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Original article

Troponin and C-reactive Protein in Risk Stratification after Myocardial Infarction

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SUMMARY

The aim of this study was to investigate the prognostic significance of troponin I, C-reactive protein and risk factors for the occurrence of complications after myocardial infarction.

Troponin I and C-reactive protein values were analyzed in 38% of patients with complications (postinfarction angina, ventricular fibrillation, heart failure and fatal outcome) and in 62% of patients without complications. Values wererecorded on admission and between the eighth and tenth day of hospitalization.

It was found that a larger number of risk factors (p = 0.00), diabetes mellitus (p = 0.02) and smoking (p = 0.01) were significantly associated with the complications. It was shown that hypertension increases the risk of developing heart failure after acute myocardial infarction (p = 0.02). It resulted with statistically non-significant difference in the observed values of troponin I between the group of patients with complications and the group without them (p = 0.22, p = 0.327).There was a statistically significant difference in the observed values of C-reactive protein in the two groups of patients (p = 0.00, p = 0.01).

It can be concluded that the values of troponin I had no prognostic significance in risk stratification, while the values of C-reactive protein, individual risk factors and a large numberof risk factors hadsignificance in risk stratification after myocardial infarction.

Key words: **myocardial infarction, troponin I, C-reactive protein, risk factors**

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INTRODUCTION

Risk stratification of patients with AMI (acute myocadial infarction) starts on presentation and is a continuous process that should predict those who are at high risk for further ischemic events or adverse outcomes (1). It takes place on three levels: in the initial clinical event, during hospitalization, and at the time of hospital discharge. In these circumstances, biochemical markers play a central role (2). Cardiac troponin I (cTnI) has the highest specificity and sensitivity for the detection of AMI and risk stratification. It is released into the blood within few hours of the onset of symptoms, and values remain elevated for several days after the attack. Complications in patients with AMI can be predicted based on the high value of troponin I that correlates with mortality (2,3). Patients with gradually increased troponin values have the tendency to develop adverse cardiac outcome in the next few weeks (1). C-reactive protein (CRP) is the most studied inflammatory marker. It has high sensitivity but low specificity. CRP has proven to be highly predictive for future cardiovascular events and useful in monitoring the evaluation of risk during cadiovascular diseases and their treatment. Higher values indicate the worsehospital and short-term posthospital prognosis (1,4).

METHODS

This was prospective and comparative study conducted in the Clinic for Cardiology at the Clinical Center of the University of Sarajevo.The study included 100 patientswith the diagnosis of myocardial infarction of both sexes, aged between 18 and 90 years,admitted to the Clinic from April 2014 to October 2014. Data on the sex, age and risk factors were taken from medical records (case history). Complications monitored in patients were post-infarction angina, ventricular fibrillation, heart failure and fatal outcome and have been reported on the basis of discharge letters.The values of cTnI and CRP were recorded on admission and between the eighth and tenth day of hospitalization. One measurement was recorded in patients who died shortly after admission. The value of cTnIwas determined by the automatic analyzer Architect ci8200 Abbott by CMIA method (Chemi-luminescent Microparticle Immunoassay). In the first step, sample, assay diluent and anti-troponin I antibody-coatedparamagneticmicroparticles are combined. Troponin I present in the sample binds to the anti-troponin I coated microparticles. After incubation and wash, anti-troponin I acridinium-labeled conjugate is added in the second step. CRP value was determined by the automatic analyzer Architect c8000 Abbott by immuneturbidi-metric method.The CRP reacts with the specific anti-body producing insoluble immune complexes. The turbiditycaused by these immune complexes is proportional to the CRP concentration in sample. Values for troponin I were from 0.00 to 0.03 ng/ml, and for CRP 0.0 to 5.0 mg/l.The procedures were in accordance with the ethical stan-dards of the institutional committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 1983.

Statistical analysis

Preparation and storage of data for statistical analysis was made in Microsoft Excel 2010. A software package that was used in the processing of data is IBM SPSS Statistics 20.0.Descriptive statistic is presented in tables by the number of cases, percentage, the mean, and median. Mann-Whitney U test for significance level of 5% (0.05) was used to test the difference between the parameters in two groups (patients with complication and patients without complications) and comparison was examined by using a Chi-square test.

RESULTS

From a total of 100 patients, 74 (74%) were male, while 26 (26%) were female with a mean age of 66.16 years.Statistically significant difference with respect to the sex of the patients was determined (p=0.01). ElevatedcTnI levels were detected in all patients on admission (100%), while 90.1% had a value of cTnI above the reference between the eighth and tenth day of hospitallization.When it comes to CRP, 70.3% of patients had a value above the reference on admission. At the second measurement elevated CRP levels were detected in 74.3% of patients. The most common risk factor was hypertension, found in 72 (72%) patients. Obesity and smoking were also dominant, in 63 (63%) patients.

Of the total number of patients, 62 (62%) did not have complications, while 38 (38%) patients had the onset of complications during hospitalization.Statistically significant difference was determined according to the occurrence of complications (p = 0.01). Complications in patients are presented in Table 1.

Table 1. Complications in patients with AMI

Complications	Total n (%)
Postinfarction angina	4 (4%)
Heart failure	26 (26%)
Ventricular fibrillation	3(3%)
Fatal outcome	5(5%)
No complications	62 (62%)

The most common complication was heart failure, registered in 26 (26%) of the total number of pati-

ents. The ventricular fibrillationwas the rarest complication during hospitalization, only in three (3%) patients.

One of the important indicators of complications is the kind of risk factors. That is why we tried to analyze the impact of certain risk factors on the occurrence of complications, and the results of the analysis are presented in Table 2.

Table 2. The influence of risk factors on the occurrence of complications

Risk factor	With complications n (%)	Without complications n (%)	p
Positive family history	10 (27.80)	26 (72.20)	0.114
Hypertension	26 (56.50)	46 (43.50)	0.533
Diabetes mellitus	17 (54.80)	14(45.20)	0.020
Obesity	18 (28.60)	45 (71.40)	0.093
Hyperlipidemia	8 (30.80)	18 (69.20)	0.377
Smoking	16 (25.40)	47 (74.60)	0.001

Results of the analysis showed that diabetes mellitus and arterial hypertension were more present in patients with complications, whereas other risk factors were found in patients without complications. Analysis also showed that there is a statistical connection between diabetes mellitus (p = 0.02) and smoking (p = 0.00) with the occurrence of complications after AMI. We also determined that there is a statistically significant correlation between the number of risk factors and complications in patients with AMI (Pearson correlation=0.33, p=0.00).

Results of testing the connection between individual risk factors and complications in AMI are given in Table 3.In patients with heart failure the most common risk factor was hypertension (30.2%). The results showed that there is a statistical association of hypertension and heart failure after AMI in patients (p = 0.02).

Table 3. Percentage distribution and statistical significance of risk factors in a variety of complications after AMI

	Total n (%)						
Complications	Positive family history	Smoking	Hypertension	Hyperlipidemia	Obesity	Diabetes mellitus	p
Post-infarction angina	1 (14.30)	1 (14.30)	2 (28.60)	2 (28.60)	1(14.30)	0 (0.00)	0.931
Heart failure	7 (11.10)	8 (12.70)	19 (30.20)	4 (6.30)	12(19.00)	13 (20.60)	**0.019**
Ventricular fibrillation	0 (0.00)	2 (33.30)	2 (33.30)	0 (0.00)	1 (16.70)	1(16.70)	0.881
Fatal outcome	2 (11.80)	3 (17.60)	3 (17.60)	2 (11.80)	4 (23.50)	3 (17.60)	0.963

Our results showed that there is no statistically significant difference between the values of cTnI on admission and between the eight and tenth day of hospitalization between the groups of patients with and without complications (p = 0.23, p = 0.33). Analysis of differences between the CRP values in the first and second measurement in the examined groups (with complications and without complications) has shown that there is a statistically significant difference between the tested parameters within these groups (p = 0.01, p = 0.01). Results are presented in Table 4.

Table 4. Results of testing the significance differences of examined parameters between groups with and without complications after AMI

	cTnI 1*	cTnI 2**	CRP 1	CRP 2
Mann-Whitney U	1008.00	983.00	796.50	745.00
Wilcoxon W	1749.00	2936.00	2749.50	2698.00
Z	-1.20	-0.98	-2.70	-2.55
p	0.227	0.327	0.007	0.011

*cTnI 1, CRP1 – on admission; **cTnI 2, CRP 2 – between eighth and tenth day of hospitalization

Table 5. Results of the measured values of cTnI in patients with and without complications

Complications	Mean / Median (25th – 75th percentile)	
	cTnI 1* (ng/ml)	cTnI 2** (ng/ml)
Postinfarction angina	48.32 / 13.75 (4.44 – 126.77)	0.23 / 0.07 (0.01 – 0.68)
Heart failure	43.74 /17.23 (1.80 – 36.28)	2.35 / 0.73 (0.13 – 4.83)
Ventricular fibrillation	33.57 / 19.70 (5.13-/)	4.11 / 2.55 (1.62-/)
Fatal outcome	31.19 / 11.70 (6.26 – 65.86)	10.38 / 5.37 (0.07-/)
With complications	41.77 / 15.71 (3.43-38.35)	2.94 / 0.85 (0.11 – 4.97)
Without complications	54.44 / 29.36 (5.56-57.87)	1.80 / 0.46 (0.11 – 1.84)

*cTnI 1 – on admission ;**cTnI 2 - between eighth and tenth day of hospitalization

Table 5 shows the results of the measured values of cTnI in patients with different types of complications that occurred during hospitalization after AMI.The average value of cTnI in the first measurement was higher in patients without complications. Mean cTnI in the second measurement was higher in patients with complications. Mean value of cTnI on admission was maximal in patients with postinfarction angina, while the minimum value was observed in patients who had a fatal outcome.

Results of the test parameter cTnI in the second measurement in patients with different types of complications indicate that the mean value was maximal in patients who had a fatal outcome, while the minimum value was in patients with postinfarction angina.

Table 6. Results of the measured values of CRP in patients with and without complications

Complications	Mean / Median (25th – 75th percentile)	
	CRP 1* (mg/l)	CRP 2** (mg/l)
Postinfarction angina	43.45 / 19.85 (1.75 – 108.75)	5.78 / 5.00 (2.00 – 10.32)
Heart failure	48.70 / 18.30 (9.77 – 48.42)	39.76 / 27.40 (11.57 – 57.80)
Ventricular fibrillation	6.13 / 6.80 (1.80/-)	18.10 /13.40 (0.00 - /)
Fatal outcome	53.94 / 39.00 (10.25 – 105.10)	150.10 / 182.30 (22.20 - /)
With complications	45.48 / 18.00 (6.77 – 48.42)	44.09 / 22.80 (8.05 – 54.92)
Without complications	26.87 / 6.10 (2.87 – 20.57)	21.47 / 9.90 (3.80 – 29.80)

*CRP 1 – on admission; **CRP 2 – between the eighth and tenth day of hospitalization

Table 6 shows the results of the measured values of CRP in patients with different types of complications that occurred during hospitalization after AMI. Results showed that the mean values of CRP on the first and second measurements were higher in patients with complications.The first measurement in patients with

different types of complications showed that the mean value of CRP was maximal in patients with fatal outcome, while the minimum value was in patients with ventricular fibrillation.Analysis of the obtained values of CRP in the second measurement in patients with different types of complications showed that the mean value was maximal in patients with fatal outcome,while the minimum value wasobserved in patients with post-infarction angina.

DISCUSSION

Acute myocardial infarction, in addition to modern methods of diagnostics and modern treatment, still remains one of the leading public health problems. Due to the high percentage of mortality, early risk stratification is very important. Patients who have a high risk of complications and unwanted outcomes tend to be identified as soon as possible, preferably already on hospital admission. We tried to identify a role of troponin I, CRP and risk factors in risk stratification after acute myocardial infarction.

Study of Tisminetzky and associates (5) aimed to describe the prevalence and characteristics, the practice of treatment and in-hospital outcomes associated with STEMI and NSTEMI in patients with diabetes and patients who did not have diabetes and were hospitalized for AMI. A review of medical records in the study included 6.903 respondents, 2.329 without and 4.514 with diabetes. The results showed that the respondents with diabetes were older, more often female, obese and with a higher frequency of comorbidity compared to participants who did not have diabetes. It has been shown that patients with diabetes are at a higher risk of development of complications, including heart failure (39% vs. 27%) and atrial fibrillation (18% vs. 16%). Subjects with diabetes had more complications and worse in-hospital outcomes compared to those who did not have diabetes.

Gerber and associates (6) investigated the difference in long-term survival after the first AMI in non-smokers, patients who stopped smoking before myocardial infarction, patients who stopped smoking after myocardial infarction and persistent smokers. The study tried to assess whether the reduction in the number of cigarettes in persistent smokers was associated with a lower mortality rate. The respondents were younger than 65 years. It has been shown that any reduction of 5 cigarettes consumed per day after AMI was significantly associated with a decreased risk of death by 18%($p < 0.001$). Quitting smoking before or after AMI is associated with improvement and survival.

Our results also showed that there is a statistical significant connection between diabetes mellitus and smoking with the occurrence of complications after AMI.

Nešić (7) investigated the presence of risk factors in patients who survived a myocardial infarction. The most common risk factor was hypertension, as presented in our study. The predominant risk factors were hyperlipidemia and smoking. The majority of patients had combined 3 risk factors and more, and in the group of patients with 3 or more risk factors the number of complications was largest. It was shown that in the group of patients with multiple risk factors, the infarcted area was larger, they had common heart rhythm disorders, and there was a larger number of patients with the signs of myocardial dysfunction.

We also determined that there was astatistically significant correlation between the number of risk factors and complications in patients with AMI.

The study of Holay and associates (8) included 120 patients with AMI who were divided into two groups: group I included the respondents under 60 years, and group II respondents over 60 years of age. In the second group of respondents, the most common risk factor was hypertension, whereas smoking was the most common in the first group. Most of the respondents in other group have developed congestive heart failure. Our results showed that there is a statistical association between hypertension and heart failure after AMI.

Joarder (3) examined the role of troponin I and CK-MB in risk stratification after acute myocardial infarction. The prospective study included 60 patients between 45 and 60 years, with the diagnosis of myocardial infarction. For each subject were collected three consecutive blood samples after admission: the first 9 hours after the onset of symptoms, the second between 9 and 24 hours of the onset of symptoms, and the third sample 24 hours after the onset of symptoms. In this research, all patients were followed up to 30 days after heart infarction by taking history, clinical examination, biochemical investigation and imaging technique. During the follow-up period, depending on the clinical and laboratory findings, the patients were categorized into low risk and high risk groups.The group of subjects with low risk had atypical symptoms, normal or non-specific ECG and normal cardiac enzyme CK-MB. Respondents in high-risk group had extended (> 20 minutes) chest pain at rest, congestive heart failure, were elderly, with ST segment changes and elevated cardiac biomarkers (troponin I and CK-MB). There was a statistically significant difference in troponin I values in all three measurements in low-risk and high-risk groups of patients. Assessment of clinical-pathological differences between the outcomes of 60 patients showed that the higher values of troponin I were significantly associated with a greater risk of developing adverse cardiac outcomes in the next few weeks.

The results of this study do not agree with the resultsobtained in our study. Our results shows that subjects were monitored during in-hospital period, 8 to

10 days and the reason for different results may be the application of different therapies, reperfusion application of fibrinolytic therapy in patients who werehospitalized in a timely manner compared to those in whom only Clexane and antiaggregate therapy were applied.

Study of Kuch and associates (9) examined the relationship between the value of CRP on admission, alone and in combination with troponin values, and short-term prognosis in patients with AMI. The study included 1.646 subjects aged 25-74 years who were hospitalized within 12 hours of the onset of symptoms. They were divided into two groups: with positive CRP (n = 919) and negative CRP (n = 727) compared to the value of CRP on admission (limit value of ≤ 0.3 mg/dl). CRP positive patients had significantly more hospital complications, and a higher rate of deaths during the 28 days ($p < 0.0001$) was reported.

Positive values of troponin on admission were also significantly associated with mortality during the follow-up period of 28 days ($p < 0.002$). The study concluded that the value of CRP onadmission was a powerful parameter for risk stratification of patients with AMI. Risk stratification by type of AMI showed that CRP was a better indicator of short-term risk in patients with NSTEMI, and troponin in patients with STEMI myocardial infarction.

In one other study (10), the prognostic value of CRP in ischemic heart diseasewas examined, including acute myocardial infarction. The aim of this study was to evaluate changes in the value of CRP in patients with ischemic heart disease and use these values as a diagnostic and prognostic tool with myocardial ischemia and infarction.Values are measured on admission, 48 hours after admission and at the end of the week. Subjects were divided into the following groups: stable angina, unstable angina, AMI and healthy groups. All subjects with AIM had increased value of CRP on admission, and 66% of them had complications (congestive heart failure, cardiogenic shock). It turned out that there is a statistically significant difference between the value of CRP on admission in the group of patients with complications compared to those who did not have compilations ($p < 0.001$). The study concluded that elevated CRP on admission and 48 hours after AMI represented the risk of complications and death. Therefore, the value of CRP may help in risk stratification and predicting prognosis.

Similar results were reported by other authors (11–15). Researches showed that there is a significant correlation between the CRP with an increased risk of cardiovascular death. CRP is an indicator of long-term development of heart failure and mortality in patients with AMI and provides prognostic information that does not provide traditional risk factors and the degree of systolic dysfunction. The value of CRP on admission is an independent indicator of mortality within 30 days and the development of heart failure in patients with AMI. These data suggest that inflammatory processes may play a role in the development of heart failure and death after myocardial infarction, independent of other traditional prognostic factors.It can be concluded that the values of CRP have prognostic significance for the development of complications after AMI. The values of troponin I have no significance for the development of complications after AMI.

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Troponin i C-reaktivni proteini u stratifikaciji rizika nakon infarkta miokarda

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SAŽETAK

Cilj ove studije bio je da se ispita prognostički značaj troponina I, C-reaktivnog proteina i faktora rizika za pojave komplikacija nakon infarkta miokarda.

Vrednosti troponina I i C-reaktivnog proteina analizirane su kod 38% bolesnika sa komplikacijama (postinfarktna angina, ventrikularna fibrilacija, srčana insuficijencija i fatalni ishod) i kod 62% bolesnika bez komplikacija. Vrednosti su zabeležene nakon prijema i između osmog i desetog dana hospitalizacije.

Utvrđeno je da je sa komplikacijama značajno bio udružen veći broj faktora rizika ($p = 0,00$), dijabetes melitus ($p = 0,02$) i pušenje ($p = 0,01$). Pokazalo se da hipertenzija povećava rizik od razvoja srčane insuficijencije nakon akutnog infarkta miokarda ($p = 0,02$). Rezultat je statistički značajna razlika u posmatranim vrednostima troponina I između grupe bolesnika sa komplikacijama i bez njih ($p = 0,22$; $p = 0,327$). Utvrđena je statistički značajna razlika u posmatranim vrednostima C-reaktivnog proteina kod obe grupe bolesnika ($p = 0,00$; $p = 0,01$).

Može se zaključiti da vrednosti troponina I nisu imale prognostički značaj u stratifikaciji rizika, dok su vrednosti C-reaktivnog proteina, pojedinačnih faktora rizika i veći broj faktora rizika imali značaj u stratifikaciji rizika nakon infarkta miokarda.

Ključne reči: **infarkt miokarda, troponin I, C-reaktivni protein, faktori rizika**