Původní sdělení | Original research article

Matrix metallopeptidase-9 prognostic role in STEMI patients after percutaneous coronary intervention (PCI) in one-year follow-up period

Mykola Kopytsya[a], Yaroslava Hilova[a], Iulia Rodionova[a], Anton Bilchenko[a], Inna Kutia[a], Borys Shelest[b]

[a] *Government Institution "L. T. Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine", Kharkiv, Ukraine*
[b] *Kharkiv National Medical University, Department of Internal and Occupational Diseases, Kharkiv, Ukraine*

ARTICLE INFO

Article history:
Submitted: 3. 7. 2022
Accepted: 14. 10. 2022
Available online: 20. 2. 2023

Klíčová slova:
Infarkt myokardu
Matrixová metaloproteináza-9
Perkutánní koronární intervence

SOUHRN

Cíl: Použití matrixové metalopeptidázy-9 (MMP-9) u pacientů s akutním infarktem myokardu s elevacemi úseku ST (STEMI) po perkutánní koronární intervenci (PCI) jako prognostického indikátoru má mnoho mezer a lékařská komunita s tím má velmi omezené zkušenosti. Cílem studie bylo zhodnotit prognostickou roli MMP-9 u pacientů se STEMI po úspěšné revaskularizaci během 12měsíčního období sledování.
Materiál a metoda: Do studie bylo zařazeno 88 pacientů, kteří splnili kritéria pro zařazení a neměli žádná vylučovací kritéria, jimž byl diagnostikován STEMI a podstoupili primární PCI. Mužů bylo 66 (75,0 %), s průměrným věkem 60,84 ± 9,68 roku. Doba sledování činila 12 měsíců. Byl použit složený cílový ukazatel, který zahrnoval výskyt srdečního selhání, které si vyžádalo hospitalizaci, úmrtí z kardiovaskulárních příčin, recidivující infarkt myokardu, akutní cerebrovaskulární příhodu. Koncentrace MMP-9 byla stanovena pomocí ELISA.
Výsledky: Kaplanova–Meierova analýza křivek ukázala významnou souvislost mezi zvýšenou MMP-9 a studovaným složeným cílovým ukazatelem, p = 0,0229. Pacienti s koncentracemi MMP-9 > 201,7 ng/ml měli signifikantně více cílových ukazatelů. Jednorozměrná regresní analýza zjistila, že MMP-9 byla indikována jako nezávislá proměnná pro nepříznivý výsledek s poměrem šancí (OR): 1,017, 95% interval spolehlivosti (CI): 1,001–1,033, p = 0,037. Multivariační logistická regresní analýza ukázala, že MMP-9 (OR: 1,019; 95% CI: 1,005–1,033; p = 0,009) spolu s glukózou nalačno (OR: 1,246; 95% CI: 1,010–1,538; p = 0,040) a leukocyty (OR: 0,751; 95% CI: 0,558–1,011; p = 0,057) zůstaly významnými nezávislými prediktory složeného cílového ukazatele u studovaných subjektů po úpravě dalších zkoumaných zkreslujících faktorů, věku, pohlaví, indexu tělesné hmotnosti, lipidových a glukózových profilů.
Závěr: U pacientů se STEMI po PCI existuje významný vztah mezi nežádoucími účinky a zvýšenými koncentracemi MMP-9. MMP-9 se během ročního sledování prokázala jako vysoce citlivý marker pro predikci nepříznivého průběhu onemocnění u pacientů se STEMI.

ABSTRACT

Objective: The use of matrix metallopeptidase-9 (MMP-9) in patients with acute myocardial infarction with ST-segment elevation (STEMI) after percutaneous coronary intervention (PCI) as a prognostic indicator has a lot of gaps and the medical community has very limited experience with it. The study aimed to evaluate the prognostic role of MMP-9 in STEMI patients after successful revascularization within a 12-month follow-up period.
Material and method: 88 patients met the inclusion criteria and had no exclusion criteria diagnosed with STEMI who underwent primary PCI were enrolled in the study. 66 (75.0%) were men, with a mean age of 60.84±9.68 years. A follow-up period was 12 months. The combined endpoint was used and it included the occurrence of heart failure, which required hospitalization, cardiovascular death, recurrent myocardial infarction, acute cerebrovascular event. The level of MMP-9 was determined by ELISA.

Address: Borys Shelest, MD, 6, Trinklera street, 61022 Kharkiv, Ukraine, e-mail: borisshelestt@gmail.com
DOI: 10.33678/cor.2022.109

Please cite this article as: Kopytsya M, Hilova Y, Rodionova I, et al. Matrix metallopeptidase-9 prognostic role in STEMI patients after percutaneous coronary intervention (PCI) in one-year follow-up period. Cor Vasa 2023;65:57–64.

Keywords:
Matrix metalloproteinase-9
Myocardial infarction
Percutaneous coronary intervention

Results: Kaplan–Meier curves analysis showed significant association between increased MMP-9 and studied combined endpoint, p = 0.0229. The patients with MMP-9 levels over 201.7 ng/ml had significantly more endpoints. Univariate regression analysis found that MMP-9 was indicated as independent variable for unfavorable outcome with odds ratio (OR): 1.017, 95 confidence interval (CI) %: 1.001–1.033, p = 0,037. The multivariate logistic regression analysis showed that MMP-9 (OR: 1.019; 95% CI: 1.005–1.033; p = 0.009) together with fasting glucose (OR: 1.246; 95% CI: 1.010–1.538; p = 0.040) and leucocytes (OR: 0.751; 95% CI: 0.558–1.011; p = 0.057) remained significant independent predictors of combined endpoint in the studied subjects after adjusting other investigated confounders, age, sex, BMI, lipid and glucose profiles.
Conclusion: There is a significant relationship between adverse events and elevated MMP-9 levels in STEMI patients after PCI. MMP-9 was evinced as a highly sensitive marker for predicting the adverse course of the disease in patients with STEMI during the one-year follow-up.

Introduction

The discovery and further implementation of new evidence-based treatments for patients with acute myocardial infarction (AMI) with ST-segment elevation (STEMI) in recent decades have led to a sharp reduction in the risk of recurrent cardiovascular events and a significant improvement in prognosis.[1–3] However, there is still an increased risk of future cardiovascular events, and it stimulates further searches for ways to optimize the prognosis for each patient who underwent AMI with ST-segment elevation and additional novel biomarkers have been intensively studied in recent years.[4,5]

Identification of biomarkers that have prognostic value is necessary for a better risk stratification in ST-segment elevation AMI. There is evidence that ST-segment elevation AMI is predicted by a variety of factors, such as dyslipidemia, smoking, hypertension, diabetes, age, male gender, and plasma levels of natriuretic peptide (NUP) and possibly by the level of matrix metalloproteinase-9 (MMP-9).[6] Among the studied biomarkers MMP-9 is unique because it is closely related to the development of atherosclerosis and plaque instability and ACS consequently.[7] Moreover, MMP-9 plays a key role in heart attack healing, tissue repair, and remodeling of the extracellular matrix after AMI with ST-segment elevation.[8]

The search for new biomarkers continues in STEMI, although in recent years the spread of new prognostic biomarkers in acute coronary syndrome has been impressive, only a few have convincingly proven their clinical value. Only some of them are promising in this regard, their role in clinical decisions has not yet been determined, in particular, treatment decisions.[9]

At the same time, very limited experience has been accumulated on the possibility of clinical use of MMP-9 in patients with STEMI after percutaneous coronary intervention (PCI) as a prognostic marker (indicator) in a one-year perspective. While this issue is very important in terms of the management of such patients and improving their survival and post-infarction recovery. Accumulated preliminary data allow us to hypothesize that the level of MMP-9 may be a significant predictor of the course of the disease and the post STEMI patient's condition after PCI.

The study aimed to evaluate the prognostic role of MMP-9 in STEMI patients after successful revascularization within a 12-month follow-up period.

Methods

Study design

130 patients diagnosed with STEMI were enrolled in the study. Patients were hospitalized in the intensive care unit of the Government Institution "L.T.Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine" (GI "L.T.Mala NIT NAMSU") during the first two days after PCI stenting of the infarct-dependent coronary artery, which was held at the Government Institution "V.T. Zaycev Institute of General and Urgent Surgery NAMSU". 88 patients met the inclusion criteria and had no exclusion criteria out of 130 enrolled patients. Among these 88 subjects, 66 (75.0%) were men and 22 (25.0%) were women, with a mean age of 60.84±9.68 years.

Patients were under supervision in a 12-month follow-up period. The combined endpoint was used and it included the occurrence of heart failure (HF), which required hospitalization, cardiovascular death, recurrent myocardial infarction, acute cerebrovascular event. The complicated course of the disease (STEMI) in the acute period was assessed by the severity of acute HF (II–III) according to Killip grade, cardiac arrhythmias (paroxysms of atrial fibrillation, ventricular tachycardia, transient atrioventricular block II–III). The diagnosis of STEMI was established in accordance with the guidelines of the European Society of Cardiology (2018).[10] The diagnosis of HF was established according to current ESC Guidelines.[11] The diagnosis of arterial hypertension was established in accordance with the current recommendations of the 2018 ESC/ESH Clinical Practice Guidelines for the Management of Arterial Hypertension.[12]

Ethical disclosure

The research was conducted in accordance with the provisions of the Declaration of Helsinki, and the protocol of the study was agreed with the GI "L.T.Mala NIT NAMSU" Commission on Ethics and Deontology (Protocol № 6 of 30.05.2017). All patients signed informed consent to participate in the study accordingly to the latest GMP ICH procedures.

Inclusion and exclusion criteria

Criteria for inclusion in the study were: established AMI with ST-segment elevation, age >35 years, no contraindications to PCI, written informed consent to participate in the study, and restore coronary blood flow at the level

of TIMI III. Exclusion criteria were age >80, severe concomitant chronic diseases (anemia, chronic obstructive pulmonary disease, bronchial asthma, liver cirrhosis, chronic kidney disease with glomerular filtration rate <35 ml/min/1.73 m^2, bleeding), known malignancy, cancer, inability to understand the study and informed consent and vulnerable segments of the population.

Patient management

Patients underwent primary PCI using a bare-metal coronary stent (BMS). The TIMI scale was used to assess the restoration of blood flow in the infarct-dependent coronary artery. 88 patients were able to restore coronary blood flow at the level of TIMI III, they were selected for further study. All patients received drug therapy in accordance with current recommendations: enoxaparin in a therapeutic dose of 0.1 mg/kg body weight twice a day, acetylsalicylic acid 100 mg once a day, ticagrelor 90 mg twice a day, rosuvastatin 40 mg or atorvastatin 80 mg once a day, β-blockers (bisoprolol or nebivolol), ACE inhibitors (ramipril or enalapril).

Ultrasound examination of patients was performed within 48 hours after hospitalization using the Toshiba Aplio 500, model TUS-A500, with the evaluation of next parameters: end-diastolic volume (EDV) of the left ventricle (LV) and end-systolic volume (ESV) of the left ventricle, myocardial mass LV (MMLV), LV ejection fraction (EF), left atrial volume (LAV), LV diastolic dysfunction – maximum early diastolic filling rate E (m/s), maximum atrial diastolic filling rate A (m/s), their E/A ratio.

Determination of troponin I, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) was carried out by the enzymatic method. The level of MMP-9 was determined by enzyme-linked immunosorbent assay using a set of Human MMP reagents – ELISA KIT, Invitrogen, Austria. Blood for determination of MMP-9 in serum was taken on day 3 after STEMI beginning.

Statistical processing of the normality of the distribution was done by Kolmogorov–Smirnov and Lilliefors tests. Normally distributed variables are presented in the form of mean (M) and standard deviation (SD) and were compared using the Student's t-test, otherwise, variables with not normal distribution are presented as medians and interquartile ranges and compared using the Mann–Whitney test and qualitative variables are presented as percentages and compared by the chi-square test (χ^2). Multivariate analysis was used to indicate the factors associated with adverse events (combined endpoint). Univariate analysis was performed for the measured variables. Predictor variables that were statistically significant when evaluated individually against a combined endpoint were included in the forward stepwise multiple logistic analysis. The results were calculated and presented as β-coefficient, standard errors (SE), odds ratio (OR), and 95% confidence interval (CI) for each factor. The level of statistical significance was set to a p <0.05. Statistical analysis was performed using the software package Statistica 8.0 (StatSoft Inc, USA), and MedCalc Statistical Software version 20.111 (Belgium).

Results

All studied patients were divided into two groups depending on the level of MMP-9 (median 201.7 ng/ml). The first group 1 included 44 patients with MMP-9 ≥201.7 ng/ml. The second one was with MMP-9 <201.7 ng/ml and included the same number of patients. The main clinical, socio-demographic, anamnestic, cardiac instrumental and laboratory parameters of these groups are presented in Table 1.

The participant subjects were predominantly male (75.0%) with a median age of 60.84±9.68 years, with coexistent commonplace risk factor for STEMI like increased blood pressure/arterial hypertension (HTN) (86.4%), followed by smoking (48.9%). On the other hand type 2 diabetes mellitus (2TDM) and increased body mass index (BMI) (>30 kg/m^2) were present only in 23.9% and 26.1% of patients consequently. It is essential to point out that all investigated indicators – age, blood pressure, glucose and lipid metabolic balance, smoking, HbA_{1c}, serum creatinine and echocardiographic parameters were not significantly different between the groups with higher MMP-9 and the lower MMP-9 one. The differences in the concentration of the studied biomarker –MMP-9 indicate the activation of MMP-9 synthesis due to acute myocardial damage, p = 0.0001. Comparing the localization of infarction and atherosclerotic vascular lesions in the groups, no statistically significant differences were found.

To identify the MMP-9 role in the development of adverse cardiovascular events (combined endpoint) and the relationship between the course of the disease and the concentration of MMP-9, a cumulative

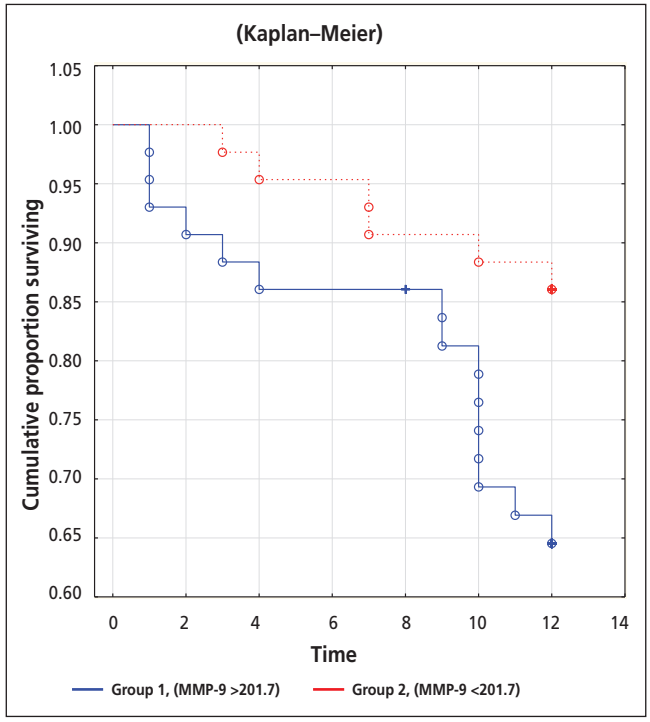

Fig. 1 – Kaplan–Meier curves showing the development of a combined endpoint in STEMI patients in a 12-month follow-up period depending on MMP-9 concentration.

Table 1 – Baseline characteristics of patients with STEMI depending on the level of MMP-9

Parameters	All patients (n = 88)	Group 1 MMP-9 ≥ median (n = 44)	Group 2 MMP-9 < median (n = 44)	x^2, *p*
Age, years (SD)	60.84±9.68	60.68±9.02	61.00±10.39	0.878
Males, n (%)	66 (75.0)	32 (72.7)	34 (77.3)	0.623
Females, n (%)	22 (25.0)	12 (27.3)	10 (22.7)	
HTN, n (%)	76 (86.4)	38 (86.4)	38 (86.4)	1.0
2TDM, n (%)	21 (23.9)	12 (27.3)	9 (20.5)	0.617
HbA_{1c}	6.71±2.01	6.89±1.78	6.51±1.99	0.678
Smoking, n (%)	43 (48.9)	20 (45.5)	23 (52.3)	0.522
BMI >30 kg/m^2, n (%)	23 (26.1)	8 (18.2)	15 (34.1)	0.0895
EDV LV, ml	123.40±24.74	121.66±26.02	125.01±23.70	0.551
LVEF, %	46.63±5.50	46.62±4.64	46.63±6.33	0.990
LAV	35.95±9.26	35.81±10.35	36.09±8.17	0.896
E/E'	13.72±4.89	12.67±4.28	14.70±5.29	0.120
TnI, ng/mL	7.56 [2.17–9.20]	7.45 [2.75–9.54]	6.81 [3.35–8.80]	0.362
TC, mmol/l	4.67±1.23	4.70±1.15	4.64±1.31	0.844
HDL-C, mmol/l	1.03±0.29	1.06±0.37	1.00±0.19	0.397
LDL-C, mmol/l	2.57±1.08	2.69±1.05	2.46±1.11	0.358
TG, mmol/l	1.99±1.11	1.81±0.86	2.15±1.28	0.164
Creatinine clearance, ml/min	77.08±28.94	77.71±29.08	76.46±29.14	0.846
MMP-9, ng/ml	193.09±59.32	238.25±31.29	147.93±44.34	0.0001

2TDM – type 2 diabetes mellitus; BMI – body mass index; E/E' – ratio between early mitral inflow velocity and mitral annular early diastolic velocity; EDV LV – end-diastolic volume of the left ventricle; HDL-C – high-density lipoprotein cholesterol; HTN – arterial hypertension; LAV – left atrium volume; LDL-C – low-density lipoprotein cholesterol; LVEF – left ventricular ejection fraction; MMP-9 – matrix metalloproteinase 9; TC – total cholesterol; TG – triglycerides; TnI – troponin I.

Table 2 – Univariate and multivariate logistic analysis of factors influencing the development of adverse events after AMI with ST segment elevation

Parameter	β-coefficient	OR	95% CI	*p*
Univariate logistic analysis				
MMP-9, ng/ml	0.017	1.017	1.001–1.033	0.037
SAP, mm Hg	0.007	1.007	0.974–1.041	0.684
DAP, mm Hg	0.0113	1.011	0.936–1.093	0.775
BMI, kg/m^2	–0.138	0.871	0.716–1.060	0.168
Complications in the acute period	0.829	2.293	0.211–24.893	0.495
2TDM	0.883	2.419	0.310–18.867	0.399
Fasting glucose, mmol/l	0.193	1.213	0.927–1.586	0.159
EDV LV, ml	0.007	1.007	0.970–1.046	0.702
Leucocytes, *10^9/l	-0.299	0.741	0.524–1.049	0.091
TC, mmol/l	0.282	1.326	0.689–2.549	0.398
TG, mmol/l	-0.617	0.539	0.161–1.805	0.317
Creatinine, mmol/l	0.0163	1.016	0.998–1.041	0.177
Multivariate logistic analysis				
MMP-9, ng/ml	0.018	1.019	1.005–1.033	0.009
Fasting glucose, mmol/l	0.220	1.246	1.010–1.538	0.040
Leucocytes, *10^9/l	–0.287	0.751	0.558–1.011	0.057
Creatinine, mmol/l	0.012	1.012	0.997–1.029	0.180

2TDM – type 2 diabetes mellitus; BMI – body mass index; DAP – diastolic arterial pressure; EDV LV – end-diastolic volume of the left ventricle; MMP-9 – matrix metalloproteinase 9; SAP – systolic arterial pressure; TC – total cholesterol; TG – triglycerides.

Kaplan–Meier curves analysis was performed. And it showed significant association between increased MMP-9 and studied endpoint, F-criteria Cox, F (12.30) = 2.848, p = 0.0099 and Log-rank criteria, p = 0.0229 (Fig. 1). Significantly more endpoints were recorded in the patients with MMP-9 levels over 201.7 ng/ml, the vast majority of which were HF decompensation, which required hospitalization. Thus wise, increased MMP-9 concentrations showed a significant direct influence on unfavorable one-year prognosis in STEMI patients after PCI (Fig. 1).

Univariate with consequent multivariate logistic regression analyses were performed to investigate independent predictors of the adverse outcome presented as reaching the combined endpoint. After providing the univariate regression analysis it was found that MMP-9 was indicated as independent variable for unfavorable outcome OR: 1.017, 95 CI%: 1.001–1.033, p = 0,037. The multivariate logistic regression analysis showed that MMP-9 (OR: 1.019; 95% CI: 1.005–1.033; p = 0.009) together with fasting glucose (OR: 1.246; 95% CI: 1.010–1.538; p = 0.040) and leucocytes (OR: 0.751; 95% CI: 0.558–1.011; p = 0.057) remained significant independent predictors of combined endpoint (bad prognosis in patients with STEMI) in the studied subjects after adjusting other confounders as is shown in Table 2.

Discussion

We consider it important to point out that our investigation was focused on the MMP-9 role in prognosis in STEMI patients who underwent PCI and this issue was not previously fully described. It was established in our work that increased level of MMP-9 at admission in those patients is an important marker for further prognosis and a concentration of this enzyme over 201.7 ng/ml is prognostically unfavorable for the post-infarction one-year follow-up period. There are some works that presented the close results with accordant patients.[13–15]

Even though MMP-9 belongs to the family of metalloproteinase and is considered to be widely studied, researchers continue to study the role of this enzyme in atherosclerosis, ACS, MI and other cardiovascular diseases (CVD).[16–19]

The most recent studies continue to investigate the MMP-9 role as a player in pathways of myocardial injury and its place in the field of prognostic markers in cardiovascular pathology.[20–23] And its role is under investigation not only in cardiovascular pathology, but also in chronic Chagas disease, ocular pathology, ischemic stroke, in diabetes.[24–28] It is worth mentioning the work studying MMP-9 in renal diseases. For example, O. Zakiyanov et al. examined the dynamics of MMPs in patients with kidney disease.[29] The authors state that metalloproteinases are one of the key players in a variety of acute and chronic variants of kidney diseases. In their review, the authors argue that a deeper understanding of the MMPs' role in the development of renal pathology will open novel ideas for advanced therapeutic approaches. And we consider that such a statement can be extrapolated to patients with CVD.

MMP-9 is regarded as a new effective marker and a possible therapeutic target for diseases based on atherosclerosis.[30,31] In addition, MMP-9 also has potential as an indicator of the early stages of atherosclerotic damage, since an increase in the level of this substance most likely evidences destabilization of the atherosclerotic plaque and destruction of myocardial tissue, and also MMP-9 shows a significant prognostic value.[14] MMP-9 levels increased in patients with acute myocardial infarction with ST-segment elevation and MMP-9 appeared to be a significant biomarker for the diagnosis of acute myocardial infarction with ST-segment elevation.[32]

MMP-9 levels have been studied as a possible predictor of risk in patients with acute coronary syndrome (ACS) by G.M. Hamed and M.F. Fattah.[33] These investigators also took into account smoking status, blood pressure levels, lipid and glucose balance, markers of myocardial necrosis, and instrumental data. These authors showed that MMP-9 levels were higher in patients with ACS than in the stable CAD group. Importantly, this study demonstrated that STEMI has the highest levels of MMP-9. And this correlates with our data, that is, the MMP-9 values were significantly higher in patients who had an unfavorable outcome of the disease (recurrent ischemic attacks, congestive heart failure or death). However, their data pointed to an MMP-9 cut-off value of 3100 pg/mL as an indicator of the difference between MI and unstable angina (UA). Such a difference in numbers is most likely due to the various reagents that were used in the study, while the influence of the time of taking the material for the study is not excluded. This may suggest that further research is needed to elucidate the timing of peak MMP-9 levels in MI. The authors argue that MMP-9 can serve as an early marker that differentiates MI from UA, which we did not investigate in our work. At the same time, this work, like our study, showed the importance of MMP-9 as a predictor of an unfavorable outcome of MI.

Another recent work by D. Opincariu et al. dedicated to the role of MMP-9 in CVD showed the importance of the mentioned enzyme in predicting the course of STEMI.[34] At the same time, the MACE indicator for 1 year was chosen as the endpoint in their work. Authors showed that the most significant predictive indicators of MACE were elevated levels of MMP-9 along with I-CAM, V-CAM at 1-year follow-up. Interestingly, none of the other investigated parameters was found to be significant in this trial. The data by Opincariu et al. also correlate with our results. In general, D. Opincariu et al. emphasized that inflammatory biomarkers are more important and significant predictors for MACE than instrumental parameters such as LVEF. Noteworthy is their conclusion that a high level of MMP-9 (greater than 1155 ng/mL, AUC –0.786, p <0.001) was the strongest predictor of STEMI recurrence even after adjusting for left ventricular ejection fraction, diabetes mellitus, acute phase complications, and other inflammatory biomarkers.

The recent work by H. Kook et al. from Korea in 2020 confirmed that MMP-9 is an important prognostic

marker in ACS.[35] However, in this paper, the authors improved the prediction model by adding soluble lectin-like oxidized low-density lipoprotein receptor-1, MMP-9, leukocyte levels, and peak levels of CK-MB to the discriminative model. They showed that such a complex model predicts plaque destabilization more effectively than single biomarkers in patients with ACS. However, their study was focused less on the long-term prognosis after STEMI and predominantly on the prognosis of plaque rupture in ACS, which distinguished this work from ours. However, in terms of studying the effect of MMP-9 on the pathogenesis of ACS, this work cannot be overestimated and it provides additional important information about the nature of the MMP-9 effects on the prognosis in STEMI patients. Their ROC analysis showed that MMP-9 (p = 0.0274) was a significant independent marker for separating the group with plaque rupture from the group without plaque rupture.[35] The mentioned work from Korea estimated that MMP-9, as an inflammatory biomarker, is actively involved in the process of destabilization of atherosclerotic plaques, and this is the basis for the development of both acute coronary syndrome and the development of subsequent adverse consequences in the post-infarction period.

Another important basic work for understanding our results can be considered a recent review by T. Li et al.[36] The authors note that increased production of MMP-9 most likely accentuates the destruction of the extracellular matrix and leads to destabilization of atherosclerotic plaques. Their work showed that high MMP-9 values are associated with greater plaque vulnerability. This review demonstrates that MMP-9 may be a predictor of destabilization of atherosclerotic plaques, and the further course of cardiovascular disease, that is in concordance with our results. The accumulated data make it possible to state that in addition to the fact that MMP-9 is a significant prognostic marker for predicting the course of atherosclerotic changes, this enzyme should also be investigated as a therapeutic target to improve the management and prognosis of such patients. It is also important that T. Li et al noted the need to take into account the influence of additional factors on the relationship between MMP-9 and atherosclerotic lesions, such as ethnicity, MMP-9 gene polymorphism, and comorbidities.[36] Further large-scale works are still required to improve our understanding of the role and place of MMP-9 in CVD.

The work of G. Jordakieva et al. is newsworthy since it is somewhat similar in general meaning to our study.[37] The authors showed that the MMP-9 values are significant in the prediction of short-term (30-day) mortality, and this was applied more specifically to patients with heart disease. However, their study design had 120 patients who were examined in the intensive care unit of the internal medicine department, which, in addition to cardiac essential patients, also included other critically ill patients. This was very different from our work since we investigated only STEMI patients after PCI. At the same time, G. Jordakieva et al. obtained results also showed that high MMP-9 values may be important prognostic markers, as well as potential therapeutic targets in systemic inflammation and the intensive care unit setting.[37]

This testifies in favor of the fact that the increased MMP-9 expression is an important pathogenetic link in various critical conditions and especially in acute cardiovascular conditions, such as STEMI or ACS.

There are several possible explanations for the association between elevated MMP-9 levels and subsequent adverse events after STEMI. Coronary atherosclerotic plaques are the pathological basis of coronary heart disease. From these considerations, we assume that the key reason is that MMP-9 is closely associated with the rupture of atherosclerotic plaques. An increased level of this enzyme reduces the fibrous cover of the plaque due to the degradation of the matrix of the fibrous cover of the atheromatous plaque, which leads to the formation and rupture of unstable plaques and the next clinical cardiovascular events. We consider that the increased synthesis of MMP-9 in the lesions in patients with STEMI is likely to suppress the rate of formation of a stable plaque and this is what affects the further course of the disease and the development of adverse events. High levels of MMP-9 support low gradient inflammation, which is the pathogenetic basis for the presence of unstable plaques in post-infarction patients.

The presented study had several limitations. First, it is worth mentioning that the study had the compact sample size to state definitive conclusions. Second, there were no series of measurements of MMP-9, to estimate the evolution of its minimum – maximum ranges. In addition, only one clinical site was involved. Also, the limitation is that predominantly males were among the investigated subjects. Additionally, we evaluated only exactly STEMI patients after PCI without any other treatment, on the other hand, this narrow target group together with appropriate statistical methods doing our best to avoid these possible biases. It can be considered as a limitation that we used a combined (composite) endpoint as an outcome, including some conditions but not an exact firm (primary) endpoint. Therewithal, the relationship between the obtained 12-month treatment and MMP-9 levels and the final outcome was not assessed. At the same time, we consider a trial's strength that it was carried out under conditions of routine clinical practice and granted us to gain real relevant data.

Our consideration is that further studies are required on the role of MMP-9 in the after PCI STEMI patients' prognosis and its pathogenetic role needs more deep investigations. Further sizable, multicenter trials are needed to confirm obtained relation between MMP-9 and prognosis in STEMI patients.

Conclusion

Based on the studied data, it can be assumed that there is a significant relationship between adverse events and elevated MMP-9 levels in STEMI patients after PCI. MMP-9 was evinced as a highly sensitive marker for predicting the adverse course of the disease in patients with STEMI during the one-year follow-up. Future investigations are needed to estimate whether MMP-9 is associated with myocardial infarction pathogenesis

and prognosis, revealed as a protective mechanism response, or unconcerned in the STEMI pathophysiological processes. Elucidating its exact and valid mechanism promisingly can lead to increasing in STEMI patients' survival and recovery and better management.

Conflict of interest
All authors declare that there is no conflict of interest.

Funding
None declared by the authors.

Ethical statement
The study was approved by the Ethics Committee of Government Institution "L.T.Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine", Kharkiv, Ukraine (Protocol № 6 of 30.05.2017).

Informed consent
Informed consent was signed by all participants accordingly to GMP ICH procedures, no vulnerable subjects were enrolled.

References

1. Mughal LH, Sastry S. Advances in the treatment of ST Elevation Myocardial Infarction in the UK. JRSM Cardiovasc Dis 2022;11:20480040221075519.
2. Dong H, Li X, Xiao D, Tang Y. Late Percutaneous Coronary Intervention is Associated with Better Prognosis of Patients with Acute Myocardial Infarction. Int J Gen Med 2022;15:2621–2627
3. Szummer K, Wallentin L, Lindhagen L, et al. Improved outcomes in patients with ST-elevation myocardial infarction during the last 20 years are related to implementation of evidence-based treatments: Experiences from the SWEDEHEART registry 1995–2014. Eur Heart J 2017;38:3056–3065.
4. Yamashita Y, Shiomi H, Morimoto T, et al. Cardiac and Noncardiac Causes of Long-Term Mortality in ST-Segment--Elevation Acute Myocardial Infarction Patients Who Underwent Primary Percutaneous Coronary Intervention. Circ. Cardiovasc Qual Outcomes 2017;10:e002790.
5. Wu Y, Pan N, An Y, et al. Diagnostic and Prognostic Biomarkers for Myocardial Infarction. Front Cardiovasc Med 2021;7:617277.
6. Kelly D, Khan SQ, Thompson M, et al. Plasma tissue inhibitor of metalloproteinase-1 and matrix metalloproteinase-9: novel indicators of left ventricular remodelling and prognosis after acute myocardial infarction. Eur Heart J 2008;29:2116–2124.
7. Zayani Y, Allal-Elasmi M, Jacob MP, et al. Peripheral blood levels of matrix and inflammatory mediators are elevated in Tunisian patients with acute coronary syndromes. Clin Lab 2013;59:169–175.
8. Becirovic-Agic M, Chalise U, Daseke MJ, et al. Infarct in the Heart: What's MMP-9 Got to Do with It? Biomolecules 2021;11(4):491.
9. Eggers KM, Lindahl B. Prognostic Biomarkers in Acute Coronary Syndromes: Risk Stratification Beyond Cardiac Troponins. Curr Cardiol Rep 2017;19:29.
10. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: 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;39:119–177.
11. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42:3599–3726.
12. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018;39:3021–3104.
13. Zhu JJ, Zhao Q, Qu HJ, et al. Usefulness of plasma matrix metalloproteinase-9 levels in prediction of in-hospital mortality in patients who received emergent percutaneous coronary artery intervention following myocardial infarction. Oncotarget 2017;8:105809–105818.
14. Lahdentausta L, Leskelä J, Winkelmann A, et al. Serum MMP-9 Diagnostics, Prognostics, and Activation in Acute Coronary Syndrome and Its Recurrence. J Cardiovasc Trans Res 2018;11:210–220.
15. Somuncu MU, Pusuroglu H, Karakurt H, et al. The prognostic value of elevated matrix metalloproteinase-9 in patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction: A two-year prospective study. Rev Port Cardiol (Engl Ed) 2020;39:267–276.
16. Olejarz W, Łacheta D, Kubiak-Tomaszewska G. Matrix Metalloproteinases as Biomarkers of Atherosclerotic Plaque Instability. Int J Mol Sci 2020;21:3946.
17. Brown BA, Williams H, George SJ. Evidence for the Involvement of Matrix-Degrading Metalloproteinases (MMPs) in Atherosclerosis. Prog Mol Biol Transl Sci 2017;147:197–237.
18. Pogorielova OS, Korniienko VV, Chumachenko YD, et al. Impact of MMP-9 Genetic Polymorphism and Concentration on the Development of Coronary Artery Disease in Ukrainian Population. Cardiol Res Pract 2022;2022:2067632.
19. Ben Braiek A, Chahed H, Dumont F, et al. Identification of biomarker panels as predictors of severity in coronary artery disease. J Cell Mol Med 2021;25:1518–1530.
20. Yabluchanskiy A, Ma Y, Iyer RP, et al. Matrix metalloproteinase-9: Many shades of function in cardiovascular disease. Physiology (Bethesda) 2013;28:391–403.
21. Hassanzadeh-Makoui R, Razi B, Aslani S, et al. The association between Matrix Metallo-proteinases-9 (MMP-9) gene family polymorphisms and risk of Coronary Artery Disease (CAD): a systematic review and meta-analysis. BMC Cardiovasc Disord 2020;20:232.
22. Holm Nielsen S, Jonasson L, Kalogeropoulos K, et al. Exploring the role of extracellular matrix proteins to develop biomarkers of plaque vulnerability and outcome. J Intern Med 2020;287:493–513.
23. Wang X, Khalil RA. Matrix Metalloproteinases, Vascular Remodeling, and Vascular Disease. Adv Pharmacol 2018;81:241–330.
24. Medeiros NI, Gomes JAS, Fiuza JA, et al. MMP-2 and MMP-9 plasma levels are potential biomarkers for indeterminate and cardiac clinical forms progression in chronic Chagas disease. Sci Rep 2019;9:14170.
25. de la Fuente M, Rodríguez-Agirretxe I, Vecino E, et al. Elevation of Tear MMP-9 Concentration as a Biomarker of Inflammation in Ocular Pathology by Antibody Microarray Immunodetection Assays. Int J Mol Sci 2022;23:5639.
26. Wu G, Cai H, Li G, et al. Influence of the Matrix Metalloproteinase 9 Geners3918242 Polymorphism on Development of Ischemic Stroke: A Meta-analysis. World Neurosurg 2020;133:e31–e61.
27. Chen L, Yang Q, Ding R, et al. Carotid thickness and atherosclerotic plaque stability, serum inflammation, serum MMP-2 and MMP-9 were associated with acute cerebral infarction. Exp Ther Med 2018;16:5253–5257.
28. Macarie RD, Vadana M, Ciortan L, et al. The expression of MMP-1 and MMP-9 is up-regulated by smooth muscle cells after their cross-talk with macrophages in high glucose conditions. J Cell Mol Med 2018;22:4366–4376.
29. Zakiyanov O, Kalousová M, Zima T, Tesař V. Matrix Metalloproteinases in Renal Diseases: A Critical Appraisal. Kidney Blood Press Res 2019;44:298–330.
30. Wang N, Yuan Y, Sun S, Liu G. microRNA-204-5p Participates in Atherosclerosis Via Targeting MMP-9. Open Med (Wars) 2020;15:231–239.

31. He Z, Wang Y, He Q, Chen M. microRNA-491-5p protects against atherosclerosis by targeting matrix metallopeptidase-9. Open Med (Wars) 2020;15:492–500.
32. Chen Z, Yan Y, Wu J, et al. Expression level and diagnostic value of exosomal NEAT1/miR-204/MMP-9 in acute ST-segment elevation myocardial infarction. IUBMB Life 2020;72:2499–2507.
33. Hamed GM, Fattah MF. Clinical Relevance of matrix metalloproteinase 9 in patients with acute coronary syndrome. Clin Appl Thromb Hemost 2015;21:705–711.
34. Opincariu D, Rodean I, Rat N, et al. Systemic Vulnerability, as Expressed by I-CAM and MMP-9 at Presentation, Predicts One Year Outcomes in Patients with Acute Myocardial Infarction-Insights from the VIP Clinical Study. J Clin Med 2021;10:3435.
35. Kook H, Jang DH, Kim JH, et al. Identification of plaque ruptures using a novel discriminative model comprising biomarkers in patients with acute coronary syndrome. Sci Rep 2020;10:20228.
36. Li T, Li X, Feng Y, et al. The Role of Matrix Metalloproteinase-9 in Atherosclerotic Plaque Instability. Mediators Inflamm 2020;2020:3872367.
37. Jordakieva G, Budge-Wolfram RM, Budinsky AC, et al. Plasma MMP-9 and TIMP-1 levels on ICU admission are associated with 30-day survival. Wien Klin Wochenschr 2021;133:86–95.