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Prognostic significance of inflammatory biomarkers in diabetic and non-diabetic patients with STEMI, treated with primary percutaneous coronary intervention

Prognostički značaj biomarkera inflamacije kod bolesnika sa i bez dijabetesa koji su lečeni primarnom perkutanom koronarnom intervencijom zbog akutnog infarkta miokarda sa elevacijom ST segmenta

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Abstract

Background/Aim. Although the prognostic significance of inflammatory biomarkers, C-reactive protein (CRP) and fibrinogen, in the patients with the ST-segment elevation myocardial infarction (STEMI) is already known, the specific difference between such patients according to diabetic status remains unknown. **Methods.** The study was conducted in a single tertiary center. The values of CRP and fibrinogen were measured during the first 48 h in consecutive patients with first STEMI treated with primary percutaneous coronary intervention (pPCI). The patients were divided into two groups: with diabetes and without diabetes. The aim of this study was to determine a prognostic significance of maximal values of these two inflammatory biomarkers for in-hospital and six-month mortality in these two groups. **Results.** Among 475 patients, 126 (26.5%) were with diabetes and 349 (73.5%) were without diabetes. The patients with diabetes had significantly higher median values of CRP and fibrinogen compared to the nondiabetic patients [29.6 (10.4–91.8) mg/L *vs* 22.4 (9.79–49.2) mg/L, $p = 0.046$ and 4.7 (3.6–6.3) g/L *vs* 4.3 (3.6–5.4) g/L, $p = 0.026$, respectively]. However, the multivariate survival analysis using the Cox regression model showed that in the nondiabetic STEMI patients CRP and fibrinogen had significant prognostic value for in-hospital mortality [hazard ratio (HR) = 1.013, 95% confidence interval (CI) (1.004–1.022), $p = 0.004$; HR = 1.529 (1.023–2.287), $p = 0.039$, respectively]. Regarding six-month mortality, no significant difference was achieved. Overall survival was the lowest in the fourth quartile of CRP in the patients without diabetes. **Conclusion.** The higher values of CRP are the significant independent predictor of in-hospital and overall mortality in the STEMI patients without diabetes treated with primary PCI. Fibrinogen can also be used as an additional prognostic inflammatory biomarker for in-hospital mortality in the non-diabetics with STEMI.

Key words:
biomarkers; c-reactive protein; diabetes mellitus; fibrinogen; mortality; percutaneous coronary intervention; prognosis; st elevation myocardial infarction.

Apstrakt

Uvod/Cilj. Iako je poznat prognostički značaj inflamatornih biomarkera kao što su C-reaktivni protein (CRP) i fibrinogen, kod bolesnika sa akutnim infarktom miokarda sa elevacijom ST-segmenta (STEMI), postojanje razlike u zavisnosti od prisustva ili odsustva dijabetesa nije poznato. **Metode**. Istraživanje je sprovedeno u medicinskom centru tercijernog nivoa. Kod bolesnika sa STEMI, lečenih primarnom perkutanom koronarnom intervencijom (pPKI) merene su vrednosti CRP-a i fibrinogena, u toku prvih 48h od prijema. Bolesnici su bili podeljeni u dve grupe: grupu sa dijabetesom i grupu bez dijabetesa. Cilj rada bio je da se utvrdi prognostički značaj maksimalnih vrednosti ta dva biomarkera zapaljenja za nastanak intrahospitalne i šestomesečne smrtnosti u svakoj od grupa. **Rezultati**. Među 475 bolesnika, 126 (26,5%) je imalo dijabetes, a 349 (73,5%) nije imalo dijabetes. Bolesnici sa dijabetesom su imali značajno veću vrednost medijane CRP-a i fibrinogena u poređenju sa bolesnicima bez dijabetesa [29,6 (10,4–91,8) *vs* 22,4 (9,79–49,2) mg/L, $p = 0,046$ i 4,7 (3,6–6,3) g/L *vs* 4,3 (3,6–5,4) g/L, $p = 0,026$]. Međutim, korišćenjem Cox regresione multivarijant-

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ne analiza smrtnosti modela pokazano je da su kod bolesnika bez dijabetesa CRP i fibrinogen imali značajnu prognostičku vrednost za nastajanje intrahospitalne smrtnosti [*hazard ratio* – stopa rizika (HR) = 1,013 95% interval poverenja (CI) (1,004–1,022), $p = 0.004$ i HR = 1,529, 1,023–2,287 95%CI, $p = 0{,}039$]. Kada je u pitanju šestomesečna smrtnost, nije pronađena statistički značajna razlika. Ukupno preživljavanje je bilo najniže u četvrtom kvartilu CRP-a u grupi bolesnika bez dijabetesa. **Zaključak**. Visoke vrednosti CRP-a su nezavisan prediktor intrahospitalne i ukupne šestomesečne smrtnosti kod bolesnika sa STEMI koji nemaju dijabetes lečenih pPKI. Fibrinogen se takođe može koristiti kao prognostički marker za intrahospitalnu smrtnost kod nedijabetičara sa STEMI.

Ključne reči:
biomarkeri; c-reaktivni protein; dijabetes melitus; fibrinogen; mortalitet; perkutana koronarna intervencija; prognoza; infarkt miokarda sa st elevacijom.

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 the ST-segment elevation (STEMI) and without STEMI (NSTEMI) [2]. C-reactive protein (CRP) and fibrinogen, the acute phase reactants, are commonly used in everyday 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 the increased inflammation. The increased inflammatory biomarkers are even suspected to cause diabetes mellitus type 2 and its complications [9]. The patients with STEMI are often treated with primary percentanous coronary intervention (pPCI) with a stent implantation. Even this intervention itself is associated with an increased inflammatory response [10, 11]. However, it is still unknown if there are any differences in the inflammatory response between the 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.

Methods

This is a retrospective and partly prospective cohort study performed in the Clinic for Emergency Internal Medicine at the Military Medical Academy in Belgrade, Republic of Serbia in the period from 2002 till 2016. Only the patients admitted due to the first, ever diagnosed STEMI who underwent pPCI and with all available data were included in the study. STEMI was diagnosed according to electrocardiogram (ECG) recorded as pre-hospital or at admission. The ST-segment elevation in two adjacent leads by ≥ 1 mm in leads I–III, aVF, aVL, V4–V6 and ≥ 2 mm 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 h from the self-reported chest pain onset. Before the PCI execution, all patients received loading doses of aspirin (300 mg) and clopidogrel (600 mg), or ticagrelor (180 mg). The venous blood samples for determination of CRP and fibrinogen were collected once a day during the first 48 h from the admission starting in the morning after the pPCI procedure. The maximal values of CRP and fibrinogen were then evaluated for the prediction of in-hospital and six-month mortality. For overall mortality, the 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 the admission after successful pPCI. Six-month mortality was considered as any cause of death starting from day 30 until day 180 from the admission.

Statistics

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

Results

Overall 475 consecutive patients with the 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. The patients with diabetes were older, more often female and more often hypertensive compared to nondiabetics. They were also presented more often with the acute heart failure (Killip class > 1) and with longer time that passed from the pain onset to reperfusion (pPCI). In opposite, the nondiabetics were more often smokers than the diabetics. Other basic characteristics of the patients were presented in Table 1.

In the diabetic group, in-hospital mortality was 11 (8.7%) patients and six-month mortality was 9 (7.1%) pa-

tients. In the nondiabetic group, in-hospital mortality was 18 (5.2%) patients and six-month mortality was 25 (7.2%) patients. The patients with diabetes had the significantly higher median values of CRP and fibrinogen compared to the nondiabetic patients [29.6 (10.4–91.8) mg/L *vs* 22.4 (9.79–49.2) mg/L, $p = 0.046$ and 4.7 (3.6–6.3) g/L *vs* 4.3 (3.6–5.4) g/L, $p = 0.026$, respectively]. Adjusted hazard ratios (HR) for the presence of two outcomes considering the maximal values of CRP and fibrinogen observed separately for the patients with diabetes and without diabetes are shown in Table 2.

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

In the patients without diabetes, overall mortality during the first six months was 12.3% and 15.9% in the patients with diabetes. A significantly lower overall survival was in the fourth quartile of CRP compared to other three quartiles among the patients without diabetes. No significant difference in overall survival between the quartiles of CRP was found among the patients with diabetes (Figure 1). The maximal values of fibrinogen did not show a significance in term of overall six-month mortality in the patients with and without diabetes (Figure 2).

Discussion

This study showed that among the STEMI patients treated with p/PCI, those with diabetes type 2 had the significantly higher values of CRP and fibrinogen compared to the patients without diabetes. However, a prognostic significance of these inflammatory biomarkers for the prediction of mortality was completely different. A higher value of CRP was a significant predictor of in-hospital mortality in the nondiabetics, but not in the diabetics. In addition, in the patients without diabetes, the higher values of fibrinogen had the additional prognostic implication on in-hospital mortality. The higher values of CRP and fibrinogen were not associated with higher six-month mortality after the patients were discharged from the clinic.

Table 1

Basic characteristics at the admission of the patients stratified by presence or absence of diabetes

Characteristics	Diabetics 126 (26.5%)	Non-diabetics 349 (73.5%)	*p*
Age, (years), mean ± SD	64.2 ± 12.2	61.6 ± 12.2	0.038
Female, n (%)	45 (35.7)	88 (25.2)	0.037
Smokers, n (%)	52 (41.2)	197 (56.4)	0.003
Hypertension, n (%)	97 (76.9)	229 (65.6)	0.034
Hypercholesterolemia > 5 mmol/L, n (%)	72 (57.1)	223 (63.9)	0.216
Modified Selvester ECG score > 15%, n (%)	53 (42.1)	126 (36.1)	0.569
Q-wave on the admission ECG, n (%)	53 (42.1)	131 (37.5)	0.448
Killip class > 1, n (%)	33 (26.1)	51 (14.6)	0.006
Time to reperfusion in hours, mediana (25th–75th IQR)	5.0 (3.0–8.0)	3.5 (2.0–6.0)	0.005
Multivessel coronary disease, n (%)	90 (70.7)	215 (61.8)	0.081
Infarction related artery, n (%)			
left main	2 (1.6)	4 (1.1)	0.660
LAD	45 (35.7)	142 (40.7)	0.340
CXa	18 (14.2)	46 (13.2)	0.764
RCA	56 (44.4)	140 (40.1)	0.463
TIMI flow at the end of pPCI, n (%)			
TIMI < 3, n (%)	18 (14.2)	62 (17.8)	0.407
Rezolution of ST-segment after pPCI < 50%, n (%)	49 (38.9)	103 (29.5)	0.068

LAD – left anterior descending artery; CXa – circumflex artery; RCA – right coronary artery; pPCI – primary percutaneous coronary intervention; TIMI – thrombolysis in myocardial infarction; IQR – interquartile range.

Table 2

The multivariate survival analysis using the Cox regression model in the STEMI patients with diabetes

Parameter	HR (95% CI); *p*	
	CRP	Fibrinogen
In-hospital mortality		
with diabetes	1.015 (0.994–1.037); 0.173	2.169 (0.879–5.351); 0.093
without diabetes	1.013 (1.004–1.022); 0.004	1.529 (1.023–2.287); 0.039
Six-month mortality		
with diabetes	1.002 (0.984–1.019); 0.856	2.506 (0.897–6.993); 0.079
without diabetes	1.005 (0.997–1.013); 0.191	1.241 (0.826–1.866); 0.298

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

CRP – C-reactive protein; HR – hazard ratio; CI – confidence interval; STEMI – ST-segment elevation myocardial infarction.

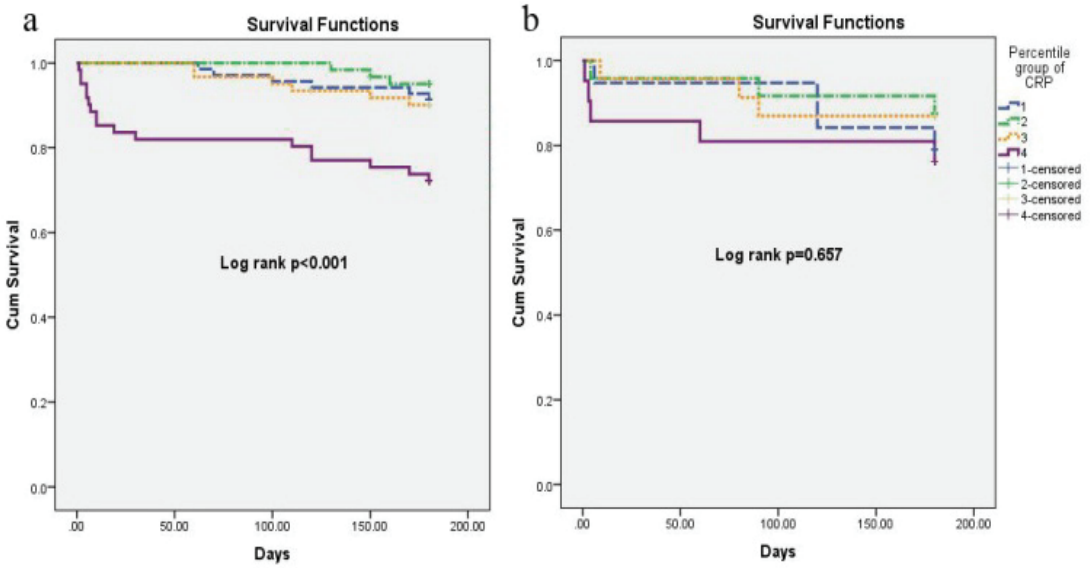

Fig. 1 – a) Kaplan-Meier curves depict overall six-month survival among: a) the nondiabetic patients and b) the diabetics patients according to the C-reactive protein (CRP) quartiles.

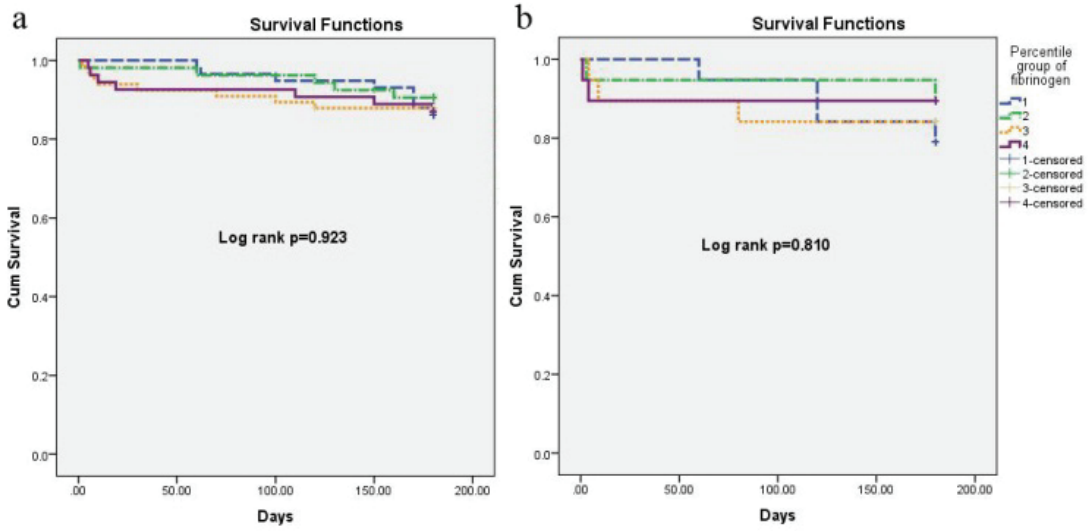

Fig. 2 – Kaplan-Meier curves depict overall six-month survival among: a) the nondiabetic (patients) and b) the diabetics patients according to the fibrinogen quartiles.

Even though the chronic inflammation increases atherosclerosis and correlates with extended cardiovascular disease, it seems that the STEMI patients without diabetes are more prone to the worst early outcome if these two inflammatory biomarkers are highly elevated. Several studies already proved a high correlation between the high values of CRP and fibrinogen at the hospital addmission in the STEMI patients and a high risk of early mortality, but neither addressed the presence, or absence of diabetes mellitus as an issue that can influence different prognostic implications of CRP or fibrinogen on mortality [4, 13–15]. Other inflammatory biomarkers are also linked to mortality in the patients with acute myocardial infarction, although their measurement is more expensive and not widely available in clinical practice [16–18]. In our study, the STEMI patients without diabetes who were in the fourth quartile value of CRP had a 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 on CRP values such as smoking cigarettes, presence of arterial hypertension, or even female gender are reported in some papers [18–20]. Prolonged ischemic time has also influence on the increased CRP levels [21]. However, in the multivariate survival analyses, when putting all these risk factors into one model using the Cox regression, CRP still emerges as the best independent predictor of early mortality in the patients without diabetes. The multivariable regression analysis also recognized fibrinogen as a significant predictor of in-hospital mortality in the patients without diabetes. However, there was no significance for six-month mortality.

The reason for this difference in a prognostic significance of inflammatory biomarkers, in particular CRP, between the STEMI patients with and without diabetes is still unknown. One of the possible answers might be that the acute glucose fluctuation in the nondiabetic STEMI patients triggers more oxidative stress compared with sustained chronic hyperglycemia in the patients with diabetes type 2 [22]. It is also known that acute hyperglycemia in STEMI is an independent risk factor for adverse events and that can even potentiate stress-induced apoptosis [19–21].

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

Study limitations

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

Conclusion

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

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