

INFLUENCE OF SYSTEMIC INFLAMMATORY RESPONSE ON IN HOSPITAL OUTCOME IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION UNDERGOING PRIMARY PERCUTANEOUS CORONARY INTERVENTION

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Subjects with type 2 diabetes mellitus (T2DM) constitute 13-25% of patients with acute myocardial infarction with ST-segment elevation (STEMI) hospitalized for myocardial reperfusion therapy. The aim of this study was to evaluate systemic inflammatory response in patients with T2DM and STEMI undergoing primary angioplasty at our clinic and to estimate prognostic significance of inflammatory markers, C-reactive protein (CRP), for in-hospital mortality in type 2 diabetics compared to those without diabetes.

The retrospective-prospective clinical study included 574 STEMI patients (122 with, and 452 without T2DM), both male and female, who underwent primary percutaneous coronary intervention (pPCI). Examination of the biochemical parameters demonstrated significantly higher concentrations of CRP [med CRP mg/L (25th-75th) 45.0 (12.0 to 101.0) to 25.8 (from 11.3 to 53.7), $p=0.013$] and glucose levels (12.4 ± 5.9 vs. 7.8 ± 1.9 , $p=0.001$) in subjects with diabetes. There were no differences between the groups regarding the activity of CK-MB fraction and LDH.

Multivariate analysis showed that CRP is an independent prognostic factor of adverse outcome in the first 30 days after primary PCI in non-diabetic group, followed by patient age and smoking (95%CI) [1.012 (1.004-1.020); $p=0,004$]. In contrast to diabetic patients, a significant mortality in non-diabetics was observed for the third tertile of (95%CI) [1.014 (1.008-1.020); $p=0.001$]. This findings were presented on the Kaplan-Meier curve.

C-reactive protein turned out to be an independent prognostic factor for hospital mortality for the patients without diabetes mellitus type 2 undergoing primary percutaneous coronary intervention. *Acta Medica Medianae 2017;56(2):5-12*

Key words: STEMI, C-reactive protein, primary percutaneous coronary intervention, type 2 diabetes mellitus, inflammation

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Introduction

Type 2 diabetes mellitus (DMT2) is present in 13-25% of patients with acute myocardial infarction with ST-segment elevation (STEMI), admitted to a hospital and undergoing myocardial reperfusion therapy (1). They have a worse clinical outcome after primary angioplasty, as well as after fibrinolytic pharmacological reperfusion therapy, compared to STEMI patients without diabetes (2,3). In these patients, elevated levels of inflammatory markers are found, associated with inflammation and adverse clinical outcome (4).

Patients with T2DM and unstable angina pectoris have an inflammatory response similar to

non-diabetic patients with STEMI. Both groups have a lower systemic inflammatory response intensity, compared to the group of diabetics with STEMI (5). Elevated levels of C-reactive protein (CRP), a systemic inflammatory response marker measured shortly after STEMI, are associated with dysregulated glucose, confirmed by OGT test during a three-month follow-up (6). C-reactive protein, as well as interleukin-6 (IL-6) and plasminogen activator inhibitor-1 (PAI-1), both have a role in the onset of insulin resistance (IR). This is indicated by a strict correlation between CRP and concentration of free fatty acids in plasma of the patients with myocardial infarction (7).

Myocardial infarction is thus associated with inflammatory response activation and insulin resistance (8), which is the main characteristic of T2DM. The results are controversial as to the importance of inflammatory response in diagnosing patients with diabetes mellitus and STEMI, who undergo primary percutaneous intervention (9). In the MONICA& CORA register,

the CRP level on patient admission is a strong risk marker for poor short-term prognosis after myocardial infarction in both diabetics and non-diabetics. However, unlike the patients without T2DM, in diabetic patients the admission CRP value was not an independent factor for long-term prognosis (10).

The aim of our study was to assess systemic inflammatory response in patients with DMT2 and STEMI who underwent primary coronary angioplasty at our clinic, and to evaluate prognostic significance of systemic inflammation response markers for in-hospital mortality in diabetic and non-diabetic patients.

Materials and methods

The retrospective-prospective clinical study included 574 patients (122 with type 2 diabetes mellitus and 452 patients without diabetes) with their first STEMI, both male and female, who were treated with primary percutaneous coronary intervention (pPCI). The procedure was performed according to the recommendations of the European Society of Cardiology, in the catheterization department of the Military Medical Academy in Belgrade.

Diabetes was defined as a history of hyperglycemia treated with insulin, hypoglycemic medications, or diet. Glycosylated hemoglobin (HbA1c) was used according to the recommendations of the American Diabetes Association (ADA). Patients with HbA1c \geq 6.5% (48 mmol/mol) were categorized among the patients with DMT2.

On admission, a standard 12-lead electrocardiogram and blood analysis were performed in order to assess creatin-kinase isoenzyme (CK-MB) activity, lactate dehydrogenase enzyme (LDH) activity, glucose blood levels, and concentration of C-reactive protein. The assessment of heart failure was conducted during clinical examination using the Killip classes, and subjects were classified as Killip class 0/1 and Killip $>$ 1. STEMI patients were immediately sent to the catheterization room, and underwent a standard pPCI procedure after medicamentous preparation.

In the next stage, the patients were monitored in the coronary care unit of the Clinic for Emergency and Internal Medicine of the Military Medical Academy. The dynamics of the enzyme LDH, CK-MB isoenzyme, glucose and CRP as a marker of inflammation was observed in the laboratory, using the Siemens Dade Behring Dimension RXL Chemistry Analyzer at the Institute of Biochemistry of the Military Medical Academy in Belgrade. In cases of a chest pain, we repeated coronary angiography to assess the occlusion of the stent. An echocardiography examination was used for each patient, using the apparatus GE Medical Systems, mod. Vivid 7 Pro, before their discharge from the hospital. Ejection fraction of the left ventricle (EFLV) was measured using the

modified Simpsons method, and Wall Motion Score Index was calculated (WMSI).

Statistic analysis

The results were statistically analyzed using a software for statistical data analysis, "IBM SPSS Statistics", version 20. Data were presented as mean \pm SD value and/or percentage. Statistical significance was evaluated by Student's t-test or Mann-Whitney U test, depending on the distribution of the obtained values. We calculated the correlation coefficient (Pearson or Spearman, depending on the distribution of the obtained parameter values) in order to determine interdependence of the monitored parameters. Time to outcome was determined by the Kaplan-Meiers method. Data will be presented in tables and graphs. A value was considered as statistically significant at $p < 0.05$.

Results

A total 574 patients with their first STEMI, who were treated with primary PCI, were monitored, 122 of which suffered from diabetes mellitus type 2 as well (Figure 1). Their basic demographic and clinical characteristics are presented in Table 1.

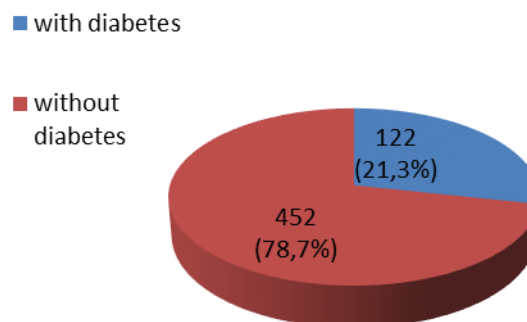


Figure 1. Examined groups

The patients with type 2 diabetes were significantly older than those without diabetes (64 ± 12 ys. vs. 60 ± 12 ys.). Both groups had more male than female patients (male-to-female ratio was approximately 2:1). Women with STEMI were more often diabetics ($p < 0.014$).

After the risk factors were examined, it was noticed that non-diabetic patients were more likely smokers (40.5% vs. 55.7%, $p = 0.004$), and that there were no significant differences in arterial hypertension (73% vs. 65.3%, $p = 0.102$) and hypercholesterolemia (62.5% vs. 68%, $p = 0.308$) between the two groups. The time „pain-reperfusion“ was the same in both groups [4h(3-7) vs. 4h(3-6), $p = 0.432$]. A significant difference was found considering heart failure at admission, which was determined as a Killip class > 1 , and appeared

to be more common in diabetic patients (24.6% vs. 15.7%, $p = 0.032$) (Table 1). There were no significant differences observed in relation to the Silvestre modified Score ($11 \pm 9\%$ vs. 11 ± 8 , $p = 0.781$), ejection fraction of left ventricle ($46 \pm 11\%$ vs. $48 \pm 10\%$, $p = 0.176$) and WMSI (1.5 ± 0.3 vs. 1.4 ± 0.3 , $p = 0.091$).

The EFLV and WMSI were not statistically different between the groups (46 ± 11 vs. 48 ± 10 , $p = 0.176$ and 1.5 ± 0.3 vs. 1.4 ± 0.3 , $p = 0.091$).

Patients with diabetes had significantly higher concentrations of CRP [med CRP mg/L (25th-75th) 45.0 (12.0-101.0) to 25.8 (11.3-53.7), $p = 0.013$] and concentrations of glucose (12.4 ± 5.9 vs. 7.8 ± 1.9 , $p = 0.001$), according to biochemical parameters. Significant differences between the two groups concerning CK-MB fraction and LDH

were not found (Table 1).

Table 2 consideration, related to the procedure itself and periprocedural complications of the primary PCI, showed the differences in TIMI 0/1 and TIMI-2 flow (56.5% vs. 66.1%, $p = 0.019$ and 24.6% vs. 14.8%, $p = 0.005$), that were more common in the group of diabetic patients, which does not apply on the TIMI-3 flow (17.2% vs. 18.8%, $p = 1.000$). There were no significant differences in multi-vessel disease (66.4% vs. 58.7%, $p = 0.156$), infarction-related artery: LAD (42.9% vs. 42.5%, $p = 0.573$), ACX (16% vs. 14%, $p = 0.595$), RCA (46.7% vs. 32.5%, $p = 0.269$). There were no differences related to the use of GP IIB/IIIa inhibitors, DES stents and TIMI-3 flow achieved after the intervention.

Table 1. Basic demographic and clinic characteristics and biochemical results

Characteristic	Group with T2DM n=122	Group without T2DM n=452	p*
Age (age \pm SD) in years	64 \pm 12	60 \pm 12	0,001
Gender: female n (%)	43 (35,2)	107 (23,7)	0,014
Artery hypertension n(%)	89 (73,0)	295 (65,3)	0,102
Hypercholesterolemia n(%)	76 (62,5)	307 (68,0)	0,308
Smoking n(%)	49 (40,5)	249 (55,7)	0,004
Time pain-reperfusion (h) med (25 th -75 th)	4 (3-7)	4 (3-6)	0,432
Killip >1 admission n (%)	30 (24,6)	71 (15,7)	0,032
Silvestre score (modif.)(%)	11 \pm 9	11 \pm 9	0,781
Ejection fraction LV (%)	46 \pm 11	48 \pm 10	0,176
WMSI	1,5 \pm 0,3	1,4 \pm 0,3	0,091
CK-MB (IU/L) med (25 th -75 th)	175,5 (95,7-334,5)	209 (108,0-377,0)	0,101
CRP (mg/L) med (25 th -75 th)	45,0 (12,0-101,0)	25,8 (11,3-53,7)	0,013
LDH (IU/L) med (25 th -75 th)	1166,0 (549,5-1878,5)	1023,5 (634,3-1700,0)	0,716
Glycemia at admission (mmol/L)	12,4 \pm 5,9	7,8 \pm 1,9	0,001

* $p < 0.05$

Table 2. PCI procedure data

Characteristic	Group with T2DM n=122	Group without T2DM n=452	p*
Multivessel disease n (%)	81 (66,4)	265 (58,7)	0,156
Infarction artery:			
LAD n(%)	52 (42,9)	192 (42,5)	0,573
ACX n(%)	25 (16,0)	63 (14,0)	0,595
RCA n(%)	57 (46,7)	99 (32,5)	0,269
TIMI flow before int.			
TIMI-0/1 n(%)	69 (56,5)	299 (66,1)	0,019
TIMI-2 n(%)	30 (24,6)	67 (13,2)	0,005
TIMI-3 n(%)	21 (17,2)	85 (18,8)	1,000
TIMI after intervention <3 n(%)	14 (11,5)	67 (14,8)	0,462
ST segment resolution <50% n (%)	46 (37,7)	100 (22,1)	0,152
Stents DES n(%)	21 (17,2)	103 (22,7)	0,211
Major bleeding n(%)	1 (0,81)	0 (0,0)	0,246
Periprocedural CVI n(%)	1 (0,81)	3 (0,66)	1,000
Reinfarction n(%)	7 (2,45)	11 (1,55)	0,713

* $p < 0.05$

The analysis of periprocedural complications in terms of major bleeding (0.81% vs. 0.0%, $p = 0.246$), periprocedural stroke (0.81% vs. 0.66%, $p = 1.00$), or reinfarction (2.45% vs. 1.55%, $p = 0.713$) showed no differences between

the groups. In hospital mortality due to all reason of death (9.8% vs. 4.6%, $p = 0.227$) and hospital death due to coronary heart disease (3.3% vs. 2.6%, $p = 0.602$) did not differ between the patients within the groups (Table 3).

Table 3. Primary and secondary outcomes

Characteristic	Group with T2DM n=122	Group without DM n=452	p*
In-hospital mortality n(%)	12 (9,8)	21 (4,6)	0,227
Hospital death due to a coronary cause n(%)	4 (3,3)	11 (2,6)	0,602

*p<0.05

Association with adverse events was tested for the following variables: gender, age, smoking, Killip> 1, CRP, blood glucose, TIMI-0/1 and TIMI-2 (Table 4).Multivariate analysis showed that CRP

is an independent prognostic factor of adverse in hospital outcome after primary PCI [CRP (95%CI): 1.012 (1.004-1.020); p=0.004] only for non-diabetic patients (Table 5).

Table 4. Patient group related prognostic significance of CRP

Characteristic	Group with T2DM n=122			Group without T2DM n=452		
	Died	Survived	p	Died	Survived	p*
n (%)	12 (9,8)	110 (90,2)		21 (4,6)	431 (95,4)	
CRP (mg/L) med (25 th -75 th)	129,9 (34,7-171,5)	43,2 (11,7-95,0)	0,101	121,8 (75,4-140,8)	24,0 (11,2-49,7)	<0,001

*p<0.001

Table 5. "Odds ratio" for CRP in non-diabetics group

Parameter	Non adjusted OR (95% CI); p*	Adjusted OR# (95% CI); p*
CRP mg/L	1,014 (1,008-1,020); 0,001	1,012 (1,004-1,020); 0,004

* p<0.05

#Adjusted to: age, smoking

A statistically significant mortality in non-diabetic patients was observed for the third tertile [CRP (95% CI): 1.014 (1.008-1.020),p<0.001]

while there was no statistical significance in diabetic group, as showed by Kaplan-Meier curves (Figure 2 and 3).

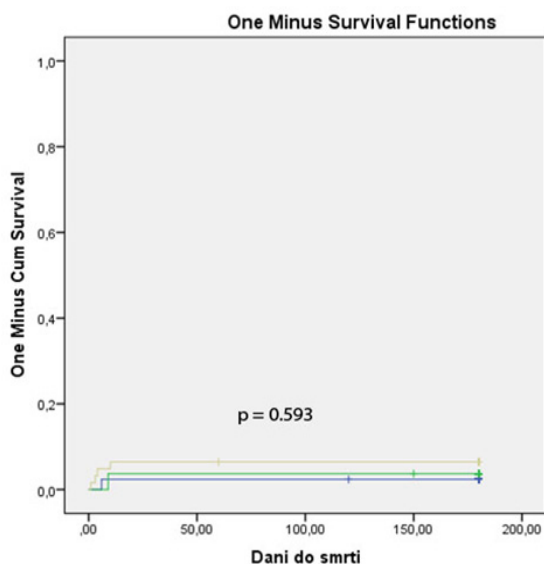


Figure 2. Mortality in the diabetes group presented in CRP tertiles

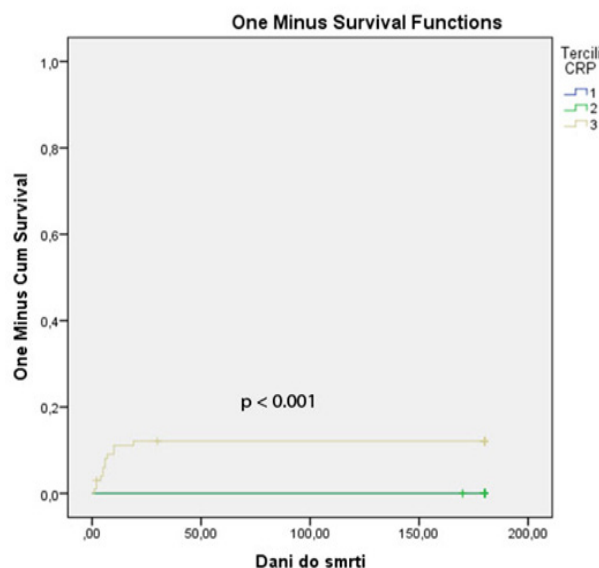


Figure 3. Mortality in non-diabetes group presented in CRP tertiles

Discussion

The results related to in-hospital mortality did not show any statistically significant difference between the groups of patients with and

without diabetes (3.4% versus 5.2%, p = 0.602). This result was not related to HORIZONS AMI study or any other study (11). In this study, 3265 patients with STEMI, of which 533 (16.3%) were with diabetes, demonstrated that mortality after

30 days was significantly higher in diabetic patients (1.8% vs. 4.5%, $p=0.0002$). The situation was similar with in-hospital mortality resulting from coronary reasons (3.4% vs. 2.6%, $p=1.000$), in contrast to the results of other studies (12,13).

However, in the HORIZONS AMI study, there were more patients with prior myocardial infarction, prior PCI or CABG in both groups, compared to the patients in our study. Most likely for this reason, a statistically significant difference in in-hospital deaths was not detected.

On the other hand, modern interventional approach to percutaneous coronary intervention is equally successful in both groups, a group of patients with diabetes, and the other group without diabetes.

The reason for higher mortality in diabetes group in these studies is less frequently achieved restoration of normal myocardial perfusion, measured by "myocardial blush grade" and ST-segment resolution, as well as a higher incidence of distal embolization (1, 14,15). Our results concerning ST segment resolution did not show any statistically significant difference (37.7% vs. 22.1%, $p=0.152$) between the groups. CRP and IL-6 and IL-10 were not correlated with the no-reflow phenomenon. There was a correlation to arachidonic acid-induced platelet aggregation (AA-IAT) and thromboxane B2 levels, measured before and after PCI. AA-IAT before a PCI proved to be a prognostic factor for the no-reflow phenomenon in diabetics, the sensitivity of which was 96.2% and specificity 38.5% (16,17).

Patients with diabetes who underwent PCI were older (64 ± 12 years, 60 ± 12 years, $p=0.001$), and were less likely to smoke, and the frequency of arterial hypertension and hypercholesterolemia was not statistically different between the groups. GUSTO IIb analysis in this study shows a similar relation between diabetics and non-diabetics treated with primary PCI. Patients with diabetes were older, more often women and less often smokers (18).

After examining data regarding the time between the event and patient admission in our study, we found no statistically significant difference in "pain-reperfusion time" between diabetics and non-diabetics ($p=0.432$). Similar results were also found in a recent study, which compared the time of reporting 62 diabetics and 204 non-diabetics patients with the first presentation of STEMI. The quality and intensity of pain were evaluated using the McGill questionnaire. It was concluded that there was no significant difference in reporting time between the two groups (χ^2 , $p=0.105$). It was noted that patients with diabetes who had had multi-vessel coronary disease (χ^2 , $p<0.01$) reported last (19). It is very likely that permanent and adequate education of the target group of diabetics could improve the outcome in these patients. On the other hand, better primary health care organization and wider network of PCI centers contribute to better prognosis in these patients.

Concerning heart failure at admission in the group of patients with diabetes, a frequent occur-

ence of heart failure was observed, ranked as Killip class >1 (24.6% vs. 15.8%, $p=0.032$). Since coronary angiography prior to intervention did not show more frequent presence of multivessel disease in the group of diabetics, as should be expected, more frequent heart failure on admission was probably the consequence of preexisting myocardial damage in terms of microcirculation disorders and increased extracellular matrix fibrosis in diabetic patients.

In general, in patients with a degree of heart failure present on admission despite pPCI and achieved TIMI-3 flow, suboptimal myocardial reperfusion was observed in a relatively large number of cases. The Killip class at admission was associated with myocardial perfusion, distal embolization, infarction size, maximum enzyme elevation, ejection fraction at discharge and one-year mortality (20).

The reason for absent differences in the measured ejection fraction and WMSI between the groups was likely to be a short monitoring period.

TIMI-0/1 flow was more common in non-diabetics, compared to TIMI flow before the intervention, while TIMI-2 flow was more frequently noticed in the group of diabetics. This appeared to be probably due to collateral circulation between the coronary arteries in the group of diabetics, causing the maintenance of retro grade filling of infarction-related artery during an infarction in diabetics, which was not present in non-diabetic patients with more frequent TIMI 0/1 flow.

After a pPCI intervention, an equal degree of TIMI 3 flow was observed in both groups, which was consistent to other studies (21).

Thanks to the progress of technology and P2Y12 receptor inhibitor application, and GP IIb/IIIa inhibitors, and with the use of modern scores for bleeding (CRUSADE, ACQUITY), periprocedural complications like major bleeding, bleeding in the brain or reinfarction in our study were not more frequent in the group of diabetics.

CRP concentrations were significantly increased in diabetic patients [medCRP mg/L (25th-75th) 45.0 (12.0 to 101.0) to 25.8 (11.3 to 53.7), $p = 0.013$]. This finding suggested the presence of an intense systemic inflammation in patients with diabetes mellitus (22), although most of myocardial necrosis assessed using CK-MB was no different. It was interesting that studies of the effect of T2DM on myocardial infarction size measured using the scintigraphy with technetium-99m-sestamibi found no significant differences in infarction size between diabetics and non-diabetics who underwent primary PCI (23).

Inflammation has an important role in acute coronary syndrome and in diabetes mellitus type 2. It was found that patients with diabetes and unstable angina have an inflammatory response similar to non-diabetic patients with STEMI. Nevertheless, both of these groups have a lower systemic inflammatory response intensity compared to the group of diabetics with STEMI (24). Although the blood glucose level at admission is significantly higher in patients with diabetes mellitus, literature data indicate that the highest risk of in-hospital death is present in non-diabetic

patients with elevated glucose at admission (25). However, in our study, the elevated levels of blood glucose did not prove to be an independent predictor of death in any of the examined groups of patients. Increased CRP levels recorded early after STEMI were associated with glucose dysregulation, confirmed using the OGT test in a three-month follow-up (6). C-reactive protein, as well as interleukin-6 (IL-6) and plasminogen activator inhibitor-1 (PAI-1), have a role in the onset of insulin resistance (IR). This is indicated by a strict correlation between IL-6 and CRP and free fatty acid concentration in the blood of patients with myocardial infarction (7).

In this manner, myocardial infarction is associated with the activation of both inflammatory response and insulin resistance (8).

C-reactive protein turned out to be an independent prognostic factor for mortality only in patients with STEMI without diabetes (95% CI [1.014 (1.008 to 1.020), $p=0.001$]). A similar conclusion was presented in a study which examined the MONICA/KORA myocardial infarction registry. In that study, CRP at admission was a powerful risk marker of a poor short-term prognosis after myocardial infarction. However, in contrast to the patients without diabetes, CRP at

admission was not an independent factor for long-term prognosis in diabetic patients (9).

These findings suggest the need for further investigation of the importance of inflammatory response in ischemic heart disease and diabetes mellitus type 2 due to its close relatedness with the occurrence, development and complications of atherosclerotic disease.

Conclusion

Our study did not reveal any statistically significant difference in total in-hospital mortality and hospital death due to coronary reasons between the groups of patients with and without type 2 diabetes who underwent pPCI due to STEMI.

The intensity of a systemic inflammatory response in patients with diabetes was statistically significantly higher, even though the size of the infarction area was not statistically different between the studied groups.

Although higher in the T2DM group, C-reactive protein turned out to be an independent prognostic factor for in-hospital mortality only for patients without type 2 diabetes mellitus who underwent pPCI due to STEMI.

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UTICAJ SISTEMSKOG INFLAMATORNOG ODGOVORA NA INTRAHOSPITALNI ISHOD KOD BOLESNIKA SA DIJABETESOM MELITUSOM TIP 2 I INFARKTOM MIOKARDA SA ELEVACIJOM ST SEGMENTA KOJI SU PODVRGNUTI PRIMARNOJ PERKUTANOJ KORONARNOJ INTERVENCIJI

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Dijabetes melitus tip 2 (DMT2) se sreće kod 13-25% bolesnika sa akutnim infarktom miokarda sa elevacijom ST segmenta (STEMI), koji se hospitalizuju radi terapijske reperfuzije miokarda. Kod ovih bolesnika se nalaze i povećane vrednosti markera inflamacije i udruženost inflamacije sa nepovoljnim kliničkim ishodom. Cilj ovog rada bio je da se proceni sistemski inflamatorni odgovor bolesnika sa DMT2 i infarktom miokarda sa ST elevacijom koji se podvrgavaju primarnoj koronarnoj angioplastici na našoj klinici, kao i da se proceni prognostički značaj markera inflamacije, CRP-a za intrahospitalnu smrtnost dijabetičara u odnosu na grupu bolesnika bez dijabetesa.

U retrospektivno-prospektivnu kliničku studiju je uključeno 574 bolesnika, od čega 122 sa dijabetesom melitusom tip 2, sa prvim infarktom miokarda sa ST elevacijom, muškog i ženskog pola koji se nakon postavljene dijagnoze podvrgavaju primarnoj perkutanoj koronarnoj intervenciji (pPKI).

Uvidom u biohemijske parametre utvrđeno je da su značajno veće koncentracije CRP-a u grupi ispitanika sa dijabetesom [med CRP mg/L(25th-75th) 45,0 (12,0-101,0) prema 25,8 (11,3-53,7), $p=0,013$], što je slučaj i sa vrednostima glukoze u krvi ($12,4\pm 5,9$ vs. $7,8\pm 1,9$ $p=0,001$). Nije viđena statistički značajna razlika među grupama u odnosu na CK-MB frakciju, kao i u odnosu na LDH. Multivarijantna analiza je pokazala da je CRP nezavisni prognostički faktor nepovoljnog intrahospitalnog ishoda nakon primarne PKI u grupi bez dijabetesa melitusa. Statistički značajna smrtnost u grupi nedijabetičara je zabeležena za treći tercil CRPom [(95%CI) 1,014(1,008-1,020), $p=0,001$], dok u grupi dijabetičara nema statistički značaj, što je prikazano Kaplan-Majerovim krivuljama.

C-reaktivni protein, iako sa značajno višim koncentracijama u grupi sa T2DM, poka-zao se kao nezavisni prognostički faktor za intrahospitalnu smrtnost samo za grupu bolesnika bez dijabetesa koji su podvrgnuti primarnoj angioplastici zbog infarkta miokarda sa ST elevacijom. *Acta Medica Medianae 20017;56(2):5-12*

Ključne reči: STEMI, C-reaktivni protein, primarna perkutana koronarna intervencija, dijabetes melitus tip 2, inflamacija