Original article

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BLEEDING RISK FACTORS IN ACUTE CORONARY SYNDROME

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The modern treatment of patients with acute coronary syndrome (ACS) is justified and effective, but carries a higher risk of bleeding. The study aimed to determine the basic risk factors for bleeding and included 177 patients with ACS who were hospitalized at the Clinic for Crdiology Niš, in the period from May to September 2013. Based on the presence of bleeding, patients were first divided into patients with bleeding and patients without bleeding. Patients with bleeding were further divided into patients with significant bleeding and patients with less significant bleeding. The study took into account: demographic and anamnestic data, a form of ACS, basic laboratory tests and applied therapy for ACS. In the group of patients with bleeding, there were statistically significantly more non-smokers (χ^2 = 6.527, p = 0.038), patients with chronic kidney disease (CKD) (χ^2 = 4.192, p = 0.041) and patients with higher CRP values (p = 0.039). In the subgroup of patients with significant bleeding, there were a statistically significantly more frequent patients with CKD (36.4% vs. 6.5%, Fisher's tests: p = 0.007) and higher CRP values (z = 2.452, p = 0.014). In the subgroup of patients with less significant bleeding, the values of hemoglobin (t = 3,496, p = 0,003) were statistically significantly lower compared to other patients. It is interesting to note that the values of hemoglobin, creatinine clearance, and leukocyte count (as a parameter of inflammation) are variables of the PRECISE-DAPT scoring system that appeared in 2017, after our study. *Acta Medica Medianae 2023;62(2): 5-14.*

Key words: *acute coronary syndrome, bleeding, risk factors*

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Introduction

According to the current data from the World Health Organization (WHO), coronary heart disease (CHD) is the leading cause of death in the world and is responsible for 16% of all deaths. In Europe, CHD kills almost 1.8 million people a year, accounting for 20% of the total annual mortality rate. (1, 2)

Acute coronary syndrome (ACS), as the most severe form of CHD, is a life-threatening condition that requires urgent hospitalization and appropriate therapy. (3) According to the NHANES (National Health and Nutrition Examination Survey) from 2013 to 2016, the overall prevalence of myocardial infarction in the United States (USA) over the age of 20 was 3.0%, namely 4.0% for males and 2.3% for females. (4)

The treatment of patients with ACS is rapidly changing and improving with the advent of newer, more potent antithrombotic agents. A more aggressive antithrombotic therapeutic approach, aimed at reducing mortality, is justified and effective but carries a higher risk of bleeding, which is relatively common in routine clinical practice (5, 6, 7).

Until recently, bleeding in ACS (except for intracranial hemorrhage) was not given much importance, because it was considered that these complications were easily resolved and did not affect the prognosis. Today, based on numerous data, it is known that bleeding in ACS has a great

impact on mortality within 30 days and other adverse events. In the Global Registry of Acute Coronary Events (GRACE) registry, significant bleeding was associated with an increased risk of in-hospital mortality and proved to be an independent predictor of mortality (8). Minor bleeding usually does not require medical attention during the acute phase, however, there is evidence that it also has an impact on mortality and ischemic events, but to a lesser extent (8).

Accordingly, it is very important to define risk factors for bleeding, assess the individual risk for the patient, and based on that choose the appropriate therapeutic approach (invasive or conservative, stent type, as well as the appropriate choice of antithrombotic drugs), which would minimize the risk of bleeding and provide the best therapeutic efficacy (8, 9).

The aim of the research

The study aimed to determine the basic risk factors for bleeding and their relationship.

Respodents and methods

The study included 177 patients diagnosed with ACS who were hospitalized at the Clinic for Cardiology in Niš, in the period from May 15 to September 10, 2013. There were 120 men (67.8%) and 57 women (32.2%) in the study population. The average age of the examined population was 63.79 ± 12.30 years (min - 26, max - 90 years). The diagnosis of ACS included both patients with myocardial infarction (IM) and ST-segment elevation (STEMI) and those without ST-segment elevation (NSTEMI), and with unstable angina pectoris (UA). Based on the presence of bleeding during hospitalization, patients were first divided into two groups: patients who had bleeding and patients who did not have bleeding. Within the group of patients with bleeding, based on the ACUITY criteria (Acute Catheterization and Urgent Intervention Triage strategy) definition of bleeding, patients were further divided into patients with significant (major) bleeding and patients with less significant (minor) bleeding. The study took into account: demographic data of patients, body weight at admission and BMI, anamnestic data, a form of ACS (STEMI, NSTEMI, UA), values of systolic and diastolic blood pressure at admission, basic laboratory tests, and complete blood count, applied therapy for ACS.

Statistical data processing

The collected data were coded and entered into a specially formed database. Statistical processing was performed in the software package SPSS 16.0. The t-test, χ^2 test, or Fisher's test of exact probability (if the absolute frequency was less than 5) and Mann-Whitney's U test were used. The statistical hypothesis was tested at the level of significance for the risk of $\alpha = 0.05$, i.e. the difference between the samples is considered significant if $p < 0.05$. Logistic regression analysis was used to prove potential risk factors for bleeding.

Research results

The number of smokers and non-smokers was equal in the examined population (38.4%). No patient had a history of previous bleeding, and one patient had a history of previous thrombosis (0.6%). Five patients (2.8%) had a history of a previous ulcer. The prevalence of diabetes mellitus in the study population was 28.8%, and the prevalence of hypertension was 77.4%. Fifteen patients (8.5%) had chronic kidney disease (CKD) history.

In the study population, there were 23 patients (13.0%) with bleeding, of which 11 patients (6%) had significant bleeding, and 12 patients (7%) had less significant bleeding (Figure 1).

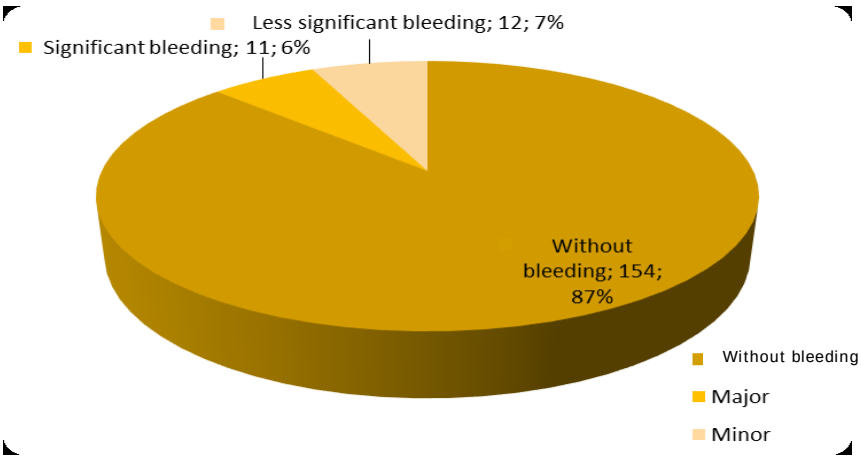

Figure 1. The prevalence of bleeding in the examined population

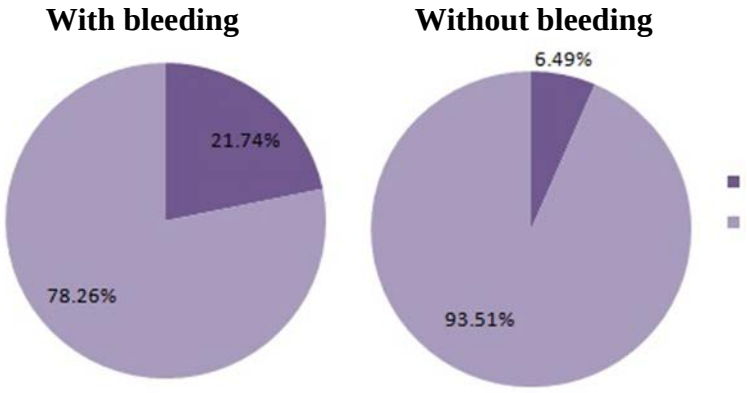

Figure 2. The presence of CKD history in relation to the occurrence of bleeding

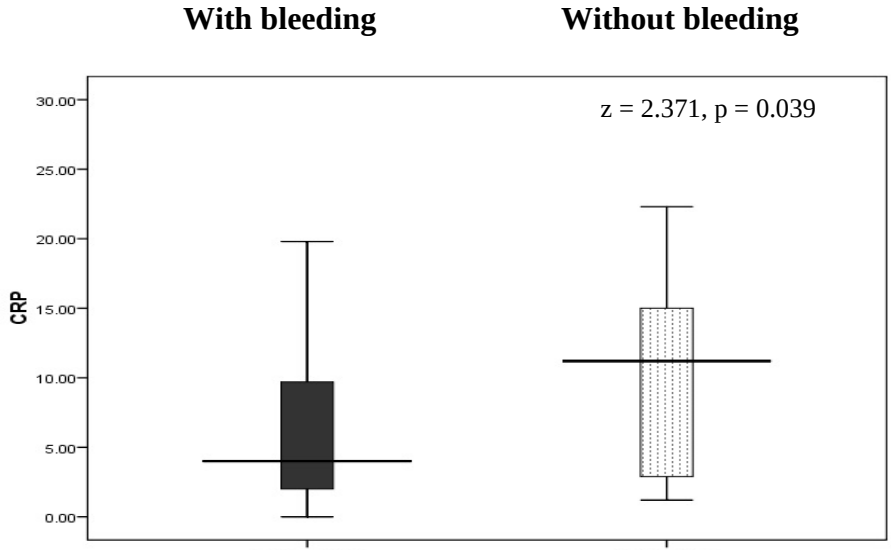

Figure 3. CRP values in relation to the occurrence of bleeding

In the group of patients with bleeding, there were statistically significantly more non-smokers (χ^2 = 6.527, p = 0.038). Further, the anamnesis of chronic kidney disease (CKD) was statistically significantly more frequent in patients with bleeding, compared to other patients (χ^2 = 4.192, p = 0.041) (Figure 2).

Likewise, in the subgroup of patients with significant bleeding, it was shown that patients with significant bleeding had a statistically significantly more frequent history of CKD compared to other patients (36.4% vs. 6.5%, Fisher's tests: p = 0.007). Comparing other demographic and clinical parameters concerning the occurrence of bleeding, no statistically significant difference was found.

It was determined that there was no statistically significant difference in the values of systolic and diastolic blood pressure, body weight, and laboratory tested parameters concerning the occurrence of bleeding, except for the value of C-reactive protein (CRP), which was statistically significantly higher in patients with bleeding compared to patients without bleeding (p = 0.039) (Figure 3).

Similarly, in the subgroup of patients with significant bleeding, CRP values (z = 2.452, p = 0.014) also proved to be statistically significantly higher compared to patients without bleeding. The values of other examined parameters did not differ statistically significantly in the occurrence of significant bleeding. In the univariate logistics model, CRP stood out as an independent risk factor (OR 1.014, p = 0.036). Non-smokers have a 5 times higher risk of bleeding than smokers. These statistically significant risk factors were then included in a multivariate logistic regression in which CRP was singled out as a statistically significant factor (OR 1.013, 95% CI 1,000-1.026, p = 0.047).

In the subgroup of patients with less significant bleeding, the values of hematocrit (t =

3.376, p = 0.004) and hemoglobin (t = 3.496, p = 0.003) were statistically significantly lower compared to patients without bleeding. Decreases in hemoglobin and hematocrit have been identified in the univariate statistical model as independent risk factors for the development of minor bleeding. These two risk factors did not prove statistically significant in the multivariate model. The values of other examined parameters did not differ statistically significantly compared to the occurrence of less significant bleeding.

It was shown that there is a statistically significant difference in the occurrence of bleeding in relation to certain forms of ACS (χ^2 = 4.12, p = 0.042). Patients with bleeding (87.0%) have statistically significantly more frequent STEMI compared to patients without bleeding (63.0%). In the bleeding group, one patient (4.3%) had newly developed atrial fibrillation (AF) and two patients had previously had AF. In the group of patients without bleeding, five patients (3.2%) had newly developed AF, and four had AF from before. No statistically significant difference was found in the frequency of newly developed AF (p = 0.572) and AF from earlier (p = 0.175) in relation to the occurrence of bleeding.

All patients from both groups received initial doses of aspirin and clopidogrel with gastroprotective therapy, at the first contact with the medical service. Patients received appropriate doses of anticoagulant therapy (unfractionated heparin or enoxaparin) according to the European guideline for ACS treatment. PCI was used in 16 patients with bleeding (69.6%) and 109 patients without bleeding (70.8%). It was determined that there is no statistically significant difference in the frequency of PCI, in relation to the occurrence of bleeding (p = 0.899).

In the subgroup of patients with less significant bleeding, it was shown that they were statistically significantly more likely to receive fibrinolysis and subsequent PCI during hospitalization compared to patients without bleeding (Fisher's test: p = 0.026).

Discussion

A review of the existing literature in order to find data related to the prevalence and risk factors for bleeding in ACS in our country did not provide the required data. The results of this research were viewed mainly in the light of data from large registers and studies.

The effect of smoking on bleeding

Smoking leads to numerous harmful effects that are manifested on both the cardiovascular system and the body as a whole. Endothelial dysfunction, dyslipidemia, elevated levels of inflammatory markers, and altered rheological properties of the blood are just some of the mechanisms that classify smokers as people at an increased risk for the occurrence and development of ischemic heart disease (10–14) .

By processing the data of a large number of studies and registers, it was shown that smokers with ACS had a higher risk of bleeding. Smoking, as a risk factor for bleeding, is also one of the variables of some scoring systems for assessing the risk of bleeding (15, 16). Smoking also affects certain drugs used in ACS. Thus, smoking affects the metabolism of clopidogrel by inducing cytochrome P450 (CYP) 12A, which converts clopidogrel to its active metabolites, and leads to a greater degree of inhibition of platelet activity (17). Some authors have shown that smokers on clopidogrel have a higher risk of bleeding, moderate to severe, but some claim that such patients are not at increased risk (10, 18).

In the examined population, it was shown that bleeding was significantly more frequent among non-smokers. In addition to numerous publications where smoking is a risk factor for bleeding, there is also a certain number of publications, in which bleeding is more common in non-smokers, as it is in our study. By analyzing the basic characteristics of patients in the GUSTO I study, which included 41,021 patients with ACS, Berkowitz et al. showed that bleeding was more common among non-smokers (19). Al-Mallah and his colleagues examined the predictors of GIT bleeding and showed that it was more common among non-smokers (20). Examining the effects of clopidogrel in ACS in smokers and non-smokers, Sibbald et al. showed that there was no greater reduction in adverse events in smokers compared to non-smokers and that major bleeding was less common among smokers (18). There are several mechanisms, which could explain the more frequent bleeding among non-smokers. Namely, due to the effects that smoking has on the cardiovascular system, primarily the occurrence of endothelial dysfunction, dyslipidemia, accelerated atherosclerosis, and increased thrombogenicity, smokers get coronary heart disease earlier than non-smokers do. Because they are younger, they usually have fewer comorbidities. Non-smokers who get coronary heart disease are in most cases older (which is the case in the study population) and have more comorbidities (DM, CKD, HTA) that were involved in the development of coronary heart disease, and which are also risk factors for bleeding. In addition, as they get older, they are at a higher risk of bleeding, because the patient's age is an independent predictor of bleeding (8). Given that thrombogenic factors are increased in smokers, then they could be expected to have a lower risk of bleeding than non-smokers. In addition, they may be less likely to have anemia that is a risk factor for bleeding because they often have polycythemia as a compensatory mechanism. Toss and associates noticed that when dalteparin is used in patients with ACS, at a dose of 120 IU/kg twice daily, there is a higher anti-Xa activity in women and non-smokers, which

increases the tendency to bleeding. Perhaps this could also be one of the mechanisms that would explain the higher frequency of bleeding among non-smokers (21).

CRP as a marker of inflammation and a risk factor for bleeding

Elevated CRP levels, detected in the first days after myocardial infarction, may reflect an elevated systemic inflammatory response, induced by myocardial necrosis, cytokine release, and activation of the inflammatory cascade (22). In the last fifteen years, several publications have been published, where CRP is an independent predictor of a bad outcome in patients with NSTEMI. Tsakiris and associates have shown that high CRP at admission is a predictor of short-term and long-term adverse events (22). Inflammation certainly has an impact on the occurrence of adverse events in ACS, including bleeding, with some authors arguing that an elevated number of white blood cells is a more powerful predictor of adverse events, including bleeding, than CRP (23). The fact that Mehran, Nikolsky, and associates in the scoring system for assessing the risk of bleeding have included elevated leukocytes as a marker of inflammation certainly shows that the inflammatory condition is a risk factor for the occurrence of bleeding in ACS (24).

In our population, it was shown that the values of CRP were significantly higher in patients with bleeding compared to those without bleeding, as well as in the group with significant bleeding compared to patients who did not bleed. This association of CRP values with bleeding did not exist in patients with less significant bleeding. In the univariate logistic model, CRP was singled out as an independent risk factor (OR 1.014, p = 0.036), and in the multivariate logistic regression, CRP was singled out as a statistically significant factor (OR 1.013, 95% CI 1,000-1.026, p = 0.047). The mechanisms by which inflammation affects the occurrence of bleeding have not been fully elucidated. One of the possible mechanisms might be damage to the integrity of endothelial cells in the process of inflammation, damage to the vascular barrier, and an increase in vascular permeability. In addition, elevated CRP values are a marker of an inflammatory condition, and inflammation may be associated with many other conditions and comorbidities, which increases the susceptibility to bleeding. Since it has been shown that there is a correlation between CRP values and infarct severity, patients with higher CRP values, and thus more severe infarction, are more likely to have more comorbidities, which affects the severity of the disease. This primarily refers to patients with long-term DM, CKD, who have more severe heart attacks due to more extensive changes in blood vessels, and it is well known that both DM and CKD are proven risk factors for bleeding. Inflammatory markers are also elevated in anemic patients, and they are also at higher risk of bleeding. In addition, elevated CRP values are associated with exacerbations of many chronic inflammatory diseases that are more common in the elderly, and age is an independent predictor of bleeding.

Chronic kidney disease as a risk factor for bleeding

It is a known fact that the frequency of adverse events is higher in patients with varying degrees of CKD, and this relationship exists throughout the ACS spectrum (25). El-Menyar et al. have shown that CKD is associated with multiple increases in mortality in patients with ACS, namely: three times higher mortality in mild CKD, ten times higher in moderate, and as much as eighteen times higher mortality in severe CKD (25). Analysis of the GRACE registry data showed that CKD is an independent risk factor for bleeding and that the risk of significant intrahospital bleeding in renal patients increases by approximately 50% (8). Similarly, Manoukian and associates confirmed that CKD is an independent risk factor for ACS bleeding (26). The parameters of renal function are also part of the scoring systems for assessing the risk of bleeding. Thus, the values of serum creatinine are part of the scoring system of Mehran and Nikolsky, and the values of creatinine clearance are part of the CRUSADE system (24, 27). Creatinine clearance is one of the five variables included in the PRECISE-DAPT (Predicting Bleeding Complications In patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy) scoring system, which emerged after our study (28).

It is of great importance to know renal function in patients with ACS because, in patients with impaired renal function, who are at risk for bleeding, by taking appropriate preventive measures, this risk can be minimized. Choosing a radial approach over the femoral can also reduce the risk of bleeding (29).

Our study also showed that patients with a history of CKD were 5.5 times more likely to have significant bleeding than patients with normal renal function. This correlation was not confirmed in patients with less significant bleeding. Several mechanisms can be used to explain the increased risk of bleeding in patients with renal dysfunction. Circulating uremic toxins are partly responsible for platelet dysfunction, affecting both platelet activation and aggregation, as well as the interaction between platelets and the arterial wall (30). In patients with ACS and CKD, due to delayed elimination of antithrombotic drugs, which are partially or completely excreted by the kidneys, there is a high possibility of overdose with these drugs if the dose is not adjusted to renal function and therefore a higher risk of bleeding. Patients with CKD very often have associated conditions that are a cause or consequence of CKD, and which are also risk factors for bleeding, such as hypertension,

diabetes, anemia. These are often elderly patients, which in turn increases the risk of bleeding.

Anemia and the risk of bleeding

Anemia is associated with an increased risk of adverse events, which exist throughout the spectrum of coronary heart disease, including stable angina pectoris, ACS, and even in patients undergoing elective PCI (29). Low hemoglobin levels at admission are an independent predictor of mortality in acute coronary syndrome, and also a risk factor for the development of heart failure and bleeding (31). The effect of anemia on the increased risk of bleeding could be explained by several mechanisms. One of the possible explanations would be the effect of hyperdynamic circulation, as a compensatory mechanism on anemia, on the more vulnerable endothelium due to hypoxia. In addition, other risk factors for bleeding are very often present in anemic patients, which further increases the risk of bleeding.

Namely, anemic patients are mostly elderly people, in whom anemia is caused by inadequate nutrition, poor absorption of essential ingredients for normal erythropoiesis, very often occult bleeding, and it is well known that age is an independent predictor of bleeding. Anemia is more common in females, and women are also at higher risk of bleeding than men.

Very often, anemia is associated with renal dysfunction, which through several mechanisms affects the occurrence of anemia, primarily due to reduced erythropoiesis, due to lack of erythropoietin, and the presence of uremic toxins that disrupt erythropoiesis. The presence of low hemoglobin on admission may reflect the presence of undetected hemorrhagic diathesis, which leads to an increased risk of bleeding after anticoagulant and antiplatelet therapy. Anemia in chronic diseases is not uncommon, therefore, low hemoglobin on admission can be a companion of an inflammatory condition that affects the occurrence of anemia through several mechanisms, primarily negatively affecting erythropoiesis and reducing the absorption of iron from the gastrointestinal tract. Inflammation is associated with an increased risk of bleeding. The inflammatory response is an integral part of the reaction to tissue damage in myocardial infarction and can persist for several weeks. Increased cytokine production may adversely affect erythropoiesis and impair intestinal iron absorption (32).

In the study population, the values of hemoglobin and hematocrit at admission were significantly lower in patients with less significant bleeding, compared to patients who did not bleed. This correlation was not found in patients with significant bleeding, which suggests that anemia is certainly a risk factor for bleeding, with less significant bleeding being mostly puncture site bleeding in our study, which could be easily controlled, so did not become significant bleeding. Another explanation could be that some other risk factors for bleeding were probably crucial in patients with significant bleeding. Decreases in hemoglobin and hematocrit were performed in a univariate statistical model as independent risk factors for the development of minor bleeding. These two risk factors did not prove statistically significant in the multivariate model.

The association of ACS with bleeding

In the examined population, bleeding was more common among patients with STEMI form of ACS, compared to NSTEMI and APNS. These results are consistent with the results of most authors. Based on data from the ACUITY and HORIZONS AMI studies, Mehran, Nikolsky, and associates formed an evaluation system for assessing the risk of bleeding, where one of the factors to be evaluated is the presence of STEMI at admission (24). Since patients with STEMI have a fibrin-rich thrombus, they also receive reperfusion therapy, in terms of PPCI or fibrinolytics. As a result, more patients receive several antithrombotic drugs simultaneously during the first few days of myocardial infarction (33). There is also an increased risk of bleeding with invasive procedures. Patients over 80 undergoing PCI are especially at high risk of bleeding (34). The incidence of bleeding in percutaneous interventions is lowest in elective PCI and highest in primary PCI (34). Based on that, it could be concluded that STEMI patients who undergo PPCI are at higher risk of bleeding compared to NSTEMI and APNS.

The concomitant use of PCI and fibrinolysis and the risk of bleeding

Reperfusion therapy, including PPCI and thrombolysis, is a standard in the treatment of patients with STEMI. Based on the results of a meta-analysis, which included data from 23 clinical studies, PPCI proved to be much more effective than thrombolytic therapy in terms of reducing mortality, reinfarction, and stroke. However, in several patients, thrombolytic therapy remains the treatment of choice, due to the fact that PPCI is not available in many centers, where there is no possibility of rapid transport of the patient to the catheterization room (35, 36). In such cases, after thrombolysis, the patient should be transported to a PCI center as soon as possible. In case of failed thrombolysis, or if there is evidence of re-occlusion or reinfarction with recurrent ST-segment elevation, the patient should be referred to emergency rescue PCI (5). However, in addition to the benefits, rescue PCI is associated with a higher incidence of non-fatal bleeding, compared to PPCI (37). This is mainly the case of an increased incidence of minor bleeding, especially at the puncture site (38, 39).

It is not so rare that after a failed attempt to open the infarct artery, the patient develops fibrinolysis. In our study, it was shown that in

patients who received both fibrinolytic and PCI, less significant bleeding was more frequent, which is in accordance with the data from the literature. Among patients with significant bleeding, there was no significant association between concomitant PCI and thrombolysis and bleeding, which is again consistent with the literature data.

Conclusion

Bleeding in patients with ACS was more common among non-smokers.

Patients with a history of CKD, as well as patients with elevated CRP values, were also statistically significantly more likely to bleed. This association also existed in a subgroup of patients with significant bleeding.

Patients with less significant bleeding were significantly more likely to have anemia on admission compared to patients without bleeding, as well as those with significant bleeding.

Bleeding was shown to be more common in patients with STEMI ACS, and concomitant use of fibrinolysis and PCI was associated with a more frequent occurrence of less significant bleeding, mainly at the puncture site.

In the univariate logistic model, CRP stood out as an independent risk factor, and in the multivariate logistic regression, CRP stood out as a statistically significant factor.

It is interesting to note that the values of hemoglobin, creatinine clearance, and leukocyte count (as a parameter of inflammation) are variables of the PRECISE-DAPT scoring system that appeared in 2017, after our study.

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FAKTORI RIZIKA ZA NASTANAK KRVARENJA U AKUTNOM KORONARNOM SINDROMU

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Savremeni terapijski pristup kod bolesnika sa akutnim koronarnim sindromom (AKS) jeste opravdan i efikasan, ali nosi sa sobom veći rizik od nastanka krvarenja. Cilj istraživanja, koje je obuhvatilo 177 bolesnika sa AKS, hospitalizovanih na Klinici za kardiovaskularne bolesti u Nišu u periodu od marta do septembra 2013. godine, bio je utvrditi osnovne faktore rizika za nastanak krvarenja. Na osnovu prisustva krvarenja, bolesnici su najpre bili podeljeni na bolesnike sa krvarenjem i bolesnike bez krvarenja. Bolesnici sa krvarenjem dalje su podeljeni na bolesnike sa značajnim krvarenjem i bolesnike sa manje značajnim krvarenjem. Prilikom istraživanja u obzir su uzeti sledeći podaci: demografski i anamnestički podaci, oblik AKS-a, osnovne laboratorijske analize, kao i primenjena terapija za AKS. U grupi bolesnika sa krvarenjem bilo je statistički značajno više nepušača (χ^2 = 6,527, p = 0,038), bolesnika sa hroničnom insuficijencijom bubrega (HBI) (χ^2 = 4,192, p = 0,041) i bolesnika sa povišenim CRP vrednostima (p = 0,039). U podgrupi bolesnika sa značajnim krvarenjem bilo je statistički značajno više bolesnika sa HBI (36,4% prema 6,5%; Fišer test: p = 0,007) i povišenim CRP vrednostima (z = 2,452, p = 0,014). U podgrupi bolesnika sa manje značajnim krvarenjima, vrednosti hemoglobina bile su statistički značajno niže u odnosu na ostale bolesnike (t = 3,496, p = 0,003). Interesantno je pomenuti da su vrednosti hemoglobina, klirens kreatinina i broj leukocita (kao marker inflamacije) sastavne komponetnte PRECISE DAPT skoring sistema, koji se pojavio 2017. godine, nakon našeg istraživanja. *Acta Medica Medianae 2023;62(2):5-14.*

Ključne reči: *akutni koronarni sindrom, krvarenje, faktori rizika*