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

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-
tion of an epithelial-mesenchymal transition, endothe-
lial-mesenchymal transition as well as activation of
resident fibroblasts and pericyte-myofibroblast transdif-
erentiation [12]. Oxidative stress also has an undeni-
able 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 compo-
nent 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 develop-
ment and progression of atherosclerotic disease. In clini-
cal studies conducted in patients with acute coronary syn-
dromes, 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 includ-
ing 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 pre-
dictors of adverse outcomes in patients with reduced glo-
merular 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, inflamma-
tory disease, malignancy, liver dysfunction), 96 patients after
PCI were enrolled. GFR was calculated using CKD-EPI
formula. Blood tests, including routine biochemical ana-
lysis and measurement of serum levels of MMP-9 and
MPO, were performed in 32 subjects with GFR lower than
60 mL/min/1.73 m² (group A) and in 64 patients with GFR
above 60 mL/min/1.73 m² (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 pa-
patients immediately after transfer from the catheterisation
laboratory. Serum was separated 1 hour after clotting. The
samples were then centrifuged for approximately 10 min-
utes 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 ac-
cording 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 tele-
phone interviews and analysis of repeated hospital admis-
sions. The primary endpoint of the study was all-cause mor-
tality and major adverse cardiovascular and cerebrovascular
events (MACCE).

Statistical analysis

Statistical analyses were carried out using SPSS ver-
sion 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 as-
sess the ability of biomarkers to predict a negative out-
come. 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. Bilat-
eral P values < 0.05 were considered to indicate statis-
tical significance.

Results

Patients’ characteristics are shown in Table 1. A cor-
relation 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 in-
significantly 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,
junction fraction, presence of PCI, LM occlusion, sex, age,
hypertension, thrombolysis in myocardial infarction blood
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

<table>
<thead>
<tr>
<th>Parameters</th>
<th>All (n = 96)</th>
<th>Group A</th>
<th>Group B</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>62 (55.25–68.75)</td>
<td>66.5 (61–70.75)</td>
<td>60 (52.5–66)</td>
<td>0.05</td>
</tr>
<tr>
<td>Males</td>
<td>71</td>
<td>52</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.96 ± 4.08</td>
<td>26.98 ± 4.26</td>
<td>28.35 ± 3.94</td>
<td>0.814</td>
</tr>
<tr>
<td>Recurrent MI, n (%)</td>
<td>1 (8.4)</td>
<td>5 (15.6)</td>
<td>3 (4.9)</td>
<td></td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>8 (8.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>38 (39.58)</td>
<td>9 (28.12)</td>
<td>29 (45.31)</td>
<td></td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>71 (73.95)</td>
<td>24 (75)</td>
<td>47 (73.4)</td>
<td></td>
</tr>
<tr>
<td>LM occlusion</td>
<td>17 (17.7)</td>
<td>6 (18.75)</td>
<td>11 (17.18)</td>
<td></td>
</tr>
<tr>
<td>Acute coronary syndrome characteristics, n (%)</td>
<td></td>
<td></td>
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<td></td>
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</tbody>
</table>

| 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 m²               | 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/m²                        | 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

<table>
<thead>
<tr>
<th>Markers</th>
<th>Group A</th>
<th>Group B</th>
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<tbody>
<tr>
<td>MPO</td>
<td>110.83 (45.19–156.33)</td>
<td>91.17 (53.10–209.89)</td>
<td>0.423</td>
</tr>
<tr>
<td>MMP-9</td>
<td>188.46 ± 56.66</td>
<td>193.68 ± 57.08</td>
<td>0.265</td>
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</tbody>
</table>
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.

References
