Association of Inflammatory and Hemostatic Parameters With Values of High Sensitive Troponin in Patients With Acute Coronary Syndrome

Sehveta Mustafic, Alma Mujic Ibralic, Daniela Loncar

ABSTRACT

Background: Acute coronary syndrome (ACS) includes a group of different clinical conditions resulting from acute ischemia and/or myocardial necrosis and may manifest as: unstable angina pectoris, acute myocardial infarction without and with ST-segment elevation on electrocardiography (ECG), or as sudden cardiac death. Their mutual differentiation is based on clinical findings and ECG characteristics, on laboratory confirmation or exclusion of myocardial necrosis on the basis of obtained values of highly sensitive and specific cardiac troponins T or I. Troponin I is a widespread marker in clinical use that possesses almost 100% specificity for myocardial tissue and is used as a highly sensitive marker even in the case of microscopically small lesions of cardiac tissue necrosis.

Objective: To investigate the association of inflammatory and hemostatic parameters with values of high sensitive troponin I (hsTnI) in patients with acute coronary syndrome.

Methods: The prospective study included 82 patients with a clinical condition of acute coronary heart disease (stable angina pectoris 23, acute coronary syndrome 59, of which 35 had non-STEMI elevation infarction and 24 had ST-segment elevation infarction (STEMI). The values of hsTnI had been measured in all patients and correlated with values of inflammatory (c reactive protein-CRP, leukocytes, neutrophils, lymphocytes, neutrophil/lymphocyte ratio) and hemostatic (platelet counts, mean platelet volume-MPV) parameters.

Results: Patients with acute coronary syndrome had significantly higher values of hsTnI, and inflammatory parameters: CRP, leukocytes and neutrophils (absolute number and percentage) as well as the neutrophil/lymphocyte ratio compared to patients with stable angina pectoris. In patients with ACS, hsTnI has significantly correlated with CRP (r=0.5; p=0.00), leukocytes (r=0.3; p=0.020) and absolute neutrophil count (r=0.27; p=0.039). In patients with non-STEMI, a significant correlation was found between hsTnI and MPV (r=0.359; p=0.034), while in the STEMI group a significant correlation existed between hsTnI and CRP (r=0.422; p=0.042) and neutrophil/lymphocyte ratio (r=0.511; p=0.011).

Conclusion: Markers of inflammation may help in early risk stratification in patients with acute coronary syndrome.

Keywords: myocardial infarction, CRP, leukocytes, platelets, MPV.

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the pathogenesis of atherosclerosis. Numerous studies indicate the role of inflammation as a key pathogenetic mechanism in all stages of this disease, from initiation through the progression of atherosclerosis and ultimately to thromboembolic complications of the disease itself (3). Inflammatory cells (monocytes, neutrophils, mast cells), platelet activation, coagulation cascade and platelet-fibrin clot formation are of central importance in this process (4).

Since numerous cellular and molecular mechanisms contribute to the development of atherosclerosis, and in the center of the pathogenetic mechanism is inflammation, there is the question of the role of individual mediators of inflammation and their application in cardiovascular risk assessment.

2. OBJECTIVE

The aim of this study has been to determine the values of inflammatory (CRP, leukocyte count, neutrophil count and proportion, lymphocyte count and proportion, neutrophil / lymphocyte ratio) and hemostatic (platelet count and mean platelet volume-MPV) parameters in patients with clinical suspicion of acute coronary events, and correlating them with the obtained values of hsTnI to predict what type of ACS it is.

3. PATIENTS AND METHODS

The prospective study has included a total of 82 patients who came to the Admission Clinic of the Internal Clinic of the University Clinical Center (UCC) Tuzla with a clinical presentation of acute coronary heart disease. According to the consensus of the European Society of Cardiology (ESC), the diagnosis of the disease was made on the basis of: anamnesis and clinical picture, ECG findings and hsTnI values (1).

Based on the findings, patients were divided into 2 groups: a) patients with stable angina pectoris—control group; b) patients with acute coronary syndrome (patients with unstable angina pectoris, non-STEMI and STEMI infarction)—examined group. The examined group was divided into 2 subgroups: a) patients with STEMI infarction; b) patients with non-STEMI infarction and unstable angina pectoris.

In all patients, in relation to the type of acute coronary syndrome and hsTnI values were evaluated: CRP concentration, total leukocyte count, total neutrophil count and proportion, total lymphocyte count and proportion, neutrophil/lymphocyte ratio, platelet count and mean platelet volume. hsTnI values (normal: women <15.6 pg/ml; men <34.2 pg/ml), CRP (normal <3.3 mg/l), total leukocyte count (normal: 3.4-9.7 x10⁹/l), total lymphocyte count (normal: 20-46%), and platelet count (normal: 158-424 x10⁹/l) and MPV (normal: 6.8-10.4 fl) were analyzed from venous blood samples of patients taken immediately after the diagnosis of acute coronary heart disease by the attending physician of the Admission Clinic of the Internal Clinic of the University Medical Center Tuzla. The analysis was performed in the Department of Biochemistry of the Polyclinic for Laboratory Diagnostics, University Medical Center Tuzla. The concentration of hsTnI and CRP was determined on the immuno-biochemical analyzer Architect ci8200 by Abbot Diagnostics, and the number of leukocytes, individual subpopulations of leukocytes, platelet count and MPV on the hematology analyzer XN-1000 by Sysmex. For the purposes of the examination, data from the patient card of the hospital and laboratory information system of the University Medical Center Tuzla were used. Patients with recent surgery, patients with known malignancy, and patients with proven systemic or inflammatory disease were excluded from the study.

Statistical analyses

Standard methods of descriptive statistics (measures of central tendency, measures of dispersion) are used in the statistical processing of results. All variables were tested for normal distribution using the Kolmogorov-Smirnov test and histogram. For testing the statistical significance of differences between samples, parametric and nonparametric significance tests were used, as well as the linear correlation method. Quantitative variables were compared by t-test with correction for unequal variances where they were distributed by normal distribution. For comparison between more than 2 groups, analysis of variance (ANOVA) with the Tukey post-hoc test was used. Category variables were analyzed by χ²-test, with Yates continuity correction for 2x2 tables. Correlations between significant variables were made by parametric Pearson correlation. The difference between the samples was considered significant if a level of statistical significance of p <0.05 was reached. Statistical processing was done in the software package SPSS 23.0 (Chicago, IL, USA).

4. RESULTS

Out of the 82 patients, 28% (23/82) had stable angina pectoris and 72% (59/82) had acute coronary syndrome, of which 59.32% (35/59) had infarction without ST-segment elevation (non-STEMI) and 40.68% (24/59) had ST-elevation infarction (STEMI). The mean age (± SD) of all patients was 62 (±15) years ranging from 16 to 87 years, with a male dominance of 1.65:1 versus female; men 51 (62%), women 31 (38%). Patients with acute coronary syndrome (non-STEMI and STEMI) were older compared to the group with stable angina pectoris (p=0.002). Patients with stable angina pectoris 52.83±18.77 versus 65.77±8.86 years patients group with non-STEMI, and versus patients with STEMI 65.67±14.64 years (p=0.002, both). There was not differences between non-STEMI and STEMI group in age (p=1.0).

By comparing all examined biochemical and hematological parameters between patients with acute coronary syndrome (STEMI and non-STEMI) and the group of patients with angina pectoris, significant differences have been found in the values of hsTnI, CRP, leukocytes and neutrophils in absolute numbers, neutrophils and lymphocytes in percentage and neutrophil/lymphocyte ratio between examined groups (Table 1).
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5. DISCUSSION

Cardiovascular diseases are the leading cause of death and one of the most important public health problems in the world. ACS is a life-threatening manifestation of atherosclerosis caused by rupture or erosion of atherosclerotic plaque and it is usually accelerated by acute thrombosis, with or without concomitant vasocostriction, resulting in a sudden and critical decrease in blood flow. The division within the ACS, based on ECG findings, into non-STEMI and STEMI largely coincides with the pathophysiology of the critical coronary lesion and determines the mode of treatment in these patients. STEMI is usually caused by complete atherothrombotic blockage of one of the epicardial coronary arteries and requires urgent percutaneous reperfusion, while in non-STEMI is usually high-grade stenosis or so-called percutaneous reperfusion and fibrinolytics are not indicated. On the other hand, differentiation based on the clinical picture of non-STEMI patients with high risk of myocardial infarction from patients with stable angina pectoris and low risk of infarction is not possible, and the ECG finding is not specific. For this reason, it is necessary, on the basis of other findings, primarily hsTnI, to make a risk stratification for patients and to start an adequate therapeutic approach as soon as possible.

Troponin release predominantly occurs due to two mechanisms. Exposure to plaque content results in platelet activation and aggregation. These aggregates are unstable and lead to distal embolization with microcalcifications followed by troponin release. Further progression to coagulation

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Angina pectoris</th>
<th>Non-STEMI*</th>
<th>STEMI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/L)*</td>
<td>0.501</td>
<td>-0.118</td>
<td>0.422</td>
</tr>
<tr>
<td>Leukocytes (x10^9/l)</td>
<td>0.303</td>
<td>-0.148</td>
<td>0.251</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>0.270</td>
<td>-0.199</td>
<td>0.261</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>-0.052</td>
<td>0.160</td>
<td>-0.357</td>
</tr>
<tr>
<td>Neutrophil/lymhpctye ratio</td>
<td>0.084</td>
<td>0.525</td>
<td>0.125</td>
</tr>
<tr>
<td>Platelets (x10^9/l)</td>
<td>-0.204</td>
<td>-0.184</td>
<td>-0.318</td>
</tr>
<tr>
<td>MPV (fL)*</td>
<td>0.182</td>
<td>0.359</td>
<td>0.122</td>
</tr>
</tbody>
</table>

Table 2: Correlation of examined biochemical and hematological parameters with hsTnI values in different forms of coronary heart disease. a) non ST-segment elevation infarction; b) ST-segment elevation infarction; c)Pearson correlation coefficient; d) c-reactive protein; e) mean platelet volume
cascade activation results in fibrin thrombus formation with blood vessel occlusion and a zone of necrosis in the area supplied by that artery, which is again accompanied by troponin release. Therefore, the pathologically elevated absolute value of troponin, as a highly sensitive and specific marker for myocardial tissue, may serve in the clinical gradation of disease risk in patients with ACS. In addition, increased cardiac troponins have a strong prognostic value for mortality in patients with acute coronary syndrome without ST elevation (5). In patients with clinically documented acute coronary syndrome, even a small increase in hsTnI and TnT concentrations identifies high-risk patients who will benefit most from early coronary angiography and revascularization (6). In our study, elevated hsTnI (> 15.6 pg/ml in women, and >34.2 pg/ml in men) was found in all patients with acute coronary syndrome, and significantly higher values were observed in patients with STEMI infarction compared to patients with unstable angina pectoris and non-STEMI infarction which is consistent with literature data. In the complex process of atheroma rupture, inflammation has been shown to be a key pathophysiological factor. Inflammation is crucial in the initiation and progression of atherosclerosis, but also in the destabilization and rupture of atherosclerotic plaque, which leads to acute cardiovascular events (7). Leukocytes, macrophages, dysfunctional endothelial cells, and smooth muscle cells of the intima play a major role (8); and among some already known markers of inflammation, the C-reactive protein was highlighted, specially measured by methods for determining very low concentrations of so-called high sensitive-hsCRP. Elevated values of various mediators of inflammation, especially CRP, are predictors of cardiovascular events, and CRP itself is a strong indicator of overall vascular risk (9).

The most important feature of leukocytosis in patients with acute coronary syndrome is an increased number of neutrophils, and their activation is one of the features of this event. Elevated neutrophil counts also mean increased cardiovascular risk. In the study by Horn et al (10) it has been showed that relative neutrophilia along with lymphopenia is associated with increased cardiovascular risk. Neutrophils may also play a crucial role in plaque rupture itself by releasing superoxide radicals, proteolytic enzymes, and arachidonic acid metabolites (11). Pathological studies have shown a much higher infiltration of macrophages and neutrophils in unstable plaques, in contrast to stable plaques with their dominance in the area of plaque rupture (12, 13). An increased number of neutrophils in patients with acute myocardial infarction is associated with the early development of congestive heart failure, and absolute and relative neutrophilia were predictors of poorer reperfusion after primary coronary angioplasty and thrombolytic therapy in patients with acute ST-elevation infarction. The neutrophil-to-lymphocyte ratio proved to be a particularly sensitive and reliable parameter. This ratio has been associated with increased long-term mortality in patients undergoing percutaneous coronary interventions, and as an independent indicator of death or myocardial infarction in high-risk patients (14, 15). Whereas the total plasma lymphocyte count in patients with ACS is reduced, and the CD4 / CD8 ratio is also significantly reduced, this reduction in lymphocytes reduces the body’s anti-inflammatory capacity, creating a short-term inflammatory status (16). On the other hand, lymphocyte apoptosis has been shown to further increase arterial stiffness (17). Our study also showed an increase in the number and proportion of neutrophils, as well as increased values of the ratio of neutrophils and lymphocytes (NLR) with a decrease in the number and proportion of lymphocytes, which confirms that these parameters, especially the NLR ratio as a cheap, easily available, biomarker may serve as an additional tool for assessing cardiovascular risk in clinical practice.

The role of CRP in the pathogenesis of atherosclerosis has been the subject of numerous studies. The findings to date indicate the proatherogenic and proinflammatory role of C-reactive protein in all stages of cardiovascular disease, from initial, asymptomatic atherosclerotic plaques to clinical manifestations and adverse cardiovascular events. CRP itself can activate phagocytic cells and is also involved in the removal of apoptotic cells from the body, the process of atherosclerosis, and has been identified as a mediator of organic damage during myocardial infarction (18) The synthesis of CRP in the liver is mainly controlled by interleukin 6 (IL-6), which also stimulates intrahepatic fibrinogen synthesis and stimulates megakaryocyteopoiesis to achieve a procoagulant effect on platelets (19). Numerous studies have been conducted emphasizing its potential role as a predictor of cardiovascular risk and the possible goal of therapeutic interventions in the prevention of adverse cardiovascular events (20). There is evidence that CRP is directly involved in the process of atherogenesis, and it has also been found in arterial plaque itself (21). Numerous prospective cohort studies have shown that elevated hsCRP values are associated with an increased risk of developing coronary heart disease in both sexes (22). The first prospective study of the association between CRP and coronary heart disease risk was published in 1996, as part of the MRFIT study (The Multiple Risk Factor Intervention Trial) (23) Since then, more than 40 similar studies of the association between CRP and coronary heart disease risk have been published (24). Riedker et al (25) confirmed in a large epidemiological study the role of CRP as a predictor of cardiovascular events associated with coronary heart disease. According to Madjid et al (22) values <1.0 mg/l represent low risk, values 1.0-3.0 mg/l moderate risk and values >3.0 mg/l high risk for coronary heart disease. Data from the Framingham study show that measuring hsCRP and using it as an additional risk factor, in addition to traditional cardiovascular risk factors, improves the ability to predict the outcome of coronary heart disease by 11.8% (26). Compared with other cardiovascular risk factors (triglycerides, LDL-cholesterol, homocysteine, lipoprotein A, apoprotein A), the predictive value of hsCRP was more significant (27). CRP can be elevated in all clinical forms of coronary heart disease. Elevated values were
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found in seemingly healthy asymptomatic individuals, patients with stable angina, those with acute coronary syndrome (unstable angina and myocardial infarction), and those after myocardial infarction. An increase in values shortly after the onset of symptoms confirms the hypothesis of the role of the inflammatory mechanism in acute coronary syndrome (28). In myocardial infarction, necrosis of the heart muscle occurs, which stimulates the formation of CRP. CRP rise is proportional to the degree of necrosis of the heart muscle, and peaks after the second day of infarction (29). Studies have shown that the measurement of hsCRP, during hospital admission as well as hospital discharge, in patients with acute coronary syndrome is significant, especially in the prediction of future complications or new events. Elevated values indicate a higher risk for the development of future cardiovascular events. It has been confirmed that CRP can be used as independent predictors of risk and, in combination with troponin, provides even better insight into a patient’s cardiovascular risk (27). Also in our study, the values of circulating CRP in the group of patients with unstable angina or myocardial infarction tended to increase and were significantly higher compared to patients with stable angina.

Activated platelets play a key role in the formation of arterial thrombus. They precipitate at the site of unstable plaque rupture and release strong platelet agonists such as adenosine 5’-diphosphate (ADP), serotonin, thromboxane A2, and superficial thrombin, which leads to additional accumulation, activation and aggregation of platelets, and consequently reduce their number in the blood (30). MPV has been accepted as an indicator of platelet activation, and as a prognostic factor in coronary heart disease (31). Increased MPV could be responsible for prothrombotic condition that leads to thrombus formation after rupture of coronary atherosclerotic plaque. Elevated MPV values have been reported in acute myocardial infarction, and have been an independent risk factor for the development of recurrent coronary events and death. Therefore, the presence of a large number of large platelets is probably a risk factor for coronary thrombosis and myocardial infarction, which can be easily determined during routine hematological analysis using automatic cell counters (32). At the beginning, MPV is a strong independent prognostic factor of poor perfusion and mortality in patients with acute myocardial infarction with ST-elevation treated by primary percutaneous coronary intervention (33). In one study, MPV was a reliable indicator of restenosis in patients undergoing percutaneous coronary angioplasty, and in patients with acute infarction, it was also associated with more frequent development of heart failure or mural thrombus formation (34). However, no changes in MPV were found in patients that would depend on infarct location or coronary disease prevalence, but MPV values were higher in patients with unstable angina pectoris compared with patients with stable angina (35). Clinical studies have unequivocally shown that MPV is a simple and easily accessible marker of the severity and outcome of coronary heart disease, although this was not confirmed by the results of our study considering relatively small number of respondents. The average platelet volume, as an indicator of platelet activity, was negatively related to platelet count (r=0.33, p<0.001), and was positively correlated with CRP values and total number of leukocytes, neutrophils, neutrophil content, and neutrophil to lymphocyte ratio (r=0.15-0.18, p <0.0019).

6. CONCLUSION

Troponin values are one of the decisive criteria in risk stratification and decision-making when it comes to therapeutic approach to a patient with acute coronary syndrome. Inflammation, systemic and local, plays an important role in the development of acute coronary syndrome. The inflammatory process itself determines the stability or instability of the plaque, which coincides with the pathophysiology of the critical coronary lesion and determines the way of their treatment. Markers of inflammation in acute coronary syndrome can help stratify risk and identify patients who may benefit from certain types of therapy.

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