Acta Clin Croat 2024; 63:733-744

doi: 10.20471/acc.2024.63.03-04.34

Original Scientific Paper

TEN-YEAR OUTCOMES AFTER ACUTE STEMI TREATED WITH PRIMARY PCI – THE ROLE OF ACUTE BIOMARKERS AND OTHER PARAMETERS IN PREDICTING CLINICAL SEVERITY AND PROGNOSIS

Marko Mornar Jelavić[1,2], Zdravko Babić[3,4,5], Dorijan Babić[3], Diana Balenović[6], Ronald Lipovšćak[7] and Hrvoje Pintarić[2,8,9]

[1] Affidea Croatia, Sveti Rok Polyclinic, Zagreb, Croatia;
[2] School of Dental Medicine, University of Zagreb, Zagreb, Croatia;
[3] School of Medicine, University of Zagreb, Zagreb, Croatia;
[4] Faculty of Kinesiology, University of Zagreb, Zagreb, Croatia;
[5] Coronary Care Unit, Division of Cardiology, Department of Internal Medicine, Sestre milosrdnice University Hospital Center, Zagreb, Croatia;
[6] Department of Cardiology, Dr. Ivo Pedišić General Hospital, Sisak, Croatia;
[7] Department of Cardiology, Karlovac General Hospital, Karlovac, Croatia;
[8] Aviva Polyclinic, Zagreb, Croatia;
[9] Traumatology Department, Sestre milosrdnice University Hospital Center, Zagreb, Croatia

SUMMARY – This rare prospective study investigated 10-year outcomes of acute ST-elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI), and evaluated the role of acute biomarkers and other parameters in predicting clinical severity and prognosis. We included 250 patients and analyzed their baseline (cardiovascular risk factors), laboratory (maximal CK/TnT, acute inflammatory (white blood cells (WBC), hs-CRP), and liver biomarkers (AST/LDH), glomerular filtration rate (eGFR)) and clinical severity parameters (length of hospital stay, in-hospital complications, coronary angiography, and echocardiography (LVEF)). After hospital discharge, 229 patients were followed-up (2011-2022) and grouped according to the presence of major adverse cardiovascular events (MACE). In the acute phase, WBC, hs-CRP, LDH and AST positively correlated with maximal CK/cTnT and total in-hospital complications, and negatively with LVEF; WBC positively correlated with cardiogenic shock and stent diameter, hs-CRP with cardiac arrest and length of hospital stay, and LDH with stent diameter; total in-hospital complications increased the risk of in-hospital mortality and number of significantly stenosed coronary arteries, risk of heart failure, whereas the length of hospital stay negatively correlated with LVEF ($p<0.05$ all). During 10-year follow-up, LDH and clinical severity parameters (stenosis of LAD/ACx, multivessel CAD, proximal coronary stenosis, Gensini score, in-hospital complications) increased, while the others (normal eGFR and LVEF) reduced the risk of total MACE ($p<0.05$). In conclusion, acute biomarkers have a role in predicting clinical severity but

Correspondence to: *Marko Mornar Jelavić, MD, PhD*, Affidea Croatia, Sveti Rok Polyclinic, Ulica grada Vukovara 284, HR-10000, Zagreb, Croatia
E-mail: mjelavic@yahoo.com

Received December 21, 2022, accepted February 12, 2024

they have no role in predicting long-term prognosis (except for LDH). Total in-hospital complications, more severe CAD, systolic dysfunction, and worse kidney function may lead to worse in-hospital and long-term outcomes.

Keywords: *Acute STEMI; Primary percutaneous coronary intervention; Long-term prognosis; Inflammation; Biomarkers*

Introduction

Acute myocardial infarction (AMI) and heart failure that sometimes follows are among the leading causes of death and disability worldwide. Following an AMI, the most effective treatment for minimizing acute myocardial ischemia/reperfusion injury, salvaging viable myocardium, and limiting myocardial infarct size, is timely myocardial reperfusion using primary percutaneous coronary intervention (PCI). However, the process of myocardial reperfusion can, paradoxically, induce cardiomyocyte death and myocardial injury by itself, a phenomenon which has been termed 'myocardial reperfusion injury', and which can contribute up to 50% of the final MI size[1,2]. As such, the mortality and morbidity following AMI remain significant with 7% of early mortality and 22% of deaths at one year, respectively[3].

Recruitment of inflammatory cells is a dynamic and superbly orchestrated process comprising sequential infiltration of the injured myocardium with neutrophils, mononuclear cells, dendritic cells (DCs), and lymphocytes[4]. Neutrophils migrate into the infarcted myocardium during the first hours after the onset of ischemia and peak after one day[5]. Thereafter, monocytes and their descendant macrophages dominate cellular infiltration and release inflammatory mediators, reactive oxygen species, and proteolytic enzymes, contributing to the initiation and resolution of inflammation, phagocytosis, proteolysis, angiogenesis, infarct healing, and ventricular remodeling[4-6]. Meanwhile, DCs and T lymphocytes are recruited into the injured myocardium, contributing to wound healing and ventricular remodeling[7,8].

The main aims of this study were as follows: to investigate 10-year outcomes of acute ST-elevation myocardial infarction (STEMI) treated with primary PCI; and to investigate the role of acute biomarkers and other parameters in predicting clinical severity and prognosis in this group of patients.

Patients and Methods

This prospective study, approved by the appropriate ethics committee, included 250 patients with acute STEMI treated with primary PCI. The inclusion criteria were presenting within 12 hours from the onset of symptoms (history of chest pain/discomfort lasting for 10-20 min or more, not responding fully to nitroglycerine), persistent ST-segment elevation on electrocardiography (ECG) in at least two consecutive leads or (presumed) new left bundle branch block, and elevated cardiac laboratory biomarkers (cardiac troponin T (cTnT) and creatine kinase (CK)). The diagnosis of acute STEMI was established and primary PCI performed using the European Society of Cardiology criteria[9,10].

During hospitalization, 19 (7.6%) patients died. After hospital discharge, 229 patients were followed-up for 10 years. They were classified into two groups according to the presence of major adverse cardiovascular events (MACE), and analyzed by the baseline and severity parameters of acute STEMI. MACE parameters include cardiac rehospitalization (reinfarction, PCI/coronary artery bypass graft (CABG), heart failure), stroke and mortality, as well as total MACE. Data were collected by medical examination, checking medical documentation, or telephone contact with patients, family members or family physicians.

Baseline demographic and medical history parameters included gender, age, hypertension, dyslipidemia, diabetes, obesity (body mass index (BMI), waist circumference (WC), waist-to-hip (WHR) and waist-to-height ratio (WHtR)), smoking, known family history of cardiovascular events, previous MI or previous PCI/CABG. Clinical severity parameters included biomarkers of necrosis (maximal CK/TnT, acute inflammatory (white blood cells (WBC), high sensitivity C-reactive protein (hs-CRP)) and liver biomarkers (aspartate aminotransferase (AST), lactate dehydrogenase (LDH)), kidney function (estimated

glomerular filtration rate (eGFR) according to the Cockroft-Gault formula), length of hospital stay, in-hospital complications (heart failure, cardiogenic shock, cardiac arrest, reinfarction, mechanical ventilation, reintervention, total), coronary angiography findings (distribution and number of significantly stenosed coronary arteries and their segments, number, length and diameter of stents, and Gensini score), and imaging of systolic function (left ventricular ejection fraction (LVEF)). Coronary angiography was performed by applying a monoplane system (Axiom Artis, Siemens, Erlangen, Germany)[9]. Patients received 70 IE/kg of unfractionated heparin, 300 mg of aspirin, a loading dose of 600 mg of clopidogrel, and a GPIIb/IIIa inhibitor according to the judgment of an interventional cardiologist. Stenosis of more than 50% was considered clinically significant. It was measured with the system software in all patients. Serum CK activity was measured by spectrophotometry (Olympus 680, Beckman Coulter Inc., California, USA), while cTnT levels were measured by electrochemiluminescence assay (Cobas e411, Roche Diagnostics, Sussex, UK). Echocardiography was performed in all patients (Acuson Sequoia 512, Siemens, Munich, Germany). Patients with other inflammatory states and malignant disease were excluded.

Statistical analysis

Qualitative data were expressed as absolute number and percentage. We used the χ^2 test with Yates correction. Quantitative data were expressed as median and range. Differences between the two groups were tested by the Mann-Whitney U test. Correlations between two variables were investigated by Spearman's correlation and classified as very weak (rho=0-0.19), weak (rho=0.20-0.39), moderate (rho=0.40–0.59), strong (rho=0.60-0.79), and very strong (rho=0.80-1.0). This guide was also applied to negative correlations. We used logistic regression analysis for analyzing the effect of independent on dependent variable; data were presented with odds ratio (OR) and confidence interval (CI). The level of statistical significance was set at $p<0.05$ (MedCalc 12.7.0.0. for Windows).

Table 1. Correlation between acute biomarkers and clinical severity of acute STEMI

Clinical severity	Parameter							
	WBC (x10³ cells/mL), rho [CI]	**p**	**hs-CRP (mg/L), rho [CI]**	**p**	**LDH (U/L), rho [CI]**	**p**	**AST (U/L), rho [CI]**	**p**
Max CK (U/I)	0.33 [0.20-0.44]	**0.000**	0.24 [0.07-0.38]	**0.005**	0.88 [0.84-0.91]	**0.000**	0.91 [0.88-0.93]	**0.000**
Max cTnT (ng/mL)	0.28 [0.15-0.40]	**0.000**	0.25 [0.10-0.40]	**0.002**	0.74 [0.67-0.79]	**0.000**	0.74 [0.67-0.79]	**0.000**
LVEF (%)	-0.24 [-0.36 to -0.11]	**0.001**	-0.28 [-0.48 to -0.12]	**0.001**	-0.51 [-0.60 to -0.40]	**0.000**	-0.47 [-0.57 to -0.36]	**0.000**
In-hospital complications (n)	0.23 [0.11-0.36]	**0.001**	0.21 [0.05-0.36]	**0.012**	0.24 [0.12-0.37]	**0.000**	0.23 [0.10-0.36]	**0.000**
Hospital stay (days)	0.07 [-0.06-0.21]	0.297	0.25 [0.10-0.40]	**0.002**	0.09 [-0.04-0.22]	0.180	0.07 [-0.07-0.20]	0.346
Stents (n)	-0.04 [-0.18-0.10]	0.566	-0.04 [-0.21-0.13]	0.610	-0.02 [-0.15-0.12]	0.801	-0.02 [-0.15-0.12]	0.781
Stent length (mm)	-0.02 [-0.15-0.12]	0.797	0.06 [-0.11-0.23]	0.491	0.06 [-0.07-0.20]	0.362	0.04 [-0.10-0.18]	0.571
Stent diameter (mm)	0.14 [0.01-0.27]	**0.042**	0.06 [-0.11-0.22]	0.512	0.15 [0.01-0.28]	**0.035**	0.12 [-0.02-0.25]	0.099

WBC = white blood cells; hs-CRP = high sensitivity C-reactive protein; LDH = lactate dehydrogenase; AST = aspartate aminotransferase; CI = confidence interval; CK = creatine kinase; cTnT = cardiac troponin T; LVEF = left ventricular ejection fraction

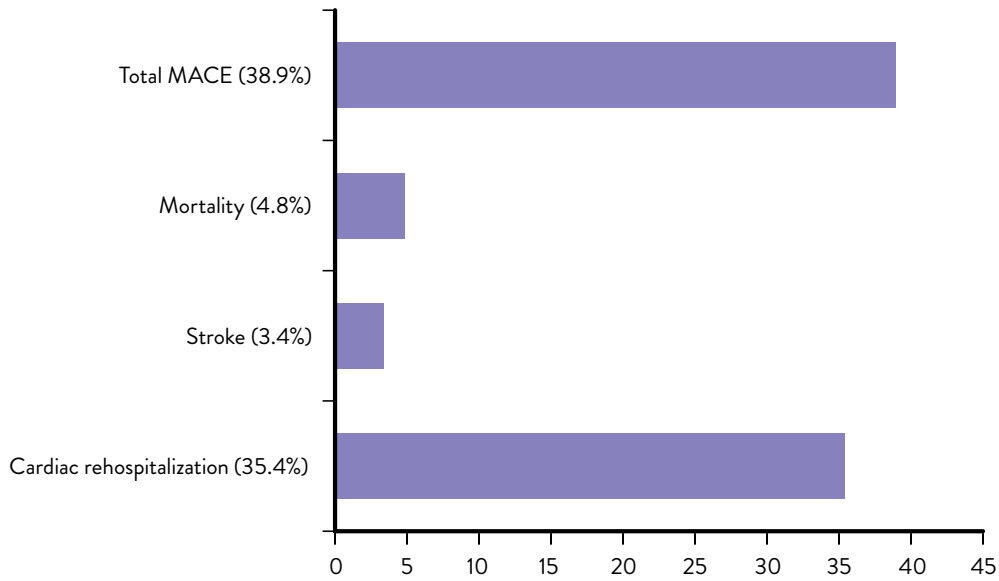

Fig. 1. Major adverse cardiovascular events (MACE) during 10-year follow-up (2011-2021).

Results

Baseline, clinical severity and prognostic data

Among the total of 250 patients at hospital admission, acute STEMI was more frequent in men (n=177, 70.8%) than in women (n=73, 29.2%). The most frequent cardiovascular risk factor was dyslipidemia (76.0%), then arterial hypertension (72.4%), metabolic syndrome (54.4%), smoking (51.6%), positive family history (42.8%), hyperglycemia (24.4%), previous PCI (9.2%), previous MI (8.8%), and CABG (0.4%). During hospital stay, 80 (32.0%) patients had total in-hospital complications and 19 (7.6%) patients died.

During 10-year follow-up (229 patients), MACE was recorded in 89 (38.9%) patients. The most common MACE parameter was cardiac rehospitalization (35.4%), then mortality (4.8%) and stroke (3.4%) (Fig. 1).

Acute biomarkers and other parameters as predictors of acute phase (primary outcome)

a) In the acute phase, WBC, hs-CRP, LDH and AST positively correlated with maximal CK/cTnT (rho=0.33/0.28, rho=0.24/0.25, rho=0.88/0.74, and rho=0.91/0.74, respectively) and total in-hospital complications (rho=0.23, rho=0.21, rho=0.24 and rho=0.23, respectively), and negatively with LVEF (rho=-0.24, rho=-0.28, rho=-0.50 and rho=-0.47, respectively) ($p<0.05$ all). Additionally, WBC positively correlated with cardiogenic shock (OR=1.25) and stent diameter (rho=0.14), hs-CRP with cardiac arrest (OR=1.12) and length of hospital stay (rho=0.25), and LDH with stent diameter (rho=0.15) ($p<0.05$ all) (Table 1);
b) total in-hospital complications increase the risk of in-hospital mortality (OR=3.07, CI [1.30-7.24], p=0.011);
c) the number of significantly stenosed coronary arteries increases the risk of heart failure (OR=2.46, CI [1.41-4.28], p=0.002); and
d) normal LVEF reduces the risk of longer hospital stay (rho=-0.14, CI [-0.28 to -0.01], p=0.040).

Acute biomarkers and other parameters as predictors of MACE during long-term follow-up (10 years) (secondary outcome)

a) Patients with MACE (n=89, 38.9%) were older (median age 63 *vs*. 59 years), they had higher rates of arterial hypertension (80.9% *vs*. 65.0%) and metabolic syndrome (62.9% *vs*. 48.6%), and previous

Table 2. Differences between study groups in baseline parameters and parameters of clinical severity of acute STEMI

	Parameter		
	MACE (N=89)	**No MACE (N=140)**	**p**
Baseline			
Age (years)	63 (56-71)	59 (54-73)	**0.049**
Male, n (%)	67 (75.3)	99 (70.7)	0.452
Hypertension, n (%)	72 (80.9)	91 (65.0)	**0.010**
Hyperlipidemia, n (%)	69 (77.6)	105 (75.0)	0.663
Diabetes mellitus type 2, n (%)	23 (25.8)	31 (22.1)	0.521
Metabolic syndrome, n (%)	56 (62.9)	68 (48.6)	**0.034**
Body mass index (kg/m^2)	28 (25-31)	28 (25-31)	0.904
WC (cm)	102 (95-108)	99 (93-108)	0.390
Waist-to-hip ratio	1.0 (0.9-1.1)	1.0 (0.9-1.1)	0.931
Waist-to-height ratio	0.6 (0.5-0.6)	0.6 (0.5-0.6)	0.627
Smoking, n (%)	42 (47.2)	80 (57.1)	0.142
Previous MI, n (%)	11 (12.4)	8 (5.7)	0.072
Previous PCI/CABG, n (%)	12 (13.5)	8 (5.7)	**0.043**
Family predisposition, n (%)	46 (51.7)	59 (42.1)	0.159
Clinical severity			
Length of hospital stay (days)	9 (7-12)	9 (7-12)	0.158
WBC (x10^3 cells/mL)	11.2 (9.5-14.0)	11.0 (8.8-13.7)	0.545
hs-CRP (mg/L)	1.2 (0.4-7.6)	0.8 (0.3-2.7)	0.151
LDH (U/L)	626 (411-1051)	563 (360-836)	**0.032**
AST (U/L)	229 (89-417)	192 (100-297)	0.094
Max CK (U/I)	2558 (1043-5724)	1809 (955-3682)	**0.010**
Max cTnT (ng/mL)	3.4 (1.9-6.4)	2.8 (1.6-5.2)	0.169
eGFR (mL/min/1.73 m^2)	63 (51-75)	73 (61-85)	**0.001**
LMCA, n (%)	4 (4.5)	3 (2.1)	0.315
RCA, n (%)	50 (56.2)	84 (60.0)	0.568
LAD, n (%)	49 (55.1)	43 (30.7)	**0.000**
ACx, n (%)	65 (73.0)	83 (59.3)	**0.034**
Multivessel CAD, n (%)	52 (58.4)	63 (45.0)	**0.048**
Proximal coronary segments, n (%)	71 (79.8)	86 (61.4)	**0.004**
Gensini score	60 (42-83)	37 (30-73)	**0.001**
LVEF (%)	50 (45-55)	55 (50-56)	**0.001**
In-hospital complications (total)	2 (1-2)	1 (1-2)	**0.049**

STEMI = ST-elevation myocardial infarction; MI = myocardial infarction; PCI/CABG = percutaneous coronary intervention/coronary artery bypass graft; WBC = white blood cells; hs-CRP = high sensitivity C-reactive protein; LDH = lactate dehydrogenase; AST = aspartate transferase; CK = creatine kinase; cTnT = cardiac troponin T; eGFR = estimated glomerular filtration rate; LMCA = left main coronary artery; RCA = right coronary artery; LAD = left anterior descending artery; ACx = left circumflex artery ; CAD = coronary artery disease; LVEF = left ventricular ejection fraction; MACE = major adverse cardiovascular events

PCI/CABG (13.5% *vs*. 5.7%) (p<0.05 all) (Table 2). They also had higher values of liver/myocardial necrosis biomarkers (median LDH 626 *vs*. 563 U/L, max CK 2558 *vs*. 1809 U/L), worse kidney function (median eGFR 63 *vs*. 73 mL/min/1.73 m^2), more severe coronary artery disease (CAD) (more frequent stenosis of left anterior descending artery (LAD) (55.1% *vs*. 30.7%), left circumflex artery (ACx) (73.0% *vs*. 59.3%), multivessel CAD (58.4% *vs*. 45.0%) and proximal coronary segments stenosis (79.8% *vs*. 61.4%), and worse Gensini score (median 60 *vs*. 37), worse systolic function (median LVEF 50% *vs*. 55%), and more in-hospital complications (median 2 *vs*. 1) (p<0.05 all) (Table 1).

b) By using logistic regression analysis (Table 3), we found that some baseline parameters (age, hypertension, metabolic syndrome, previous PCI/CABG), laboratory (LDH, max CK) and clinical severity parameters (significant stenosis of LAD and ACx, multivessel CAD, proximal coronary stenosis, Gensini score, total in-hospital complications) increase, while others (normal eGFR and LVEF) reduce the risk of total MACE (p<0.05 all).

Discussion

This is one of the rare studies which investigated the impact of acute biomarkers, imaging and clinical parameters on long-term (10-year) prognosis after acute STEMI treated with primary PCI. Briefly, we found a positive correlation of acute (inflammatory and liver) biomarkers with clinical severity of acute STEMI (maximal CK/TnT and LVEF values, cardiogenic shock, cardiac arrest, death, total in-hospital complications, length of hospital stay, and stent diameter). They had no direct predictive value for prognosis (except for LDH), but indirectly, through myocardial necrosis and impaired systolic function, led to adverse long-term outcomes.

Núñez *et al*. conclude that WBC on admission is an independent predictor of long-term mortality in both non-STEMI and STEMI patients[11]. Other studies report on an association between increased WBC and higher incidence of complications following AMI, in particular, heart failure and short- and long-term mortality[12-22]. A number of mechanisms have been proposed to explain this association, such as resistance to thrombolytic therapy due to alterations in the microcirculation, hypercoagulable state, a no-reflow phenomenon caused by leukocytes, indirect cardiotoxicity mediated by proinflammatory cytokines, promoters of ischemia-reperfusion injury, and expansion of the AMI[23-27]. Regarding this final point, it is important to bear in mind that the leukocyte response that occurs following AMI is a central part of the inflammatory reparative response that is initiated to replace the necrotic tissue with scar tissue. Elevation in WBC count was associated with reduced epicardial blood flow and myocardial perfusion, thromboresistance (arteries open later and have a greater thrombus burden), and a higher incidence of new congestive heart failure and death. These observations provide a potential explanation for the higher mortality rate observed among AMI patients with elevated WBC counts and helps explain the growing body of literature that links inflammation and cardiovascular disease[12]. WBC count within 24 h of admission for an AMI is a strong and independent predictor of in-hospital and 30-day mortality, as well as in-hospital clinical events[13]. Canon *et al*. observed in a study of 7,651 patients with acute coronary syndromes that a WBC count of >10,000 was associated with increased 30-day and 10-month mortality. With its simplicity and widespread availability, WBC count could serve as a simple and inexpensive tool for risk stratification in acute coronary syndromes[14]. In patients with unstable angina/NSTEMI, elevations in a simple, widely available blood test, the WBC count, were associated with impaired epicardial and myocardial perfusion, more extensive CAD, and higher six-month mortality[15]. The results reported by Menon *et al*. suggest that peripheral total leukocyte count is strongly associated with the development of heart failure, cardiogenic shock, and death during hospitalization for AMI. These findings suggest that the WBC count should be considered an important prognostic factor associated with adverse hospital outcomes in patients with AMI[17]. An elevated WBC count at hospital admission, although only a crude index of inflammation, nevertheless is an independent predictor of death at 6 months in patients with acute coronary syndromes[18]. WBC is a strong independent predictor of short- and long-term mortality after non-ST elevation-acute coronary syndrome (NSTE/ACS)

Table 3. Effect of various baseline and clinical severity parameters on MACE during 10-year follow-up after acute STEMI

	Parameter	
	MACE, OR [CI]	**p**
Baseline		
Age (years)	1.02 [1.00-1.05]	**0.049**
Males	1.26 [0.69-2.31]	0.451
Hypertension	2.28 [1.21-4.29]	**0.011**
Hyperlipidemia	1.15 [0.61-2.15]	0.663
Diabetes mellitus type 2	1.23 [0.66-2.28]	0.521
Metabolic syndrome	1.80 [1.04-3.10]	**0.034**
BMI (kg/m^2)	0.97 [0.92-1.04]	0.405
WC (cm)	1.00 [0.98-1.02]	0.739
WHR	1.63 [0.07-36.08]	0.759
WHtR	0.92 [0.03-30.80]	0.961
Smoking	0.67 [0.39-1.14]	0.142
Previous MI	2.33 [0.90-6.03]	0.082
Previous PCI/CABG	2.57 [1.01-6.57]	**0.048**
Family predisposition	1.47 [0.86-2.51]	0.159
Clinical severity		
Hospital stay (days)	1.04 [0.99-1.10]	0.144
WBC (x10^3 cells/mL)	1.03 [0.99-1.11]	0.520
hs-CRP (mg/L)	1.04 [0.98-1.10]	0.247
LDH (U/L)	1.00 [1.00-1.01]	**0.038**
AST (U/L)	1.00 [0.99-1.01]	0.172
Max CK (U/I)	1.00 [1.00-1.02]	**0.012**
Max cTnT (ng/mL)	1.06 [0.98-1.16]	0.163
eGFR (mL/min/1.73 m2)	0.97 [0.96-0.99]	**0.001**
LMCA	2.15 [0.47-9.82]	0.324
RCA	0.86 [0.49-1.46]	0.568
LAD	2.76 [1.59-4.80]	**0.000**
ACx	1.86 [1.05-3.31]	**0.035**
Multivessel CAD	1.71 [1.00-2.94]	**0.048**
Proximal coronary segments	2.48 [1.33-4.60]	**0.004**
Gensini score	1.01 [1.00-1.02]	**0.001**
LVEF (%)	0.94 [0.91-0.98]	**0.001**
In-hospital complications (total)	1.50 [1.00-2.23]	**0.049**

STEMI = ST-elevation myocardial infarction; MACE = major adverse cardiovascular events; OR = odds ratio; CI = confidence interval; BMI = body mass index; WC = waist circumference; WHR = waist-to-hip ratio; WHtR = waist-to-height ratio; MI = myocardial infarction; PCI/CABG = percutaneous coronary intervention/coronary artery bypass graft; WBC = white blood cells; hs-CRP = high sensitivity C-reactive protein; LDH = lactate dehydrogenase; AST = aspartate aminotransferase; CK = creatine kinase; cTnT = cardiac troponin T; eGFR = estimated glomerular filtration rate; LMCA = left main coronary artery; RCA = right coronary artery; LAD = left anterior descending artery; ACx = left circumflex artery; CAD = coronary artery disease; LVEF = left ventricular ejection fraction

treated with very early revascularization[19]. Relative neutrophilia on admission to the hospital in patients with AMI is significantly associated with early development of congestive heart failure (CHF). This association may help in the identification of individuals at a high risk who might benefit from more aggressive interventions to prevent or reduce the risk of CHF[20]. In men and women of all ages with the spectrum of ACS, initial leukocyte count is an independent predictor of hospital death and development of heart failure[21].

An acute increase in hs-CRP shortly after STEMI reaches its peak value within 48-72 h and gradually decreases over the next several weeks to reference range <10 mg/L[28,29]. In patients with AMI, the level of hs-CRP may correspond to the extent of coronary artery lesion, the size of myocardial necrosis area, the risk of recurrent acute coronary syndrome, the risk of new-onset atrial fibrillation, ventricular tachycardia, heart failure decompensation/development, and death. It should be acknowledged that CRP is a marker of inflammation, and it is a nonspecific sign of many acute and chronic diseases that may coexist in patients with AMI[30].

Once again, our study showed that long-term (10-year) prognosis was influenced by several parameters during acute phase, i.e., age, arterial hypertension, metabolic syndrome, previous PCI/CABG, kidney function, max CK and LDH, LVEF, severity of CAD, and total in-hospital complications. Fournier *et al.* and Yahoud *et al.* report that the strongest independent predictor of the long-term mortality rate is ejection fraction[31,32]. In the study by Smolina *et al.*, older age, higher deprivation, no revascularization procedures, and presence of comorbidities were associated with a higher risk of AMI recurrence[33]. Botkin *et al.* found that advancing age, female sex, presence of prior diabetes, stroke, heart failure or myocardial infarction, and occurrence of several clinical complications during hospital stay were significantly related to an adverse post-discharge prognosis[34]. Timoteo *et al.* conclude that elderly patients represent a substantial proportion of the population admitted with MI and receive less evidence-based therapy. Age is an independent predictor of short- and medium-term mortality[35]. According to the studies by Lekston *et al.* and Dziewierz *et al.*, the presence of multivessel disease in patients with STEMI is a strong and independent risk factor for higher long-term mortality[36,37]. It should be emphasized that the lack of influence of inflammatory parameters (WBC and hs-CRP) in this study on long-term prognosis may have been due to the relatively small number of examined patients and that conducting studies with a larger number of subjects is recommended. Finally, as in our previous investigations performed on short-term follow-up (12-month), we did not find any influence of anthropometric parameters on long-term prognosis[38-40]. It may be explained with variations of body weight and composition during short- and long-term follow-up period.

The first biomarker used to aid in the diagnosis of acute MI was AST[41-45]. In 1954, Ladue *et al.* proposed that AST released from cardiomyocytes undergoing necrosis would be useful in diagnosing acute MI[42]. AST increases in the blood 3 to 4 hours after an acute MI, peaks at 15 to 28 hours, and returns to baseline within 5 days. In current clinical practice, AST has fallen out of favor for diagnosing acute MI because it is not a specific marker for cardiac myocytes. AST levels in the blood elevate in hepatic disease (e.g., hepatitis, hepatic congestion), pericarditis, pulmonary embolism, and shock, and therefore they are not used in the diagnosis of acute MI anymore. After discovering that AST was released from ischemic cardiac myocytes, LDH emerged as another potential biomarker for detecting myocardial ischemia. LDH increases in the blood 6 to 12 hours after an acute MI, peaks within 24 to 72 hours, and normalizes within 8 to 14 days. In the past, a ratio of LDH1 (an isoform found in the heart) to LDH2 greater than 1 was considered to be specific for an acute MI[41-45]. Since it is not a specific marker for cardiac myocytes and its levels can also increase in many other conditions, LDH is no longer used in the diagnosis of MI. Nowadays, the only usage of LDH in the evaluation of acute MI is to differentiate acute from subacute MI in patients with elevated troponin levels and normal creatine kinase-myocardial band (CK-MB) levels[41-45]. It is worth emphasizing once again that in patients with AMI complicated by cardiogenic and other types of shock, and with some other conditions, AST and LDH may be elevated, they are monitored as an indicator of the course of the disease, and are associated with a more complicated clinical course and worse prognosis[41-45]. In this study, AST and

LDH correlated with several parameters of clinical severity (maximal CK/TnT, LVEF, heart failure, cardiogenic shock, total in-hospital complications) and may serve for in-hospital risk stratification. Also, only LDH had a role in predicting prognosis.

Conclusion

Acute biomarkers have a role in predicting clinical severity (myocardial necrosis, LVEF, cardiac arrest, cardiogenic shock, total in-hospital complications, length of hospital stay, and stent diameter), but they cannot be used for prediction of the long-term prognosis (except for LDH). Total in-hospital complications, more severe CAD, systolic dysfunction, and worse kidney function may lead to worse in-hospital (primary) and long-term (secondary) outcomes. Finally, primary prevention measures should be directed on timely treatment of arterial hypertension and metabolic syndrome, two modifiable risk factors with impact on long-term prognosis.

References

1. Yellon DM, Hausenloy DJ. Myocardial reperfusion injury. N Engl J Med. 2007 Sep 13;357(11):1121-35. doi: 10.1056/NEJMra071667.
2. Ong SB, Hernández-Reséndiz S, Crespo-Avilan GE, Mukhametshina RT, Kwek XY, Cabrera-Fuentes HA, *et al*. Inflammation following acute myocardial infarction: multiple players, dynamic roles, and novel therapeutic opportunities. Pharmacol Ther. 2018 Jun;186:73-87. doi: 10.1016/j.pharmthera.2018.01.001.
3. Cung TT, Morel O, Cayla G, Rioufol G, Garcia-Dorado D, Angoulvant D, *et al*. Cyclosporine before PCI in patients with acute myocardial infarction. N Engl J Med. 2015 Sep 10;373(11):1021-31. doi: 10.1056/NEJMoa1505489.
4. Liu J, Wang H, Li J. Inflammation and inflammatory cells in myocardial infarction and reperfusion injury: a double-edged sword. Clin Med Insights Cardiol. 2016 Jun 1;10:79-84. doi: 10.4137/CMC.S33164. PMID: 27279755; PMCID: PMC4892199.
5. Yellon DM, Hausenloy DJ. Myocardial reperfusion injury. N Engl J Med. 2007 Sep 13;357(11):1121-35. doi: 10.1056/NEJMra071667.
6. Nahrendorf M, Swirski FK, Aikawa E, Stangenberg L, Wurdinger T, Figueiredo JL, *et al*. The healing myocardium sequentially mobilizes two monocyte subsets with divergent and complementary functions. J Exp Med. 2007 Nov 26;204(12):3037-47. doi: 10.1084/jem.20070885.
7. Anzai A, Anzai T, Nagai S, Maekawa Y, Naito K, Kaneko H, *et al*. Regulatory role of dendritic cells in postinfarction healing and left ventricular remodeling. Circulation. 2012 Mar 13;125(10):1234-45. doi: 10.1161/CIRCULATIONAHA.111.052126.
8. Hofmann U, Beyersdorf N, Weirather J, Podolskaya A, Bauersachs J, Ertl G, *et al*. Activation of CD4+ T lymphocytes improves wound healing and survival after experimental myocardial infarction in mice. Circulation. 2012 Apr 3;125(13):1652-63. doi: 10.1161/CIRCULATIONAHA.111.044164.
9. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, *et al*.; ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018 Jan 7;39(2):119-77. doi: 10.1093/eurheartj/ehx393.
10. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, *et al*. 2014 ESC/EACTS Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J. 2014 Oct 1;35(37):2541-619. doi: 10.1093/eurheartj/ehu278.
11. Núñez J, Fácila L, Llàcer A, Sanchís J, Bodí V, Bertomeu V, *et al*. Valor pronóstico del recuento leucocitario en el infarto agudo de miocardio: mortalidad a largo plazo [Prognostic value of white blood cell count in acute myocardial infarction: long-term mortality]. Rev Esp Cardiol. 2005 Jun;58(6):631-9.
12. Barron HV, Cannon CP, Murphy SA, Braunwald E, Gibson CM. Association between white blood cell count, epicardial blood flow, myocardial perfusion, and clinical outcomes in the setting of acute myocardial infarction: a thrombolysis in myocardial infarction 10 substudy. Circulation. 2000 Nov 7;102(19):2329-34. doi:10.1161/01.cir.102.19.2329.
13. Barron HV, Harr SD, Radford MJ, Wang Y, Krumholz HM. The association between white blood cell count and acute

myocardial infarction mortality in patients > or =65 years of age: findings from the cooperative cardiovascular project. J Am Coll Cardiol. 2001 Nov 15;38(6):1654-61. doi: 10.1016/s0735-1097(01)01613-8.

14. Cannon CP, McCabe CH, Wilcox RG, Bentley JH, Braunwald E. Association of white blood cell count with increased mortality in acute myocardial infarction and unstable angina pectoris. OPUS-TIMI 16 Investigators. Am J Cardiol. 2001 Mar 1;87(5):636-9, A10. doi: 10.1016/s0002-9149(00)01444-2.
15. Sabatine MS, Morrow DA, Cannon CP, Murphy SA, Demopoulos LA, DiBattiste PM, *et al*. Relationship between baseline white blood cell count and degree of coronary artery disease and mortality in patients with acute coronary syndromes: a TACTICS-TIMI 18 (Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy – Thrombolysis in Myocardial Infarction 18 trial) substudy. J Am Coll Cardiol. 2002 Nov 20;40(10):1761-8. doi: 10.1016/s0735-1097(02)02484-1.
16. Yen MH, Bhatt DL, Chew DP, Harrington RA, Newby LK, Ardissino D, *et al*. Association between admission white blood cell count and one-year mortality in patients with acute coronary syndromes. Am J Med. 2003 Sep;115(4):318-21. doi: 10.1016/s0002-9343(03)00358-9.
17. Menon V, Lessard D, Yarzebski J, Furman MI, Gore JM, Goldberg RJ. Leukocytosis and adverse hospital outcomes after acute myocardial infarction. Am J Cardiol. 2003 Aug 15;92(4):368-72. doi: 10.1016/s0002-9149(03)00651-9.
18. Bhatt DL, Chew DP, Lincoff AM, Simoons ML, Harrington RA, Ommen SR, *et al*.; PURSUIT Investigators. Effect of revascularization on mortality associated with an elevated white blood cell count in acute coronary syndromes. Am J Cardiol. 2003 Jul 15;92(2):136-40. doi: 10.1016/s0002-9149(03)00527-7.
19. Mueller C, Neumann FJ, Perruchoud AP, Buettner HJ. White blood cell count and long term mortality after non-ST elevation acute coronary syndrome treated with very early revascularisation. Heart. 2003 Apr;89(4):389-92. doi: 10.1136/heart.89.4.389.
20. Kyne L, Hausdorff JM, Knight E, Dukas L, Azhar G, Wei JY. Neutrophilia and congestive heart failure after acute myocardial infarction. Am Heart J. 2000 Jan;139(1 Pt 1):94-100. doi: 10.1016/s0002-8703(00)90314-4.
21. Furman MI, Gore JM, Anderson FA, Budaj A, Goodman SG, Avezum A, *et al*.; GRACE Investigators. Elevated leukocyte count and adverse hospital events in patients with acute coronary syndromes: findings from the Global Registry of Acute Coronary Events (GRACE). Am Heart J. 2004 Jan;147(1):42-8. doi: 10.1016/j.ahj.2003.07.003.
22. Hung MJ, Cherng WJ. Comparison of white blood cell counts in acute myocardial infarction patients with significant versus insignificant coronary artery disease. Am J Cardiol. 2003 Jun 1;91(11):1339-42. doi: 10.1016/s0002-9149(03)00325-4.
23. Wong CK, French JK, Gao W, White HD. Relationship between initial white blood cell counts, stage of acute myocardial infarction evolution at presentation, and incidence of Thrombolysis In Myocardial Infarction-3 flow after streptokinase. Am Heart J. 2003 Jan;145(1):95-102. doi: 10.1067/mhj.2003.64.
24. Neumann FJ, Zohlnhöfer D, Fakhoury L, Ott I, Gawaz M, Schömig A. Effect of glycoprotein IIb/IIIa receptor blockade on platelet-leukocyte interaction and surface expression of the leukocyte integrin Mac-1 in acute myocardial infarction. J Am Coll Cardiol. 1999 Nov 1;34(5):1420-6. doi: 10.1016/s0735-1097(99)00350-2.
25. Engler RL, Dahlgren MD, Morris DD, Peterson MA, Schmid-Schönbein GW. Role of leukocytes in response to acute myocardial ischemia and reflow in dogs. Am J Physiol. 1986 Aug;251(2 Pt 2):H314-23. doi: 10.1152/ajpheart.1986.251.2.H314.
26. Irwin MW, Mak S, Mann DL, Qu R, Penninger JM, Yan A, *et al*. Tissue expression and immunolocalization of tumor necrosis factor-alpha in postinfarction dysfunctional myocardium. Circulation. 1999 Mar 23;99(11):1492-8. doi: 10.1161/01.cir.99.11.1492. PMID: 10086975.
27. Cotter G, Kaluski E, Milo O, Blatt A, Salah A, Hendler A, *et al*. LINCS: L-NAME (a NO synthase inhibitor) in the treatment of refractory cardiogenic shock: a prospective randomized study. Eur Heart J. 2003 Jul;24(14):1287-95. doi: 10.1016/s0195-668x(03)00193-3.
28. Osman R, L'Allier PL, Elgharib N, Tardif JC. Critical appraisal of C-reactive protein throughout the spectrum of cardiovascular disease. Vasc Health Risk Manag. 2006;2:221-37. doi: 10.2147/vhrm.2006.2.3.221.
29. Kang DO, Park Y, Seo JH, Jeong MH, Chae SC, Ahn TH, *et al*.; KAMIR-NIH Registry Investigators. Time-dependent prognostic effect of high sensitivity C-reactive protein with statin therapy in acute myocardial infarction. J Cardiol. 2019 Jul;74(1):74-83. doi: 10.1016/j.jjcc.2018.12.022.
30. Polyakova EA, Mikhaylov EN. The prognostic role of high-sensitivity C-reactive protein in patients with acute myocardial infarction. J Geriatr Cardiol. 2020 Jul 28;17(7):379-83. doi: 10.11909/j.issn.1671-5411.2020.07.007.

31. Fournier JA, Cabezón S, Cayuela A, Ballesteros SM, Cortacero JA, Díaz De La Llera LS. Long-term prognosis of patients having acute myocardial infarction when ≤40 years of age. Am J Cardiol. 2004 Oct 15;94(8):989-92. doi: 10.1016/j.amjcard.2004.06.051.
32. Yahud E, Tzuman O, Fink N, Goldenberg I, Goldkorn R, Peled Y, *et al*. Trends in long-term prognosis according to left ventricular ejection fraction after acute coronary syndrome. J Cardiol. 2020 Sep;76(3):303-8. doi: 10.1016/j.jjcc.2020.03.012.
33. Smolina K, Wright FL, Rayner M, Goldacre MJ. Long-term survival and recurrence after acute myocardial infarction in England, 2004 to 2010. Circ Cardiovasc Qual Outcomes. 2012 Jul 1;5(4):532-40. doi: 10.1161/CIRCOUTCOMES.111.964700.
34. Botkin NF, Spencer FA, Goldberg RJ, Lessard D, Yarzebski J, Gore JM. Changing trends in the long-term prognosis of patients with acute myocardial infarction: a population-based perspective. Am Heart J. 2006 Jan;151(1):199-205. doi: 10.1016/j.ahj.2005.03.016.
35. Timóteo AT, Ramos R, Toste A, Lousinha A, Oliveira JA, Ferreira ML, *et al*. Impacto da idade no tratamento e resultados após enfarte agudo do miocárdio em particular nos muito idosos [Impact of age on treatment and outcomes after acute myocardial infarction, particularly in very elderly patients]. Rev Port Cardiol. 2011 Dec;30(12):897-903. doi: 10.1016/j.repc.2011.09.013.
36. Lekston A, Tajstra M, Gąsior M, Gierlotka M, Pres D, Hudzik B, *et al*. Impact of multivessel coronary disease on one-year clinical outcomes and five-year mortality in patients with ST-elevation myocardial infarction undergoing percutaneous coronary intervention. Kardiol Pol. 2011;69(4):336-43.
37. Dziewierz A, Siudak Z, Rakowski T, Zasada W, Dubiel JS, Dudek D. Impact of multivessel coronary artery disease and noninfarct-related artery revascularization on outcome of patients with ST-elevation myocardial infarction transferred for primary percutaneous coronary intervention (from the EUROTRANSFER Registry). Am J Cardiol. 2010 Aug 1;106(3):342-7. doi: 10.1016/j.amjcard.2010.03.029.
38. Jelavic MM, Babic Z, Pintaric H. The importance of two metabolic syndrome diagnostic criteria and body fat distribution in predicting clinical severity and prognosis of acute myocardial infarction. Arch Med Sci. 2017 Jun;13(4):795-806. doi: 10.5114/aoms.2016.59703.
39. Mornar Jelavić M, Babić Z, Pintarić H, Mišigoj-Duraković M. The role of anthropometry in acute ST-elevation myocardial infarction treated with primary percutaneous coronary intervention. Acta Clin Croat. 2016 Jun;55(2):224-32. doi: 10.20471/acc.2016.55.02.07.
40. Jelavic MM, Babic Z, Pintaric H. Interrelation between the relative fat mass index and other obesity indices in predicting clinical severity and prognosis of acute myocardial infarction. Postepy Kardiol Interwencyjnej. 2020 Jun;16(2):198-201. doi: 10.5114/aic.2020.96064.
41. Patibandla S, Gupta K, Alsayouri K. Cardiac Enzymes. 2021 Aug 11. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan. PMID: 31424800.
42. LADUE JS, WROBLEWSKI F, KARMEN A. Serum glutamic oxaloacetic transaminase activity in human acute transmural myocardial infarction. Science. 1954 Sep 24;120(3117):497-9. doi: 10.1126/science.120.3117.497.
43. Mythili S, Malathi N. Diagnostic markers of acute myocardial infarction. Biomed Rep. 2015 Nov;3(6):743-8. doi: 10.3892/br.2015.500.
44. Schmiechen NJ, Han C, Milzman DP. ED use of rapid lactate to evaluate patients with acute chest pain. Ann Emerg Med.1997 Nov;30(5):571-7.
45. Yun DD, Alpert JS. Acute coronary syndromes. Cardiology. 1997 May-Jun;88(3):223-37. doi: 10.1159/000177335.

Sažetak

DESETOGODIŠNJI ISHODI NAKON AKUTNOG STEMI-a LIJEČENOG PRIMARNOM PCI – ULOGA AKUTNIH BIOMARKERA I DRUGIH PARAMETARA U PREDVIĐANJU KLINIČKE TEŽINE I PROGNOZE

M. Mornar Jelavić, Z. Babić, D. Babić, D. Balenović, R. Lipovšćak i *H. Pintarić*

Ova rijetka prospektivna studija istraživala je 10-godišnje ishode akutnog infarkta miokarda sa ST-elevacijom (STEMI) liječenog primarnom perkutanom koronarnom intervencijom (PCI) i procjenjivala je ulogu akutnih biomarkera i drugih parametara u predviđanju kliničke težine i prognoze. Uključeno je bilo ukupno 250 bolesnika koje smo analizirali prema njihovim bazičnim (čimbenici kardiovaskularnog rizika), laboratorijskim (maksimalni CK/TnT, akutni upalni (leukociti (LKC), hs-CRP) i jetreni biomarkeri (AST/LDH), brzina glomerularne filtracije (eGFR)) i parametrima kliničke težine (trajanje hospitalizacije, bolničke komplikacije, parametri koronarne angiografije i ehokardiografije (LVEF)). Nakon otpusta 229 bolesnika praćeno je tijekom 10 godina (2011.-2022.) i grupirano prema glavnim neželjenim kardiovaskularnim događajima (MACE). U akutnoj fazi LKC, hs-CRP, LDH i AST pozitivno su korelirali s maksimalnim CK/cTnT, ukupnim bolničkim komplikacijama, a negativno s LVEF. Dodatno, LKC su pozitivno korelirali s kardiogenim šokom i promjerom stenta, hs-CRP sa srčanim zastojem i trajanjem hospitalizacije, a LDH s promjerom stenta ($p<0,05$). Ukupne bolničke komplikacije povećavaju rizik od bolničke smrtnosti, broj značajno stenoziranih koronarnih arterija, rizik od zatajenja srca, dok je trajanje hospitalizacije bilo u negativnoj korelaciji s LVEF ($p<0,05$). Tijekom 10-godišnjeg praćenja LDH i parametri kliničke težine (stenoza LAD i ACx, višežilna koronarna bolest, proksimalna koronarna stenoza, Gensinijev zbroj, ukupne bolničke komplikacije) povećavaju, dok ostali (normalni eGFR i LVEF) smanjuju rizik od ukupnih MACE ($p<0,05$). Zaključno, akutni biomarkeri imaju ulogu u predviđanju kliničke težine, ali se ne mogu rabiti za predviđanje dugoročne prognoze (osim LDH). Ukupne bolničke komplikacije, teža koronarna bolest, sistolička disfunkcija i lošija funkcija bubrega mogu dovesti do lošijih bolničkih i dugoročnih ishoda.

Ključne riječi: *Akutni STEMI; Primarna perkutana koronarna intervencija; Dugoročna prognoza; Upala; Biomarkeri*