



CORRELATES OF IN-HOSPITAL MORTALITY IN PATIENTS WITH ACUTE CORONARY SYNDROME IN KOSOVO

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SUMMARY – It has been demonstrated that pre-hospital emergency care reduces in-hospital mortality in patients admitted with acute coronary syndrome (ACS). The aim of this study was to analyze the relationship between pre-hospital emergency care and in-hospital mortality in ACS patients treated at the University Clinical Centre of Kosovo Emergency Department (UCCCK ED). This observational clinical study included 1498 ACS patients treated at UCCCK ED and followed-up by phone call for one year after discharge from the hospital. According to multivariate Cox regression analysis, age (HR=2.37, 95% CI 1.67-3.52), pre-hospital emergency care (HR=3.92, 95% CI 2.35-6.54), STEMI (HR=6.17, 95% CI 3.22-15.31), diabetes mellitus (HR=3.01, 95% CI 1.98-3.78), left ventricular ejection fraction <40% (HR=17.63, 95% CI 11.2-30.54) and ex-smoking (HR=2.34, 95% CI 1.57-3.85) were significant predictors of mortality in ACS patients. In-hospital mortality of patients admitted with ACS remains high in Kosovo as compared with developed countries. A better strategy for pre-hospital emergency care in Kosovo is recommended to save lives in these high-risk patients.

Key words: *In-hospital mortality; Acute coronary syndrome; Emergency department*

Introduction

Acute coronary syndrome (ACS) is the leading cause of cardiovascular morbidity and mortality, resulting in substantial health care utilization and costs¹. Most of deaths from ACS occur in the first few hours after the onset of symptoms, mainly from fatal arrhythmias which could be prevented by rapid access to specialized care². ACS is a clinical condition related to reduction or complete cessation of blood

flow in coronary arteries and consequently with heart muscle necrosis. An updated classification of ACS has introduced the following conditions: unstable angina (UA), ST-elevation myocardial infarction (STEMI), and non-ST-elevation myocardial infarction (NSTEMI)³. The main objective of treating patients with ACS is to re-establish myocardial perfusion within few hours from the onset of pain in order to save the ischemic myocardium and increase the chance of survival^{4,5}. The emergency physician's role in the stabilization, evaluation and treatment of the patient with ACS is critical. ACS is one of the main causes of death in Kosovo⁶, and it is among the medical emergencies that mostly benefit from an efficient pre-hospital care system⁷. Recent studies⁸⁻¹¹ have demonstrated the effectiveness of pre-hospital

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emergency in reducing the time between the onset of symptoms, diagnosis and beginning of treatment, and reducing mortality of these patients^{8,9}.

The aim of the study was to analyze the correlates of in-hospital mortality of patients with ACS treated at the University Clinical Center of Kosovo Emergency Department (UCCK ED), especially according to pre-hospital emergency care, clinical presentation as UA, NSTEMI or STEMI, and risk factors.

Patients and Methods

This observational clinical study included all consecutive patients admitted to UCCK ED for ACS. The ACS was defined according to the criteria of the 2000 Consensus Document Myocardial Infarction Redefined issued by the ESC/ACC Joint Committee¹². The inclusion criteria were clinical signs and symptoms of ACS, electrocardiography (ECG) changes, and cardio-specific enzyme blood levels. The location of myocardial infarction (MI) was determined according to ECG changes. ST elevation of more than 1 mm and increased level of troponins were denoted as STEMI, whereas ST denivelation of more than 1 mm and T wave inversion with increased level of troponins were denoted as NSTEMI. Patients were divided into two groups, depending on whether pre-hospital emergency care was used, and into three groups based on different clinical ACS presentation, i.e. UA, NSTEMI or STEMI. For the purposes of this study, we defined the pre-hospital emergency (PHE) group including those patients that were referred to the ED *via* PHE treatment, whereas all other patients regardless of the mode of transportation were included in the control group.

The research was conducted according to ethical principles and was approved by the UCCK Ethics Committee, No. 661.

Statistical analysis

Data were expressed as median and interquartile range (IQR) for continuous variables and as percentage for categorical ones. Pearson's χ^2 -test or Fisher exact test were used to test differences between categorical variables. Mann Whitney U test or Student's t-test was used to test differences between quantitative variables according to distribution. Survival was compared between the two patient groups using Kaplan Meier estimate with the log-rank test. Univariate and multivariate Cox regression hazard analysis was

employed to detect risk factors. The level of statistical significance was set at $p < 0.05$. Data analysis was performed with the Statistical Package for Social Sciences 20.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Of the total number of ACS patients (N=1498) admitted through the UCCK ED, 30.6% were aged ≥ 70 years, median age 64 (IQR 18-99) years; female 65.5 (IQR 20-92) years and male 63 (IQR 18-99) years. Female patients admitted for ACS were older compared with male patients ($p < 0.0001$). According to residence, 67.0% of patients lived in town, with the same percentage for the two genders ($p > 0.05$).

There were 338 (22.6%) patients with UA, 499 (33.3%) with STEMI, and 661 (44.1%) with NSTEMI. According to the type of ACS, the percentage of ACS patients was similar in two years without statistical significance ($p > 0.05$). Only 170 (11.3%) of all ACS patients had received PHE treatment, i.e. 13.4% of female and 10.2% of male patients, without statistically significant gender difference ($p > 0.05$). The in-hospital mortality rate of patients admitted with ACS was 10.3%, and it was higher in female (12.5%) compared to male (9.0%) patients, yielding a statistically significant difference ($p < 0.05$) (Table 1).

The in-hospital mortality rate was found to be higher in patients aged ≥ 70 (18.3%), female patients (12.5%), patients with STEMI (21.4%), PHE treated patients (28.8%), patients that did not have arterial hypertension before hospitalization (15.4%), diabetics (17.0%), non-obese patients (10.8%) and ex-smokers (18.8%). The mortality rate did not differ between patients that were living in urban and rural setting (Table 2).

According to univariate Cox regression analysis, age, female sex, STEMI, NSTEMI, PHE treatment, diabetes, hyperlipidemia, smoking and low left ventricular ejection fraction (LVEF) were significant risk factors for in-hospital mortality in patients admitted for ACS (Table 3). However, on multivariate Cox regression analysis, only age, presence of STEMI, the lack PHE treatment, diabetes mellitus, low LVEF and smoking remained independent predictors of mortality in patients admitted for ACS (Table 4).

The Kaplan-Meier survival curve showed that STEMI patients had higher in-hospital mortality rate

Table 1. Basic characteristics of patients with acute coronary syndrome

	Female	Male	Total	p-value
Total, n (%)	546	952	1498	
Age (years)				
<70	343 (62.8)	696 (73.1)	1039 (69.4)	<0.001
≥70	203 (37.2)	256 (26.9)	459 (30.6)	
Median (IQR)	65.5 (20-92)	63 (18-99)	64 (18-99)	<0.001
Residence				
Rural	185 (33.9)	309 (32.5)	494 (33.0)	0.612
Urban	361 (66.1)	643 (67.5)	1004 (67.0)	
Acute coronary syndrome				
UA	123 (22.5)	215 (22.6)	338 (22.6)	0.279
STEMI	169 (31.0)	330 (34.7)	499 (33.3)	
NSTEMI	254 (46.5)	407 (42.8)	661 (44.1)	
Group				
PHE group	73 (13.4)	97 (10.2)	170 (11.3)	0.063
Control group	473 (86.6)	855 (89.8)	1328 (88.7)	
Status at discharge, n (%)				
Survived	478 (87.5)	866 (91.0)	1344 (89.7)	0.041
Deceased	68 (12.5)	86 (9.0)	154 (10.3)	
Hypertension				
Yes	385 (70.5)	461 (48.4)	846 (56.5)	<0.001
No	161 (29.5)	491 (51.6)	652 (43.5)	
Diabetes				
Yes	218 (39.9)	240 (25.2)	458 (30.6)	<0.001
No	328 (60.1)	712 (74.8)	1040 (69.4)	
Obesity				
Yes	83 (15.2)	70 (7.4)	153 (10.2)	<0.001
No	463 (84.8)	882 (92.6)	1345 (89.8)	
Smoking				
Current smoker	80 (14.7)	463 (48.6)	543 (36.2)	<0.001
No smoker	441 (80.8)	376 (39.5)	817 (54.5)	
Ex-smoker	25 (4.6)	113 (11.9)	138 (9.2)	

IQR = interquartile range; UA = unstable angina; STEMI = ST-elevation myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction; PHE = pre-hospital emergency

compared with patients that were admitted for ACS and had NSTEMI or UA (Fig. 1). The log rank test yielded a significant difference in in-hospital mortality between STEMI and NSTEMI patients, STEMI and

UA patients, and NSTEMI and UA patients ($p < 0.001$ all). After one year, patients were called by phone, yielding a 19.4% mortality rate at 12 months from admission (Fig. 2).

Table 2. Correlates of in-hospital mortality from acute coronary syndrome

	Status at discharge		p-value
	Survived	Death	
Total, n (%)	1344 (89.7)	154 (10.3)	
Gender			
Female	478 (87.5)	68 (12.5)	0.041
Male	866 (91.0)	86 (9.0)	
Clinical presentation			
UA	329 (97.3)	9 (2.7)	<0.001
STEMI	392 (78.6)	107 (21.4)	
NSTEMI	623 (94.3)	38 (5.7)	
Group			
PHE group	121 (71.2)	49 (28.8)	<0.001
Control group	1223 (92.1)	105 (7.9)	
Age group			
<70	969 (93.3)	70 (6.7)	<0.001
≥70	375 (81.7)	84 (18.3)	
Residence			
Rural	444 (89.9)	50 (10.1)	0.928
Urban	900 (89.6)	104 (10.4)	
Hypertension			
Yes	774 (93.9)	50 (6.1)	<0.001
No	570 (84.6)	104 (15.4)	
Diabetes			
Yes	380 (83.0)	78 (17.0)	<0.001
No	964 (92.7)	76 (7.3)	
Obesity			
Yes	85 (98.8)	1 (1.2)	0.001
No	1259 (89.2)	153 (10.8)	
Smoking			
No smoker	732 (89.6)	85 (10.4)	<0.001
Current smoker	500 (92.1)	43 (7.9)	
Ex-smoker	112 (81.2)	26 (18.8)	
Duration of symptoms			
<6 hours	468 (34.8)	68 (44.2)	0.027
6-12 hours	110 (8.2)	13 (8.4)	
>12 hours	766 (57.0)	73 (47.4)	

IQR = interquartile range; UA = unstable angina; STEMI = ST-elevation myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction; PHE = pre-hospital emergency

Table 3. Univariate Cox regression analysis of mortality predictors

	HR	95% CI	p-value
Age \geq 70 years	2.81	1.99-3.97	<0.001
Female sex	1.39	1.00-1.93	0.041
UA	1.00	-	-
STEMI	8.51	5.88-12.31	<0.001
NSTEMI	2.18	1.19-3.98	<0.001
PHE group	3.92	2.35-6.54	<0.001
Urban residence	1.02	0.73-1.43	0.928
Hypertension	0.36	0.26-0.49	<0.001
Diabetes	2.39	1.69-3.37	<0.001
Hyperlipidemia	1.68	1.22-2.31	0.032
Obesity	0.06	0.03 - 0.09	0.001
No smoker	1.00	-	-
Current smoker	0.76	0.53-1.08	0.130
Ex-smoker	1.86	1.09-3.17	0.006
LVEF <40%	15.95	9.11-27.91	<0.001

UA = unstable angina; STEMI = ST-segment elevation myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction; LVEF = left ventricular ejection fraction; PHE = pre-hospital emergency treatment; HR = hazard ratio; 95% CI = 95% confidence interval

Table 4. Multivariate Cox regression analysis of in-hospital mortality

	HR	95% CI	p-value
Age \geq 70 years	2.37	1.67-3.52	<0.001
Female sex	1.01	0.87-1.23	0.067
STEMI	6.17	3.22-15.31	<0.001
PHE group	3.92	2.35-6.54	<0.001
Diabetes	3.01	1.98-3.78	<0.001
Hyperlipidemia	1.2	0.98-1.89	0.054
Ex-smoker	2.34	1.57-3.85	0.01
LVEF < 40%	17.63	11.2-30.54	<0.001

STEMI = ST-segment elevation myocardial infarction; LVEF = left ventricular ejection fraction; PHE = pre-hospital emergency treatment; HR = hazard ratio; 95% CI = 95% confidence interval

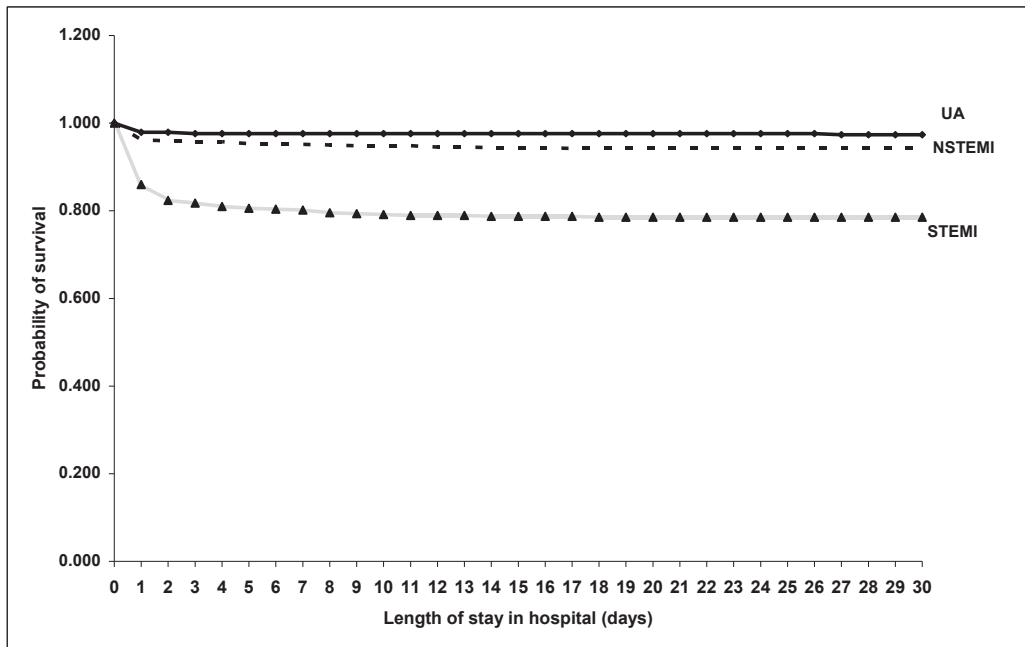


Fig. 1. Kaplan Meier survival curve of patients with STEMI, NSTEMI and UA.

STEMI = ST-segment elevation myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction; UA = unstable angina

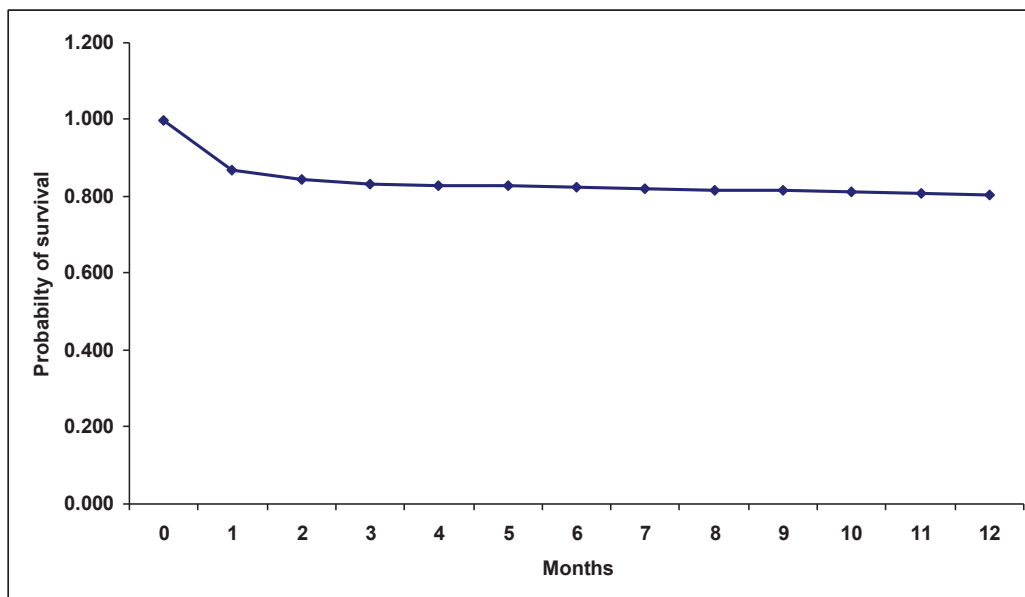


Fig. 2. Kaplan Meier survival curve of patients with STEMI and NSTEMI at 1-year follow up.

STEMI = ST-segment elevation myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction

Discussion

Main findings

The main finding of our study was that in-hospital mortality of patients admitted with ACS in Kosovo remained high. Another important finding was that in Kosovo, as compared with developed countries, the lack of PHE treatment was an independent predictor of in-hospital mortality in ACS patients.

Data interpretation

The performance of Kosovo emergency system relating to the acute treatment of ACS patients has not been thoroughly studied. Emergency medicine is a relatively new field, even in the most developed societies¹³, whereas in Kosovo it is in its infancy. An Anglo-American model of the emergency medicine in Kosovo was developed after the war conflict in 1999, with the involvement of international governmental and non-governmental organizations. These organizations have built or renovated hospital emergency departments, donated ambulances and equipment, and trained healthcare professionals¹⁴. The World Health Organization has built up a health policy to help recuperation and recovery of the post-war health system in Kosovo¹⁵. The results of assessment showed that the emergency medicine in Kosovo is under-developed. There has been minimal formal training, lack of organization of Emergency Medicine System, lack of equipment and a solid communication system, and all of these were inadequate also for the emergency center of UCKK¹⁶⁻¹⁸, thus it was expected to find a specific death rate of ACS patients during their hospital stay.

Based on our findings, there was a higher in-hospital mortality in our patients. The lack of full time primary percutaneous coronary intervention (PCI) procedures in patients with ACS may have contributed to the high in-hospital mortality rate of our population. Analysis of in-hospital mortality rate of patients with ACS treated with primary PCI demonstrated that the total mortality rate was 5.7%; the mortality rate of women was 2.5-fold the mortality rate of men (10% *vs.* 4.2%)¹⁹. A significantly higher percentage of in-hospital deaths was found in women with acute myocardial infarction (AMI) compared to men. Women have a lower possibility of MI incident in fertility period because of the role of estrogen. In menopause, when the protective role of estrogen

decreases, the incidence of MI in women rises^{20,21}. We could conclude that women have a lower incidence of MI but after the incident, mortality is significantly higher. In the study by Novak *et al.*²², women were older than men (71±11 years *vs.* 64±12 years, $p < 0.001$) and as a result of this disparity in age had higher rates of complications and in-hospital mortality. Women had a lower prevalence of smoking and higher prevalence of hypertension and history of angina pectoris, regardless of their age. The use of coronary catheterization and percutaneous transluminal coronary angioplasty (PTCA) significantly reduced in-hospital mortality and complications while thrombolytic therapy was associated with 3.3 times increased mortality odds ratio (OR, $p = 0.01$). STEMI (OR 4.5, $p < 0.001$) and in-hospital complications (OR 25, $p < 0.001$) also were significant predictors of in-hospital mortality. In the study by Bajraktari *et al.*²³ from 2008, the in-hospital mortality rate for AMI patients in a cardiology department without primary PCI center was 10.3% (12.3% for women and 9.5% for men). In our study, the in-hospital mortality rate for ACS was 10.3%, higher in female than male patients (12.5% *vs.* 9.0%), with a significant difference ($p < 0.05$). Females were at a higher risk than males (OR 1.242, 95% CI 1.025-1.504). Between 1999 and 2012, the age of AMI patients increased but the mortality rate remained constant. The in-hospital mortality rate for UA patients was 2.7%, STEMI patients 21.4% and NSTEMI patients 5.7%. Different studies²⁴⁻²⁶ found important variations among STEMI, NSTEMI and UA patients in the incidence of heart failure and mortality. In other conditions, the in-hospital mortality rate was also higher before PCI²⁷⁻³⁴.

The rise in the cardiovascular disease (CVD) burden is primarily the result of both the rising prevalence of risk factors and a relative lack of access to treatments that improve survival after CVD. The prevalence of risk factors (hypertension, diabetes, obesity) is higher. AMI patients in Kosovo belong to younger age groups compared to developed countries.

The American Heart Association states that the best option in the case of a suspected ACS event is to activate the mobile emergency medical service². This recommendation is based on the fact that this could provide safer transportation and shorter time-to-treatment intervals. In our study, only 11.3% of patients received PHE care (13.4% of female and 10.2% of male patients).

According to the study performed at the Medical Center University of Alabama³⁵, the in-hospital mortality rate was 8% in patients with a pre-hospital ECG and 12% in those without a pre-hospital ECG ($p < 0.001$). In our study, the in-hospital mortality rate among the PHE group patients (28.8%) was higher as compared with the control group (7.9%). This could be explained by the fact that the usage of PHE service was very scarce (11.3%) and it was only used in patients with more severe health conditions. The STEMI-self-transport patients have prolonged treatment periods compared to the patients transported by the emergency medical service³⁶.

In our study, smoking was associated with a lower risk of death in ACS, primarily because of the younger age of smokers with ACS and less severe coronary artery disease. Similar data have also been reported elsewhere³⁷⁻³⁹. Obesity at ACS presentation is associated with lower in-hospital mortality. The 'obesity paradox' may be a function of younger age at presentation, referral for angiography at an earlier stage of disease, and more aggressive management of ACS.

The established CVD risk factors including high blood pressure, adverse blood lipid profile⁴⁰, diabetes mellitus, obesity and smoking have been addressed in recommendations and guidelines half a century ago or even earlier. These commonly recognized risk factors jointly account for 80% of the burden of ischemic heart disease⁴¹.

The in-hospital mortality rate of ACS in North America during the last 30 years has decreased from 25%-30% to 7%-10%. This decline can be due to the advent of Coronary Care Unit (1960s), beta blocker administration (1970s), fibrinolytic therapy initiation (1980s) and PCI (1990s)⁴², improvements in risk factor modification, organization of healthcare systems, and disease management that have substantially attenuated the adverse prognosis of both STEMI and NSTEMI⁴³. The British Heart Foundation estimates that ACS remains one of the major causes of premature deaths for men and women in the United Kingdom⁴⁴. The risk factors for ACS include older age groups, male sex, hypertension, smoking, diabetes, hypercholesterolemia, previous atheromatous CVD, and a family history of premature ischemic heart disease. In patients with ACS, about one-half of deaths occur within 30 days, and 9% to 19% of ACS patients die during the first 6 months after being diagnosed⁴⁵.

Limitations of the study

The main limitation of our study was that we did not have a national register⁴⁶ for ACS because of the lack of electronic Health Information System. At the same time, another important study limitation was the small sample size in the PHE group, which made it impossible to obtain statistically significant differences in some of the parameters studied.

Clinical implications

We believe that the findings of this survey will help the policymakers in developing policy and programs to reduce the mortality rates of patients with ACS, especially by developing a better strategy for the PHE in Kosovo.

In-hospital mortality of patients admitted with ACS remains high in Kosovo compared with developed countries. The lack of PHE treatment, in addition to old age, diabetes, STEMI type and compromised LV systolic function, was shown to be an independent predictor of in-hospital mortality in ACS patients. A better strategy for the PHE in Kosovo is recommended for saving lives in these high-risk patients.

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Sažetak

KORELACIJE U BOLNIČKOJ SMRTNOSTI BOLESNIKA S AKUTNIM KORONARNIM SINDROMOM NA KOSOVU

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Pokazano je da predbolnička hitna skrb smanjuje bolničku smrtnost u bolesnika s akutnim koronarnim sindromom (AKS). Cilj ove studije bio je analizirati odnos između predbolničke hitne skrbi i bolničke smrtnosti bolesnika s AKS-om liječenih na Odjelu za hitne slučajeve Univerzitetskog kliničkog centra Kosova (UKCK). Ovo opservacijsko kliničko istraživanje obuhvaćalo je 1498 bolesnika s AKS-om liječenih na Odjelu za hitne slučajeve UKCK, koji su praćeni godinu dana nakon otpusta telefonskim pozivom. Multivarijatna Coxova regresijska analiza pokazala je da su dob (HR=2,37, 95% CI 1,67-3,52), predbolnička hitna skrb (HR=3,92, 95% CI 2,35-6,54), STEMI (HR=6,17, 95% CI 3,22-15,31), šećerna bolest (HR=3,01, 95% CI 1,98-3,78), istisna frakcija lijeve klijetke <40% (HR=17,63, 95% CI 11,2-30,54) i pušenje (HR=2,34, 95% CI 1,57-3,85) značajni prediktori smrtnosti u bolesnika s AKS-om. Bolnička smrtnost bolesnika primljenih s AKS-om i dalje je visoka na Kosovu u usporedbi s razvijenim zemljama. Preporuča se bolja strategija za predbolničku hitnu skrb na Kosovu radi spašavanja života ovih bolesnika visokog rizika.

Ključne riječi: *Bolnička smrtnost; Akutni koronarni sindrom; Odjel hitne medicine*