>895 [573–1098]</td>
<td>0.026</td>
</tr>
<tr>
<td>MPO/PON-1</td>
<td>1.12 [0.14–18.74]</td>
<td>0.70 [0.04–4.09]</td>
<td>0.004</td>
</tr>
<tr>
<td>MPO/ARES</td>
<td>0.15 [0.05–1.48]</td>
<td>0.12 [0.01–1.06]</td>
<td>0.097</td>
</tr>
<tr>
<td>MPO/HDL</td>
<td>3.66 [1.02–28.29]</td>
<td>2.49 [0.11–20.53]</td>
<td>0.029</td>
</tr>
</tbody>
</table>

*Data are expressed as median and minimum-maximum value. AU, arbitrary unit; ARES, arylesterase; CK-M, creatine kinase MB; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; IMA, ischemia modified albumin; LDL-C, low-density lipoprotein cholesterol; MPO, myeloperoxidase; OSI, oxidative stress index; PON-1, paraoxonase-1; TAS, total antioxidant status; TOS, total oxidant status; TC, total cholesterol; TG, triglyceride.*
group with spontaneous reperfusion, the TAS value was higher and the TOS and OSI values were lower than the non-spontaneous reperfusion group. In our study, a significant relationship was found only between OSI and spontaneous reperfusion. We found that the OSI value was higher in the group with spontaneous reperfusion compared to the group with non-spontaneous reperfusion. Our findings were not similar to the only previous study [21]. OS, which increases suddenly with the sudden occlusion, may affect the coronary thrombus by increasing inflammation and may also mediate blood flow. In addition, spontaneous reperfusion may have increased reperfusion injury and OS. TOS was also found to be higher in patients with spontaneous reperfusion, but this difference did not reach to a statistically significant level.

When the current literature was reviewed, no relationship was found between well-known OS biomarkers (TAS, TOS and OSI) and mortality in STEMI patients. We also could not find any relationship between the OS parameters

Table 3: Correlations between oxidative stress parameters, lipid profile, MPO/PON and MPO/HDL-C among patients.

<table>
<thead>
<tr>
<th>Variables</th>
<th>MPO/PON-1</th>
<th>MPO/HDL</th>
<th>MPO/PON-1</th>
<th>MPO/HDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAS</td>
<td>0.170</td>
<td>0.081</td>
<td>0.171</td>
<td>0.078</td>
</tr>
<tr>
<td>TOS</td>
<td>0.302</td>
<td>0.002</td>
<td>0.279</td>
<td>0.004</td>
</tr>
<tr>
<td>OSI</td>
<td>0.209</td>
<td>0.030</td>
<td>0.176</td>
<td>0.069</td>
</tr>
<tr>
<td>IMA</td>
<td>-0.140</td>
<td>0.150</td>
<td>-0.045</td>
<td>0.645</td>
</tr>
<tr>
<td>ARES</td>
<td>-0.280</td>
<td>0.003</td>
<td>-0.245</td>
<td>0.011</td>
</tr>
<tr>
<td>TC</td>
<td>0.070</td>
<td>0.472</td>
<td>0.075</td>
<td>0.442</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.056</td>
<td>0.566</td>
<td>0.075</td>
<td>0.445</td>
</tr>
<tr>
<td>TG</td>
<td>0.432</td>
<td>&lt;0.001</td>
<td>0.472</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C</td>
<td>-0.296</td>
<td>0.002</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PON-1</td>
<td>-</td>
<td>-</td>
<td>-1.39</td>
<td>0.153</td>
</tr>
</tbody>
</table>

ARES, arylesterase; HDL-C, high-density lipoprotein cholesterol; IMA, ischemia modified albumin; MPO, myeloperoxidase; LDL-C, low-density lipoprotein cholesterol; PON-1, paraoxonase-1; OSI, oxidative stress index; TAS, total antioxidant status; TC, total cholesterol; TG, triglyceride; TOS, total oxidant status.

Figure 2: Box plot presentation comparison of MPO/HDL cholesterol among patients and control groups (2.49 vs. 3.66, p=0.029).

Figure 3: Box plot presentation of oxidative stress index (OSI) value among TIMI flow groups, TIMI 3 and TIMI 0–2 (2.42 vs. 1.63, p=0.016).
and in-hospital mortality. In a study examining the relationship between early systolic dysfunction and OS parameters such as total thiol groups, catalase, superoxide dismutase, and glutathione reductase. Catalase was found to be associated with early systolic dysfunction and acute heart failure in STEMI patients. In conclusion, catalase and thiol groups were reported as independent predictors of acute myocardial infarction [22]. However, early systolic dysfunction and other OS parameters have not been investigated in STEMI patients. In our study, no significant relationship was found between the studied OS parameters and early systolic function, that is, reduced ejection fraction.

MPO is a heme protein playing a role in the oxidative modification of lipoproteins. This enzyme is highly expressed from macrophages, neutrophils and monocytes in the atherosclerotic plaques [23]. This leukocyte derived enzyme catalyses the production of ROS. It has been found that the MPO levels are high in STEMI patients and may predict all cardiac events including death [24, 25]. In our study, no significant relationship was found between the studied OS parameters and early systolic function, that is, reduced ejection fraction.

IMA is a biomarker that can be used in the diagnosis of ACS [26]. The rapidly increasing IMA level following the development of ischemia in the tissue returns to normal blood value within 48 h. It has been determined that the most important mechanism in IMA formation is the stimulation of free radicals in the ischemic tissue [27]. For this reason, IMA is considered as one of the OS parameters. In addition, it was concluded that high IMA levels in STEMI patients can be used to predict incomplete ST segment resolution, which is a poor prognostic criterion [28]. In our study, IMA levels were found to be statistically significantly higher in the STEMI group than the control group. We found that IMA was an independent risk factor when regression analysis was performed by adjusting between groups. However, it failed to predict in-hospital short term prognosis.

PON-1 and AREase are the two antioxidant enzymes which have been defined as calcium dependent esterase/lactonase. They bind on HDL cholesterol and prevent atherosclerosis by detoxifying lipid peroxidation [29]. In addition to reverse cholesterol transport activity, which is responsible for the anti-atherogenic effect of HDL cholesterol, the activity mainly takes place through PON-1 [30]. PON-1 and AREase activities were found to be significantly lower in people with angiographic coronary artery disease than those with normal coronary arteries, and these low enzyme activities were reported to be more common in those with occlusion in all three coronary arteries. The reason why these antioxidant enzymes decrease is the elevation of OS in these patients which correlates with the severity of the disease [31]. Also, in our study, PON-1 and AREase enzyme activities were found to be lower in STEMI patients than the control group. This had no effect on the prognostic biomarkers examined.

In coronary artery disease, the elevation of MPO serum level at the time of a reduction in PON-1 and AREase activities, brings to mind a question of whether the ratios of these parameters are related with the prognosis of coronary artery disease or not. It was concluded that high MPO/PON-1 ratio predicted stent restenosis in patients with coronary stent [32]. In patients with ACS, the MPO/PON-1 ratio was examined in a single study in his study performed by Emami Razavi et al., MPO level was examined by immunoassay and PON-1 activity was measured by a colorimetric method. MPO/PON-1 ratio was found to be significantly higher in patients with ACS compared to the control group (p<0.01). The investigators assert the idea that MPO/PON-1 ratio could be the predictor of ACS [33]. In our study, both enzymes (MPO and PON-1) were examined by using an immunoassay method and the ratio of MPO/PON-1 was found to be significantly increased in STEMI patients. In addition, these values were found to be positively correlated with TOS and triglyceride levels and negatively correlated with IMA in the patient group. Despite this significant relationship in STEMI patients, MPO/PON-1 ratio did not show any superiority compared to only MPO and PON-1 values in predicting in-hospital short-term prognosis.

The MPO/HDL cholesterol ratio has so far been evaluated only in the Dallas Heart study performed by Khine et al. [34]. In this study, almost three thousand individuals without coronary artery disease have been followed up for 9.4 years to understand the development of coronary artery disease. When MPO/HDL cholesterol particle concentration was examined, it was found that this ratio had a negative relationship with serum HDL cholesterol level, HDL cholesterol size and PON-1 activity. As a result, in this study, it was concluded that the incidence of atherosclerotic heart disease was increased in nearly 74% of the patients with high MPO/HDL cholesterol particle concentration (HR=1.74, 95% CI 1.12–2.70). According to our knowledge, MPO/HDL has not been investigated in patients with stable coronary artery disease or acute coronary artery disease before. In our study, MPO/HDL cholesterol ratio was found to be significantly increased in the STEMI group compared to the control group. This ratio was also in correlation with TOS, AREase and triglyceride levels in the patient group. However, in determining in-hospital prognosis, MPO/HDL cholesterol ratio was not found to be superior compared to other OS parameters.

Some drugs can also affect OS parameters. Statins, antioxidant beta blockers (carvedilol, nebivolol), and anti-
oxidant angiotensin converting enzyme inhibitors (captopril, zofenopril) affect PON-1, AREase activities and OS [35, 36]. However, in our study, no significant difference was found when the patients on medications were compared with the patients who were not taking medications.

Our study had some limitations. Not only hyperlipidaemia but also smoking were significantly high in the patient group. Hyperlipidaemia and smoking are two important factors that increase OS. Studies have shown that smoking increases OS by decreasing PON-1 activity [37]. Although the use of statins was similar in both the patient and the control groups, the patient group was found to have elevated lipid levels. The relationship between hyperlipidaemia and high MPO level, as well as, low PON-1 level has been previously reported [38]. These two risk factors may have affected the level of OS parameters studied. In addition, moderate alcohol intake has been shown to increase PON-1 activity [39]. The alcohol intake of our patients was not questioned and this might be another limitation of our study. However, it was not possible to equate the patients included in this cross-sectional study in terms of all risk factors.

Sample size of our study can also be considered as the limitation of the study. It was not too large for mortality assessment. However, the main aim of our study was to examine the relationship between OS parameters and STEMI. Our second goal was to examine the effects of these parameters on short term prognosis. We believe that the findings of this study will shed light on future studies with larger population.

In conclusion, the decrease in HDL cholesterol and HDL cholesterol-related enzymes, PON-1 and AREase, may demonstrate that the pro-oxidant HDL is an independent predictor of both long-term and short-term mortality in STEMI patients. On the other hand, the elevated levels of both the well-known (TOS, OSI, and MPO) and proportional (MPO/PON-1 and MPO/HDL cholesterol ratios) oxidative stress markers were found to be significantly elevated and can be considered as having a role in the pathogenesis of STEMI. IMA was found as an independent risk factor when regression analysis was performed by adjusting between groups. In terms of short term prognosis, among the well-known and proportional parameters, we found a relationship only between OSI and spontaneous complete revascularization.

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**Informed consent:** Informed consent was obtained from all individuals included in this study.

**Ethical approval:** This study was initiated in accordance with the principles stated in the Helsinki Declaration and after the approval of the local Ethics Committee (date: October 16, 2019, decision no: 2019-175-16/10).

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