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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Dynamic thiol/disulphide homeostasis and its prognostic value in patients with non-ST elevation-acute coronary syndromes

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Abstract

Background: Cardiovascular diseases are still one of the leading causes of death in industrialised countries, and oxidative stress plays an important role in the pathogenesis of acute coronary syndromes (ACS). The dynamic thiol/disulphide homeostasis plays an important role in maintaining the oxidant-antioxidant balance.

Aim: We aimed to demonstrate the relationship between dynamic thiol/disulphide homeostasis parameters and non-ST elevation ACS (NSTE-ACS).

Methods: Patients with NSTE-ACS (n = 210) and a control group (n = 185) were included in the study. The GRACE risk score and the development of major adverse cardiovascular event (MACE) were used to evaluate the prognosis.

Results: Native thiol, total thiol, disulphide/native thiol, disulphide/total thiol, and native thiol/total thiol levels were found to be lower in the NSTE-ACS group ($p < 0.001$). There was a statistically significant difference between native and total thiol levels in the GRACE risk score subgroups ($p < 0.001$). There was a correlation between MACE and native thiol levels ($p = 0.04$).

Conclusions: Consequently, the dynamic thiol/disulphide homeostasis parameters were significantly different in the NSTE-ACS group and may be used to predict prognosis in this patient group.

Key words: non-ST elevation acute coronary syndrome, GRACE risk score, dynamic thiol/disulphide homeostasis, oxidative stress, major adverse cardiovascular event

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INTRODUCTION

Non-ST elevation acute coronary syndromes (NSTE-ACS) involve non-ST elevation myocardial infarction (NSTEMI) and unstable angina, and are associated with increased risk of morbidity and mortality [1]. Various scoring systems have been developed to carry out the risk stratification and prognostic prediction of these clinical situations. GRACE risk score is a system with high accuracy among these scoring systems [2].

Thiols (RSH) can undergo oxidation reaction via oxidants and form disulphide (RSSR). Under conditions of oxidative stress, the oxidation of cysteine residues can lead to a reversible formation of disulphide bond between protein thiol groups and low-molecular-mass thiols. The resulting disulphide bonds can again be reduced to thiol groups; thus, dynamic thiol-disulphide homeostasis is maintained [3]. The dynamic thiol disulphide homeostasis status plays a critical role in antioxidant protection, detoxification, signal transduction, apoptosis, regulation of enzymatic activity, and transcription factors and cellular signalling mechanisms [4].

The aim of our study is to compare the dynamic thiol/disulphide homeostasis, as an oxidative stress marker, between patients with NSTE-ACS and a control group, and secondly to assess the relationship between the dynamic thiol/disulphide homeostasis and GRACE risk scoring and major adverse cardiovascular event (MACE).

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METHODS

Study population

The study was performed in the cardiology clinic of our hospital between February 2015 and March 2016. Our study prospectively included 210 patients who were admitted to our emergency department with chest pain, without a prior history of coronary artery disease (CAD), and diagnosed with NSTE-ACS (126 patients with NSTEMI and 74 patients with unstable angina) as a result of clinical, electrocardiographic, laboratory, and imaging studies. Subjects matched for age and comorbidities such as diabetes mellitus (DM), hypertension, chronic obstructive pulmonary disease (COPD), and obesity were assigned as the control group. Individuals who met the criteria for recruitment were included in the study after signing the consent form.

The exclusion criteria of our study included the lack of patient consent, previously known CAD, significant valvular heart disease or valve surgery history, chronic renal failure, acute and chronic infection, autoimmune disease, recent surgery, malignancy, vitamin or antioxidant support, malnutrition, and steroid and nonsteroidal anti-inflammatory treatment.

We recorded cardiovascular (CV) and systemic medical history and performed physical examinations of all patients included in the study. The patients' age, gender, Killip and New York Heart Association classes, mean heart rate, and arterial blood pressures were recorded from the time of hospitalisation. The presence of CV risk factors such as hypertension, DM, COPD, family history of CV disease, dyslipidaemia, and obesity were questioned and recorded. The GRACE risk score was calculated during admission to the hospital. During the 180-day follow-up, the development of MACE was followed based on outpatient clinic controls and via phone calls for patients who could not refer to the outpatient clinic.

The study was approved by the Ethics Committee of our hospital.

Determination of the risk categories of the patients

Among patients who were diagnosed with NSTE-ACS, those with a GRACE risk score of 108 and lower, 108 to 140, and 140 and higher were classified as low, moderate, and high risk, respectively.

Measurement of biochemical markers

For all patients, complete blood count, troponin levels, liver and kidney function tests, and bleeding profile were routinely studied at admission. The 12-h fasting serum lipid profiles were measured by standard enzymatic methods. Thiol/disulphide homeostasis was measured with a newly developed method by Erel and Neselioglu. Reducible disulphide bonds were reduced to compose free functional thiol groups. Unused reductant sodium borohydride was used up and extracted with formaldehyde, and all thiol groups containing native and reduced ones were determined after reaction with 5,5′-dithiobis-(2-nitrobenzoic) acid. Half of the difference between native and total thiols ensured the dynamic disulphide quantity (–S-S). After detection of the native thiol (–SH) and disulphide (–S-S) amount, the ratio of disulphide-to-native-thiol (–S-S–/–SH) ratio was calculated [5].

Statistical analysis

Data of individuals who participated in the study were recorded in previously prepared study forms. Then, our data were saved in the database of the SPSS v. 22.0 software for Windows (SPSS Inc., Chicago, İllinois, USA) for the analysis to be used in the study. The normal distribution of the data was evaluated by Kolmogorov-Smirnov and Shapiro-Wilk test. Nonparametric methods were used for the analysis of non-normally distributed variables. Nonparametric variables between groups were compared with the Mann-Whitney U test. Data were presented as numbers, percentages, and arithmetic mean ± standard deviation. Spearman correlation analysis was used to compare the GRACE score and accompanying variables. Univariate and multivariate logistic regression analysis were used to determine the independent variables of MACE. Receiver operating characteristics (ROC) curve was used for the determination of the sensitivity and specificity of native thiol and its optimal cut-off value in predicting MACE. The results were considered statistically significant when a p-value < 0.05.

RESULTS

Demographic and biochemical characteristics of NSTE-ACS (210 patients) and control groups (185 subjects) are shown in Table 1.

The mean age of the NSTE-ACS group (61.94 years) was comparable with that of the control group (59.84 years) ($p = 0.219$). The incidence of CV risk factors such as hypertension, DM, COPD, and obesity were comparable between both groups. During the 180-day follow-up period, MACE was observed in 11 (5.2%) patients in the NSTE-ACS group (cardiac death in six patients, non-fatal MI in two patients, and acute heart failure in three patients). Development of MACE in the treatment strategy subgroups was not statistically significant (two [5.5%] patients in the medical therapy group, six [5.3%] patients in the percutaneous coronary intervention [PCI] group, three [4.9%] patients in the coronary artery bypass grafting group, $p > 0.05$). The mean GRACE score in the NSTE-ACS group was 161.40 (39–319).

In the NSTE-ACS group, the neutrophil/lymphocyte ratio (NLR) was statistically significantly higher, while the platelet/lymphocyte ratio (PLR) was also higher but without statistical significance ($p = 0.763$). The mean troponin and creatinine kinase-myocardial band levels were 394.55 (3–11135) pg/mL and 14.62 (0.40–300) ng/mL in the NSTE-ACS group, respectively.

Table 1. Demographic and biochemical characteristics of non-ST elevation acute coronary syndromes (NSTE-ACS) and control groups

Variables	NSTE-ACS group (210 patients)	Control group (185 people)	p
Age [years]	61.94 ± 12.52	59.84 ± 12.74	0.219
Diabetes mellitus	74 (35.2%)	63 (34.0%)	0.127
Hypertension	141 (67.1%)	115 (62.1%)	0.356
Obesity	30 (14.3%)	23 (12.4%)	0.443
COPD	34 (16.2%)	25 (13.5%)	0.536
MACE	11 (5.2%)	–	–
GRACE score	161.40 (39–319)	–	–
White blood cell [K/μL]	9.13 ± 4.38	8.02 ± 2.13	0.002
Neutrophil [K/μL]	6.06 ± 2.99	4.74 ± 1.68	< 0.001
Lymphocyte [K/μL]	2.17 ± 1.19	2.49 ± 0.69	0.001
Platelet [K/μL]	220.71± 70.51	266.87 ± 62.71	< 0.001
MPV [fL]	9.69 ± 1.46	10.70 ± 0.93	< 0.001
PLR	121.86 (10–397.5)	112.89 (40.68–225.79)	0.763
NLR	3.68 (0.33–20.29)	2.00 (0.81–5.80)	< 0.001
Glucose [mg/dL]	158.81 ± 79.10	106.18 ± 54.47	< 0.001
Creatinine [mg/dL]	1.07 ± 0.71	0.89 ± 0.77	0.102
Total cholesterol [mg/dL]	184.87 ± 45.97	196.26 ± 40.33	0.015
LDL cholesterol [mg/dL]	109.09 ± 39.32	118.09 ± 34.89	0.025
HDL cholesterol [mg/dL]	40.83 ± 14.39	45.65 ± 12.96	0.001
Triglyceride [mg/dL]	181.61 (35–1677)	165.22 (34–584)	0.310
Troponin [pg/mL]	394.55 (3–11135)	–	–
CK-MB [ng/mL]	14.62 (0.40–300)	–	–
Native thiol [μmol/L]	379.46 ± 68.10	495.76 ± 58.80	< 0.001
Disulphide [μmol/L]	19.16 ± 7.54	19.04 ± 6.28	0.861
Total thiol [μmol/L]	417.06 ± 69.72	534.54 ± 60.23	< 0.001
Disulphide/native thiol	0.053 ± 0.030	0.039 ± 0.013	< 0.001
Disulphide/total thiol	0.046 ± 0.021	0.035 ± 0.011	< 0.001
Native thiol/total thiol	0.908 ± 0.044	0.927 ± 0.023	< 0.001
Treatment strategy:			
Medical therapy	36 (17%)	–	–
PCI	113 (53%)	–	–
CABG	61 (29%)	–	–

Data are given as mean ± standard deviation, median (interquartile range), or number (percentage). CABG — coronary artery bypass grafting; CK-MB — creatinine kinase-myocardial band; COPD — chronic obstructive pulmonary disease; HDL — high-density lipoprotein; LDL — low-density lipoprotein; MACE — major adverse cardiovascular event; MPV — mean platelet volume; NLR — neutrophil-to-lymphocyte ratio; PCI — percutaneous coronary intervention; PLR — platelet-to-lymphocyte ratio

Native thiol, total thiol, and native thiol/total thiol values were statistically significantly lower and disulphide/native thiol and disulphide/total thiol values were statistically significantly higher in the NSTE-ACS group when compared to the control group ($p < 0.001$ for each). The disulphide levels were similar in both groups.

Correlation analysis of variables related to GRACE score

In the NSTE-ACS group, the correlation analysis between the GRACE score and thiol/disulphide homeostasis parameters and variables such as NLR, PLR, and troponin showed a negative and significant correlation with native thiol ($r = –0.595$,

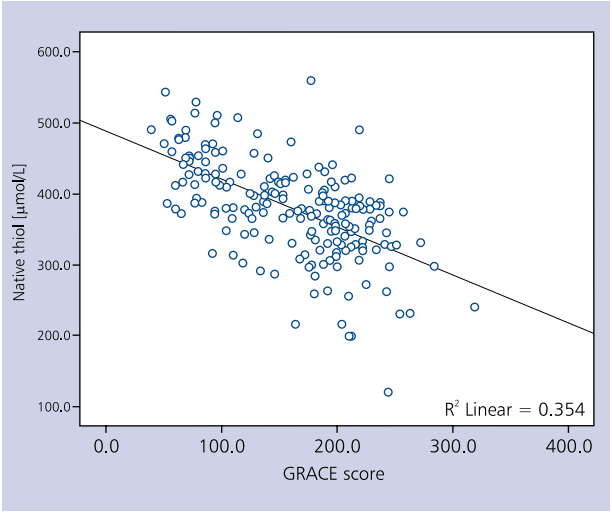

Figure 1. Negative correlation between GRACE score and native thiol

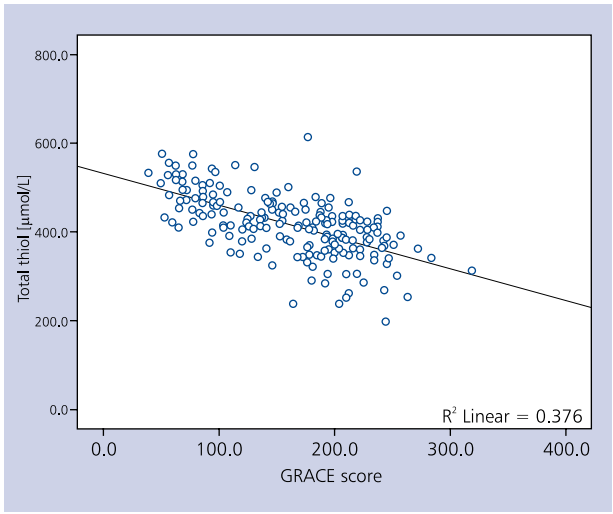

Figure 2. Negative correlation between GRACE score and total thiol

$p < 0.001$) and total thiol ($r = -0.613$, $p < 0.001$) levels (Figs. 1, 2). A positive and significant correlation was found with the variables including disulphide/native thiol ($r = 0.167$, $p = 0.015$), disulphide/total thiol ($r = 0.157$, $p = 0.023$), PLR ($r = 0.244$, $p < 0.001$), NLR ($r = 0.348$, $p < 0.001$), and troponin ($r = 0.624$, $p < 0.001$) values (Table 2).

Analysis of variance (ANOVA) analysis for GRACE score risk groups

NSTE-ACS group was divided into three subgroups: GRACE score < 108 points (n = 52), 108–140 points (n = 22), and > 140 points (n = 135). ANOVA analysis was performed between these subgroups and thiol/disulphide homeostasis parameters and variables such as NLR, PLR, and troponin values (Table 3).

A statistically significant difference was observed between the subgroups for the variables including native thiol ($p < 0.001$), total thiol ($p < 0.001$), troponin ($p = 0.026$), PLR ($p = 0.013$), and NLR ($p = 0.001$) values.

Table 2. Correlation analysis of variables related to GRACE score

	GRACE
Native thiol	Pearson's cor. –0.595; $p < 0.001$
Disulphide	Pearson's cor. –0.112; $p = 0.107$
Total thiol	Pearson's cor. –0.613; $p < 0.001$
Disulphide/native thiol	Pearson's cor. 0.167; $p = 0.015$
Disulphide/total thiol	Pearson's cor. 0.157; $p = 0.023$
Native thiol/total thiol	Pearson's cor. –0.112; $p = 0.108$
Neutrophil to lymphocyte ratio	CC 0.348; $p < 0.001$
Platelet to lymphocyte ratio	CC 0.244; $p < 0.001$
Troponin	CC 0.624; $p < 0.001$

CC — correlation coefficient; Pearson's cor. — Pearson's correlation

Univariate and multivariate logistic regression analysis of MACE and affecting variables

The univariate regression analysis demonstrated a significant correlation between MACE and variables including age (odds ratio [OR] 0.938, 95% confidence interval [CI] 0.891–0.988, $p = 0.015$), GRACE score (OR 0.958, 95% CI 0.935–0.980, $p < 0.001$), troponin (OR 0.999, 95% CI 0.998–1.000, $p = 0.015$), and native thiol (OR 1.022, 95% CI 1.012–1.033, $p < 0.001$) values (Table 4).

The multivariate regression analysis demonstrated a significant correlation between MACE and variables including GRACE score (OR 0.92, 95% CI 0.85–0.99, $p = 0.028$) and native thiol levels (OR 1.01, 95% CI 1.00–1.03, $p = 0.040$) (Table 5).

ROC curve analysis

Receiver-operating characteristic curve analysis was used for the determination of the sensitivity and specificity of native thiol and its optimal cut-off value in predicting MACE. A native thiol value of < 326 µmol/L showed a sensitivity of 0.839 and a specificity of 0.727 in predicting MACE (area under curve 0.896; 95% CI 0.839–0.953; $p < 0.001$; Fig. 3).

DISCUSSION

In our study, the comparison of the control and NSTE-ACS groups showed that native thiol, total thiol, and native thiol/total thiol values were lower and disulphide/native thiol and disulphide/total thiol values were higher in patients with NSTE-ACS. Furthermore, serum native thiol and total thiol levels were found to be correlated with GRACE risk score. In

Table 3. ANOVA analysis of biochemical parameters by GRACE score subgroups

Variables	GRACE < 108 points (52 patients)	GRACE 108–140 points (22 patients)	GRACE > 140 points (135 patients)	P total	P+	P++	P+++
Native thiol	440.03 ± 47.98	384.68 ± 52.70	354.80 ± 62.03	< 0.001	0.001	< 0.001	0.066
Disulphide	20.77 ± 6.78	19.72 ± 4.84	18.43 ± 8.12	0.156	0.849	0.142	0.738
Total thiol	481.55 ± 47.07	423.63 ± 53.46	390.62 ± 62.69	< 0.001	< 0.001	< 0.001	0.039
Disulphide/native thiol	0.048 ± 0.018	0.052 ± 0.015	0.055 ± 0.036	0.372	0.857	0.341	0.911
Disulphide/total thiol	0.043 ± 0.014	0.047 ± 0.012	0.048 ± 0.024	0.399	0.786	0.365	0.971
Native thiol/total thiol	0.913 ± 0.029	0.906 ± 0.026	0.906 ± 0.051	0.656	0.852	0.634	0.999
Troponin	49.11 (3–2070)	125.28 (3–959)	569.27 (3–11135)	0.026	0.969	0.035	0.270
Platelet-to-lymphocyte ratio	102.97 (29.25–214.00)	111.23 (10–232.5)	131.46 (40.22–397.5)	0.013	0.861	0.013	0.338
Neutrophil-to-lymphocyte ratio	2.38 (0.51–12.60)	2.98 (0.33–10.33)	4.27 (0.85–20.29)	0.001	0.741	0.001	0.181

P total: Total comparison between all GRACE subgroups; P+: Comparison between the groups of GRACE < 108 and GRACE 108–140; P++: Comparison between the groups of GRACE < 108 and GRACE > 140; P+++: Comparison between the groups of GRACE 108–140 and GRACE > 140

Table 4. Univariate regression analysis of major adverse cardiovascular event and affecting variables

Variables	Odds ratio	95% CI	P
Age	0.938	0.891–0.988	0.015
GRACE	0.958	0.935–0.980	< 0.001
PLR	1.005	0.993–1.017	0.433
NLR	0.958	0.805–1.140	0.626
LDL	1.010	0.986–1.036	0.408
Troponin	0.999	0.998–1.000	0.015
CK-MB	0.993	0.985–1.000	0.051
Native thiol	1.022	1.012–1.033	< 0.001

CK-MB — creatinine kinase-myocardial band; LDL — low-density lipoprotein; MPV — mean platelet volume; NLR — neutrophil-to-lymphocyte ratio; PLR — platelet-to-lymphocyte ratio

Table 5. Multivariate logistic regression analysis of major adverse cardiovascular event and affecting variables

Variables	Odds ratio	95% CI	P
Age	1.13	0.95–1.33	0.157
GRACE	0.92	0.85–0.99	0.028
Troponin	0.99	0.98–1.00	0.722
Native thiol	1.01	1.00–1.03	0.040

CI — confidence interval

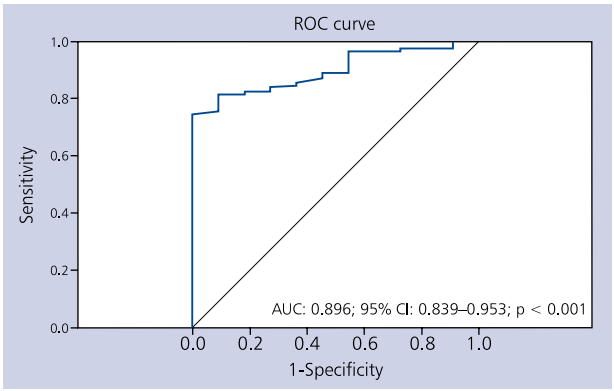

Figure 3. Sensitivity and specificity of the native thiol variant in predicting major adverse cardiovascular event ; AUC — area under curve; CI — confidence interval

addition, serum native thiol levels were shown to be a strong independent prognostic marker in the prediction of MACE.

Acute coronary syndrome is a common and life-threatening complication of CAD. In these cases, the initiator is the intracoronary thrombosis associated with atherosclerotic plaque rupture or erosion [1]. In the process of CAD development, accumulation of the oxidised lipid particles in the subendothelial cells contributes to the development of atheromatous plaque. The oxidative stress in plaque microenvironment

leads to further oxidation of lipid molecules and formation of free radicals [6, 7]. While the resulting free radicals are normally detoxified by antioxidant defence mechanisms, the deterioration of the balance due to increased free radical formation and inadequacy of antioxidant mechanisms results in oxidative stress [8].

The study conducted by Koprivica et al. [9] investigated the role of oxidative stress in the development of endothelial dysfunction and atherosclerotic disease, and also the relationship between the oxidative stress and different types of ACS. As a result, the lipid peroxidation index was significantly higher and nitric oxide, hydrogen peroxide, superoxide dismutase, and catalase activities were significantly lower in patients diagnosed with ACS [9]. In addition, two different studies on patients with acute MI and NSTEMI demonstrated increased oxidative stress in these patients by using the thiol/disulphide homeostasis parameters [10, 11].

Thiols, also known as mercaptans, are a group of organic compounds containing a sulfhydryl group (–SH) composed of a sulphur atom attached to a carbon atom and a hydrogen atom [12]. The plasma thiol pool is mainly formed by albumin thiols and protein thiols and slightly formed by low molecular-weight thiols, such as cysteine, cysteinylglycine, glutathione, and homocysteine [13]. They can be reduced and oxidised by dynamic thiol/disulphide homeostasis in the case of oxidative stress. There is an increasing body of evidence for the presence of abnormal thiol/disulphide homeostasis in the pathogenesis of diseases such as diabetes mellitus [14], cardiovascular diseases [10, 11], cancer [15], rheumatoid arthritis [16], chronic kidney disease [17], obstructive sleep apnoea [18], and Parkinson's disease [19]. In the present study, we also demonstrated that oxidative stress levels are higher in patients with NSTE-ACS using dynamic thiol/disulphide parameters.

The GRACE risk score has been developed from a multinational registry study conducted on patients with all ACS subtypes. The GRACE risk scoring ensures a risk stratification with high accuracy during both referral and discharge [2] and provides direct estimation of sixth month, first year, and third year in-hospital mortality. It also shows the combined risk of death and MI in the first year [20]. It constitutes a criterion for early intervention and revascularisation thanks to the risk stratification [1]. In our study, we showed that higher GRACE scores could be an independent predictor of MACE. We also showed that there was a positive correlation between the GRACE score and PLR and NLR parameters, which were previously shown to be useful as a prognostic marker in diseases where oxidative stress is increased [21, 22]. These results were consistent with the results of Acet et al. [23]. Furthermore, as far as we know, we first found a correlation between the dynamic thiol/disulphide homeostasis parameters and GRACE score in the literature.

In a study conducted by Karim et al. [24], 251 patients with a diagnosis of ACS were divided into two groups, as hyperuricaemic and normouricaemic patients, and were followed for seven days for the development of cardiogenic shock, acute heart failure, stroke, reinfarction after early revascularisation, sudden cardiac death, and recurrent PCI, considered as MACE. They showed that uric acid, an an oxidative stress indicator, is associated with the risk of developing MACE [24]. In addition, Xia et al. [25] reported a correlation between MACE and oxidative stress parameters such as myeloperoxidase and ischaemia-modified albumin, as well as serum NT-pro-B-type natriuretic peptide, high-sensitivity C-reactive protein, and high-sensitivity troponin T levels, in a study with 201 patients with unstable angina. In the literature, there is no previous clinical study investigating the correlation between MACE and dynamic thiol/disulphide haemostasis parameters, which are the indicators of oxidative stress. In this context, our research is the first to demonstrate that native thiols can independently predict MACE.

Limitations of the study

Our study findings should be interpreted with some limitations. First, it is a single-centre, small-scale study. Secondly, no comparison was made with other oxidative stress markers such as myeloperoxidase, paraoxonase, and ischaemia-modified albumin because they were not included in the analysis. Third, the GRACE risk score was derived and validated externally in cohorts of STEMI/NSTEMI patients [20], while our results were demonstrated only on a NSTE-ACS population.

CONCLUSIONS

In conclusion, serum thiol levels (native and total) were decreased in patients with NSTE-ACS. In addition, serum thiol levels showed a negative correlation with the GRACE score, whereas they independently predicted MACE within the six-month period. These results suggest that dynamic thiol/disulphide homeostasis may predict prognosis in NSTE-ACS patients. However, its prognostic performance needs to be confirmed in the future.

Conflict of interest: *none declared*

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