Original Article

PREDICTORS FOR LONG-TERM PROGNOSIS AFTER ACUTE CORONARY SYNDROME

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Summary

Cardiovascular diseases (CVD) are the leading cause of invalidity and death in developed countries. Among them, the main cause of death is coronary artery disease. In this retrospective study, 172 patients with acute coronary syndrome (STEMI, NSTEMI, UA) are included. They had been hospitalized on an emergency basis in the Cardiology Department, Invasive Sector of Prof. Dr. St. Kirkovich Hospital in Stara Zagora, and the Cardiology Hospital - Yambol between January 2009 and February 2010. We found a significant difference in the age at acute coronary syndrome (ACS) occurrence by sex: earlier manifestation was observed in men (p=0.018). The univariant regression analysis showed that elderly age (p=0.005, OR 1.024), glomerular filtration <90 ml/h (p=0.006, OR 0.964), GRACE-score > 140 pt (p<0.001, OR 1.045), HF (Killip class ≥ II) (p=0.002, OR 15.6) and EF<40% (p=0.003, OR 1) were factors for adverse prognosis in the first, fifth and ninth year. Only GRACE-score was an independent predictor of death obtained by multivariate regression analysis in the study (p=0.002, OR 1.052). The factors influencing long-term survival adversely after ACS are age, smoking, chronic kidney disease, previously experienced myocardial infarction, diabetes mellitus, three-vessel coronary disease, and decreased systolic function of the left ventricle, and GRACE > 140 p.

Keywords: risk factors, survival, mortality, acute coronary syndrome

Introduction

Cardiovascular diseases (CVD) are the leading cause of invalidity and death in the developed countries [1,2,27,28]. The leading cause for death is coronary artery disease and acute coronary syndrome (ACS) in particular. Data from the National Statistical Institute (NSI) show that 65% of the deaths in Bulgaria are due to CVDs, i.e., approximately 60 thousand deaths per year. Despite the modern treatment methods, the mortality from ACS worldwide remains high in the short- and long-term. There are insufficient data about studies in Bulgaria that identify the factors influencing survival and prognosis in patients after ACS in the short- and long term. Identifying factors influencing survival is essential for a fast and early stratification of the risk at patients with ACS and prompt treatment.

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The Framingham Heart Study is the first-ever long-term epidemiology study [1,2]. It analyses prospectively 5209 men and women aged 30 to 62, and every two years, the risk factors for cardiovascular diseases have been followed up. The study, published in 1957, defined arterial hypertension as measured systolic arterial pressure ≥ 160/95 mm Hg. The researchers reported that there is a four-fold increase in coronary incidents frequency in people with arterial hypertension. In 1971, the Framingham researchers analyzed 14-year follow-up data and determined a dependency between the output arterial blood pressure and coronary disease incidence. In the first half of the XX century, researchers highlighted the cardiovascular risk factors, namely arterial hypertension, hyperlipidemia, and diabetes mellitus [2,3]. The term "risk factor" was promoted in the medical literature by T. Dawber and U. Kannel in 1961 in their publication about risk factors in coronary heart disease development. In 1976, Kannel and collaborators published the first risk profile [2,4]. Twenty years later, Wilson and collaborators published a risk profile for coronary heart disease. It provided a 10-year risk assessment presenting a convenient approach for classifying individuals with a low, moderate, or high risk of coronary heart disease [2,4,5]. The latter study underlay the group's risk scale for treating adults in the National Cholesterol Education Program in the United States (NCEP) to assess a 10-year risk, classifying them with a low, moderate, or high risk. During the over 10-year monitoring, the researchers found that arterial hypertension precedes > 50% of the newly discovered heart failure. Acute myocardial infarction is related to a 6-fold higher risk of developing heart failure. The published data from the prospective follow-up study of this sub-group showed poor prognosis, survival, and increased mortality, with every 2 of 5 men surviving and only one in 10 staying until the tenth year [2].

There are currently many studies proving the role of the risk factors in the genesis of CAD. The global INTERHEART study, covering 27098 participants from 52 countries, demonstrates the connection of nine modifiable risk factors (>90%) with the acute myocardial infarction in young and older persons (women and men) in all ethnic groups. The researchers concluded that the average age of first acute myocardial infarction

(AMI) is higher among women compared to men (65 vs. 56 years; P<0.0001). The modifiable risk factors for both sexes are related to AMI. The presence of risk factors has a higher predictive value in younger patients compared to older patients. The relative risk (PAR) of all nine risk factors exceeds 94% and is similar in women and men (96 vs. 93%) [25]. The risk factors (RF) - arterial hypertension (AH), physical inactivity, and alcohol consumption are significantly higher in women than men. Metabolic risk factors greatly increase the risk of AMI, regardless of sex [24,25].

The Romanian register of STEMI for the period 2000-2007 included 9186 consecutive patients. The average age in the group was 63.8 years (SD 11.8) [6]. The risk profile of the patients was: 4986 (54.3%) had arterial hypertension, 1974 (21.5%) had diabetes mellitus, 3545 (38.6%) had lipid disorders, 4653 (50.7%) were smokers, and 935 (10.2%) had had a myocardial infarction. The frequency of arterial hypertension and diabetes mellitus was significantly higher in women, and the higher percentage of smokers was among men. The rate of nosocomial mortality was 12.7% (1170 death cases). In the prospective study ACSIS conducted in Israel, within the period February-March 2000-2010, every two years, 11 536 patients were included with ACS, of whom 4558 were diagnosed with STEMI and the remaining - with NSTEMI. The distribution of the risk factors in patients, randomized in groups by systolic cardiac function and the gravity of the mitral insufficiency, was studied. Of these patients, 4470 (49.7%) had moderately severe mitral insufficiency (EF<50%), 854 (9.6%) - severe (EF<30%) and 3659 (40.7%) were with preserved systolic function. The researchers found that older patients (p<0.001) had severe systolic dysfunction and a high rate of comorbidity (arterial hypertension, diabetes mellitus, heart failure, chronic kidney disease, peripheral arterial disease, and cerebrovascular disease) [7]. The one-year mortality significantly correlated with the gravity of pump dysfunction, respectively 36%, 4%, and 10% [7].

The Japanese Multicenter Registry analyzed data from 10,220 patients who passed through a cath-lab for an interventional procedure between 2008 and 2013. The researchers found that women were older, underweight, and more likely

to have AH, hyperlipidemia, insulin-dependent diabetes mellitus, renal and heart failure than men (p <0.001) [31].

Multivariate analysis in the general group found that the female gender was an independent predictor of general complications (p <0.001) and bleeding complications (p <0.001). A similar trend was observed in the middle-age group (≥55 and <75 years) and the advanced age group (≥ 75 years). There were significantly more bifurcation lesions and chronic total occlusions in the men`s group on the coronary angiogram than in the women`s group [29]. In the study of Parhomenko et al., patients with diabetes mellitus, renal disease, and known coronary heart disease were found to have a higher mortality rate in NSTEMI [28].

In 2005-2007, a study was conducted in Bulgaria among a sample of the population. It included 4598 healthy residents of large cities (age range 25 - 74) with at least one cardiovascular risk factor [8]. The general 10-year risk of a fatal cardiovascular event was assessed using the systematic method for evaluating coronary risk (SCORE). The average age of the participants was 56.9 ± 9.8. Most participants were within the age group 55-64 years (39.97%). A high general cardiovascular risk (over 5%) existed in 48.7% of the persons in the group. According to the European recommendations, almost half of the participants are considered at high risk for a fatal cardiovascular event over the following ten years. The risk increased with age for both sexes. The riskiest participants (SCORE≥5%) were in age groups over 45 years, particularly over 55 years. The highest risk existed in 24.3% of the subjects examined within the range 45-54 years and in more than half of the participants aged 55 to 64 years (58.5% and 28%, respectively). The common cardiovascular risk in men was significantly higher than the risk in women aged 35-44 and 45-54 (*P*%), 001 for both). Almost half of the men aged 45-54 years (42.4%) had a high common risk (SCORE≥5%). The overall cardiovascular risk increased sharply in the age groups over 45 years. Only 6.6% of men aged 65-74 years were at a low and medium common risk (SCORE <5%). However, the percentage of participants with a very high risk (SCORE≥15%) was 46.6%, i.e., almost half of men over 65 years were at a very high common risk of developing a fatal cardiovascular event

over the following ten years [8]. The results of the most extensive epidemiological studies held in Bulgaria - the Sofia Heart Study (1994-1999), the Bulgaria Heart Study 1998, and the CINDI study showed that the spread of the major risk factors was significantly higher among the Bulgarian population compared to the other European countries [30].

In a study of Kanazirev, following up prospectively for two years 145 persons with left ventricular dysfunction and heart failure after AMI at standard outpatient therapy and retrospectively for eight years, it was determined overall mortality of 14.9% in the first year, 32.12% - the second year, 55.1% - the third year, 71.43% - the fifth year and 91.84% in the eighth year. Cardiovascular mortality accounted for a significant part of the overall mortality. By the end of the follow-up, the cumulative cardiovascular mortality accounted for 73.25% of the overall mortality. The most significant part of cardiovascular mortality was sudden cardiac death (61.19%) and 46.51% of the overall mortality rate in the eighth year. Acute heart failure was the second most significant cause of death, and at the end of the follow-up in the eighth year, it was 18.56%. The fatal myocardial infarction was the cause of death in 10.44% of the cases by the end of the follow-up period. The highest frequency of death occurrence was during the first 40 months, then the mortality curve decreased significantly [9].

The purpose of the present study was to define factors influencing the short-term (1-year) and long-term (9-year) prognosis in patients with ACS by studying many indicators: demographic (sex, age), clinical laboratory (creatinine, glomerular filtration, LDL, HDL, TG), clinical (heart rate, arterial hypertension, acute left ventricular heart failure - Killip II-IV, ST deviation of ECG), smoking, echocardiography (EF (</>40%, mitral insufficiency), concomitant diseases (diabetes mellitus, stable angina pectoris, experienced ACS, rhythm/conduction disorders, cerebrovascular disease).

Materials and Methods

A retrospective study was conducted on 172 patients with acute coronary syndrome (STEMI - 103 patients, NSTEMI - 25 patients, UA - 44 patients) hospitalized on an emergency

basis in the Invasive cardiology department of the University Hospital in Stara Zagora and the Cardiology Clinics in Yambol between January 2009 and February 2010. The criteria for inclusion, distribution, and treatment of the patients in the groups are consistent with the guidelines of ESC (2010). The GRACE-score of all patients was calculated for assessing the nosocomial and 6-month mortality. The patients were followed up prospectively during the 1st year, and retrospectively in the 3rd, 5th, and 9th year after ACS. The risk factors for analyzing the mortality included age, sex, diagnosis, arterial hypertension, diabetes mellitus, dyslipidemia, smoking, CAD family history, experienced AMI, decreased systolic function of the left ventricle, and kidney function.

The statistical analyses were performed by specialized statistical software SPSS v16.0 (IBM, Chicago, IL). We used standard statistical descriptive methods to analyze demographic and clinical characteristics, laboratory, echocardiography, and angiography indicators. The dichotomous variables were reported as numbers and percentages and were compared using x2 tests, and univariant and multivariate regression analyses were performed to identify the significant risk factors. The Spearman's rank correlation was also applied to find out correlations between the continuous variables. Cox regression was used to identify independent prognostic factors.

Results

The distribution of the patients by demographic criteria and risk factors is shown in Table 1.

Clinical-demographic characteristics of patients with ACS with ST-elevation are presented in Table 2.

Clinical-demographic characteristics of patients with ACS without ST elevation are presented in Table 3.

Demographic characteristics, risk factors, clinical and instrumental data of the patients in the three groups are shown in Table 4.

The average age of the hospitalized patients with ACS was 61.5±11.9 (32.0-86.0) and 60.9±12.1 (32.0;85.0) with a STEMI diagnosis. The group of men was twice as big as the group of women and approximately five years younger. Among the hospitalized patients with NSTEMI and unstable angina (UA), the men were 50% more, as seen from the above data. The average age of the NSTEMI group was 66.2±12.3 and 60.2±10.7 for the UA group. The age of women with NSTEMI was 69.9±15.3, and of men – 64.5±10.6, and the same tendency was seen in the group with unstable angina pectoris: 63.7±8.6 for men and 58.6±11.3 for women.

A statistically significant age difference (p=0.018) was found at the occurrence of an acute coronary event in women (n=59) and men (n=113). No statistically significant age difference was found by diagnosis (p=0.097). The age of onset of a coronary incident was significantly higher in women, regardless of the diagnosis (p=0.09). We found a relation between the average age and arterial hypertension (p<0.001) as a risk factor regardless of sex. In 62.8% (91) of the men, arterial hypertension was present, while the women's percentage was 37.2% (54). Smoking rates in the group was as follows: non-smokers (67.7± 11.0 (34.0; 86.0)),

Table 1. Output characteristics of patients: modifiable and non-modifiable risk factors

Risk factors	Number (percentage)
Sex	Women - 59 (34.3%); Men - 113(65.7%)
Age	61.5±11.9(32.0-86.0)
Arterial hypertension	145 (84.3%)
Dyslipidemia	101(58.7%)
Overweight; Obesity	85(69.1%); 38(30.9%)
Smoking	62(36%)
Diabetes mellitus	45(26.2%)
Family history	43(25)
Experienced ACS	27(15.7%).

Table 2. Clinical-demographic characteristics of patients with ACS with ST-elevation

Demographic and clinical indicators	STEMI (n=103)
Sex	
Women	37 (35.9)
Men	66 (64.1)
Age	
General:	60.9±12.1(32.0;85.0)
Women	63.6±11.1(42.0;85.0)
Men	59.4±12.5(32.0;83.0)
Experienced ACS	6 (5.8)
Family history	25 (24.3)
Smoking	
Smokers	37 (35.9)
Ex-smokers	5 (4.9)
Non-smokers	58 (56.3)
Failed to indicate	3 (2.9)
Dyslipidemia	56 (54.4)
Arterial hypertension	
Women	34 (91.9) or (40.0)*
Men	51 (77.3) or (60.0)
Diabetes mellitus (known and newly discovered)	
Non-insulin-dependent diabetes mellitus	17 (16.5)
Insulin-dependent diabetes mellitus	6 (5.8)
NGT	5 (4.9)
BMI**	30.0±4.3 (19.0; 55.4) or 26.5(19.0; 55.4)
Glomerular filtration	
Women	60.9±257(4.8;108.6)
Men	73.7±273(11.4;158.8)

ex-smokers (57.9±7.9(46.0; 73.0)) smokers (53.6±8.5 (32.0; 71.0)). No dependency was observed between smoking and the type of ACS ($\chi^2(2)$=2.747; p=0.253). We found a dependency in the subgroup distribution by age (χ^2=57.602; p<0.001). There were more smokers in the three age groups under 60 and significantly more non-smokers in the age groups over 70. Comparison between sexes showed that smoking as a risk factor was significantly more widely spread among men (p<0.001). There was a significant correlation between the number of patients with known stable angina pectoris in the group with unstable angina pectoris, unlike the group with STEMI ($\chi^2(2)$=16.159; p<0.001). The presence of risk factors among the patients was the following: with one RF - 15 (8.7%), with two RFs - 47 (27.3%), and with three and more - 106 (61.6%). The highest number was that of patients with >3 RFs with STEMI, followed by those with UAP and NSTEMI.

No difference was observed in the frequency of diabetes mellitus for both sexes ($\chi 2(1)$=0.275; p=0.600) and diagnosis –$\chi 2(2)$=1.929; p=0.381. By age distribution, significantly more patients with diabetes mellitus were found in the age group 70-79 years - ($\chi 2(5)$=13.923; p=0.017) compared to younger patients. The highest value of the total cholesterol and LDL was in the group with STEMI with no significant difference from the other two groups. No significant difference was found in the total cholesterol value by sex (p=0.2) and the groups (p=0.14). No significant difference was found in the levels of LDL by sex (p=0.17) and by diagnosis (p=0.3), as well as at TG, p=0.1 and p=0.36, respectively. The HDL value differs significantly in the groups with STEMI and UAP (p=0.005). Our group's total cholesterol and LDL values did not correlate with BMI using Spearman's rank correlation coefficient. We found a low positive correlation between the increased TG and BMI (Rho=-0.292, p<0.001) and a low negative correlation between HDL and BMI (Rho=-0.159, p=0.039).

35

Table 3. Clinical-demographic characteristics of patients with ACS without ST elevation

	NSTEMI (n=44)	UA (n=25)
Sex		
Women	14 (31.8)	8 (32.0)
Men	30 (68.2)	17 (68.0)
Age		
General:	66.2±123(42.0;86.0)	60.2±10.7(39.0;86.0)
Women	69.9±153(42.0;82.0)	63.7±8.6(49.0;76.0)
Men	64.5±10.6(48.0;86.0)	58.6±113(39.0;86.0)
Experienced ACS	10 (40.0)	11 (25.0)
Previous coronary angiography		
Family history	6 (24.0)	12 (27.3)
Smoking		
Smoker	6 (24.0)	19 (43.2)
Ex	5 (20.0)	5 (11.4)
Non-smoker	14 (56.0)	20 (45.5)
Failed to indicate		
Dyslipidemia	28 (63.6)	17 (68.0)
Arterial hypertension		
Women	7 (87.5) or (33.3)	13 (92.9) or (33.3)
Men	14 (82.4) or (66.7)	26 (86.7) or (66.7)
Diabetes mellitus (known and newly discovered)		
Non-insulin-dependent diabetes mellitus	4 (16.0)	11 (25.0)
Insulin-dependent diabetes mellitus	2 (8.0)	4 (9.1)
NGT	-	2 (8.0)
BMI**	28.3±4.3 (21.5; 41.9)	27.0±3.3 (19.0; 33.8)
Glomerular filtration		
Women	62.9±31.3 (28.2; 125.0)	62.3±10.6 (52.8; 91.5)
Men	70.9±19.1 (40.6; 105.5)	83.7±16.2 (57.9; 116.6)

Table 4. Demographic characteristics, risk factors, clinical and instrumental data of the patients in the three groups

	Total	STEMI	NSTEMI	UA
Number of patients	172	103(59.9%)	25(14.5%)	44(25.6%)
Sex (% men)		66(64.1%)	17(68.0%)	30(68.2%)
Age	61.5±11.9 (32.0-86.0)	60.9±12.1 (32.0-85.0)	66.2±12.3 (42.0-86.0)	60.2±10.7 (39.0-86.0)
Risk factors:				
1 RF (% yes)	15(8.7%)	9(8.7%)	2(8.0%)	4(9.1%)
2 RF (% yes)	47(27.3%)	29(28.2%)	8(32.0%)	10(22.7%)
>3 RF (% yes)	106(61.6%)	61(59.2%)	15(60.0%)	30(68.2%)
Known heart failure				
>II F.C.	11(6.4%)	6(5.8%)	3(12.0%)	2(4.5%)
Previous stable angina pectoris	86(50.0%)	39(37.9%)	15(60.0%)	32(72.7%)
Anemia	19(11.1%)	14(13.6%)	2 (8.0)	3(6.8%)
Cerebrovascular disease	14(8.3%)	9(8.7%)	1 (4.0)	4(9.1%)

Laboratory indicators:				
Acute hypertension	5.4±1.7 (1.4-16.1)	5.6±1.9 (1.4-16.1)	5.3±1.6 (3.0-11.1)	5.0±1.0 (3.0-7.8)
LDL	3.1±1.4 (0.7-12.1)	3.3±1.6 (1.2-12.1)	3.0±1.4 (0.7-8.0)	2.8±0.9 (1.2-5.0)
HDL	1.7±0.4 (0.7-3.3)	1.8±0.4 (0.8-3.3)	1.6±0.3 (1.2-2.5)	1.6±0.4 (0.7-2.8)
TG	1.4±0.9 (0.3-5.8)	1.3±0.9 (0.3-5.8)	1.6±1.0 (0.6-3.7)	1.4±0.9 (0.3-3.8)
Creatinine	107.2±85.8 (50.0-815.7)	117.1±107.8 (54.2-815.7)	101.1±30.5 (50.0-163.5)	86.4±12.7 (63.0-124.2)
CPK	723.9±1179.4 (25.0-6491.0)	1011.5±1405.5 (64.0-6491.0)	506.9±575.7 (25.0-1827.0)	161.2±297.1 (34.0-2020.0)
CPK-MB	103.2±161.2 (1.2-1108.1)	143.5±191.3 (2.5-1108.1)	74.4±86.4 (2.7-270.7)	25.5±42.8 (1.2-251.2)
Tn I	6.9±27.8 (0.01-226.0)	8.5±34.6 (0.01-226.0)	5.4±8.2 (0.09-28.1)	2.6±3.2 (0.1-9.6)
ECG:				
ST-elevation	96(55.8%)	90(87.4%)	4(16.0%)	2(4.5%)
ST depression	31(18.0%)	8(7.8%)	13(52.0%)	10(22.7%)
Neg. T wave	39(22.7%)	9(8.7%)	9(36.0%)	21(47.7%)
Pathological Q-waves	51(29.7%)	35(34.0%)	6(24.0%)	10(22.7%)
Without ST-T changes	5(2.9%)	0(0.0%)	1(4.0%)	4(9.1%)
Rhythm/conduction disorders:				
Full left bundle branch block	4(2.3%)	1(1.0%)	1(4.0%)	2(4.5%)
Right bundle branch block	8(4.7%)	3(2.9%)	4(16.0%)	1(2.3%)
Left anterior hemiblock	17(9.9%)	9(8.7%)	3(12.0%)	5(11.4%)
AV block	13(7.6%)	10 (9.7%)	1(4.0%)	2(4.5%)
Atrial fibrillation/flutter	19(11.0%)	10 (9.7%)	4(9.1%)	5(20.0%)
Ventricular tachycardia	7(4.1%)	6(5.8%)	1(2.3%)	-
SP	137.4±26.8 (70.0-260.0)	138.9±29.7 (70.0-260.0)	141.8±26.4 (100.0-210.0)	131.4±18.0 (80.0-170.0)
DP	85.0±15.4 (40.0-143.0)	86.0±17.2 (40.0-143.0)	85.8±14.2 (60.0-118.0)	82.3±10.8 (50.0-106.0)
HR	79.0±16.1 (40.0-145.0)	80.2±16.3 (40.0-135.0)	78.6±12.9 (59.0-104.0)	76.3±17.1 (50.0-145.0)
LVHF				
Killip II-IV	27 (15.7%)	14(13.6%)	2(8.0%)	11 (25.0%)
Echocardiography indicators:				
EDV	50.3±7.5 (24.0-80.0)	50.7±7.4 (31.0-80.0)	48.5±8.1 (24.0-66.0)	50.3±7.4 (39.0-71.0)
ESV	34.0±7.8 (21.0-60.0)	35.0±7.4 (21.0-55.0)	35.4±8.1 (23.0-55.0)	34.6±8.6 (23.0-60.0)
EF (%): >55-50%				
49-40%	96(55.8%)	49 (47.6%)	12(48.0)	35(79.5%)
39-30%	55(32.0%)	39(37.9%)	11(44.0)	5(11.4%)
<30%	9 (5.2%)	6(5.8%)	1(4.0)	2(4.5%)

Coronary anatomy:				
LM	18(10.5%)	9(8.7%)	4(16.0%)	5(11.4%)
LAD	96(55.8%)	62(60.2%)	17(68.0%)	17(38.6%)
LCx	64(37.2%)	34(33.0%)	17(68.0%)	13(29.5%)
RCA	88(51.2%)	57(55.3%)	18(72.0%)	13(29.5%)
Single-vessel disease	51(29.7%)	40(38.8%)	4(16.0%)	7(15.9%)
Two-vessel disease	46(26.7%)	33(32.0%)	7(28.0%)	6(13.6%)
Three-vessel disease	48(27.9%)	26(25.2%)	13(52.0%)	9(20.5%)
Directed for coronary artery bypass	14(8.1%)	10 (9.7%)	-	4(9.1%)
Nosocomial mortality	13(7.6%)	11(10.7%)	-	2(4.5%)
Outpatient therapy: Total:				
ACE/ARB	81(47.1%)	34(33.0%)	18(72.0%)	29(65.9%)
Beta-blockers	65(37.8%)	22(21.4%)	12(48.0%)	31(70.5%)
Statin	31(18.0%)	7(6.8%)	9(36.0%)	15(34.1%)
Acetylsalicylic acid	48(27.9%)	17(16.5%)	12(48.0%)	19(43.2%)
Clopidogrel	11(6.4%)	4(3.9%)	4(16.0%)	3(6.8%)
Trimetazidine	9(5.2%)	5(4.9%)	2(8.0%)	2(4.5%)
High ceiling diuretics	10(5.8%)	4(3.9%)	4(16.0%)	2(4.5%)
GRACE				
<=108 p-	89(51.7%)	25	64	89
109-140 p	51(29.7%)	17	34	51
>140 p - high	32(18.6%)	17	15	32

Therefore, in patients with high BMI, there were decreased HDL levels. The heart rate was significantly higher in women (p=0.045).

No significant difference in creatinine levels was observed for the three diagnoses (p=0.1). The average glomerular filtration, calculated by MDRD, was 71.8ml/min (Mean±SD71.8±24.1 (5.1-158.8). We found a statistically significant difference in the average value of GFR between the two sexes: men (76±24.0) and women (62.7±23.6), t(168)=-3.435; (p=0.001), respectively. We did not find a correlation between average GFR and diagnosis, but there was such a difference for the group with GFR<60ml/min. The number of patients with STEMI diagnosis with GFR<60ml/min was significantly higher than the number of patients in the group with UAP (p=0.006), and those with NSTEMI had lower values of GFR than UAP (p=0.041). In the subgroup analysis, a significant difference of GFR was found in the age groups (p<0.001): patients aged 30-39 years towards patients within the range 60-69, and 70-79 years or over 80 years. No association was found between the average value of creatinine and GFR with nosocomial mortality (p=0.3).

Rhythm or conduction disorders or both were found in 57 (33.1%) of the patients. The most frequent arrhythmia was atrial fibrillation - 19 (11.0%), represented by the highest percentage in the group with AMI with ST-elevation (9.7%), followed by ventricular tachycardia in 7 (4.1%). The highest proportion of conductive disorders included atrioventricular block - 13 (7.6%), followed by the right bundle branch block 8 (4.7%).

Of the echocardiography parameters measured at hospitalization, mitral insufficiency was more frequent in the group with STEMI vs. UAP (p=0.002). The gravity of the mitral insufficiency did not correlate with the diagnosis of our study (p=0.8). The ejection fraction (EF) measured at hospitalization did not differ significantly in the three groups either, as the EF was not significantly lower, depending on the onset of chest pain (p=0.12), regardless of the presence of single-vessel, two-vessel, and three-vessel disease (p=0.38, p=0.62, p=0.38).

During hospitalization, 19 patients (11%) were found with cardiac asthma, eight patients (4.7%) had pulmonary edema, and 27 (15.7%) were with cardiogenic shock.

The cumulative nosocomial mortality was 7.6%. Cardiac arrest was registered in 13 patients (7.6%). There was a statistically significant correlation between the presence of LVHF and the death during hospitalization (p=0.017), regardless of the failed vessel (LM, LAD, LCx, RCA), as a cause for ACS. No significant correlation was found between the onset of the chest pain and the registered LVHF on admission to the hospital (p= 0.3). No correlation was found between the value of TnI and CPK-MB, both depending on the intervened failed vessel and nosocomial mortality.

The risk of nosocomial mortality was significantly higher in women ($\chi^2(2)$=6.576; p=0.037). Significantly more women (28.8%) were exposed to high risk than men (13.3%). The highest chance of nosocomial mortality was registered in patients from the STEMI group compared to the other two groups - $\chi^2(4)$=11.882; p= 0.018. Significantly more patients with UAP (70.5%) were exposed to lower risk than patients with STEMI (46.6%) and NSTEMI (40.0%). A statistically significant difference was found between the risk from nosocomial mortality regarding the treatment outcome –$\chi2(2)$=24.852; p<0.001. The number of patients who survived (55.3%) had been at low risk, while deceased patients (69.2%) were exposed to high risk. A statistical significance was found for the risk of mortality on the 6th month after the acute

event between the sexes –$\chi2(2)$=6.004; p=0.048. Significantly more women (47.5%) were found at higher risk than men (29.2%).

There was a strong connection between the risk of mortality at the 6th month after discharge from hospital compared to the diagnosis -$\chi^2(4)$=17.514;p=0.002. Significantly more patients with UAP (45.5%) were exposed to low risk (<89) compared to patients with STEMI (17.5%). A significant correlation was found between the calculated GRACE-score and treatment outcome -$\chi^2(2)$=15.145; p=0.001. Significantly more surviving patients (25.8%) were exposed to low risk (<89 points), while no low risk was identified among the deceased patients. Significantly more deceased patients (84.6%) had been exposed to high risk (>118 points), as compared to those who survived (31.4%).

The cumulative survival during the 1st year was 82%, in the 2nd year it was 79%, at the 3rd - 76% (Figure 1). At the end of the third and the fifth year of the follow-up, the survived patients were respectively 126 and 118 (74.1%, 69.4%), and those that had not survived were 44 (25.9%) and 52 (30.6%), respectively.

Related to the diagnosis, the cumulative survival during the first year was as follows: STEMI –75%, NSTEMI – 88%, UA – 93%.

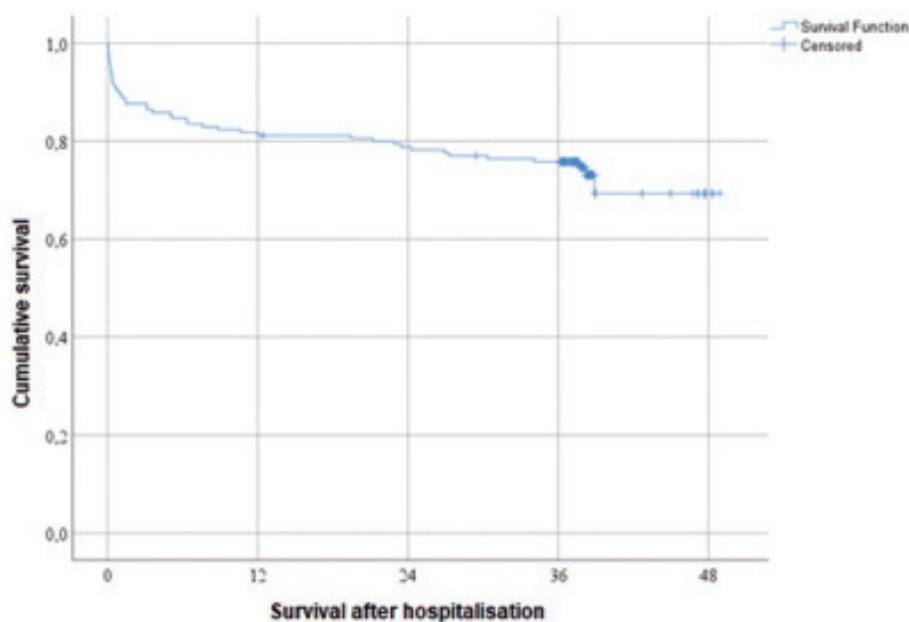The analysis of the variables shows that advanced age (p = 0.005, OR=1.024),

Figure 1. The overall survival curve for a period of 48 months

experienced myocardial infarction (p=0.006, OR=3.066), three-vessel coronary disease (p=0.008,OR=2.571), glomerular filtration <90ml/h (p = 0.006, OR=0.964), GRACE-score > 140pt (p < 0.001, OR=1.045), HF (Killip's class > = II)(p = 0.002, OR=15.6) are factors for adverse prognosis at the first and the fifth year after ACS. Only the GRACE-score is an independent predictor of death, as demonstrated by multiregression analysis in the study (p=0.002, OR= 1.052). (Table 5)

At the 60th month (the 5th year), after dichotomizing, the analyzed variables changed their significance as predictive factors – Table 6.

In the 9th year of the follow-up, the overall mortality is 39.2% (67), the patients surviving were 61.2% (104). The risk factors: diabetes mellitus, dyslipidemia, and smoking were poor prognostic markers for long-term survival. In smokers, the probability of adverse outcomes was 4.5 times higher compared to non-smokers in the 9th year. The presence of advanced age, diabetes mellitus, CKD, experienced AMI were predictors for poor prognosis. The univariant analysis of the variables in the 9th year of the follow-up is shown in the table below (Table 7).

Ejection fraction is a prognostic marker in the 12th, 60th, and 98th months of the follow-up. Patients with decreased systolic function (EF<40%) had poorer survival (p=0.006,p=0.006,p=0.015). Patients with a decreased systolic function of the left ventricle (EF <40%) and three-vessel coronary disease tended to have poorer survival and prognosis (p = 0.003) as compared to those without decreased EF or three-vessel coronary disease. (Tables 6 and 7).

Table 5. Univariant analysis of the 1st year after discharge from hospital

Factor	Univariant analysis (p-value)	Univariant analysis (p-value)
Sex	0.649	
Women		1
Men		0.819(0.347; 1.934)
Diagnosis	0.029	
STEMI		1
NAP		4.260(1.210; 14.997)
NSTEMI		3.584(0.787; 16.320)
Age	0.011	0.954(0.920; 0.989)
Dyslipidemia	0.972	
No		1
Yes		1.015(0.445; 2.313)
Smoking	0.916	
Non-smoker		1
Ex		1.387(0.285; 6.756)
Smoker		1.088(0.457; 2.588)
LDL-C	0.433	1.140(0.822; 1.580)
HDL	0.731	1.189(0.443; 3.186)
Triglyceride	0.933	1.020(0.648; 1.604)
Creatinine	0.044	0.995(0.991; 1.000)
Anemia	0.267	
No		1
Yes		0.533(0.176; 1.619)
Glomerular filtration	0.014	1.022(1.005;1.040)
GRACE score	<0.001	0.975(0.963; 0.987)
Acute left-sided heart failure	0.006	
No		1

Yes		0.045(0.005; 0.416)
Diabetes mellitus	0.286	
No		1
Yes		0.627(0.267; 1.476)
Stable angina pectoris	0.838	
No		1
Yes		0.920(0.414; 2.047)
Experienced AMI	0.039	
No		1
Yes		0.379(0.151; 0.953)
Ejection fraction (EF)	0.006	
< 40%		1
>= 40%		4.561(1.539;13.514)
Cerebrovascular disease	0.788	
No		1
Yes		1.238(0.261; 5.864)
Killip-II-IV	0.838	
No		1
Yes		0.895(0.308; 2.598)

Table 6. Univariant analysis of the 5th year after discharge from hospital

Factor	Univariant analysis (p-value)	Univariant analysis (p-value)
Sex	0.495	
Women		1
Men		1.266(0.643; 2.493)
Diagnosis	0.125	
STEMI		1
NAP		2.386(1.001; 5.689)
NSTEMI		0.943(0.378; 2.351)
Age	<0.001	0.940(0.911; 0.970)
Dyslipidemia	0.241	
No		1
Yes		1.489(0.766; 2.898)
Smoking	0.031	
Non-smoker		1
Ex		1.250(0.394; 3.962)
Smoker		2.841(1.306; 6.181)
LDL-C	0.166	1.215(0.923; 1.600)
HDL	0.278	1.574(0.694; 3.571)
Triglyceride	0.424	1.171(0.795; 1.725)
Creatinine	<0.001	0.976(0.964; 0.988)
Anemia	0.102	
No		1

Yes		0.447(0.170; 1.175)
Glomerular filtration	<0.001	1.036(1.019;1.053)
GRACE score	<0.001	0.973(0.962; 0.985)
Acute left-sided heart failure	0.044	
No		1
Yes		0.103(0.011; 0.941)
Pon_poly	0.541	
LL		1
LM		0.648(0.239; 1.756)
MM		1.296(0.273; 6.155)
Diabetes mellitus	0.007	
No		1
Yes		0.377(0.185; 0.769)
Stable angina pectoris	0.184	
No		1
Yes		0.640(0.311; 1.237)
Experienced AMI	<0.001	
No		1
Yes		0.217(0.096; 0.493)
Ejection fraction (EF)	0.006	
< 40%		1
>= 40%		4.472(1.528;13.086)
Cerebrovascular disease	0.673	
No		1
Yes		0.781(0.248; 2.459)
Killip-II-IV	0.553	
No		1
Yes		1.325(0.523; 3.361)

Table 7. Univariant analysis of the variables at the 9th year of the follow-up

Factor	Univariant analysis (p-value)	Univariant analysis (p-value)
Sex	0.307	
Women		1
Men		1.398 (0.735; 2.662)
Diagnosis	0.090	
STEMI		1
NAP		2.411 (1.097; 5.297)
NSTEMI		1.205 (0.494; 2.939)
Age	<0.001	0.920 (0.891; 0.951)
Dyslipidemia	0.095	
No		1

Yes		1.716 (0.910; 3.236)
Smoking	<0.001	
Non-smoker		1
Ex		2.233 (0.707; 7.049)
Smoker		4.558 (2.145; 9.684)
LDL-C	0.134	1.214 (0.942; 1.564)
HDL	0.999	0.999 (0.471; 2.119)
Triglyceride	0.130	1.340 (0.918; 1.955)
Creatinine	<0.001	0.970 (0.957; 0.983)
Anemia	0.027	
No		1
Yes		0.328 (0.122; 0.883)
Glomerular filtration	<0.001	1.044 (1.027;1.062)
GRACE score	<0.001	0.964 (0.950; 0.977)
Acute left-sided heart failure	0.094	
No		1
Yes		0.150 (0.016; 1.377)
Pon_poly	0.334	
LL		1
LM		0.522 (0.195; 1.395)
MM		1.125 (0.259; 4.893)
Diabetes mellitus	0.008	
No		1
Yes		0.390 (0.195; 0.784)
Stable angina pectoris	0.529	
No		1
Yes		0.820(0.442; 1.521)
Experienced AMI	0.001	
No		1
Yes		0.260 (0.114; 0.590)
Ejection fraction (EF)	0.015	
< 40%		1
>= 40%		3.952 (1.305; 11.971)
Cerebrovascular disease	0.053	
No		1
Yes		0.324 (0.103; 1.015)
Killip-II-IV	0.791	
No		1
Yes		0.893 (0.386; 2.066)

Discussion

Throughout the years, many models of close and long survival of patients after ACS have been reported. Most of the studies include patients in selected groups, excluding persons with comorbidities and at an advanced age. In this study, we included patients from real clinical

practice consecutively hospitalized with ACS. Our results approximate those in the literature [10,11,12,13]. The age of an acute coronary event was approximately five years earlier in men than in women. Arterial hypertension was a more frequent risk factor among Bulgarian patients compared to the published data. In our group, arterial hypertension, dyslipidemia, smoking, diabetes mellitus, and family history were more frequent in men than reported in other studies.

The cumulative nosocomial mortality was 7.6%. The overall survival and mortality during the 1st years were 82.9% (141) and 17.1%, respectively [28]. At the end of the third and the fifth year of the follow-up, the survived patients were respectively 126 and 118 (74.1%, 69,4%), and those that had not survived were 44 (25.9%) and 52 (30.6%). In the 9th year of the follow-up, the overall mortality was 67 (39.2%), and the patients who survived were 104 (61.2%). In the 12th month, we identified eight predictors for poor prognosis, stratified by diagnosis, age, creatinine value, GFR, GRACE-score, presence of acute left-sided heart failure on admission, experienced myocardial infarction, and EF<40%. Over the five years, the predictors remained the same, regardless of the diagnosis, and the presence of smoking and diabetes mellitus worsened the survival rate. The Brazilian study ERICO reported 12% one-year mortality after ACS [14]. The study included a sample of individuals with different social-economical status: 269 (27.9%) persons with STEMI, 378 (39.2%) with NSTEMI, and 317 (32.9%) with UA, who were followed up in the 1st, 6th, and 12th months using questionnaires on the phone. The researchers found a high frequency of AH (77.2%), dyslipidemia (54.9%) and diabetes mellitus (39.6%), and physical inactivity (71.9% [14].

The persons with a history of acute myocardial infarction are exposed to increased risk of future cardiovascular incidents (repeated AMI, heart failure, life-threatening arrhythmia, CV death) [10, 15, 16,17]. The increased risk of recurrent CV incidents draws attention to studies on survival and prognosis in patients with AMI, focused on the acute phase throughout the 1st year [18]. A systematic review for identifying the epidemiological studies of long-term (≥

10-years) tendencies for incidence and mortality in persons who experienced AMI more than one year was published by Renet al. [18]. The authors analyzed the relative risk of all causes of death after the first year from a study in Denmark, in which the patients were randomized in two groups - healthy (>30 years) without data for diabetes mellitus and history of AMI, and a second group - patients with experienced ACS [18,19]. The relative risk of all causes f[of death increased to 1-3 years and 3-5 years after AMI, compared to the reference population, and was higher in women than in men [18,19]. These data are supported by a meta-analysis including>100 000 persons aged over 65 years, demonstrating a higher risk during the first year after experienced AMI [20]. Although the risk was lower during the next three years than during the first year, it remained relatively high, and approximately one of five patients who had not had a combined endpoint during the first year had a fatal AMI, a non-fatal stroke, or death for cardiac reasons during the next three years [11]. During the 1st year, approximately one-third of the patients had experienced repeated AMI, stroke, or death for cardiac reasons [10, 20]. The same study found an increased relative risk of recurring cardiovascular incidents up to the 5th year compared to the reference group, especially in women [10,19]. The presence of advanced age, smoking, AH, diabetes mellitus, peripheral arterial disease, cardiovascular disease, CKD, COPD, hepatic insufficiency, and cancer increases the all-cause mortality in persons who experienced STEMI/NSTE-ACS [10,21]. Swedish data from the meta-analysis of 97 254 has demonstrated 18.3% mortality in the first year [11,24]. The high risk of cardiovascular events after the first year implies continuous monitoring and secondary prevention, and continuous double anti-thrombosis therapy (DAPT) after the first year after AMI prevents vascular incidents [22]. In the DAPT study on patients treated by implanting a drug-eluting stent (DES), the continuous double anti-aggregation therapy after the 12th month leads to a significant decrease of the cumulative mortality at the expense of the frequency of late stent thrombosis, cardiovascular and cerebrovascular incidents during the next 18 months, as compared to monotherapy with acetylsalicylic acid [18,23]. The current ESC

recommendations are DAPT for 12 months in case of secondary prevention, which could be extended for specific patients.

Conclusion

Our study results show that the identification on admission to a hospital of factors like old age, women, CKD, documented data for experienced AMI, systolic dysfunction of left ventricular, and three-vessel coronary disease represent risk factors in poor prognosis during hospital treatment and after discharge. The presence of these factors on admission could be of use for faster and earlier identifying high-risk patients. A disadvantage of our study is the lack of information about all causes of mortality. Such information could allow for more accurate identification of predictors of survival and mortality in patients with ACS.

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