OXIDATIVE STRESS IN ACUTE MYOCARDIAL INFARCTION PATIENTS

Jovan Jovanovic[1*], Katarina Pantic[2*], Dragan Milojevic[3], Andjela Milojevic[4], Petar Canovic[5], Milan Zaric[5], Natasa Zdravkovic[6,7], Marija Andjelkovic[5], Marko Ravic[8] and Vladimir Miloradovic[6,1]

[1] *Clinic of Cardiology, University Clinical Center Kragujevac, Kragujevac, Serbia*
[2] *Clinic of Pulmolonogy, University Clinical Center Kragujevac, Kragujevac, Serbia*
[3] *Institute for Emergency Medical Aid, Kragujevac, Serbia*
[4] *University of Kragujevac, Faculty of Medical Sciences, Department of Dentistry, Kragujevac, Serbia*
[5] *University of Kragujevac, Faculty of Medical Sciences, Department of Biochemistry, Kragujevac, Serbia*
[6] *University of Kragujevac, Faculty of Medical Sciences, Department of Internal Medicine, Kragujevac, Serbia*
[7] *Clinic of Internal Medicine, University Clinical Centre "Kragujevac", Kragujevac, Serbia*
[8] *University of Kragujevac, Faculty of Medical Sciences, Department of Clinical Pharmacy, Kragujevac, Serbia*

[*]both authors contributed equally to this work

Received: 21.1.2021.
Accepted: 25.1.2021.

Corresponding author:

Vladimir Miloradovic, MD, PhD

University of Kragujevac, Faculty of Medical Sciences, Head of Clinic of Cardiology, Clinical Center of Kragujevac

E-mail: vanja.miloradovic@gmail.com

ABSTRACT

The aim of this study was to assess and compare the oxidative stress status in STEMI and NSTEMI patients by measuring markers of free radical production and levels of antioxidant. The research was designed as an observational study with a cohort of 83 AMI hospitalized patients divided into a case (STEMI) and control (NSTEMI) group. In the study, we used the data from the patients' electronic medical records and paper files and two scores (TIMI, and GRACE) analyzed routine biochemical parameters and biochemical assays for ROS. The statistical analysis included descriptive methods, hypothesis testing and bivariate correlation. In our research, the results clearly showed that patients with STEMI had an increased activity of vSOD compared with NSTEMI patients ($p<0.01$). Also, the levels of TBARS in plasma of patients with STEMI were significantly increased compared to the NSTEMI patients ($p<0.01$). Importantly, there were no differences between STEMI patients and NSTEMI patients, for the levels of O_2^-, H_2O_2, NO, CAT, GSH. In STEMI patients, we found a positive correlation between TBARS and troponin level and a positive correlation between SOD and troponin level. In addition, our results also showed a positive correlation between AST levels and TBARS and a positive correlation between AST levels and SOD. We also found a positive correlation between GRACE score values and TBARS and SOD. Our study demonstrated that the levels of TBARS and SOD were significantly higher in STEMI patients than in NSTEMI.

Keywords: *Acute myocardial infarction, oxidative stress, free radical, troponin.*

sciendo

UDK: 616.127-005.8:
616-008.9:[577.344:546.21
Eabr 2024; 25(1):051-056
DOI: 10.2478/sjecr-2021-0008

INTRODUCTION

Acute myocardial infarction denotes the presence of acute myocardial injury with the detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and with at least one of the following: symptoms of acute myocardial ischaemia, new ischaemic ECG changes, development of pathological Q waves, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology, and/or identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy (1).

In general, myocardial infarction is divided into STEMI (infarction with ST segment elevation) which requires the reperfusion therapy as soon as possible and NSTEMI (infarction without ST segment elevation), which does not require the reperfusion therapy, except in the following situations: hypotension or shock, repeated and progressive chest pain refracted on the medicamentous therapy, malignant arrhythmias or cardiac arrest, mechanical complications of acute MI, acute heart failure, intermittent ST segment elevation (2). The pathophysiological substrate is represented by the acute, unstable atherosclerotic plaque complicated by occlusive thrombosis (complete interruption of the blood flow in myocardial infarction) (3). STEMI occlusion is long-lasting and necrosis is transmural (it covers the entire wall) and with NSTEMI, the occlusion is of shorter duration, with less necrosis that does not include the entire wall (2,4).

ROS are spontaneously produced as by-product during the electron transfer in oxidative phosphorylation (5,6). ROS molecules include superoxide, peroxide, hydroxyl radicals, and reactive nitrogen species (RNS) (7). Furthermore, ROS oxidize various cellular and extracellular components, including nucleotides, DNA, proteins, polysaccharides, and lipids (5,8). The antioxidant activity is accomplished as a result of the antioxidant scavenger system which includes enzymes superoxide dismutase, catalase and glutathione peroxidase and antioxidant vitamins C, E, A (5,9).

The oxidative stress process involving the increased oxidant production with impairment of antioxidant mechanisms plays an essential role in the pathogenesis of atherosclerosis, and it is increased by the cardiovascular risk factors such as smoking, diabetes mellitus, dyslipidemia, etc (10,11).

The aim of this study was to assess and compare the oxidative stress status in two main groups of acute MI (STEMI and NSTEMI) by measuring markers of free radical production and levels of antioxidant, as well as to analyze patients' redox state considering the diseases activity and other clinical characteristics. We also recorded further treatment strategies after the diagnosis, primary percutaneous coronary intervention, thrombolytic therapies, delayed rescue PCI, or conservative therapy.

MATERIALSAND METHODS

Patients

The research was designed as an observational study which included a cohort of 83 patients

with AMI hospitalized in the Clinic of Cardiology, University Clinical Center "Kragujevac", Kragujevac, between September the 17th and December the 30th, 2019. The study group was divided into case (patients with STEMI) and control patients (patients with NSTEMI). We extracted the data retrospectively from the patients' electronic medical records and paper files (such as years, sex, risk factors, hypertension, hyperlipidemia, diabetes, smoking, heredity, previous vascular disease, Killip classification, etc). The diagnosis of STEMI was defined as the concurrence of prolonged chest pain or discomfort with persistent ST-segment elevation in 2 or more consecutive leads or with the presumed new left or right bundle-branch block with increased cardiac enzymes and presence of symptoms of myocardial ischeamia (12).

The diagnosis of NSTEMI was defined as the concurrence of prolonged chest pain or discomfort without ST segment elevation, (ECG changes can be presented as ST segment depression, transitory ST-segment elevation, T wave changes, or normal ECG findings) and with increased values of cardiac enzymes (13).

The routine biochemical parameters, troponin, CK, CK-MB, hemoglobin, platelets, CRP, lipid status, pro-BNP, AST were analyzed in patients. In our study, we used two scores (Thrombolysis In Myocardial Infarction – TIMI, and Global Registry of Acute Coronary Events – GRACE) in order to assess the prognosis of recurrence of myocardial ischaemia and mortality, and also to select patients who needed urgent revascularization (14). NSTEMI patients with GRACE score of 140 or higher underwent early revascularization (within 24h) and were hospitalized in the ICU, those with GRACE score between 109 – 140 were hospitalized in the hospital ward, and required revascularization within 72 hours of diagnosis, and those with GRACE score less than 109 underwent the conservative treatment (15).

An echocardiographic examination was also performed to determine the ejection fraction and segments mobility (16).

Biochemical Assays

Blood samples were taken from an antecubital vein into the Vacutainer test tube containing sodium citrate anticoagulant. Blood samples were analyzed immediately. Blood was centrifuged to separate plasma and red blood cells (RBCs). Biochemical parameters were measured spectrophotometrically.

Superoxide anion radical determination

The level of superoxide anion radical (O_2^-) was measured using nitro blue tetrazolium (NBT) reaction in TRIS-buffer combined with plasma samples and read at 530 nm.

Hydrogen peroxide determination

The protocol for measurement of hydrogen peroxide (H_2O_2) is based on oxidation of phenol red in the presence of horseradish peroxidase. 200 µl sample with 800 µl PRS (phenol red solution) and 10 µl POD (Horseradish Peroxidase) were combined (1:20). The level of H_2O_2 was measured at 610 nm.

Nitric oxide determination

Nitric oxide (NO) decomposes rapidly to form stable metabolite nitrite/nitrate products. Nitrite (NO_2^-) was determined as an index of the nitric oxide production with Griess reagent. 0.1 ml 3 N PCA (Perchloride acid), 0.4 ml 20 mM ethylenediaminetetraacetic acid (EDTA), and 0.2 ml plasma were put on ice for 15 min, then centrifuged 15 min at 6,000 rpm. After pouring off the supernatant, 220 µl K_2CO_3 was added. Nitrites were measured at 550 nm. Distilled water was used as a blank probe.

Index of lipid peroxidation (thiobarbituric acid reactive substances, TBARS)

The degree of lipid peroxidation in plasma was estimated by measuring of TBARS using 1 % TBA (thiobarbituric Acid) in 0.05 NaOH, incubated with plasma at 100 ^{0}C for 15 min and read at 530 nm. Distilled water was used as a blank probe. TBA extract was obtained by combining 0.8 ml plasma and 0.4 ml trichloroacetic acid (TCA), then the samples were put on ice for 10 min, and centrifuged for 15 min at 6,000 rpm. This method was described previously.

Determination of antioxidant enzymes

Isolated RBCs were washed three times with three volumes of ice-cold 0.9 mmol/l NaCl, and hemolysates containing about 50 g Hb/l (prepared according to McCord and Fridovich) were used for the determination of CAT activity. The CAT activity was determined according to Beutler. Then 50 ll CAT buffer, 100 µl sample, and 1 ml 10 mM H_2O_2 were added to the samples. Detection was performed at 360 nm. Distilled water was used as a blank probe. The SOD activity was determined by the epinephrine method of Misra and Fridovich. A hundred µl lysate and 1 ml carbonate buffer were mixed, and then 100 µl of epinephrine was added. Detection was performed at 470 nm.

Statistics

The statistical analysis was performed with SPSS 15.0 for Windows. The results are expressed as the mean ± standard error of the mean. The data distribution was checked with the Shapiro–Wilk test, and depending on its results, the appropriate parametric or nonparametric test was used. The differences between two groups were assessed using T test or Man-Whitney test, while the differences between the values of means from more than two groups were assessed by ANOVA or Kruskal–Wallis test. The correlation between various variables was found using Bivariate correlation, i.e., Spearman's coefficient of correlation.

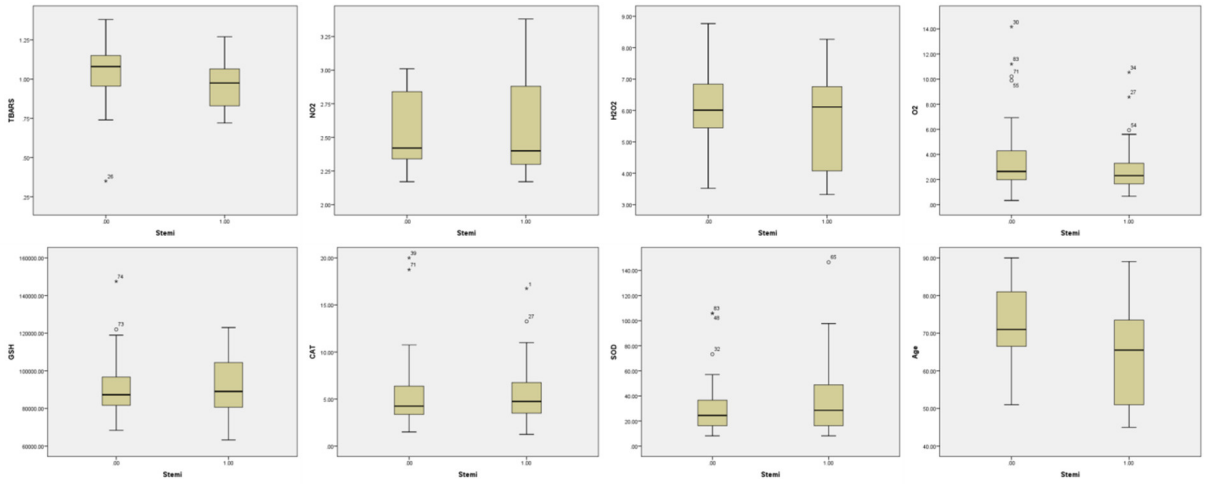
Table 1. Demographic and clinical characteristics of patients with NSTEMI (control) and STEMI. *p<0.01

	NSTEMI	STEMI
Number of patients	34 (41%)	49 (59%)
Age	71.46±1.64	64.5±2.27
AST	49.59±6.52	158.46±30.42*
Troponine	3.64±0.95	42.17±10.57*
CK-MB	29.44±4.83	151.53±21.42*
CK	397.14±96.97	1738.25±287.19*
ProBNP	5769±1271	5162±1457
Haemoglobin	123.72±3.59	128.65±3.68
thrombocytes	242.91±14.54	247.53±15.84
CRP	44.9±9.94	40.96±9.83
Total Chloesterol	5.12±0.22	5.15±0.23
LDL	3.07±0.16	3.27±0.2
HDL	1.1±0.04	1.06±0.04
Triglycerides	1.69±0.16	1.68±0.13
GRACE Score	147.06±4.55	143.37±6.21

Table 2. Parameters of oxidative stress in NSTEMI and STEMI patients.

	TBARS	NO_2	H_2O_2	O_2^-	GSH	CAT	SOD
NSTEMI	1.08±0.03	2.42±0.06	6.01±0.97	3.51±2.54	87278±1492	5.42±4.25	24.42±22.82
STEMI	0.97±0.02	2.4±0.1	6.1±2.21	2.99±2.17	91138±1735	5.53±4.75	28.49±32.49

Figure 1. Oxidative stress parameters in NSTEMI (0) and STEMI (1) patients. *p<0.01.



RESULTS

Eighty-three patients with AMI (mean age 71.46 years, SD ± 11.29, range 51 - 90) had a clear diagnosis of STEMI or NSTEMI based on the clinical characteristics, troponin values and ST segment deviation on ECG. The median duration of hospitalization for STEMI was 4 days (2 to 6 days) and for NSTEMI was 8 days (6 to 10 days). The demographic and clinical characteristics of patients with STEMI and NSTEMI (controls) are summarized in Table 1. STEMI was diagnosed in 49 patients (59%), while NSTEMI was diagnosed in 34 patients (41%). The parameters of oxidative stress are shown in Table 2 (comparison of the status of free radicals and antioxidant in STEMI and NSTEMI).

In terms of the oxidative stress parameters, STEMI and NSTEMI patients differed in two out of seven investigated parameters which included the index of lipid peroxidation, and activity of SOD (Figure 1). In our research, the results clearly showed that patients with STEMI had an increased activity of SOD compared with NSTEMI patients ($p<0.01$). Also, the levels of TBARS in plasma of patients with STEMI were significantly increased compared to the NSTEMI patients ($p<0.01$). Importantly, there were no differences between STEMI patients and NSTEMI patients, for the levels of O_2^-, H_2O_2, NO, CAT, GSH (Figure 1).

In STEMI patients, we found a positive correlation between TBARS and troponin level and a positive correlation between SOD and troponin level. In addition, our results also showed a positive correlation between AST levels and TBARS and a positive correlation between AST levels and SOD (Suppl. 1).

We also found a positive correlation between GRACE score values and TBARS and SOD (Suppl. 1).

DISCUSSION

Many studies have demonstrated a role of ROS in the pathogenesis of acute coronary syndrome (17, 18). In the basis of formation of atherosclerotic plaque, there is a complex process involving several mechanisms, including the endothelial dysfunction, neovascularization, vascular proliferation, apoptosis, matrix degradation, inflammation, and thrombosis (19,20,21). The key process in atherosclerotic plaque formation includes destruction of well-balanced homeostatic mechanisms, which incurs the oxidative stress (11,22).

For that reason, it is essential to investigate the role of oxidative stress in cardiovascular disease processes, such as atherogenesis, ischemic-reperfusion injury and cardiac remodeling (23,24). Currently, an increasing number of studies suggest that the levels of oxidative stress markers in body fluids had a positive correlation with the atherosclerotic disease activity (25, 26).

Koprivica et al. study demonstrated that ACSs patients had a significantly less efficient antioxidative defense system

compared to healthy subjects, significantly lower levels of SOD and CAT activity which resulted in significantly increased levels of lipid peroxidation. Moreover, this study clearly showed that the oxidative status between STEMI and NSTEMI patients differed only in the SOD level (27). Our results also undoubtedly showed that the SOD level is higher in STEMI patients compared to NSTEMI patients which is analogous to the previously mentioned research.

Lavall et al. study included the oxidative profile of patients with ST segment elevation and patients with non-ST-segment elevation (NSTEMI). The results of this study showed that plasma TBARS and SOD activity were significantly higher in STEMI patients compared to the control (NSTEMI) (28). Also, Yosri Noichri et al. results showed that patients with AMI compared to healthy subjects had a significantly lower catalase activity and significantly higher TBARS levels (29). Our research showed that STEMI patients had a higher level of SOD activity and also had a higher level of plasma TBARS compared to NSTEMI patients which is also in correlation with the previously mentioned researches.

Bagatini et al. results demonstrated an increase in substances reactive to thiobarbituric acid (TBARS) and carbonyl protein levels in AMI and the risk groups. In addition, the research showed a positive correlation between TBARS, carbonyl protein levels, and troponin in AMI patients (30). Moreover, in our study, the results clearly showed a positive correlation between TBARS and troponin, which is also in correlation with the previously mentioned study. These findings reinforce the fact that the increased lipid peroxidation is associated with the infarct size and degree of cellular damage (31, 32).

The previous studies have clearly indicated that AMI patients are under higher oxidative stress compared with the control (healthy subjects), no matter which type of AMI they have (27,33). The results of our study demonstrated that the oxidative profile generated by STEMI and NSTEMI is similar regardless of the size of arterial occlusion. The results associated with the investigation of oxidative stress in STEMI and NSTEMI patients suggest that the antioxidant supplementation is needed to improve the antioxidant defense, since the antioxidant defense is compromised and lipid peroxidation is increased in those patients (34, 35).

The study of Shahzad et al found a positive correlation between the level of oxidative stress markers and Grace score, which is in agreement with our results that TBARS and SOD rise were associated with high Grace score values (36).

CONCLUSION

Our study demonstrated that the levels of TBARS and SOD were significantly higher in STEMI patients than in NSTEMI. They were also statistically significantly higher in STEMI patients with high values of AST and troponin. In addition, the value of Grace score and age of a patient were associated with the value of mentioned markers of oxidative stress. Other parameters of oxidative stress didn't show a significant correlation with AMI type.

ACKNOWLEDGEMENT

The authors would like to thank the Faculty of Medical Sciences of the University of Kragujevac, Kragujevac, Serbia, for supporting the research with the Junior Project JP 04-19.

CONFLICT OF INTEREST

The authors declare no financial or commercial conflict of interest.

REFERENCES

1. Agirbasli M. Universal definition of MI: Above 99 percentile of upper reference limit (URL) for hs-cTn: Yes, but which URL?. Am J Emerg Med. 2019;37(3):510.
2. Kotecha T, Rakhit RD. Acute coronary syndromes. Clin Med (Lond). 2016;s43-s48.
3. Andrews JPM, Fayad ZA, Dweck MR. New methods to image unstable atherosclerotic plaques. Atherosclerosis. 2018;272:118-128.
4. Kanjuh V, Ostojic M, Lalic N, et al. Koronarne aterotrombotične lezije. Histopatologija, klasifikacija, korelacija sa kliničkim sindromima ishemijske bolesti srca I dijagnostika invivo I postmortem. U knjizi: Novi pogledi u prevenciji I tretmanu ateroskleroze. Glavni urednik: Kuzmanović R, et al. Banja Luka: ANURS (naučni skupovi knjiga XI, Odjelj med nauka Knjiga 2) 2007; 33-100.
5. Jakubczyk K, Dec K, Kałduńska J, Kawczuga D, Kochman J, Janda K. Reactive oxygen species - sources, functions, oxidative damage. Pol Merkur Lekarski. 2020 Apr 22;48(284):124-127.
6. Kanaan GN, Harper ME. Cellular redox dysfunction in the development of cardiovascular diseases. Biochim Biophys Acta Gen Subj. 2017;1861(11 Pt A):2822-2829.
7. Li H, Horke S, Förstermann U. Vascular oxidative stress, nitric oxide and atherosclerosis. Atherosclerosis.2014;237(1):208-19.
8. Li R, Jia Z, Trush MA. Defining ROS in Biology and Medicine. React Oxyg Species (Apex). 2016;1(1):9-21.
9. Salehi B, Martorell M, Arbiser JL, et al. Antioxidants: Positive or Negative Actors?. Biomolecules. 2018;8(4):124.
10. Burtenshaw D, Kitching M, Redmond EM, Megson IL, Cahill PA. Reactive Oxygen Species (ROS), Intimal Thickening, and Subclinical Atherosclerotic Disease. Front Cardiovasc Med. 2019;6:89.
11. Yang X, Li Y, Li Y, et al. Oxidative Stress-Mediated Atherosclerosis: Mechanisms and Therapies. Front Physiol. 2017;8:600.
12. Ibanez B, James S, Agewall S, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST –segment elevation. Eur Heart J 2018;39:119-177

13. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014. AHA/ACC guidelines for the management of patients with non-ST-elevation acute cocronary syndromes. J Am Coll Cardiol. 2014; 24:e139-228
14. Poldervaart JM, Langedijk M, Backus BE et al. Comparison of the GRACE, HEART and TIMI score to predict major adverse cardiac events in chest pain patients at the emergency department. Int J Cardiol. 2017;227:656-661.
15. Rahmani R, Majidi B, Ariannejad H, Shafiee A. The Value of the GRACE Score for Predicting the SYNTAX Score in Patients with Unstable Angina/Non-ST Elevation Myocardial Infarction. Cardiovasc Revasc Med. 2020;21(4):514-517.
16. Alizadehasl A, Sadeghpour A, Behjati M. The role of echocardiography in acute myocardial infarction. Indian Heart J. 2017;69(4):563.
17. Gökdemir MT, Kaya H, Söğüt O, Kaya Z, Albayrak L, Taşkın A. The role of oxidative stress and inflammation in the early evaluation of acute non-ST-elevation myocardial infarction: an observational study. Anadolu Kardiyol Derg. 2013;13(2):131-6.
18. Förstermann U, Xia N, Li H. Roles of Vascular Oxidative Stress and Nitric Oxide in the Pathogenesis of Atherosclerosis. Circ Res. 2017;120(4):713-735.
19. Camaré C, Pucelle M, Nègre-Salvayre A, Salvayre R. Angiogenesis in the atherosclerotic plaque. Redox Biol. T2017;12:18-34.
20. Quillard T, Franck G, Mawson T, Folco E, Libby P. Mechanisms of erosion of atherosclerotic plaques. Curr Opin Lipidol. 2017;28(5):434-441.
21. Badimon L, Vilahur G. Thrombosis formation on atherosclerotic lesions and plaque rupture. J Intern Med. 2014;276(6):618-32.
22. Marchio P, Guerra-Ojeda S, Vila JM, Aldasoro M, Victor VM, Mauricio MD. Targeting Early Atherosclerosis: A Focus on Oxidative Stress and Inflammation. Oxid Med Cell Longev. 2019;2019:8563845..
23. Fuentes E, Moore-Carrasco R, de Andrade Paes A M, Trostchansky A. Role of Platelet Activation and Oxidative Stress in the Evolution of Myocardial Infarction. J Cardiovasc Pharmacol Ther. 2019;24(6):509-520.
24. Münzel T, Camici GG, Maack C, Bonetti NR, Fuster V, Kovacic JC. Impact of Oxidative Stress on the Heart and Vasculature: Part 2 of a 3-Part Series. J Am Coll Cardiol. 2017;70(2):212-229.
25. Vichova T, Motovska Z. Oxidative stress: Predictive marker for coronary artery disease. Exp Clin Cardiol. 2013;18(2):e88-91.
26. Neri M, Fineschi V, Di Paolo M, Pomara C, Riezzo I, Turillazzi E, et al. Cardiac oxidative stress and inflammatory cytokines response after myocardial infarction. Curr Vasc Pharmacol. 2015;13(1):26-36.
27. Koprivica Z, Djordjevic D, Vuletic M, et al. Von Willebrand factor and oxidative stress parameters in acute coronary syndromes. Oxid Med Cell Longev. 2011:2011:918312..
28. Lavall MC, Bonfanti G, Ceolin RB, Schott KL, Gonçalves Tde L, Moresco RN, et al. Oxidative Profile of Patients with ST Segment Elevation Myocardial Infarction. Clin Lab. 2016;62(5):971-3.
29. Noichri Y, Chalghoum A, Chkioua L, Baudin B, Ernez S, Ferchichi S, et al. Low erythrocyte catalase enzyme activity is correlated with high serum total homocysteine levels in Tunisian patients with acute myocardial infarction. Diagn Pathol. 2013:8:68.
30. Bagatini MD, Martins CC, Battisti V, Gasparetto D, da Rosa CS, Spanevello RM, Ahmed M, Schmatz R, Schetinger MR, Morsch VM. Oxidative stress versus antioxidant defenses in patients with acute myocardial infarction. Heart Vessels. 2011;26(1):55-63.
31. Lee SH, Fujioka S, Takahashi R, Oe T. Angiotensin II-Induced Oxidative Stress in Human Endothelial Cells: Modification of Cellular Molecules through Lipid Peroxidation. Chem Res Toxicol. 2019;32(7):1412-1422.
32. Zhong S, Li L, Shen X, Li Q, Xu W, Wang X, et al. An update on lipid oxidation and inflammation in cardiovascular diseases. Free Radic Biol Med. 2019;144:266-278.
33. Kitano D, Takayama T, Nagashima K, et al. A comparative study of time-specific oxidative stress after acute myocardial infarction in patients with and without diabetes mellitus. BMC Cardiovasc Disord. 2016;16:102.
34. Wasyanto T, Yasa' A, Jalaludinsyah A. Effect of Oral N-Acetylcysteine Supplementation on the Immunity System in Patients with Acute Myocardial Infarction. Acta Med Indones. 2019;51(4):311-317.
35. Pasupathy s, Tavella R, Grover S, et al. Early Use of N-acetylcysteine With Nitrate Therapy in Patients Undergoing Primary Percutaneous Coronary Intervention for ST-Segment-Elevation Myocardial Infarction Reduces Myocardial Infarct Size (the NACIAM Trial [N-acetylcysteine in Acute Myocardial Infarction]). Circulation. 2017;136(10):894-903.
36. Shahzad S, Mateen S, Hasan A, Moin S. Grace score of myocardial infarction patients correlates with oxidative stress index, hsCRP and inflammation. Immunobiology. 2019;224(3):433-439.