МЕДИЦИНА НЕВІДКЛАДНИХ СТАНІВ ®

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Predictive role of MMP-9 and MPO in patients with reduced glomerular filtration rate after acute coronary syndrome

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Abstract. ***Background.*** *Coronary artery disease (CAD) persistently remains the leading cause of mortality globally. Given the severity and impact of this condition, researchers have been meticulously studying the pathogenesis of atherosclerosis, a principal cause behind CAD. The pathogenesis stages are complex and multifaceted, including factors such as lipid accumulation, inflammation, and plaque formation. A particular area of active exploration pertains to the influence and role of different biomarkers, including matrix metalloproteinase 9 (MMP-9) and myeloperoxidase (MPO), on these processes. These biomarkers have been associated with the progression and destabilization of atherosclerotic plaques, which are central to CAD. However, the use of these biomarkers in the context of comorbidities, such as chronic kidney disease, remains an open area of research, especially in patients after myocardial infarction.* ***Materials and methods.*** *In our study, 96 patients who had acute coronary syndrome and subsequently undergone percutaneous coronary intervention were enrolled. They were stratified into groups (A and B) based on respective glomerular filtration rates. The primary endpoint of the study was all-cause mortality and major adverse cardiovascular and cerebrovascular events.* ***Results.*** *Our analysis revealed that serum levels of MPO in group B were insignificantly higher than those in group A. Conversely, the area under the receiver operating characteristic (ROC) curve for MMP-9 in group A exhibited a significant difference, standing at 0.8 (95% confidence interval 0.609–0.991; $p = 0.039$). However, the ROC curve for MPO did not yield a significant result in any group. A combined ROC curve was also generated, with the area under this curve showing a significantly higher value of 0.890 (95% confidence interval 0.805–0.975; $p < 0.001$).* ***Conclusions.*** *We found that plasma levels of the above-mentioned biomarkers do not seem to influence a decrease in glomerular filtration rate. Nonetheless, MMP-9 levels offered significant prognostic information regarding predicted outcomes.*

Keywords: *matrix metalloproteinase 9; myeloperoxidase; acute coronary syndrome; glomerular filtration rate; outcome*

Introduction

Coronary artery disease (CAD) is a multifactorial disease with a high mortality rate worldwide [1]. The main cause of CAD is atherosclerosis, which is accompanied by the formation of plaques in the endothelium of the arteries [2].

In cardiovascular diseases, changes in extracellular matrix breakdown and regeneration occur due to arterial wall instability secondary to the damage seen in this type of disease [3].

Abnormalities of matrix metalloproteinase (MMP) production and activity have been shown to be involved in several vascular diseases in many previous studies [4–10]. In the past few decades, growing evidence from basic and clinical studies have demonstrated the important role of MMPs in the progression of left ventricular dysfunction, remodeling and mortality following acute myocardial infarction (MI) [11].

MMP-9 is also one of the trigger factors for renal fibrosis and influences its progression through activa-

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tion of an epithelial-mesenchymal transition, endothelial-mesenchymal transition as well as activation of resident fibroblasts and pericyte-myofibroblast transdifferentiation [12]. Oxidative stress also has an undeniable influence on the rate of fibrosis progression, which in turn influences the activation of factors MMP-2 and 9 [13].

Myeloperoxidase (MPO) is the most abundant component of primary neutrophil azurophilic granules and is rapidly released upon activation by various agonists [14]. First identified in human atherosclerotic plaques almost a decade ago, MPO has become an important factor in the development and progression of atherosclerotic disease. In clinical studies conducted in patients with acute coronary syndromes, elevated MPO levels were associated with an adverse prognosis and the occurrence of major cardiovascular events.

Although these markers have been extensively studied in patients after myocardial infarction and risk factors including decreased glomerular filtration rate (GFR) have been assessed for prognosis, the impact of MMP-9 and MPO on this cohort has not been studied in detail.

Aim. The aim of our work was to identify potential predictors of adverse outcomes in patients with reduced glomerular filtration rate after myocardial infarction.

Materials and methods

Patient recruitment

We prospectively analysed patients who were admitted to our department after percutaneous coronary intervention (PCI) between January 2019 and May 2020.

After excluding people with other factors that could affect the accuracy of biomarker measurements (fever, inflammatory disease, malignancy, liver dysfunction), 96 patients after PCI were enrolled. GFR was calculated using CKD-EPI formula. Blood tests, including routine biochemical analysis and measurement of serum levels of MMP-9 and MPO, were performed in 32 subjects with GFR lower than 60 mL/min/1.73 m^2 (group A) and in 64 patients with GFR above 60 mL/min/1.73 m^2 (group B). Informed consent was obtained from all 96 included subjects based on a protocol approved by the ethics committee.

Biochemical analysis

Venous blood samples (10 ml) were taken from all patients immediately after transfer from the catheterisation laboratory. Serum was separated 1 hour after clotting. The samples were then centrifuged for approximately 10 minutes and placed in Eppendorf tubes. The tubes were labelled with number, name and date. MMP-9 and MPO levels were evaluated using a solid phase enzyme immunoassay kit according to the manufacturer's instructions. If blood samples were not processed immediately, the serum was stored at –20 °C until analysis.

Echocardiography

Echocardiography was performed in all included patients (Canon Aplio 500; Canon Medical Systems Corporation, Otawara, Japan). Certified specialists performed the study according to standard operating procedures in a specially prepared room. Left ventricular ejection fraction (LVEF) was recorded. Left ventricular mass (LVM) and left ventricular mass index (LVMI) were calculated according to formulas proposed by Devereux[15].

Follow-up and outcomes

All subjects had 2 follow-up visits during the year. In addition to visits at 6 months and one year, there were telephone interviews and analysis of repeated hospital admissions. The primary endpoint of the study was all-cause mortality and major adverse cardiovascular and cerebrovascular events (MACCE).

Statistical analysis

Statistical analyses were carried out using SPSS version 26.0. The Shapiro-Wilk test was used to assess the normality of the distribution. The mean was compared using the t-test for a normal distribution and the Mann-Whitney U test for a non-normal distribution. Receiver operating characteristic (ROC) curves were used to assess the ability of biomarkers to predict a negative outcome. The Youden index was calculated for each point of the ROC curves, and the point with the maximum Youden index was considered the cut-off point. Bilateral P values < 0.05 were considered to indicate statistical significance.

Results

Patients' characteristics are shown in Table 1. A correlation analysis of the indices with markers was performed. A significant correlation was found between MMP-9 and low-density lipoproteins (LDL) (0.272, $p = 0.018$). There was a significant negative correlation between MPO and triglyceride levels (–0.282, $p = 0.007$) and very low-density lipoprotein (VLDL) levels (–0.266, $p = 0.014$). Also, MPO and MMP-9 showed a significant correlation with each other (0.483, $p < 0.001$).

Serum levels of MMP-9 in group A and group B were almost identical (186.46 ± 65.66 vs 193.68 ± 57.08 ng/mL; $p = 0.265$). Serum levels of MPO in group B were insignificantly higher than in group A (Mdn = 110.83, Q1-Q3 (45.19–156.33) vs Mdn = 91.17, Q1-Q3 (53.10–209.89), $p = 0.423$) (Table 2).

The combined endpoint numbered 12 patients. The all-cause mortality rate was 33.3 % and the MACCE rate was 66.7 %.

Prognostic value of MMP-9 and MPO in predicting 1-year adverse events

The area under the ROC curve of MMP-9 in group A was significant, 0.8 (95% confidence interval 0.609–0.991; $p = 0.039$). The area under the ROC curve of MMP-9 in group B showed a poor non-significant result. The ROC curve of MPO did not show a significant result in any of the groups. The combined effect of both biomarkers also did not show any significant result.

A combined ROC curve was calculated (Fig. 1), the model of which included the following parameters: MMP-9, ejection fraction, presence of PCI, LM occlusion, sex, age, hypertension, thrombolysis in myocardial infarction blood

flow, BMI, LVMI, GFR. The area under the ROC curve was significant, 0.890 (95% confidence interval 0.805–0.975; $p < 0.001$).

Discussion

Despite the encouraging results of MMP-9 prognosis obtained by ROC analysis, there was still no significant difference in levels between the comparison groups, divided by glomerular filtration rate. Several factors could have contributed to this. Despite the absence of any relationship between glucose levels, the presence of type 2 diabetes mellitus in patients with elevated MMP-9 and MPO levels, one can observe some publications that highlight this problem. There is also evidence of an association between an increase in the level of MMP-9 [16] in patients with heart failure with a reduced ejection fraction. Despite this, we did not have a sufficient number of patients to assess the effect of reduced ejection fraction on prognosis. There is also evidence on the effect of hypertension and hypertensive emergencies on MMP-9 levels. The authors emphasise a significant decrease in glomerular filtration rate in patients with hypertensive emergencies, but it was not an independent predictor [17]. In earlier publications with larger samples, MMP-9/TIMP-1 ratio was an independent predictor of decreased glomerular filtration rate (Modification of Diet in Renal Disease study) and albuminuria [18]. The analysis of the combined

Table 1. Patients' characteristics

Parameters	All (n = 96)	Group A	Group B	P
Age, years	62 (55.25–68.75)	66.5 (61–70.75)	60 (52.5–66)	0.05
Males	71	52	19	
BMI, kg/m^2	27.96 ± 4.08	26.98 ± 4.26	28.35 ± 3.94	0.814
Recurrent MI, n (%)	1 (8.4)	5 (15.6)	3 (4.9)	
Stroke, n (%)	8 (8.3)			
Smoking, n (%)	38 (39.58)	9 (28.12)	29 (45.31)	
Acute coronary syndrome characteristics, n (%)				
Multivessel disease	71 (73.95)	24 (75)	47 (73.4)	
LM occlusion	17 (17.7)	6 (18.75)	11 (17.18)	
Biological data				
Fasting glucose, mmol/L	6.05 (5.295–8.025)	5.98 (5.14–8.32)	6.14 (5.37–7.9875)	0.642
HbA1c, %	5.92 ± 0.62	5.77 ± 0.76	5.99 ± 0.57	0.331
Creatinine, mmol/L	98.0 (82.8–118)	118 (99.8–137)	92.2 (79.0–112)	< 0.001
GFR, mL/min/1.73 m^2	71.8 (56.9–92.6)	49.3 (43.4–53.7)	86.7 (71.4–102)	< 0.001
Total cholesterol, mmol/L	4.495 (3.795–5.445)	4.7 (4.2925–5.405)	4.38 (3.585–5.4825)	0.667
HDL, mmol/L	1.02 ± 0.26	0.99 ± 0.19	1.04 ± 0.28	0.572
LDL, mmol/L	2.71 ± 1.14	2.55 ± 0.89	2.76 ± 1.19	0.314
VLDL, mmol/L	0.830 (0.655–1.02)	0.800 (0.660–0.955)	0.815 (0.640–1.022)	0.876
Triglycerides, mmol/L	1.675 (1.2975–2.1925)	1.62 (1.3075–2.2)	1.685 (1.295–2.1925)	0.965
Clinical data				
LVEF, %	46.5 (44–49)	46 (44–48)	47 (44–49.5)	0.530
LVM, g	47.0 (44.0–51.0)	46.0 (43.5–48.0)	47.0 (44.0–51.0)	0.154
LVMI, g/m^2	115.35 (93.3–126.35)	118.15 (96.1–131.25)	114.65 (92.175–125.625)	0.321
Events, n (%)	12 (12.5)			

Notes: BMI — body mass index; LM — left main coronary artery; HDL — high-density lipoproteins.

Table 2. Average marker scores between groups, ng/mL

Markers	Group A	Group B	P
MPO	110.83 (45.19–156.33)	91.17 (53.10–209.89)	0.423
MMP-9	186.46 ± 65.66	193.68 ± 57.08	0.265

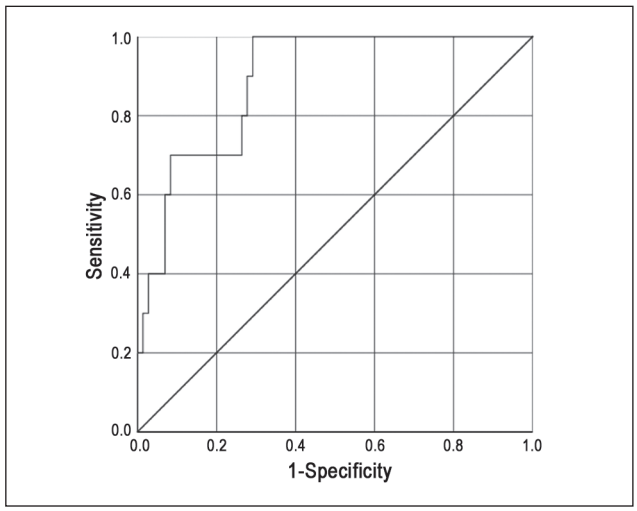

Figure 1. Combined ROC curve for prognostic model after 1 year: area 0.890, std error 0.043, asymptotic sig. < 0.001, asymptotic 95% confidence interval 0.805–0.975

ROC curve is also modestly optimistic, but further investigations will undoubtedly require a larger sample, which is also complicated by the large spectrum of comorbidity in these patients. It is also necessary to consider the method for assessing the glomerular filtration rate, since the GFR scale was used without the assessment of novel markers such as cystatin C. Despite the sufficient accuracy of the chosen method, this, however, may affect the accuracy of the result and should be taken into account in further studies. With a further decrease in the glomerular filtration rate in this sample, an increase in the predictive accuracy of MMP-9 was also noted, which gives rise to a detailed study of this issue in a larger sample of patients. The main interest of MPO in this cohort is from several angles. The effect of MPO on the progression of atherosclerosis has been shown. There is also evidence that MPO acts as an autocrine modulator of neutrophil function, recruiting previously unstimulated neutrophils. In addition, MPO attaches to leukocytes by binding to CD11B/CD18, which in turn contributes to the inflammatory effect of MPO by accumulating leukocytes at the site of inflammation [19]. MPO also showed no significant difference in levels between the comparison groups. Experiments with mice have shown an increase in MPO activity together with impaired macrophages in the arterial wall of a model of atherosclerosis in CKD, which may exacerbate the atherosclerosis process [20]. In a study involved a group of patients on hemodialysis, higher concentrations of MPO-dependent oxidised LDL were confirmed as a potential marker of MPO activity in plasma [21]. This may also be indirectly indicated by the weak correlation found with triglyceride levels and VLDL.

Study limitations

Firstly, as the department does not specialise in patients with renal pathology and the institution does not have a catheterisation laboratory, we were unable to completely cover the full spectrum of these patients, including those with renal failure.

Secondly, the sample of patients with this comorbidity was small, which also affected the result.

Conclusions

Our study showed that plasma MPO and MMP-9 levels were not involved in the reduction of glomerular filtration rate. However, MMP-9 levels showed prognostic information in relation to predicted outcomes after 1 year.

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Прогностична роль ММП-9 та МПО в пацієнтів зі зниженою швидкістю клубочкової фільтрації після гострого коронарного синдрому

Резюме. ***Актуальність.*** Ішемічна хвороба серця (ІХС) залишається основною причиною смертності в усьому світі. Враховуючи тяжкість та вплив цього захворювання, дослідники ретельно вивчають патогенез атеросклерозу, що є основною причиною ІХС. Етапи патогенезу є складними й багатогранними і включають такі фактори, як акумуляція ліпідів, розвиток запалення і формування бляшок. Особлива сфера активних досліджень стосується впливу на ці процеси й ролі в них різних біомаркерів, включаючи матриксну металопротеїназу-9 (ММП-9) та мієлопероксидазу (МПО). Ці біомаркери пов'язані з прогресуванням і дестабілізацією атеросклеротичних бляшок, що є центральним елементом ІХС. Однак використання цих біомаркерів у контексті супутніх захворювань, таких як хронічна хвороба нирок, залишається відкритою галуззю досліджень, особливо в пацієнтів після інфаркту міокарда. ***Матеріали та методи.*** У наше дослідження було включено 96 пацієнтів із гострим коронарним синдромом, які в подальшому перенесли черезшкірне коронарне втручання. Вони були розподілені на групи (А та Б) залежно від показників швидкості клубочкової фільтрації. Первинною кінцевою точкою дослідження була смертність від усіх причин та серйозні небажані серцеві та цереброваскулярні події. ***Результати.*** Наш аналіз показав, що сироваткові рівні МПО в групі Б були незначно вищими, ніж у групі А. І навпаки, продемонстровано значну різницю в площі під кривою операційних характеристик приймача (ROC) для ММП-9 в групі А, що становила 0,8 (95% довірчий інтервал 0,609–0,991; p = 0,039). Однак ROC-крива для МПО не дала значущого результату в жодній групі. Також була побудована комбінована ROC-крива, площа під якою показала вірогідно більше значення — 0,890 (95% довірчий інтервал 0,805–0,975; p < 0,001). ***Висновки.*** Ми виявили, що рівні вищезгаданих біомаркерів у плазмі крові не впливають на зниження швидкості клубочкової фільтрації. Тим не менш рівень ММП-9 надає значну прогностичну інформацію щодо прогнозованого результату.

Ключові слова: матриксна металопротеїназа-9; мієлопероксидаза; гострий коронарний синдром; швидкість клубочкової фільтрації; результат