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Please cite this article: PROGNOSTIC SIGNIFICANCE OF INFLAMMATORY BIOMARKERS IN DIABETIC AND NON-DIABETIC PATIENTS WITH STEMI, TREATED WITH PRIMARY PERCUTANEOUS CORONARY INTERVENTION

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UDC:

DOI: https://doi.org/10.2298/VSP170905175M

When the final article is assigned to volumes/issues of the Journal, the Article in Press version will be removed and the final version appear in the associated published volumes/issues of the Journal. The date the article was made available online first will be carried over.
Prognostic significance of inflammatory biomarkers in diabetic and non-diabetic patients with STEMI, treated with primary percutaneous coronary intervention

Prognostički značaj inflamatornih biomarkera kod pacijenata sa dijabetesom i bez dijabetesa koji su lečeni primarnom perkutanom koronarnom intervencijom zbog akutnog infarkta miokarda sa elevacijom St segmenta

Veljko Milic*, Boris Dzudovic*, Slobodan Obradovic*

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Uvod. Iako je poznat prognostički značaj inflamatornih biomarkera kao što su C-reactivni protein (CRP) i fibrinogen, kod pacijenata sa akutnim infarktom miokarda sa elevacijom ST-segmenta (STEMI), postojanje razlike u zavisnosti od prisustva ili odsustva dijabetesa nije poznato.

Metodologija. U medicinskom centru tercijernog nivoa, merene su vrednosti CRP-a i fibrinogena, u toku prvih 48h od prijema, kod pacijenata sa STEMI lečenih primarnom perkutanom koronarnom intercenciom (pPKI). Pacijenti su podeljeni u dve grupe: grupu sa dijabetesom i grupu bez dijabetesa. Procenjivan je prognostički značaj maksimalnih vrednosti ova dva biomarkera zapaljenja za nastanak intrahospitalne i šestomesečne smrtnosti u svakoj od grupa.

Rezultati. Među 475 pacijenata, 126 (26.5%) je imalodijabetes, a 349 (73.5%) nijemalodijabetes. Pacijenti sa dijabetesom su imali značajno veću vrednost medijane CRP-a i fibrinogena u poređenju sa pacijentima bez dijabetesa [29.6(10.4-91.8) vs. 22.4(9.79-49.2), p=0.046 i 4.7 (3.6-6.3) vs. 4.3 (3.6-5.4), p=0.026]. Pa ipak, multivarijantna analiza smrtnosti koristeći Cox regresioni model je pokazala da kod pacijenata bez dijabetesa CRP i fibrinogen imaju značajn upragnostičku vrednost za nastajanje intrahospitalne smrtnosti [HR= 1.013 95% CI (1.004-1.022), p=0.004 i HR=1.529 (1.023-2.287), p=0.039]. Kada je u pitanj ušestomesečna smrtnost, nije pronađena statistički značajna razlika. Ukupno preživljavanje je bilo najniže u četvrtom kvartilu CRP-a u grupi pacijenata bez dijabetesa.

Zaključak. Visoke vrednosti CRP-a su nezavisna prediktor intrahospitalne i ukupne šestomesečne smrtnosti kod pacijenata sa STEMI koji nemaju dijabetes i koji su lečeni pPKI. Fibrinogen se takođe može koristiti kao prognostički marker za intrahospitalnu smrtnost kod nedijabetičara sa STEMI.
**Background.** Although the prognostic significance of inflammatory biomarkers, C-reactive protein (CRP) and fibrinogen, in patients with ST-segment elevation myocardial infarction (STEMI) is already known, the specific difference between such patients according to diabetic status remains unknown.

**Methodology.** In a single tertiary center, values of CRP and fibrinogen were measured during the first 48 hours in consecutive patients with first STEMI treated with primary percutaneous coronary intervention (pPCI). Patients were divided into two groups: with diabetes and without diabetes. Prognostic significance of maximal values of these two inflammatory biomarkers for in-hospital and six-month mortality was evaluated among the two groups.

**Results.** Among 475 patients, 126 (26.5%) were with diabetes and 349 (73.5%) were without diabetes. Patients with diabetes had significantly higher median values of CRP and fibrinogen compared to non-diabetic patients [29.6 (10.4-91.8) vs. 22.4 (9.79-49.2), p=0.046 and 4.7 (3.6-6.3) vs. 4.3 (3.6-5.4), p=0.026, respectively]. However, multivariate survival analysis using Cox regression model showed that in non-diabetic STEMI patients CRP and fibrinogen had significant prognostic value for in-hospital mortality [HR= 1.013 95%CI (1.004-1.022), p=0.004 , HR= 1.529 (1.023-2.287), p=0.039, respectively]. Regarding the six-month mortality, no significant difference was achieved. Overall survival was lowest in the fourth quartile of CRP in patients without diabetes.

**Conclusion.** Higher values of CRP are significant independent predictor of in-hospital and overall mortality in STEMI patients without diabetes treated with primary PCI. Fibrinogen can also be used as additional prognostic inflammatory biomarker for in-hospital mortality in non-diabetics with STEMI.

**Key words:** CRP; fibrinogen; diabetes; STEMI; prediction; mortality.
Introduction

Inflammation is the inevitable companion of acute myocardial infarction and plays a key role in wound healing and scar formation (1). Different patterns of inflammatory response are detected between myocardial infarction with ST-segment elevation (STEMI) and without ST-segment elevation (NSTEMI) (2). C-reactive protein (CRP) and fibrinogen, the acute phase reactants, are commonly used in every-day clinical praxis. The role of CRP and fibrinogen as predictors of heart failure development and mortality after acute myocardial infarction are already investigated (3-8). Diabetes is well known risk factor for cardiovascular disease, but it is also associated with increased inflammation. Increased inflammatory biomarkers are even accused to cause diabetes mellitus type 2 as well as complications (9). Patients with STEMI are often treated with primary PCI (pPCI) with stent implantation. Even this intervention itself is associated with increased inflammatory response (10,11). However, it is still unknown are there any differences in inflammatory response between patients with and without diabetes and with acute myocardial infarction treated with pPCI. In addition, it is still unclear whether the prognostic value of some inflammatory biomarkers in these two subgroups of patients observed separately is different.

We measured CRP and fibrinogen during the first two days of hospitalization in consecutive STEMI patients treated with pPCI, and depending on their diabetic status, we evaluated the prognostic value of these two biomarkers for early (in-hospital) and late (six-month) mortality.
Methodology

This is retrospective and partly prospective cohort study performed in the Clinic for emergency internal medicine at Military Medical Academy in Belgrade, Republic of Serbia in the period from 2002 till 2016. Only patients admitted due to first ever diagnosed STEMI who underwent pPCI and with all available data were included in the study. STEMI was diagnosed according to ECG recorded as pre-hospital or at admission. ST-segment elevation in two adjacent leads by ≥1mm in leads I-III, aVF, aVL, V4-V6 and ≥2mm in leads V1-V3, were considered as significant for the diagnosis (12). All patients included in the study underwent pPCI in the time frame no longer than 12 hours from the self-reported chest pain onset. Before PCI execution, all patients received loading doses of aspirin (300mg) and clopidogrel (600mg) or ticagrelor (180mg). Venous blood samples for determination of CRP and fibrinogen were collected once daily during the first 48 hours from admission starting the morning after pPCI procedure. Maximal values of CRP and fibrinogen were then evaluated for the prediction of in-hospital and six-month mortality. For overall mortality quartiles of maximal values of these inflammatory biomarkers were compared for the frequencies of event. In-hospital mortality was considered as death during the hospital stay starting from the first day from admission after successful pPCI. Six month mortality was considered as any cause of death starting from day 30 until day 180 from admission.

Statistics

For data analysis, maximal values of CRP and fibrinogen were expressed as median with interquartile range. Categorical data were expressed as numbers (percentages). Fisher exact test for qualitative variables and the Mann-Whitney U test for quantitative variables were used to test difference between groups. For multivariate survival analysis Cox Regression
model was used and overall survival was depicted by Kaplan-Meier curve using log-rank test to compare survival distributions among the quartile groups. All statistics were performed with SPSS for Windows, version 20.0. P value < 0.05 was considered significant.

Results

Overall 475 consecutive patients with first STEMI treated with pPCI were included in the study. Among them, 126 (26.5%) were diagnosed with diabetes type 2 and 349 (73.5%) did not have diabetes. Patients with diabetes were older, more often female and more often hypertensive compared to non-diabetics. They also presented more often with acute heart failure (Killip class > 1) and with longer time passed from pain onset to reperfusion (pPCI). In opposite, non-diabetics were more often smokers then diabetics. Other basic characteristics of the patients were presented in table 1.
Table 1. Basic characteristics on admission of the patients stratified by presence or absence of diabetes

<table>
<thead>
<tr>
<th></th>
<th>Diabetics</th>
<th>Non-diabetics</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age – years ± SD</strong></td>
<td>64,2±12,2</td>
<td>61,6±12,2</td>
<td>0,038</td>
</tr>
<tr>
<td><strong>Female n (%)</strong></td>
<td>45 (35,4)</td>
<td>88 (25,3)</td>
<td>0,037</td>
</tr>
<tr>
<td><strong>Smokers n (%)</strong></td>
<td>52 (41,1)</td>
<td>197 (56,8)</td>
<td>0,003</td>
</tr>
<tr>
<td><strong>Hypertension n (%)</strong></td>
<td>97 (76,2)</td>
<td>229 (65,8)</td>
<td>0,034</td>
</tr>
<tr>
<td><strong>Hypercholesterolemia &gt;5 mmol/L n (%)</strong></td>
<td>72 (57,0)</td>
<td>223 (64,1)</td>
<td>0,216</td>
</tr>
<tr>
<td><strong>Modified SelvesterECG score &gt;15% n (%)</strong></td>
<td>53 (39,6)</td>
<td>126 (36,4)</td>
<td>0,569</td>
</tr>
<tr>
<td><strong>Q-wave on the admission ECG n (%)</strong></td>
<td>53 (42,1)</td>
<td>131 (37,8)</td>
<td>0,448</td>
</tr>
<tr>
<td><strong>Killip class &gt;1</strong></td>
<td>33 (26,0)</td>
<td>51 (14,7)</td>
<td>0,006</td>
</tr>
<tr>
<td><strong>Time to reperfusion in hours mediana (25th-75th)</strong></td>
<td>5.0 (3.0 – 8.0)</td>
<td>3.5 (2.0 – 6.0)</td>
<td>0,005</td>
</tr>
<tr>
<td><strong>Multivessel coronary disease n (%)</strong></td>
<td>90 (70,7)</td>
<td>215 (61,8)</td>
<td>0,081</td>
</tr>
<tr>
<td><strong>Infarction related artery n (%)</strong></td>
<td>2 (1,6)</td>
<td>4 (1,1)</td>
<td>0,660</td>
</tr>
<tr>
<td><strong>Left main</strong></td>
<td>45 (35,4)</td>
<td>142 (40,8)</td>
<td>0,340</td>
</tr>
<tr>
<td><strong>CXa</strong></td>
<td>18 (14,2)</td>
<td>46 (13,2)</td>
<td>0,764</td>
</tr>
<tr>
<td></td>
<td>CRP</td>
<td>Fibrinogen</td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
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<td></td>
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<tr>
<td>In-hospital mortality</td>
<td>1.015 (0.994 – 1.037); 0.173</td>
<td>2.169 (0.879 – 5.351); 0.093</td>
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<td>six-month mortality</td>
<td>1.002 (0.984 – 1.019); 0.856</td>
<td>2.506 (0.897 – 6.993); 0.079</td>
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</table>

LAD – left anterior descending artery, CXa – circumflex artery, RCA – right coronary artery, pPCI- primary percutaneous coronary intervention.

In diabetic group, in-hospital mortality was 11 (8.7%) patients and six-month mortality was 9 (7.1%) patients. In non-diabetic group, in-hospital mortality was 18 (5.2%) patients and six-month mortality was 25 (7.2%) patients. Patients with diabetes had significantly higher median values of CRP and fibrinogen compared to non-diabetic patients [29.6 (10.4–91.8) vs. 22.4 (9.79–49.2), p=0.046 and 4.7 (3.6–6.3) vs. 4.3 (3.6–5.4), p=0.026, respectively].

Adjusted hazard ratios (HR) for the presence of two outcomes considering maximal values of CRP and fibrinogen observed separately for patients with diabetes and without diabetes are shown in table 2a and 2b.

Table 2a. Multivariate survival analysis using Cox regression model in STEMI patients with diabetes

<table>
<thead>
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<th>Fibrinogen</th>
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</table>

adjusted for age, gender, smokers, hypertension, Killip class and time to reperfusion.
Table 2b. Multivariate survival analysis using Cox regression model in STEMI patients without diabetes

<table>
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<th>CRP</th>
<th>Fibrinogen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR* (95%CI); p</td>
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</tr>
<tr>
<td>In-hospital mortality</td>
<td>1.013 (1.004 – 1.022); 0.004</td>
<td>1.529 (1.023 – 2.287); 0.039</td>
</tr>
<tr>
<td>six-month mortality</td>
<td>1.005 (0.997 – 1.013); 0.191</td>
<td>1.241 (0.826 – 1.866); 0.298</td>
</tr>
</tbody>
</table>

adjusted for age, gender, smokers, hypertension, Killip class and time to reperfusion.

When using stepwise regression model, CRP emerges as the best independent predictor of in-hospital mortality, followed by the years of age, in patients without diabetes. When fibrinogen was included in the stepwise regression model, years of age has advantage as independent predictor of in-hospital mortality, followed by fibrinogen, in patients without diabetes.

In patients without diabetes, overall mortality during the first six months was 12.3% and 15.9% in patients with diabetes. Significantly lower overall survival was in the fourth quartile of CRP compared to other three quartiles among patients without diabetes. No significant difference in overall survival between quartiles of CRP was achieved among patients with diabetes (Figure 1a and 1b). Maximal values of fibrinogen did not show significance in term of overall six-month mortality in patients with and without diabetes (Figure 2a and 2b).
Figure 1. Kaplan-Meier curves depict overall six-month survival among non-diabetic (panel a) and diabetics (panel b) patients according to CRP quartiles.

Figure 2. Kaplan-Meier curves depict overall six-month survival among non-diabetic (panel a) and diabetics (panel b) patients according to fibrinogen quartiles.
Discussion

This study showed that among STEMI patients treated with primary PCI, those with diabetes type 2 had significantly higher values of CRP and fibrinogen compared to patients without diabetes. However, prognostic significance of these inflammatory biomarkers for the prediction of mortality is completely different. Higher value of CRP is significant predictor of in-hospital mortality in non-diabetics, but not in diabetics. In addition, in patients without diabetes, higher values of fibrinogen have additional prognostic implication on in-hospital mortality. Higher values of CRP and fibrinogen were not associated to higher six-month mortality after patients were discharged from the clinic. Even though chronic inflammation increases atherosclerosis and correlates with extended cardiovascular disease, it seems that STEMI patients without diabetes are more prone to worst early outcome if these two inflammatory biomarkers are highly elevated. Several papers have already proved high correlation between high values of admission CRP and fibrinogen in STEMI patients and high risk of early mortality, but neither addressed the presence or absence of diabetes mellitus as an issue that can influence different prognostic implication of CRP or fibrinogen on mortality (13-16). Other inflammatory biomarkers are also linked to mortality in patients with acute myocardial infarction, although their measurement is more expensive and not widely available in clinical practice (16-18). In our study, STEMI patients without diabetes who were in the fourth quartile value of CRP had higher incidence of overall mortality and fibrinogen did not have prognostic implications on six-month overall mortality in both groups. The influence of other risk factors as smoking the cigarettes and presence of arterial hypertension or even female gender on CRP values are reported in some papers (19-21). Prolonged ischemic time has
also influence on increased CRP levels (22). However, in multivariable survival analyses, when putting all these risk factors into one model using Cox regression, CRP still emerges as the best independent predictor of early mortality in patients without diabetes.

Multivariable regression analysis recognized also fibrinogen as a significant predictor of in-hospital mortality in patients without diabetes. However, there was no significance for six-month mortality.

The reason for this difference in prognostic significance of inflammatory biomarkers, in particular CRP, between STEMI patients with and without diabetes is still unknown. One of the possible answers might be that acute glucose fluctuation in non-diabetic STEMI patients triggers more oxidative stress compared with sustained chronic hyperglycemia in patients with diabetes type 2 (23). It is also known that acute hyperglycemia in STEMI is independent risk factor for adverse events and that can even potentiate stress-induced apoptosis (20-22).

The importance of laboratory measurement of inflammatory biomarkers for the assessment of mortality risk in STEMI patients after percutaneous angioplasty could help in individualizing the treatment and follow up schedules of these patients.

**Study limitations**

This study included relatively low number of STEMI patients with diabetes leading to low number of events in this group of patients. Data for six-month mortality is obtained mostly by telephone contact with patients family and do not include the cause of death, although injuries and other similar accidents are excluded. Our laboratory also did not use hs-CRP tests which were unavailable.
Conclusion

Although STEMI patients with diabetes, treated with primary PCI, have higher values of CRP and fibrinogen on admission, compare to patients without diabetes, these inflammatory biomarkers, in particular CRP, are significant predictors of in-hospital mortality only in patients without diabetes. Regarding overall six-month mortality in STEMI patients without diabetes treated with primary PCI, those with CRP values in fourth quartile have significantly higher incidence of death compare to lower quartiles.

REFERENCES


