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The association of myeloperoxidase and SYNTAX score in patients with ST-elevation myocardial infarction

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ABSTRACT

Aims: There is evidence that myeloperoxidase (MPO) is a significant biomarker in various cardiovascular diseases. This work explored the relationship between MPO serum levels and SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery trial) score in patients with ST Elevation Myocardial Infarction (STEMI) after percutaneous coronary intervention.

Methods: The study design was observational and cross-sectional with prospective patient enrollment. Patients were divided into two groups: those with a SYNTAX score >32 and those with a SYNTAX score ≤32. The SYNTAX score was calculated based on the SYNTAX 2.2 score calculator (syntaxscore.org). Patients were analyzed for demographic, and clinical characteristics, including body mass index, carbohydrate and lipid metabolic balance, troponin, and MPO levels. The MPO was measured by ELISA.

Results: Ninety-three patients with STEMI were enrolled with a mean age of 63.77±8.55 years, and 50.5% were males. The MPO level had a significant positive correlation with the SYNTAX score in patients with SYNTAX score >32, r=0.58, p<0.001, and in low SYNTAX score ≤32 patients: r=0.42, p=0.006. Multivariate regression analysis showed that MPO was a significant predictor for SYNTAX score >32 [odds ratio (OR): 1.055, 95% confidence interval (CI): 1.007-1.101, p=0.009], also age (OR: 1.129, 95% CI: 1.031-1.401, p=0.007), high sensitivity of C-reactive protein (OR: 1.309, 95% CI: 1.167-2.878, p=0.030), and triglycerides (OR: 1.181, 95% CI: 1.077-1.992, p=0.021) were significant predictors.

Conclusions: The elevated MPO levels are related to a higher SYNTAX score and may help predict further STEMI development.

Introduction

Myeloperoxidase (MPO) is a protein from the heme peroxidase superfamily and is deposited primarily in leukocytes (1). This enzyme is secreted upon the activation of leukocytes and is an essential player in innate immunity (2). Additionally, MPO can also be found in the endothelial cells (3). MPO has several important functions, such as the antimicrobial activity of neutrophils and phagocytosis (4). Studies have also shown that MPO is a local mediator of tissue damage due to inflammation in various pathologies (1,5,6). Recent studies have shown that changes in the concentration of MPO lead to an inflammatory response and affect the production of cytokines, and it has also been reported that increased oxidative stress and inflammation are associated with an increased level of MPO (7).

MPO is among the biomarkers defined for cardiovascular diseases (CVD), including acute coronary syndrome (ACS), atherosclerosis, heart failure (HF), and hypertension (8-10). On the other hand, the current knowledge is also conflicting. For instance, some studies have reported a positive relationship between high MPO levels and poor prognosis and an increased risk of death in CVD (5,11). In contrast, other studies have not found such a clear correlation (12). Therefore, the existing data do not provide an unambiguous answer to the certainty of MPO as a prognostic marker.

Researchers and cardiologists increasingly use the SYNTAX (from the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery trial) scale in routine clinical practice to assess patients with ST Elevation Myocardial Infarction (STEMI). This scale effectively predicts the future course of patients with STEMI after percutaneous coronary intervention (PCI) since numerous studies have confirmed that patients with a high SYNTAX score are more likely to have a poor prognosis (13,14). This scale is also a significant independent predictor of severe cardiovascular outcomes (15-17). However, there is no data on the relationship of MPO with the SYNTAX scale, while it may be useful from a practical perspective to consider MPO as a factor in determining the complexity of patients with STEMI.

We hypothesized that high levels of MPO may be associated with SYNTAX scores and subsequently with serious adverse cardiovascular events during the post-infarction period.

Therefore, this study investigated the relationship between MPO level and SYNTAX score in patients with STEMI patients after PCI.

Methods

Study population

The study design was observational and cross-sectional with prospective patient enrollment. The patients were diagnosed with STEMI and underwent coronary angiography. All participants were hospitalized and examined during the first 12 h at the Department of Prevention and Treatment of Emergency Conditions in Government Institution "L.T. Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine", Kharkiv May 2021 to December 2021. We diagnosed STEMI according to the European Guidelines for the Diagnosis and Treatment of STEMI, 2017. All patients received therapy according to the current recommendations of the European Society of Cardiology.

STEMI, hospital admission within 24 h after the onset of the first signs, age ≥40 ≤80 years, and informed consent to participate in the study were the inclusion criteria. Exclusion criteria were informed consent refusal, prior coronary bypass surgery, diabetes mellitus, body mass index >39 kg/m^2, glomerular filtration rate <60 mL/min/1.73 m^2, malignancy, infectious and inflammatory diseases in the acute stage, type 1 diabetes mellitus, hypertrophic cardiomyopathy, life-threatening arrhythmias, thyroid disease, inability to follow the study protocol.

This study conformed to the principles outlined in the Declaration of Helsinki. The National Institute of Therapy named after A.I. L.T. Malaya NAMS of Ukraine Local Ethics and Deontology Commission approved the study protocol (no. 12 from 21/10/2020), and all patients gave informed consent.

Laboratory and instrumental investigations

The investigator team assessed the clinical and biochemical parameters in the first 24 h of admission, including smoking status, body mass index, blood pressure, and medications. Laboratory tests were performed according to standard methods to determine white blood cell count, platelet count, hemoglobin level, blood glucose, lipids, serum creatinine, glycated hemoglobin (HbA1c), high sensitivity of C-reactive protein (hs-CRP) and highly sensitive cardiac troponin I (hs-cTnI), MPO.

Whole blood (10 mL) was taken for MPO measurement. Then, the sample was centrifuged, and the serum samples were stored at -80 °C until assayed. MPO was measured using reagents (Ref. BMS2038INST Human MPO Instant ELISA kit) from Invitrogen, Austria, as recommended by the manufacturer.

Echocardiography was performed using the Medison SonoAceX6 apparatus (Korea) to evaluate end-systolic and end-diastolic volumes of the left ventricle (LV), maximum early diastolic filling velocity E (m/s), the maximum speed of atrial diastolic filling A (m/s), their ratio E/A, and LV ejection fraction (EF).

Coronary angiography was performed through the femoral or radial artery according to the approved protocol immediately after hospitalization using the Integris Allura system (Philips Healthcare, Best, the Netherlands). Each coronary artery was visualized with two to three orthogonal projections according to the usual protocol. An automatic contrast injector was used to support the procedure with "Ultravist-370" contrast (Bayer Pharma GmbH, Germany). Primary PCI was performed with a bare-metal Rebel TM stent (Platinum Chromium Coronary Stent System, Boston Scientific, USA) for infarction of the dependent artery.

The SYNTAX score was calculated by interventional cardiologists based on the SYNTAX 2.2 score calculator (syntaxscore.org). The patients were divided into two groups according to the SYNTAX score >32 and ≤32.

Statistical Analysis

The MedCalc® Statistical Software version 20.111 (MedCalc Software Ltd., Ostend, Belgium) was used for statistical analysis. Continuous variables with a normal distribution are presented as mean±standard deviation. Skewed continuous variables are presented as median (interquartile range). Categorical variables are expressed as percentages and numbers. The Shapiro-Wilk test was used to test the normality of distribution. T-test was used to compare normally distributed continuous variables, and the Mann-Whitney U test to compare nonnormal distribution. Categorical variables were compared using a χ^2 test or Fisher's exact test. Univariate and multivariate analyses with the forward stepwise method were performed to determine the independent predictors of a high SYNTAX score. The results of the regression analyses were presented as odds ratios (OR)

and 95% confidence intervals (CI). A p-value of <0.05 was considered statistically significant.

Results

The study included 93 patients with a mean age of 63.77±8.55 years and 50.5% of males. As shown in Table 1, patients who were more severely ill with a high SYNTAX level (score >32) were older than the low SYNTAX group (score ≤32) (67.23±8.89 vs. 60.95±9.02; p=0.001). Additionally, patients with high SYNTAX scores had significantly higher hs-CRP levels (p=0.004), body mass index (p=0.021), systolic blood pressure (SBP) (p=0.007), and triglyceride level (p=0.012) and lower LV EF (p<0.001) compared with those in the low SYNTAX group.

Table 1 shows the comparison of the baseline characteristics of the study participants accordingly to the SYNTAX score. Smoking, diastolic blood pressure, creatinine, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, HbA1c, and hs-cTnI on admission were not statistically different between the high and low SYNTAX groups. Also, both groups were statically similar by gender.

Patients with STEMI with a high SYNTAX score had significantly increased serum MPO levels (81.05±16.33 ng/mL) compared to patients with STEMI who had a low SYNTAX score (69.81±15.07 ng/mL) (p<0.001). MPO level showed a significant positive correlation with the SYNTAX score in patients with STEMI (r=0.65, p<0.001). In patients with a SYNTAX score ≤32 correlation was weaker but still significant (r=0.42, p=0.006); and in patients with a SYNTAX score >32, it was also significant (r=0.58, p<0.001) (Figure 1A, 1B, 1C).

To assess the impact of MPO on the SYNTAX results, we performed univariate and multivariate logistic regression analyses (Table 2). Univariate associations were found between higher SYNTAX score >32 and age (OR: 1.151, 95% CI: 1.040-1.331, p=0.003), MPO (OR: 1.067, 95% CI: 1.011-1.153, p=0.010), SBP (OR: 1.155, 95% CI: 1.097-3.121, p=0.022); hs-CRP (OR: 1.547, 95% CI: 1.121-3.109, p=0.012), triglycerides (OR: 1.210, 95% CI: 1.090-2.021, p=0.019), and left ventricle EF (LVEF) (OR: 0.902, 95% CI: 0.587-0.963, p=0.042) in patients with STEMI.

Multivariate logistic regression analyses showed that MPO was an independent predictor of SYNTAX score >32 in patients with STEMI (OR: 1.055, 95% CI: 1.007-1.101, p=0.009) as shown in Table 2. In addition to MPO, age (OR: 1.129, 95% CI: 1.031-1.401, p=0.007), hs-CRP (OR: 1.309, 95% CI: 1.167-2.878, p=0.030), and triglycerides (OR: 1.181, 95% CI: 1.077-1.992, p=0.021) were the other predictors of SYNTAX score >32.

Discussion

This study showed that higher MPO levels were associated with higher SYNTAX scores in patients with STEMI. An increased MPO level was also an independent predictor of STEMI

Table 1. Comparison of baseline characteristics of the study participants accordingly to the SYNTAX score level

Parameters	All patients (n=93)	SYNTAX score ≤32 (n=47)	SYNTAX score >32 (n=46)	p
Age, years, mean±SD	63.77±8.55	60.95±9.02	67.23±8.89	0.001
Gender, males, n (%)	47 (50.5)	24 (51.1)	23 (50)	0.919
BMI, kg/m^2, mean±SD	24.31±2.15	23.57±2.31	22.44±2.32	0.021
Smoking, n (%)	43 (43.87)	20 (42.55)	22 (47.83)	0.610
HbA1c, %, mean±SD	5.89±1.23	5.77±1.34	6.02±1.19	0.344
SBP, mmHg, mean±SD	149.11±12.75	147.84±13.09	154.99±11.82	0.007
DBP, mmHg, mean±SD	90.04±8.91	88.59±8.12	91.70±7.65	0.060
Creatinine, mg/dL, mean±SD	0.95±0.19	0.95±0.17	1.01±0.15	0.075
TC, mg/dL, mean±SD	186.75±33.91	183.34±29.78	193.61±28.55	0.093
HDL, mg/dL, mean±SD	41.02±8.44	42.05±7.89	39.08±9.32	0.100
LDL, mg/dL, mean±SD	133.03±31.80	131.91±34.65	140.88±31.22	0.193
Triglyceride, mg/dL, mean±SD	170.96±47.53	159.81±51.91	185.35±43.17	0.012
hs-CRP, mg/L, mean±SD	15.99±3.22	15.05±3.63	17.38±3.89	0.004
LVEF, %, mean±SD	58.70±7.99	59.88±7.51	54.32±6.81	<0.001
hs-cTnI on admission ng/mL, median (interquartile range)	76.99 (58.11-89.79)	72.21 (55.17-85.16)	83.91 (59.98-89.21)	0.062
MPO, ng/mL, mean±SD	78.11±16.85	69.81±15.07	81.05±16.33	<0.001

P-level of significance comparing high SYNTAX score and low SYNTAX score groups.
BMI: Body mass index, LVEF: Left ventricle ejection fraction, HbA1c: Glycated hemoglobin, TC: Total cholesterol, HDL: High-density lipoprotein-cholesterol, LDL: Low-density lipoprotein-cholesterol, hs-CRP: High-sensitive C-reactive protein, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, hs-cTnI: High sensitive-cardiac troponin I, MPO: Myeloperoxidase, SD: Standard deviation

complexity. Our results highlight the significance of MPO, as well as in immune response, inflammation, and oxidative stress in patients with STEMI.

MPO is a widely studied biomarker suspected to be important in evaluating the severity of CVD. Several recent studies have reported a significant connection between MPO and CVD. Increased circulating MPO levels were found to be associated with poor prognosis and increased risk of mortality from CVD (5,8).

Several authors have suggested that due to its involvement in oxidative stress and inflammation, MPO may play an important role in destabilizing atherosclerotic plaques in coronary arteries (18), which in turn determines the clinical value of this marker.

MPO has been studied as a diagnostic indicator for chest pain in ACS (8,18) and as a prognostic marker for acute coronary events (19). We compared the obtained data with the findings of Omran et al. (18) who showed that MPO was very effective in diagnosing myocardial infarction in patients with ACS with suspected infarction. They noted that the combination of MPO, creatine kinase-MB, and TnI was the most useful in patients with ACS. They have attributed such a high diagnostic value to its significant role in the inflammatory response.

Trentini et al. (20) have evaluated the role of MPO in patients with myocardial infarction. They studied patients with acute myocardial infarction (AMI), patients with stable coronary artery disease (CAD), and controls. AMI patients had significantly higher MPO levels than controls, but they also showed that

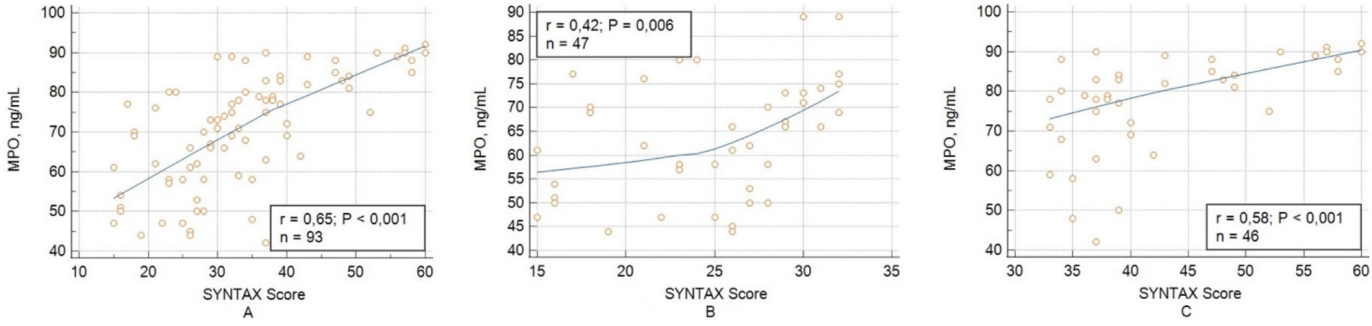

Figure 1. Correlations between myeloperoxidase serum levels and SYNTAX score. **A)** In all enrolled patients, n=93; **B)** In the first group with SYNTAX score <32, n=47; **C)** in the second group with SYNTAX score ≥32, n=46
MPO: Myeloperoxidase

Table 2. Univariate and multivariate linear regression analysis showing independent predictors of the SYNTAX score

Variables	Univariate regression analysis		Multivariate regression analysis	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
BMI	1.073 (0.993-1.069)	0.105		
Age	1.151 (1.040-1.331)	0.003	1.129 (1.031-1.401)	0.007
LVEF	0.902 (0.587-0.963)	0.042	0.902 (0.571-1.212)	0.069
Creatinine	1.049 (0.922-1.881)	0.237		
HbA1c	1.183 (0.879-1.599)	0.190		
Triglyceride	1.791 (0.879-2.625)	0.483		
HDL	0.810 (0.323-2.052)	0.654		
LDL	1.553 (0.930-1.980)	0.091		
Triglyceride	1.210 (1.090-2.021)	0.019	1.181 (1.077-1.992)	0.021
hs-CRP	1.547 (1.121-3.109)	0.012	1.309 (1.167-2.878)	0.030
Smoking	1.311 (0.903-1.566)	0.107		
SBP	1.155 (1.097-3.121)	0.022	1.161 (0.988-3.418)	0.072
DBP	1.030 (0.925-1.088)	0.158		
hs-cTnI	1.034 (0.980-1.059)	0.083		
MPO	1.067 (1.011-1.153)	0.010	1.055 (1.007-1.101)	0.009

Significant p-values are shown in bold.
CI: Confidence interval, BMI: Body mass index, LVEF: Left ventricle ejection fraction, HbA1c: Glycated hemoglobin, HDL: High-density lipoprotein-cholesterol, LDL: Low-density lipoprotein-cholesterol, hs-CRP: High-sensitive C-reactive protein, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, hs-cTnI: High sensitive-cardiac troponin I, MPO: Myeloperoxidase

MPO was higher in patients with stable CAD compared with AMI, although the patients with CAD had concomitant chronic obstructive pulmonary disease.

Based on data from previous studies that have shown an association of MPO with atherosclerosis (21-23), Tan et al. (24) studied the relationship of MPO with plaque erosion in 252 patients with STEMI, of whom 37% and 32% were diagnosed with plaque rupture and erosion, respectively. They found significantly higher levels of MPO in patients with plaque erosion compared with those with plaque rupture. Also, plasma MPO level was independently associated with plaque erosion (OR: 3.25, 95% CI: 1.37-7.76, p<0.01). MPO level correlated significantly with plaque erosion in patients, as well.

A recent, small study showed that patients with AMI correlated significantly with MPO with lesion size and microvascular obstruction (25). Higher MPO levels were observed in patients who had a larger infarct size, more prominent LV remodeling, and greater microvascular obstruction. MPO was directly correlated with cardiac troponin and peak creatine kinase (25). These results are to some extent comparable to our results.

Khalil et al. (26) have also observed results close to our investigation. In 215 patients with STEMI patients admitted for primary PCI, the authors showed that a higher level of MPO was an independent predictor of the severity of the disease and mortality. MPO levels significantly increased the quality of the prediction of adverse events and disease severity in patients with STEMI, which broadly coincides with the results obtained from us.

The large CLARITY-TIMI study with a 30-day observation found that MPO, along with two other markers (suppression of tumorigenicity 2 protein and troponin T), was a significant predictor of cardiovascular death or HF in patients with STEMI (27). These markers, when added to the TIMI risk scale, significantly improved the prognosis. Thus, MPO provided additional information for predicting death from CVD or HF.

In another study, investigators evaluated MPO levels as a predictor of long-term adverse cardiac events in patients with STEMI patients who underwent PCI (28). They found that during 14 months of follow-up, 20% of 127 patients experienced serious adverse cardiovascular events (unscheduled coronary revascularization procedure, stroke, re-infarction, or death from all causes). Higher MPO levels were independent predictors of all adverse events studied. That work has shown that MPO levels were more predictive of major cardiovascular adverse events than NT-proBNP levels.

Kolodziej et al. (29) analyzed 13 studies with 9090 participants and showed that high levels of MPO were significantly associated with mortality (OR: 2.03, 95% CI: 1.40-2.94, p<0.001). However, the author did not identify MPO as a significant predictor of serious adverse cardiac events and recurrent myocardial infarction. Similar to our study, this analysis showed that diabetes mellitus did not affect the predictive value of MPO, whereas, gender and smoking status had a strong influence on the predictive value of MPO regarding mortality and recurrence of myocardial infarction.

Cheng et al. (30) found that patients with CAD had elevated plasma levels of MPO, and MPO was positively correlated with the severity of CAD and the risk of major adverse cardiovascular events (MACE) during 6 months of follow-up. In this regard, the prognostic value of MPO was higher than that of homocysteine and hs-CRP. Thus, it was assumed that MPO could predict MACE and that this protein played an important role and showed clinical significance in assessing the patient's condition to improve the prognosis of patients.

Simultaneously, some data do not confirm the diagnostic and prognostic role of MPO and some works did not find a significant correlation between the level of MPO and clinical results in patients with CVD (31,32). For instance, a recent study by Pek et al. (31) evaluated MPO in predicting 30-day and 6-month adverse cardiac events, defined as HF-related death, myocardial infarction, and ventricular fibrillation. The results showed that MPO levels were almost the same with and without adverse cardiac events, both after 30 days and after 6 months. Thus, MPO did not show its effectiveness as a marker for the diagnosis and prognosis of ACS. On the other hand, that work was different from our study because the patients had concomitant renal pathology. The presence of such severe comorbidity could reduce the diagnostic and prognostic efficacy of MPO. Additionally, there was only one stage and not a serial measurement of MPO.

In the study by Liu et al. (32), which studied the prediction of short-term and long-term outcomes in patients with ACS, the researchers found that MPO could not significantly predict short-term or long-term outcomes. Simultaneously, the authors found that patients with STEMI had significantly higher plasma MPO levels than patients with ACS without ST-segment elevation.

Study Limitations

Our study has several limitations. First, we had a small sample size, and thus the conclusions deserve reconfirming. We also believe that only a single center can be considered a limitation. Third, the study design was cross-sectional. Additionally, we only measured the MPO concentration on admission and did not have serial measurements. Finally, we measured only the SYNTAX score without considering other possible markers of severity and prediction. However, this scale is the most relevant from our viewpoint of view.

Conclusion

In conclusion, this is the first study showing that elevated MPO levels are associated with a higher SYNTAX score and may help predict further STEMI development. Our findings may provide a new approach to the prognosis of patients with STEMI patients and make an additional tool for early risk stratification and management. However, further research is needed to elucidate the mechanism through which the observed relationship between the MPO level and severity of STEMI is realized (e.g., a reactive response to inflammation, a consequence of a more extensive endothelial lesion, response to atherosclerotic rupture, and destabilization). Identifying this pathogenic mechanism would likely lead to a better understanding of the role of MPO in the clinical management of patients with STEMI patients.

Ethics

Ethics Committee Approval and Informed Consent: The L.T. Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine Local Ethics and Deontology Commission approved the study protocol (no. 12 from 21/10/2020), and all patients gave informed consent.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: I.R., I.K., Concept: M.K., Design: M.K., I.K., Data Collection or Processing: N.T., Y.H., Analysis or Interpretation: I.R., N.T., Y.H., Literature Search: I.K., B.S., Writing: I.R., N.T., Y.H., B.S.

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