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Original article

# Elevated serum osteoprotegerin levels predict in-hospital major adverse cardiac events in patients with ST elevation myocardial infarction

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ABSTRACT

The aim of our study was to investigate whether osteoprotegerin (OPG) is related to in-hospital major adverse cardiac events (MACE) and reperfusion parameters in patients with ST elevation myocardial infarction (STEMI). The OPG/receptor activator of nuclear factor-κB (RANK)/RANK ligand pathway has recently been associated with atherosclerosis. OPG is a predictor of cardiovascular events in patients with acute coronary syndrome. This study included 96 consecutive patients with STEMI undergoing primary percutaneous coronary intervention (PCI). Two groups with equal number of patients were formed according to median OPG level. The association of OPG levels on admission with post-procedural reperfusion parameters, and in-hospital MACE were investigated. Patients with higher OPG levels displayed higher neutrophil/lymphocyte ratio, admission troponin, admission glucose, and high-sensitive C-reactive protein. Higher OPG levels were associated with increased thrombolysis in myocardial infarction (TIMI) risk score, TIMI risk index, pain to balloon time, need for inotropic support, shock, and MACE, mainly driven by death. Reperfusion parameters were not different between the two groups. TIMI risk score, TIMI risk index, myocardial blush grade, estimated glomerular filtration rate (eGFR), number of obstructed vessels, and OPG significantly predicted adverse cardiac events. Multiple logistic regression analysis revealed OPG as an independent predictor of MACE as well as eGFR, number of obstructed vessels, and corrected TIMI frame count. OPG, a bidirectional molecule displaying both atheroprotective and pro-atherosclerotic properties, is currently known as a marker of inflammation and a predictor of cardiovascular mortality. The present study, for the first time, demonstrated that an increased OPG level is related to in-hospital adverse cardiovascular events after primary PCI in patients with STEMI.



## Introduction

Osteoprotegerin (OPG), a glycoprotein and a member of the tumor necrosis factor (TNF) receptor superfamily, forms the molecular link between skeletal, immune, and vascular systems [1,2]. OPG prevents osteoclast-mediated bone resorption, by binding the receptor activator of nuclear factor-κB ligand (RANKL), acting as a decoy receptor to competitively inhibit the interaction of RANKL with its receptor, receptor activator of nuclear factor-κB (RANK) [3]. In addition, OPG demonstrated anti-apoptotic activity by binding to another receptor of the TNF family, TNF-related apoptosis-inducing ligand (TRAIL) [4]. Recently, OPG has gained considerable interest in the cardiovascular discipline due to its association with inflammation and atherosclerosis. Increased OPG levels have been associated with endothelial dysfunction [5], coronary calcium score [6], presence and severity of coronary artery disease (CAD) [7], peripheral vascular disease [8], and cerebrovascular disease [9].

ST elevation myocardial infarction (STEMI) is a major cause of cardiovascular mortality and morbidity. Despite advances in emergent revascularization including primary percutaneous coronary intervention (PCI), acute heart failure, shock, and mechanical complications are still encountered as major problems during hospital care [10,11]. The prognosis of STEMI is quite variable depending on a number of clinical, echocardiographic, and biochemical markers. Thus, identification of new molecules for risk stratification to select patients at high risk for adverse clinical end-points is important. In

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addition, these molecules may help to reveal new aspects in the pathophysiology of acute and chronic vascular events.

Preliminary studies investigating the relationship between STEMI and OPG documented increased OPG levels in patients with STEMI compared to patients with stable CAD and normal controls [12]. Prominent immunostaining of OPG/RANK/RANKL were demonstrated within the thrombus material, aspirated during primary PCI for acute STEMI [13]. Although OPG is a strong predictor of mortality and heart failure (HF) in patients with acute coronary syndrome (ACS) [14], whether OPG is related to in-hospital major adverse cardiac events (MACE) and reperfusion parameters in patients with STEMI has not been clarified until now. We intended to investigate OPG levels in patients with STEMI and evaluate its relationship with reperfusion parameters and in-hospital MACE.

## Methods

This study was conducted prospectively, in the cardiology clinic at Rize Education and Research Hospital, Rize, Turkey. Ninety six patients with STEMI with no history of previous CAD, who underwent primary PCI at our institution between May 2011 and January 2012, were enrolled consecutively. The diagnosis of acute STEMI was made as previously described [15]. The diagnosis of acute STEMI was also confirmed by demonstrating the culprit lesion by coronary angiography. Informed consent was obtained from all patients prior to the study. The study was performed in accordance with the principles stated in the Declaration of Helsinki and approved by the Local Ethics Committee.

Clinical characteristics, which consisted of multiple descriptors from each patient's history and physical examination, were collected by physicians from cardiology clinics of each patient and were stored in the database of the coronary angiography laboratory. We recorded the baseline characteristics, which include hypertension, diabetes mellitus, smoking status, family history of premature CAD and lipid parameters. Killip score [16], thrombolysis in myocardial infarction (TIMI) risk index [17], and TIMI risk score [18] was also calculated and used for risk stratification.

Patients with significant organic valvular heart disease, known history of CAD or prior MI, malignancy, collagen vascular disease, chronic kidney and hepatic failure, pulmonary embolism, and sepsis were excluded from the study. The exclusion criteria were selected to avoid confounding factors other than STEMI origin and location.

A 12-lead surface electrocardiogram (ECG) was obtained from all patients in the supine position immediately after their admission to the emergency care unit (ECU). The 12-lead ECG (Cardiofax S ECG-1250K, filter range 0.5–150 Hz, AC filter 60 Hz, 25 mm/s, 10 mm/mV; Nihon Kohden, Tokyo, Japan) was analyzed by two independent clinicians who were blind to study design and data. A repeat ECG was obtained 60 min after primary PCI. A special ruler was used to measure the difference (in mm) between isoelectric line and ST-segment elevation at 20 ms after the J-point. Jeopardized myocardium was determined by the sum of ST elevations (in mm) on each ST-elevated derivation on pre- and post-PCI ECGs (total ST elevation score). Percentage of total ST resolution was calculated by the following formula: (sum of ST elevations on pre-PCI ECG) − (sum of ST elevations on post-PCI ECG)/(sum of ST elevations on pre-PCI ECG) × 100.

Cardiac biomarkers levels including creatine kinase (CK), CK-MB fraction (CK-MB), troponin-I, and inflammatory markers including leukocytes were measured at our emergency department and used in the analyses as admission values. The lipid samples were evaluated after fasting for at least 8 h. Glucose, creatinine, and lipid profile were determined by the standard methods. White blood cell (WBC, leukocyte) counts were obtained from an automated cell counter (Coulter Gen-S, Coulter Corp., Miami, FL, USA). Estimated glomerular filtration rate (eGFR) was calculated by Cockroft–Gault formula [19].

Blood samples for OPG were drawn prior to primary PCI and serum, isolated by centrifugation within 1 h at 2500 × *g* for 10 min, and stored at −80 °C. Serum levels of OPG were quantified by enzyme-linked immunosorbent assay (ELISA) using commercially available matched antibodies (eBioscience, San Diego, CA, USA). The intra-assay and inter-assay coefficients of variation (CV) were 7.0% and 8.0%, respectively. The sensitivity was calculated to be 2.5 pg/mL.

Admission serum specimens for high sensitivity C-reactive protein (hsCRP) were frozen at −20 °C before analysis. Serum levels of hsCRP were determined by an immunoturbidimetric method performed on the Abbott auto-analyzer (Architect C1600, Abbott, Abbott Park, IL, USA).

All of the patients received 300 mg aspirin and a loading dose of 600 mg clopidogrel prior to the procedure. After sheath insertion via femoral approach, an intravenous bolus of unfractionated heparin at a dose of 70 IU/kg was administered. Coronary stenting directly, or after balloon angioplasty, was performed where eligible. Glycoprotein IIb–IIIa inhibitor (tirofiban) was administered at the preference of the operator. After the procedure, all patients were treated according to the current recommendations by clinicians blinded to OPG concentrations and followed-up in the coronary care unit and cardiology clinics until discharge. MACE were defined as recurrent myocardial infarction, stroke, decompensated HF, and cardiac death. In hospital re-infarction was defined as recurrent chest pain lasting more than 30 min, associated with new Q waves or recurrent ST-segment elevation ≥0.1 mV in at least two contiguous leads and an increase in CK-MB levels to at least twice the upper limit of normal value and/or more than 50% above the previous value after the index procedure.

Preprocedural and postprocedural TIMI flow grade [20], corrected TIMI frame count (TFC) [21], and myocardial blush grade [22] were assessed by two cardiologists blinded to patient data.

### *Statistical analyses*

Continuous variables were given as mean ± SD; categorical variables were defined as percentage. Data were tested for normal distribution using the Kolmogorov–Smirnov test. The Student's *t*-test was used for the univariate analysis of normally distributed continuous numerical variables and Mann–Whitney *U*-test was used for non-normally distributed numerical variables, and the $\chi^2$-test for the categorical variables. Spearman's rank correlation coefficient was used to analyze the relationship between numerical and ordinal variables. For presentation of data, two groups were formed as above and below the median OPG level. Moreover, additional groups were made up according to the presence or absence of MACE. Logistic regression analysis was used for multivariate analysis of independent variables. All tests of significance were two-tailed. Statistical significance was defined as $p < 0.05$. The Statistical Program for Social Sciences (SPSS for windows 15, Inc., Chicago, IL, USA) was used for all statistical calculations.

## Results

The baseline clinical characteristics are presented in Table 1. The study population consisted of 96 patients with STEMI who underwent primary PCI. Blood samples were obtained within 30 min after admission, before administration of any medication. The mean plasma OPG level was 109 ± 134 pg/mL, with a median value of 70 pg/mL. The baseline clinical characteristics of the subgroups,

**Table 1**
Baseline demographics and clinical characteristics.

| Characteristic (median OPG: 70 pg/mL) *N* (96) | OPG < median (48) | OPG ≥ median (48) | *p*-Value |
|---|---|---|---|
| Age (yrs) | 53 ± 29 | 63 ± 34 | <0.001 |
| BMI (kg/m$^2$) | 27.6 ± 4.1 | 27.8 ± 4.1 | NS |
| Gender (male) | 85% | 79% | NS |
| Hypertension | 35% | 35% | NS |
| Diabetes mellitus | 8% | 29% | 0.009 |
| Smoking | 69% | 67% | NS |
| Hyperlipidemia | 19% | 17% | NS |
| Family history of premature CAD | 15% | 4% | 0.080 |
| Heart rate (bpm) | 82 ± 15 | 82 ± 19 | NS |
| Admission blood glucose (mg/dl) | 145 ± 62 | 192 ± 137 | 0.025[a] |
| Fasting blood glucose (mg/dl) | 119 ± 40 | 148 ± 77 | 0.023 |
| Creatinine (mg/dl) | 0.93 ± 0.29 | 1.03 ± 0.32 | NS[a] |
| eGFR (mL/min) | 105 ± 34 | 83 ± 28 | 0.001 |
| Total cholesterol (mg/dl) | 184 ± 47 | 182 ± 41 | NS |
| LDL (mg/dl) | 120 ± 37 | 120 ± 35 | NS |
| HDL (mg/dl) | 37 ± 10 | 39 ± 8 | NS |
| Triglyceride (mg/dl) | 133 ± 80 | 119 ± 72 | NS |
| Leukocytes ($10^3$/mm$^3$) | 11 ± 3 | 13 ± 5 | 0.067 |
| Neutrophils ($10^3$/mm$^3$) | 7 ± 3 | 9 ± 5 | 0.024[a] |
| Lymphocyte ($10^3$/mm$^3$) | 2.9 ± 1.4 | 2.1 ± 1.1 | 0.002[a] |
| Monocyte (/mm$^3$) | 0.68 ± 0.26 | 0.68 ± 0.35 | NS[a] |
| *N*/*L* ratio | 3.4 ± 3.2 | 5.4 ± 4.0 | 0.007 |
| Hemoglobin (mg/dl) | 14.4 ± 1.4 | 13.4 ± 1.4 | 0.001 |
| Platelet count ($10^9$/L) | 260 ± 57 | 245 ± 54 | NS |
| CK-MB (U/L) (Adm.) | 25 ± 63 | 50 ± 81 | 0.098 |
| CK-MB (U/L) (peak) | 210 ± 96 | 213 ± 100 | NS[a] |
| Troponin I (ng/mL) (Adm.) | 2.8 ± 8.2 | 10.1 ± 16.9 | 0.012 |
| Troponin I (ng/mL) (peak) | 45 ± 11 | 46 ± 11 | NS[a] |
| C-reactive protein (mg/dl) | 0.83 ± 1.23 | 2.1 ± 3.6 | 0.002[a] |
| Q wave on ECG % | 61% | 74% | NS |
| Left ventricular ejection fraction (%) | 44 ± 10 | 43 ± 10 | NS |
| *Medications* | | | |
| Aspirin | 13% | 21% | NS |
| Clopidogrel | 0% | 4% | NS |
| Beta blockers | 6% | 17% | NS |
| Statins | 4% | 13% | NS |
| ACEI/ARB | 23% | 17% | NS |
| CCB | 6% | 15% | NS |
| Tirofiban | 10% | 21% | NS |
| OAD/insulin | 8% | 21% | NS |

ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; Adm., admission value; BMI, body mass index; CAD, coronary artery disease; CCB, calcium channel blocker; CK, creatinine kinase; CK-MB, creatinine kinase muscle/brain; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; *N*/*L*, neutrophil/lymphocyte; NS, not significant; OAD, oral anti-diabetic; OPG, osteoprotegerin; PCI, percutaneous coronary intervention.

[a] Nonparametric variables were analyzed by Mann–Whitney *U*-test.

**Table 2**
Angiographic characteristics and procedural results.

| Characteristic | OPG < median | OPG ≥ median | *p*-Value |
|---|---|---|---|
| *Pre-procedural characteristics* | | | |
| TIMI risk score | 3.3 ± 2.7 | 5.4 ± 2.8 | 0.001 |
| TIMI risk index | 21 ± 11 | 31 ± 16 | 0.001 |
| Pain to balloon time (min) | 278 ± 234 | 439 ± 374 | 0.001[a] |
| Baseline TIMI grade 0 or 1 | 89% | 85% | NS |
| Thrombus score 4 or 5 | 96% | 90% | NS |
| Anterior MI | 48% | 48% | NS |
| Total ST elevation on admission (mm) | 9.5 ± 7.3 | 10.4 ± 7.6 | NS[a] |
| Number of obstructed vessels ≥50% | 2.0 ± 0.8 | 2.2 ± 0.8 | NS[a] |
| *Post-procedural results* | | | |
| TIMI flow grade (2, 3) | 94% | 90% | NS |
| Corrected TIMI frame count | 27 ± 21 | 30 ± 24 | NS[a] |
| Myocardial blush grade (2, 3) | 73% | 63% | NS |
| ST resolution % | 56 ± 52 | 53 ± 33 | NS[a] |
| *In-hospital course* | | | |
| MACE | 8% | 29% | 0.009 |
| Death | 0% | 13% | 0.011 |
| Re-MI | 4% | 10% | NS |
| Stroke | 0% | 0% | NS |
| Decompensated HF | 6% | 19% | 0.064 |
| Shock | 0% | 13% | 0.011 |
| Need for inotropic support | 2% | 17% | 0.014 |
| CPR | 0% | 19% | 0.002 |
| Atrial fibrillation | 6% | 10% | NS |
| Major/minor bleeding | 4% | 8% | NS |
| Pre-PCI cardiac arrest | 2% | 13% | 0.05 |
| VT/VF | 4% | 8% | NS |

CPR, cardiopulmonary resuscitation; HF, heart failure; MACE, major adverse cardiac event; MI, myocardial infarction; OPG, osteoprotegerin; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction; VF, ventricular fibrillation; VT, ventricular tachycardia.

[a] Nonparametric variables were analyzed by Mann–Whitney *U*-test.

with OPG levels higher and lower than the median, are compared in Table 1. Patients with higher OPG levels were more likely to be older, to have history of diabetes mellitus, to have lower hemoglobin levels, and eGFR. In addition, in patients with higher OPG, higher values of leukocyte count, neutrophil/lymphocyte (*N*/*L*) ratio, admission troponin, admission glucose, CRP, and hsCRP were also documented.

Angiographic characteristics and procedural results are detailed in Table 2. Higher OPG levels were associated with increased TIMI risk score ($p = 0.001$), TIMI risk index ($p = 0.001$), pain to balloon time ($p = 0.014$), need for inotropic support ($p = 0.014$), shock ($p = 0.011$), and MACE ($p = 0.009$), mainly driven by increased mortality in this group ($p = 0.011$) (Fig. 1). There was a trend for increased decompensated HF, although not reaching significance. Reperfusion parameters including TIMI flow grade, corrected TFC, myocardial blush grade, and percentage of ST segment resolution was not different between the two groups. Correlation analysis demonstrated that OPG related to *N*/*L* ratio ($r = 0.364$, $p < 0.001$), and hsCRP ($r = 0.337$, $p = 0.001$) significantly.

Female gender, plasma creatinine, glucose, hemoglobin, neutrophil/leukocyte count, eGFR, left ventricular ejection fraction (LVEF), TIMI risk score, Killip score, TIMI risk index, myocardial blush grade, number of obstructed vessels, corrected TFC, and OPG significantly predicted adverse cardiac events (Table 3). Multiple logistic regression analysis including age, gender, eGFR, hemoglobin, admission glucose level, *N*/*L* ratio, number of obstructed vessels ≥50%, corrected TFC, hs-CRP, LVEF, and OPG levels revealed OPG as an independent predictor of MACE (odds ratio: 1.008, 95% CI: 1.003–1.015, $p = 0.016$) as well as eGFR, number of obstructed vessels, and corrected TFC (Table 4).

## Discussion

We demonstrated for the first time that increased OPG levels are associated with higher in-hospital MACE in patients with STEMI. Higher OPG concentrations also indicated increased TIMI risk score, pain to balloon time, need for inotropic support, shock, and hsCRP potentially delineating a high-risk group. Furthermore, corrected TFC and myocardial blush grade did not differ significantly between the two groups, formed according to OPG levels. Despite the lack of association with reperfusion parameters, OPG correlated with hsCRP, *N*/*L* ratio, and remained as the strongest independent parameter in the multivariate analysis.

Data regarding the relationship between STEMI and OPG in the current medical literature are scarce. A previous study documented increased OPG levels in patients with STEMI compared to patients with CAD and normal controls [12]. Prominent immunostaining of OPG/RANK/RANKL were demonstrated within the thrombus material, aspirated during primary PCI for acute STEMI, implicating a

**Table 3**
Relationship of major adverse cardiovascular events with prognostic parameters in study.

| Parameters | Major adverse cardiovascular events | | *p*-Value |
|---|---|---|---|
| | Absence | Presence | |
| Age (yrs) | 60 ± 13 | 66 ± 10 | 0.062 |
| BMI (kg/m$^2$) | 27 ± 4 | 28 ± 6 | NS |
| Gender (male) | 87% | 65% | 0.023 |
| Hypertension | 34% | 50% | NS |
| Diabetes mellitus | 16% | 30% | NS |
| Smoking | 73% | 50% | NS |
| Hyperlipidemia | 16% | 20% | NS |
| Family history of CAD | 10% | 5% | NS |
| Heart rate (bpm) | 80 ± 17 | 86 ± 21 | NS |
| Creatinine (mg/dl) | 0.9 ± 0.3 | 1.3 ± 0.6 | 0.001[a] |
| eGFR (mL/min) | 98 ± 32 | 69 ± 31 | 0.001 |
| Admission blood glucose (mg/dl) | 154 ± 72 | 219 ± 183 | 0.017[a] |
| Fasting blood glucose (mg/dl) | 124 ± 52 | 166 ± 72 | 0.076 |
| Leukocytes ($10^3$/mm$^3$) | 11 ± 3 | 15 ± 7 | 0.005 |
| Neutrophils ($10^3$/mm$^3$) | 7 ± 3 | 12 ± 7 | 0.005[a] |
| Hemoglobin (mg/dl) | 14.1 ± 1.5 | 13.3 ± 1.8 | 0.06 |
| EF% | 45 ± 10 | 39 ± 8 | 0.012 |
| Troponin I (peak) | 1.6 ± 0.2 | 1.7 ± 0.1 | NS[a] |
| HsCRP | −0.3 ± 0.5 | −0.1 ± 0.7 | NS[a] |
| *N*/*L* ratio | 3.9 ± 3.0 | 6.2 ± 5.4 | 0.079 |
| Killip score | 1.1 ± 0.3 | 2.1 ± 1.0 | <0.001 |
| TIMI risk score | 3.8 ± 2.5 | 7.5 ± 3.1 | <0.001 |
| TIMI risk index | 23 ± 11 | 40 ± 18 | 0.001 |
| Osteoprotegerin (pg/mL) | 85 ± 66 | 215 ± 257 | 0.002[a] |
| Total ST elevation on admission (mm) | 10 ± 7 | 12 ± 10 | NS[a] |
| ST segment resolution % | 54 ± 45 | 60 ± 30 | NS[a] |
| Corrected TIMI frame count | 26 ± 19 | 44 ± 31 | 0.001[a] |
| Myocardial blush grade (2, 3) | 72% | 50% | 0.018 |
| Number of obstructed vessels ≥50% | 2.0 ± 0.8 | 2.5 ± 0.8 | 0.012[a] |

BMI, body mass index; CAD, coronary artery disease; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HsCRP, high-sensitivity C-reactive protein; *N*/*L*, neutrophil/lymphocyte; TIMI, thrombolysis in myocardial infarction.

[a] Nonparametric variables were analyzed by Mann–Whitney *U*-test.

potential causative role [13]. Previous studies identified OPG as an independent predictor of HF and mortality in patients with myocardial infarction complicated with HF and ACS [14,23]. Moreover, higher OPG levels were associated with a larger infarct size after STEMI [24].

In the present study, despite the documented association between increased OPG levels and in-hospital MACE in patients with STEMI, the exact cause of this relationship is still unknown. Whether OPG has an independent active pathophysiologic effect or is just a marker of severity has not been clarified. In vitro studies identified OPG to have anti-atherosclerotic properties by inhibiting vascular calcification, regulating B-cell maturation, and demonstrating anti-apoptotic activity [1,25]. However, regardless of the convincing evidence for antiatherogenic effects in animal models, OPG seems to be associated with CAD and a marker of mortality in human studies [9,26]. There may be several explanations for this association. Endothelial and vascular smooth muscle cells secrete OPG in response to TNF-α [27]. Previous studies reported increased expression of RANK in monocytes, RANKL mRNA in T-cells in patients with unstable angina, and OPG/RANK/RANKL specifically in the atherosclerotic plaques. Moreover, supported with the evidence that RANKL increases matrix metalloproteinase (MMP) activity, OPG/RANK/RANKL axis seems to be a crucial factor in unstable coronary syndromes [13]. Therefore, OPG alone may not be effective in neutralizing RANK/RANKL interaction, particularly at high RANKL concentrations. In addition, binding of OPG may possibly hinder clearance of RANKL which increases RANKL actions. Thus, higher OPG concentration, corresponding to a low OPG/RANKL ratio, could indicate overall activity in the OPG/RANK/RANKL system.

In contrast to protective properties, higher OPG levels are associated with increased endothelial cell adhesion and migration of inflammatory cells [28], enhanced MMP-mediated matrix degradation [13], diminished endothelial nitric oxide synthase activity [29], and blocked potential anti-inflammatory activity of TRAIL [30];

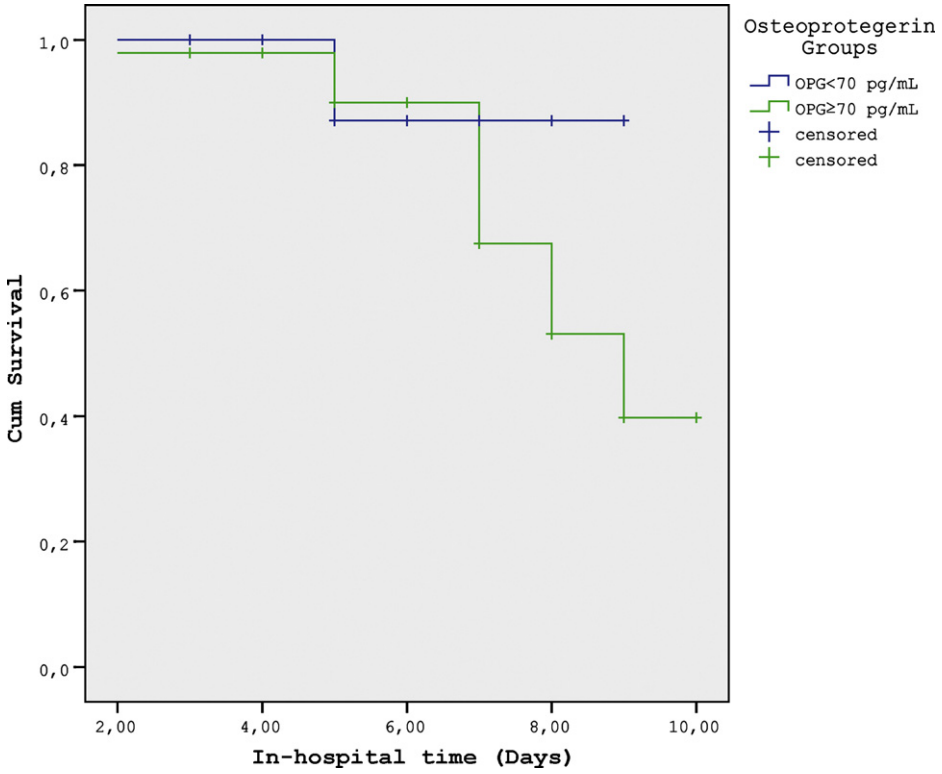


**Fig. 1.** Kaplan–Meier survival plot documenting increased major adverse cardiac event rate in patients with higher osteoprotegerin (OPG) concentrations; Cum, cumulative.

**Table 4**
Multivariate logistic regression analysis: predictors for major adverse cardiovascular events.

| Predictors | OR | 95% CI | *p*-value* | OR | 95% CI | *p*-Value[a] |
|---|---|---|---|---|---|---|
| *Major adverse cardiovascular events* | | | | | | |
| Age (yrs) | 0.996 | 0.916–1.082 | 0.918 | | | |
| Gender (male) | 0.384 | 0.041–3.575 | 0.400 | | | |
| Admission blood glucose (mg/dl) | 0.999 | 0.991–1.007 | 0.868 | | | |
| Hemoglobin (mg/dl) | 1.549 | 0.713–3.365 | 0.269 | | | |
| eGFR (mL/min) | 0.950 | 0.905–0.997 | 0.037 | 0.971 | 0.944–0.999 | 0.042 |
| *N*/*L* ratio | 0.960 | 0.800–1.153 | 0.663 | | | |
| C-reactive protein (mg/dl) | 1.278 | 0.957–1.707 | 0.096 | | | |
| Osteoprotegerin (pg/mL) | 1.011 | 1.001–1.021 | 0.034 | 1.008 | 1.003–1.015 | 0.016 |
| LVEF (%) | 0.935 | 0.850–1.030 | 0.173 | | | |
| Number of obstructed vessels ≥50% | 2.974 | 0.928–9.536 | 0.067 | 2.906 | 1.051–8.037 | 0.040 |
| Corrected TIMI frame count | 1.039 | 1.006–1.073 | 0.021 | 1.039 | 1.011–1.069 | 0.006 |
| Constant | 0.009 | – | 0.497 | 0.020 | – | 0.041 |
| $R^2$ | 0.593 | | | 0.516 | | |

CI, confidence interval; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; *N*/*L*, neutrophil/lymphocyte; OR, odds ratio; TIMI, thrombolysis in myocardial infarction.

[a] Logistic regression analysis with Backward: LR method was used for multivariate analysis of independent causative variables including age, gender, eGFR, hemoglobin, admission glucose level, *N*/*L* ratio, number of obstructed vessels ≥50%, corrected TIMI frame count, high-sensitivity C-reactive protein, LVEF, and osteoprotegerin levels; and after pre-elimination with Enter method.

all in favor of an advanced atherosclerotic process. Consequently, increased OPG concentration may be an ineffective compensatory mechanism in order to heal vascular insult, and a marker of inflammation in cardiovascular disease. Similarly, hsCRP and *N*/*L* ratio was increased in patients with higher OPG levels and correlated to OPG in our study.

A recent study, investigating the relationship between microvascular perfusion and higher OPG levels, revealed increased angiographic no-reflow, microvascular obstruction, and microcirculatory resistance after primary PCI in patients with STEMI [31]. We could not demonstrate a significant association between OPG and reperfusion parameters in our study. However, we did not measure index of microcirculatory resistance, a better marker of microvascular obstruction, as in the referenced study.

Our study includes a small group of patients, which could have diminished the statistical significance of relationship between reperfusion and acute decompensated HF. In addition, we could not measure RANKL level, however OPG may be a more reliable and stable marker of OPG/RANKL/RANK activity [2].

OPG, a multifaceted molecule displaying both atheroprotective and pro-atherosclerotic properties, is a marker of inflammation and a predictor of cardiovascular mortality. We, for the first time, demonstrated that increased OPG level is related to in-hospital adverse cardiovascular events after primary PCI in patients with STEMI.

## Conflict of interest

The authors do not declare any conflict of interest.

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