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ORIGINAL ARTICLE

Acute Coronary Syndrome (STEMI, NSTEMI and Unstable Angina Pectoris) and Risk Factors, Similarities and Differences

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Abstract

Introduction: Acute coronary syndrome (ACS) is one of the most common and most dramatic manifestations of ischaemic heart disease and distinguishing of ACS from non-cardiac chest pain represents a diagnostic challenge. Objective: Determine the frequency of ACS types: NSTEMI, STEMI and unstable angina pectoris (UAP) and examine the frequency and significance of risk factors and cardiospecific enzymes in patients with ACS.
Methods: The analysis included patients who were referred from the prehospital level of the Banja Luka Primary Healthcare Centre (Emergency Department and Family Medicine Department) and treated under the ACS diagnosis in the coronary unit of the Cardiovascular Diseases Clinic of the Banja Luka University Clinical Centre of the Republic of Srpska (UCCRS) in the first 6 months of 2011. The study included patients older than 18, with recorded information on their gender, age, smoking status, hypertension, diabetes, obesity and family burden. Values of cholesterol, triglycerides, serum potassium, creatine kinase (CK), CK-MB, cardiac troponin T (cTnT) were measured.
Results: The total of 192 patients were referred under the referral diagnosis of ACS and treated in the coronary unit of the CVD Clinic of the Banja Luka UCCRS. At the same time, ACS was confirmed in 178 cases. STEMI was confirmed in 86 patients (48.31 %), NSTEMI in 55 (30.90 %) and UAP in 37 (20.79 %). ACS was statistically significantly more common in men (112 men and 66 women), in particular younger men (average age for men was 62.7 and 69.2 for men and women, respectively) ($U = 2.472 \cdot 10^3$, $p < 0.001$). Among the risk factors, it was found that smoking was more often associated with STEMI ($p = 0.014$) and hypertension with UAP ($p = 0.041$). Among all parameters, all three examined cardiac biomarkers showed statistical significance ($p < 0.001$), namely: values at STEMI > NSTEMI > UAP.
Conclusion: Half of patients with ACS did not have STEMI (which is presumably easy to diagnose). Third of patients with ACS reported atypical symptoms, which further complicates the early recognition of MI without ST elevation. Precaution is needed in women and in elderly. Determination of cTnT should be available in every examination room.

Key words: Acute coronary syndrome; NSTEMI; Risk factors; CK-MB; cTnT.

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Introduction

Cardiovascular disease (CVD) is the leading cause of death globally.[1] About 17.9 million people died from CVD in 2016, representing 31 % of all deaths.[2] Slightly less than half of CVD deaths were caused by ischaemic heart disease, of which 1.8 million people die in Europe every year.[3, 4]

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About 1,500 patients with acute myocardial infarction are registered in the Republic of Srpska annually.[5]

Most CVDs are preventable by reducing risk factors. The main and independent risk factors for CVD include smoking cigarettes to any extent, high blood pressure, elevated total cholesterol and LDL-cholesterol, low HDL-cholesterol, diabetes and older age. The main risk factors have an additive effect on the occurrence of CVD.[5]

Symptom of ischaemic myocardium is pain (*angere* means strangle in Latin and thus the term angina).[6] Pain is usually described as a heavy chest pressure, tightness or squeezing, it often radiates to the left shoulder, neck, or arm. Pain is intense and prolonged for more than 30 minutes. Patients with chest pain represent a very significant part of all acute medical hospitalisations in Europe.

ACS is a consequence of subacute or acute reduction of myocardial oxygen supply due to a disruption of atherosclerotic plaque of the coronary artery with consequent thrombosis, inflammation, vasoconstriction and microembolisation.[7, 8]

ACS is one of the most common and most dramatic manifestations of ischaemic heart disease. It is defined as a set of clinical syndromes caused by circulatory disorders in coronary arteries with consequent ischaemia.[9, 10] The term ACS includes three different entities of acute manifestation of coronary heart disease: unstable angina pectoris (UAP), non-ST elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction (STEMI). The term myocardial infarction (MI) can be used in cases where there is evident myocardial necrosis within the clinical features indicating myocardial ischaemia.[11, 12] The term ACS is used because the initial demonstration and early treatment of UAP, STEMI and NSTEMI are often similar. Distinguishing ACS from non-cardiac chest pain is primarily a diagnostic challenge.[13] Despite modern treatment, the MI mortality rate and readmission of patients remains high.[14]

Based on electrocardiographic (ECG) changes, patients can be divided into 2 groups:

- Patients with typical acute chest pain and persistent (> 20 min) ST segment elevation or newly formed left branch block in ECG. These patients have acute complete occlusion of the coronary artery. In this case, it is ACS with STEMI. These patients require urgent reperfusion therapy with fibrinolytic medications or primary PCI.[14]
- Patients with acute chest pain but without persistent elevation of the ST segment or left branch block on ECG record. They have permanent or transient ST-segment depression or inversion, flattening or pseudo-normalization of the T-wave, or no changes in the ECG. The initial strategy in these patients is to alleviate the symptoms of ischemia, to monitor patients with serial ECG and to monitor markers of myocardial necrosis. Depending on the value of troponin, it will qualify as NSTEMI or UAP.[15, 16] In a certain number of these patients, coronary artery disease will be ruled out as the cause of these symptoms.

All patients coming to the emergency departments with chest discomfort and other symptoms indicative of ACS should be considered a high priority for case triage.[17] Initial evaluation includes assessment of the following parameters: patient history including risk factor assessment, physical examination, 12-channel ECG, measurement of specific cardiac biomarkers, primarily cardio-specific troponins T (cTnT) and I (cTnI).[14, 16, 18]

Chest pain is the most characteristic symptom in patients with ACS. Women, the elderly, people with diabetes and hypertension are likely to report to the emergency room later and for this reason their symptoms tend to be more frequent and non-specific.[16]

ECG is one of the most important diagnostic procedures in ACS evaluation.[19, 20] Cardiac biomarkers have revolutionised the diagnosis, risk assessment and treatment of patients with ACS. Besides, the European Society of cardiology (ESC), American College of cardiology/American heart Association (ACC/AHA) working group and the World Cardiology Federation formulated in 2007 a redefinition of myocardial infarction in which biomarkers play a central role.[21, 22] Although conventional markers of necrosis have high diagnostic value, their sensitivity is weak in the first few hours after the onset of pain.[23] Today, cTnI and cTnT are considered as markers of the highest diagnostic specificity for the final diagnosis of AIM. An increase in serum concentration is observed 3-8 hours after the onset of pain, a maximum is reached after 12-24 h and the

increased concentration is maintained for about 7-14 days. Considering that the concentration of cTnI in the serum of healthy individuals is very low, the diagnostic sensitivity of this marker is very high and it can detect even a very small myocardial damage.[14, 16, 24] If determination of myoglobin and cardiac troponin levels is not possible, it is considered that the best substituting laboratory marker is measurement of CK-MB.[16] CK-MB is an isoenzyme of creatine kinase (CK) and is much more specific for the heart than CK. Its concentration in the serum rises after 4-6 h, peaks after 12-24 h and normalises after 2-3 days.

Objective

Determine the frequency of NSTEMI in the population, relative to STEMI and UAP. To examine the frequency and significance of risk factors and cardio-specific enzymes in patients with ACS.

Methods

It was a retrospective cross-sectional study. It included patients who were referred from the prehospital level of the Banja Luka Primary Healthcare Centre (including patients from family clinics and patients from the Emergency Room) and treated under the diagnosis of ACS in the coronary unit of the CVD Clinic of the Banja Luka University Clinical Centre in the first six months of 2011.

Patients with the established diagnosis of ACS were divided into 2 groups (according to the ECG record and the present symptoms):

- STEMI ACS - Patients with typical acute chest pain (> 20 min) and persistent ST-segment elevation or newly formed left branch block in electrocardiogram. The elevated markers of myocardial necrosis have been additionally found in these patients.

- NSTEMI ACS (NSTEMI or UAP) - Patients with acute chest pain but without persistent elevation of ST segment or left branch block in electrocardiogram. They have persistent or transient ST-segment depression or inversion, flattening or pseudonormalisation of the T-wave, or no changes in the ECG. Depending on additional troponin values (whether they have elevated or normal values), they were qualified as NSTEMI or UAP.

The study included people of both sexes aged over 18. Data were taken from the medical records of patients treated in the Coronary Unit of the Clinic for CVD of UCCRS during the first 6 months of 2011. In addition to gender and age, the recorded data included smoking status, presence of hypertension, diabetes, obesity, family burden. Obesity as a risk factor existed if the Body Mass Index (BMI) was ≥ 30.0 kg/m^2.[25] The presence of hypertension or diabetes has been validated based on the use of therapy for these diseases (oral or parenteral therapy).

Laboratory parameters performed during hospitalisation were used (values of blood lipids, ie values of total cholesterol (Chol) and values of triglycerides (Tgl), potassium (K^+), and values of cardio-specific enzymes: CK, CK-MB, cTnT. CTnT were determined on the Roche Elecsys E 411 and other parameters on the Olympus AU 680. The methods used included kinetic UV test for: CK, CK-MB, enzyme staining test for: Chol and Tgl, ion selective electrical determination for: K, and immune-chemiluminescence method for cTnT. Lipid status (cholesterol and lipids) was assessed during the hospitalisation of patients, since in most cases, there were no data on previous values of the parameters mentioned.

ECGs were recorded on first encounter with doctor and ECG monitoring was performed during hospitalisation, but ECGs that were recorded at admission and at the discharge of every patient were preserved and described. At admission, the ECG was performed at the internist's outpatient clinic, and at the discharge it was performed at the coronary unit of the CVD Clinic of the Banja Luka UCCRS. In both cases, those were twelve-channel devices with a paper speed of 25 mm/s, and a correct calibration of 1 mV.

To examine the significance of the difference between the ACS type and risk factors, the category data were compared using the Chi-square test, and in the case of numerical data, the One-Way ANOVA, ie the on parametric Kruskal-Wallis H test. To examine the association of ACS and CK type, a generalised linear model was used, since the normal reference values of this enzyme were different in men and women, in order to make adjustments for the gender of the patient. The statistical conclusion was made on the basis of two-way (2-tailed) p values, as well as the level of significance $p < 0.05$. Statistical data processing was performed by using IBM SPSS 16.0 software.

Results

In the period from January to June 2011, under the referral diagnosis of ACS, a total of 192 patients were referred to the coronary unit of the CVD Clinic of the Banja Luka UCCRS. At the same time, the ACS diagnosis was not confirmed in 14 cases. The frequency of individual types of ACS and their distribution by gender is shown in Table 1.

Table 1: Frequency of individual types of ACS and their distribution by gender

ACS	N (%)	Gender	
		Female (%)	Male (%)
STEMI	86 (48.31)	56 (31.46)	30 (16.85)
NSTEMI	55 (30.90)	34 (12.36)	21 (11.80)
UAP	37 (20.79)	22 (12.36)	15 (8.43)
Total	178 (100.00)	112 (62.92)	66 (37.08)

ACS: acute coronary syndrome, STEMI: ST segment elevation myocardial infarction; NSTEMI: non-ST segment elevation myocardial infarction; UAP: unstable angina pectoris;

There was no statistically significant difference in frequencies between NSTEMI and UAP (p = 0.061), while the differences between STEMI/NSTEMI and STEMI/UAP were statistically significant with the level of significance p<0.01.

No statistically significant difference was found between individual types of ACS and patient's gender (Chi square: 0.396, p = 0.820). Men were statistically more likely to suffer from all types of ACS, but there is no difference between the types of ACS.

The average age of men was 62.72 and women 69.29. A nonparametric Mann-Whitney U test was used to analyse the significance of the mean age differences in ACS patients depending on patient's gender, as there was a statistically significant deviation of the age distribution from the normal pattern. ACS in women was found to occur in older age groups ($U = 2.472 \cdot 10^3$, $p < 0.001$).

The relationship between risk factors in individual ACS is shown in Table 2.

Smoking as a risk factor was not evaluated in 11 patients (due to absence of data in the medical records). A statistically significant difference was found between certain types of ACS and cigarette consumption ($\chi^2 = 7.279$, p = 0.026). By using Bonferroni adjustment and significance level $\alpha = 0.017$, it was found that cigarette consumption was more associated with STEMI than with UAP myocardial damage (smoking STEMI 58.2 %: smoking UAP 32.4 %) (p = 0.014).

No statistically significant difference was found between individual types of ACS and diabetes ($\chi^2 = 1.622$, p = 0.444).

No statistically significant difference was found between individual types of ACS and obesity in patients ($\chi^2 = 1.018$, p = 0.601).

A statistically significant difference was found between certain types of ACS and hypertension ($\chi^2 = 6.372$, p = 0.041). By using Bonferroni adjustment and significance level $\alpha = 0.017$, hypertension was found to be more associated with UAP than with STEMI ACS (hypertension UAP 81.1 % vs hypertension STEMI 58.1 %) (p = 0.014).

No statistically significant difference was found between certain types of ACS and positive family history in view of cardiovascular diseases ($\chi^2 = 1.630$, p = 0.443).

Table 2: Risk factors and ACS

Risk factor		STEMI	NSTEMI	UAP	Total	χ^2 test	*p* value
Tobacco use	Yes	46 (57.50)	23 (28.75)	11 (13.75)	80 (47.90)		
	No	33 (37.93)	31 (35.63)	23 (26.44)	87 (52.10)	7.279	0.026
Diabetes	Yes	20 (40.82)	18 (36.73)	11 (22.45)	49 (27.53)		
	No	66 (51.16)	37 (28.68)	26 (20.16)	129 (72.47)	1.622	0.444
Obesity	Yes	21 (53.85)	12 (30.77)	6 (15.38)	39 (21.91)		
	No	65 (46.76)	43 (30.94)	31 (20.79)	139 (78.09)	1.018	0.601
Hypertension	Yes	50 (42.37)	38 (32.20)	30 (25.42)	118 (66.29)		
	No	36 (60.00)	17 (28.33)	7 (11.67)	60 (33.71)	6.372	0.041
Heredity	Yes	20 (40.82)	18 (36.73)	11 (22.45)	49 (27.53)		
	No	66 (51.16)	37 (28.68)	26 (20.16)	129 (72.47)	1.622	0.444

ACS: acute coronary syndrome, STEMI: ST segment elevation myocardial infarction; NSTEMI: non-ST segment elevation myocardial infarction; UAP: unstable angina pectoris;

Values of lipid status and K^+ in serum depending on the type of ACS are shown in Table 3.

No statistically significant differences in cholesterol values were found depending on the type of ACS (One-Way ANOVA: F = 0.332, p = 0.718).

No statistically significant differences were determined in triglyceride values depending on the type of ACS (Kruskal-Wallis H test: χ^2 = 0.658, p = 0.720).

No statistically significant differences in K^+ concentration values were found depending on the ACS type (χ^2 = 2,858, p = 0.240).

Table 3: Lipid status and K^+ in serum depending on the type of ACS

ACS	Mean ± SD (mmol/L)		
	Chol	Tgl	K^+
STEMI	5.87 ± 1.16	2.25 ± 2.06	4.16 ± 0.54
NSTEMI	5.66 ± 1.46	1.95 ± 1.29	4.13 ± 0.55
UAP	5.67 ± 1.31	2.21 ± 1.46	4.36 ± 0.63
Total	**5.77 ± 1.50**	**2.16 ± 1.74**	**4.19 ± 0.57**

ACS: acute coronary syndrome, STEMI: ST segment elevation myocardial infarction; NSTEMI: Non-ST segment elevation myocardial infarction; UAP: Unstable angina pectoris; Chol: cholesterol, Tgl: triglycerides, K^+: potassium, Reference values: Chol: 2.8-5.2 mmol/L, Tgl: 0-1.7 mmol/L, K^+: 3.2-5.2 mmol/L

A generalised linear model was used to calculate the significance of the difference in serum creatine CK values, considering the impaired assumption on the normal distribution and homogeneity of variance (Levene test: p < 0.001). Gender adjustment was also performed as normal CK reference values are different in men and women. Statistically significant differences in CK values depending on the type of ACS were found. The highest mean CK values were found in STEMI (1,520.78 U/L), lower in NSTEMI (735.04 U/L), and the lowest in UAP (114.80 U/L) (Wald χ^2 = 8058.26, p < 0.001). All three differences were statistically significant with sequential Sidak significance p < 0.001. Biomarker values are shown in Figure 1.

Statistically significant differences in CK-MB values were found depending on the ACS type (Kruskal Wallis test, χ^2 = 72.07, p < 0.001). Mutual comparison by using the Mann-Whitney U test resulted in statistical significance (p < 0.001) among all parameters.

Highest mean CK-MB values were observed in STEMI (141.70 U/L), lower in NSTEMI (89.91 U/L) and lowest in UAP (13.36 U/L).

Statistically significant differences in cTnT values depending on the type of ACS were found (χ^2 = 87.06, p < 0.001). Mutual comparison by using the Mann-Whitney U test and in accordance with the Bonferroni adjustment and the significance level α = 0.017, all three comparisons were statistically significant (p < 0.001). The highest mean cTnT values were observed in STEMI (3,694 pg/ml), lower in NSTEMI (1,152 pg/ml), and lowest in UAP (45.68 pg/ml).

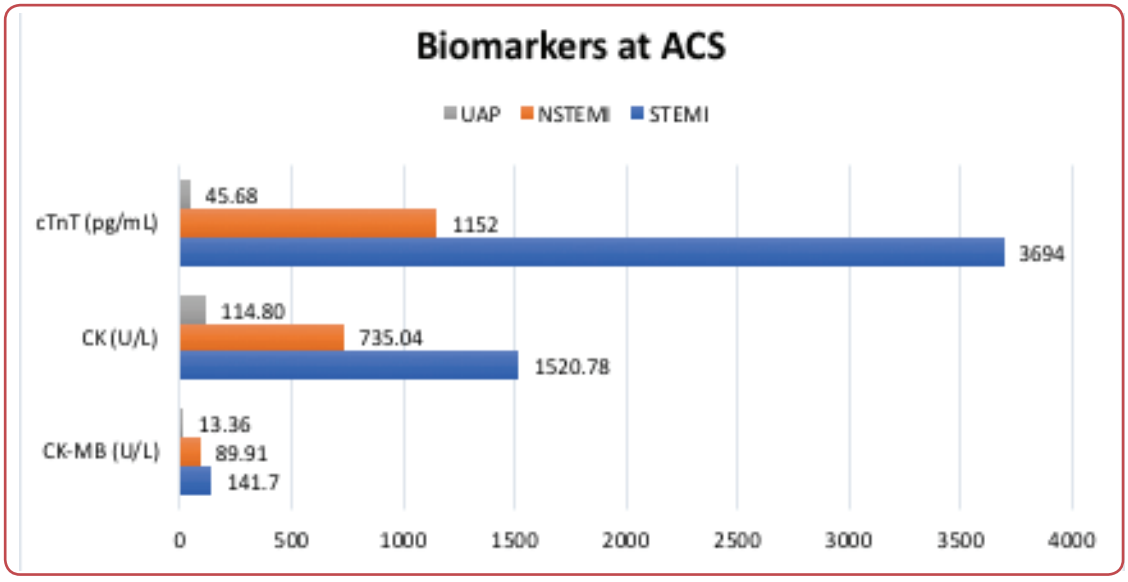

Figure 1: Cardiac biomarkers depending on the type of ACS.

ACS: acute coronary syndrome, STEMI: ST segment elevation myocardial infarction; NSTEMI: Non-ST segment elevation myocardial infarction; UAP: Unstable angina; Chol: cholesterol, Tgl: triglycerides, K^+: potassium,
Reference values: CK men up to 171 U/L, CK women up to 145 U/L, CK-MB 0-24 U/L, cTnT 12.8-24.9 pg/ml.

Discussion

In a period of six months, a total of 192 patients were referred from the Banja Luka Primary Healthcare Centre under the referral diagnosis of ACS. According to the ACS registry in Serbia, during 2009, this acute form of ischaemic heart disease was registered in 63 people every day. In the same year, 18 people died every day from acute myocardial infarction.[26]

The frequency of certain types of ACS, ie myocardial damage in this study was as follows: STEMI 48.31 %, NSTEMI 30.90 %, UAP 20.79 %. In some other studies, data showed a smaller share of STEMI in total ACS.[27, 28] These data suggest that there is a high percentage of patients with acute coronary events in whom no characteristic ST-elevation is found on the ECG. This means that medical staff, primarily doctors, must be well educated, be able to use their knowledge and available diagnostic tools to establish a timely diagnosis of ACS or to suspect ACS. The incidence of STEMI has been decreasing for years, while at the same time the incidence of NSTEMI has slightly increased, which is explained as a consequence of the introduction of biomarkers of high sensitivity and specificity, so that infarctions that affected a small part of the heart muscle were diagnosed that could not have been detected or diagnosed previously.[29-31] Encouraging trends in reducing mortality in both STEMI and NSTEMI in the first year after myocardial infarction suggest that methods of treating acute MI have improved significantly.

In this study, the age structure of patients with ACS depending on gender was also analysed. The average age was found to be 62.7 for men and 69.2 for women (average 65.16) suffering from ACS. This age breakdown corresponds approximately to the age breakdown in studies done by other authors.[32] The explanation for the fact that ASC occurs later in women, as has been established previously, relates to the protective effect of female sex hormones on the development of atherosclerotic heart disease.

Individual types of ACS were compared depending on patient's gender. No statistically significant difference was found between individual types of ACS and patient's gender, although it was found that men were more likely to suffer from all three subtypes of ACS (62.9 % vs 37.1 %), which again can be explained by hormonal differences in men and women, in addition to other risks factors, eg, higher number of male smokers. These data agree with large GRACE study data[33] covering the ten-year period, from 1999 to 2009, where approximately two-thirds of men are found in the STEMI and NSTEMI groups, as well as with other studies confirming that STEMI is more common in younger population and in men.[34-37]

Smoking, as one of the leading risk factors, has been compared with certain types of ACS. It was found that cigarette smoking was more associated with STEMI (58.2 %) than with UAP (32.4 %), while 42.5 % of patients with NSTEMI were smokers. In this study, out of 167 patients, almost half of them smoked cigarettes (N = 80), while in the Filipiak et al[38] study, 36.41 % of the examined number of patients were smokers. Different data could be explained by different lifestyle habits in different regions. In 11 patients the smoking status could not be retrieved from the documentation. Although it is just 11 out of 192 (5.7 %), as it is easy to obtain this data, this represents poor history taking. If universal information software would be implemented as planned (to all medical institutions, of every level in whole of the Republic of Srpska), it is justified to believe that would improve data management.

Of the 178 patients in this study, 49 (27.5 %) had diabetes. No statistically significant difference was found between certain types of ACS and obesity in patients. Diabetes is not only an independent risk factor for coronary heart disease, but it also has a major impact on other risk factors. More than a billion adults worldwide are overweight. Out of this number, 300 million are clinically obese. Improper diet, combined with reduced physical activity, is the cause of an increased incidence of obesity.[39]

Arterial hypertension is the most important independent factor for coronary heart disease. High blood pressure is one of the most dangerous widespread diseases of the modern age, with significant morbidity and mortality and immeasurable social and oeconomic consequences in the world and in our country. In age groups older than 20, it is present in as many as 10 - 20 % of cases.[40] Out of 178 patients, 118 (66.2 %) had high blood pressure. Hypertension was found to be more associated with UAP than with STEMI ACS (hypertension/

UAP 81.1 %, hypertension/STEMI 58.1 %, hypertension/NSTEMI 69 %). This can be explained by higher blood pressure values in UAP due to a lower degree of myocardial damage (higher left ventricular ejection fraction). Some other researchers report that in patients with ACS, the incidence of hypertension varies from 31 % to 59 %.[32] In the general population, the prevalence of hypertension increases progressively with age in both men and women. The paper of Picarella et al. of 2011 established that NSTEMI and UAP ACS associated with chronic hypertension affect about 2/3 of the population (70 % to 75 %), compared to patients with STEMI (30 % to 40 %).[41] From this perspective, the association of hypertension/NSTEMI and UAP ACS in this study and the previous study is approximately the same, while the association of hypertension/STEMI is different (30 % to 40 % in Picarella and 58.1 % in this study). The mentioned author explains the obtained results by the fact that in his study, patients with NSTEMI are older and suffering from more comorbidities compared to patients with STEMI.

Among electrolytes, K^+ was observed primarily, ie the possibility of increased K^+ levels in blood, as the most important intracellular cation, after ACS. Namely, one of the factors that leads to a tendency to cardiac fibrillation after ACS is the fact that acute cessation of myocardial blood flow causes K^+ to begin to rapidly flow out of ischaemic cells and to increase the concentration of K^+ in extracellular fluid.[42] Since 98 % of total K^+ is located in intracellular region, the assumption was that with the death of cardiomyocytes in the infarcted area, the level of K^+ in the extracellular fluid, ie in blood, would thus increase.[43] A larger increase in this intracellular ion was expected in transmural myocardial damage (STEMI) than in partial (NSTEMI). However, this study did not establish any differences in K^+ values between individual types of ACS, which can be explained by relatively low heart mass (250-300 g) in relation to the total body weight, so that heart damage is not accompanied by visible electrolyte imbalances.

The highest mean CK values were found in STEMI (1,520 U/L), lower in NSTEMI (735 U/L), and lowest in UAP (114 U/L). CK, as a non-specific biomarker, although still used, is not recommended as a diagnostic parameter for ACS.[1, 44] By observing the mean values of serum CK-MB in relation to ACS subtypes, the following conclusions were also obtained: highest mean values of CK-MB observed are in STEMI (141 U/L), lower in NSTEMI (89 U/L), and lowest in UAP (13 U/L), which corresponds to data from other sources.[45, 46] cTnT was also correlated with previous enzymes. Namely, the highest mean values of cTnT were observed in STEMI (3,694 pg/mL), lower in NSTEMI (1,152 pg/ml), and the lowest in UAP (45 pg/mL). Therefore, the largest increase in cardio-specific enzymes was in STEMI and this is explained by the fact that this type of ACS usually represents the major, transmural myocardial damage, while NSTEMI usually represents the minor, subendocardial heart damage. Slightly higher values of serum biomarkers than the reference ones in UAP are explained by comorbidities affecting these patients (most often chronic renal failure but also other diseases, such as the use of cytostatics in cancer patients, patients with autoimmune diseases, chronic alcohol addicts, etc.).

There are few limitations to this study. It is a retrospective study from the single centre and from one region, with aged data. This study could be base for prospective study with clear protocol that would eliminate limitations of this study.

Conclusion

In their daily work, doctors at the prehospital level meet with patients who have symptoms of acute chest pain. The registries show that about 30 % of patients with ACS report atypical symptoms, which further complicates the early recognition of MI without ST elevation. According to all recommendations, such patients need an ECG, cTnT, medical treatment and follow-up. Given the seriousness of this diagnosis, failure to recognise it early can even be fatal, which makes this topic even more important for the primary care physician.

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Conflict of interest

None.

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