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ORIGINAL ARTICLE

Predictors for major adverse cardiovascular events among patients with acute coronary syndrome in Bosnia and Herzegovina

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ABSTRACT

Aim Despite advancements in the diagnosis, treatment and monitoring of patients with acute coronary syndrome (ACS), morbidity and mortality following ACS remain high. The aim of this study was to actively seek possible predictors of adverse outcomes after ACS aiming to identify high-risk patients promptly.

Methods This retrospective cohort study investigated patients with ACS hospitalized at Clinical Centre of the University of Sarajevo from 2019 to 2021. Patients were followed up for a period of 12 months post-discharge to assess major cardiovascular events (MACE) and MACE associated independent predictors.

Results. The study included 121 patients, mostly male 102 (84.3%), with a mean age of 60.83±12.61 years; prevalent risk factors were hypertension 94 (77.7%), dyslipidaemia 84 (69.4%), diabetes mellitus 91 (75.2%), active smoking 67 (55.4%) and positive family history of cardiovascular diseases 81 (66.9%). MACE occurred in 33 (27.3%) patients since the initial ACS, and those patients were older (p=0.012), had higher level of creatinine (p<0.001), lower ejection fraction at discharge (p<0.001) and larger left atrial diameter (p=0.032). Serum creatinine (OR=1.014, 95% CI 1,003-1,026, p=0.017) and ejection fraction (OR=0.924, 95% CI 0,869-0,984, p=0.013) were independent predictors associated with a 12-month follow up MACE following ACS.

Conclusion A monitoring of serum creatinine level, left atrial diameter, and ejection fraction post-acute coronary syndrome as potential indicators of future MACE within a 12-monnth follow-up period is of great importance. These findings emphasize the need for tailored management strategies to mitigate risks in this patient population.

Keywords: cardiovascular diseases, creatinine, echocardiography, heart disease risk factors, myocardial infarction

INTRODUCTION

Despite advancements in the diagnosis, treatment, and monitoring of patients with acute coronary syndrome (ACS), morbidity and mortality following ACS remain high (1). This ongoing challenge has prompted researchers to actively seek possible predictors of adverse outcomes after ACS aiming to identify high-risk patients promptly (2). The latest available report from the Public Health Institute of the Federation of Bosnia and Herzegovina (FB&H) on diseases as causes of death in the population in 2018 revealed acute myocardial infarction as a leading cause, with the rate of 93.5 per 100,000 population (3). Numerous prognostic factors (4–11) for survival are delineated.

Age emerges as the strongest predictor of adverse outcomes, with the risk of adverse outcomes increasing by

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1.7 times for every 10 years of patient age (4,5). Subsequent to age, systolic blood pressure and serum creatinine levels are the next crucial predictors of adverse outcomes, demonstrating that a rise in creatinine levels by 1 mg/dL elevates the risk of mortality by 1.2 times. Other researchers (5,6) proved that left ventricular ejection fraction (LVEF), and creatinine levels are independent predictors of five-year survival rates, suggesting that patients post-ACS with reduced LVEF, as well as chronic kidney disease, should have more frequent check-ups and actively adjust therapy to treat cardiovascular disease complications. Furthermore, red blood cell distribution width (RDW) was highlighted as a significant predictor of systolic and diastolic dysfunction after ST-segment elevation myocardial infarction (STEMI) and primary coronary intervention (PCI), linking high RDW with the development of atrial fibrillation (AF) and heart failure after STEMI (7). Elevated platelet activity is also correlated with the risk of major adverse cardiovascular events (MACE) and it exhibits circadian variations, with peak platelet adhesion occurring in the morning hours, coinciding with a circadian pattern observed in the frequency of ACS and sudden cardiac death, which shows increased cardiovascular event frequency during the early morning hours (8,9). Also, the platelet-to-lymphocyte ratio (PLR) can be used as a predictor of survival (10). Some studies (11) indicated that hyperuricemia may be a risk factor for cardiovascular disease with increased oxidative stress, and serum uric acid is an independent predictor of mortality in coronary artery disease, morbidity in acute myocardial infarction, or congestive heart failure.

At present, there have been no comparable studies in Bosnia and Herzegovina (B&H) that specifically address the identification of risk factors and predictors associated with MACE following ACS. Given the importance of this area of study, gaining deeper insights into the predictors of poor outcomes following ACS is essential for enhancing the quality of patient treatment and care within our local context. This gap underscores the need for further investigation and analysis to better inform clinical practices and interventions tailored to our population's needs.

The aim of this study was to assess the prevalence of risk factors for coronary artery disease in patients with ACS, investigate the occurrence of MACE, explore the association between various biochemical parameters and the incidence of MACE, investigate the correlation between different haematological parameters and the occurrence of MACE, and examine the relationship between different echocardiographic parameters and the incidence of MACE during the 12-month follow-up period after ACS among patients in Bosnia and Herzegovina.

PATIENTS AND METHODS

Patients and study design

This retrospective cohort study that included patients hospitalized with a working diagnosis of ACS between 2019 and 2021, was conducted at the Clinic for Cardiovascular Diseases, Vascular Diseases, and Rheumatism of the Clinical Centre of the University of Sarajevo, B&H. Exclusion criteria were: inadequate or absent medical documentation, patients who underwent primary percutaneous coronary intervention (pPCI) and were not followed up by cardiologists from our Centre, but rather from different regional hospitals, patients who did not give an informed consent to participate in the study, and patients with fatal outcomes not related to ACS.

The participants were followed up for a period of 12 months after discharge due to the occurrence of an adverse outcome defined as MACE (12), which included recurrent ACS requiring PCI or coronary artery bypass grafting (CABG), hospitalization due to anginal symptoms, heart failure, or cardiovascular death. Data on MACE were collected through the analysis of regular follow-up visits, reporting to the Cardiology Outpatient Clinic, or rehospitalization. For the purpose of confirming MACE, an analysis of medical records from the Hospital Information System generated at the Clinic for Cardiovascular Diseases, Vascular Diseases, and Rheumatism, Emergency Medicine Clinic, and other internal medicine clinics within the Clinical Centre of the University of Sarajevo, internal medicine departments of Health Centres, and Emergency Medical Services, as well as mortality records within and outside healthcare facilities, was conducted.

The study was approved by the Ethics Committee of the Institute for Scientific Research of the Clinical Centre of the University of Sarajevo and School of Medicine in Sarajevo.

Methods

Upon admission, each patient underwent a 12-lead electrocardiogram (ECG), and ACS was defined as new-onset ST-segment elevation at the J point in at least two contiguous leads of ≥2 mm (0.2 mV) in males or ≥1.5 mm (0.15 mV) in females in case of STEMI, or NON-STEMI in case of ST segment depression. Additionally, each patient had positive biomarkers for myocardial necrosis: cardiac troponin I (cTnI), aspartate aminotransferase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), potassium (K), and creatine kinase myoglobin binding (CKMB). Data were collected on gender, age, and risk factors: hypertension, dyslipidaemia, smoking, diabetes mellitus, positive family history.

A venous blood sample was taken from each patient, and the following laboratory tests were performed: haematological parameters - white blood count (WBC),

red blood cell count (RBC), platelet count (PLT), haemoglobin (HGB), haematocrit (HCT), and red blood cell distribution width (RDW); biochemical parameters - AST, ALT, CK, LDH, C reactive protein (CRP), cTnI, CKMB, uric acid, Na, K, glucose, glycated haemoglobin (HbA1c), creatinine, lipid profile (total cholesterol, low-density lipoprotein LDL cholesterol - LDL, HDL-cholesterol, triglycerides); protein profile (total proteins, albumin, and globulins).

During hospitalization, each patient underwent two-dimensional (2D), M-mode, and Doppler transthoracic echocardiographic evaluation according to the recommendations of the American Society of Echocardiography Guidelines (13–15). The examination was performed using a Philips Affinity IE 30 machine (Amsterdam, Netherlands) in the echocardiography laboratory. All parameters were measured over 3 cardiac cycles if the patient was in sinus rhythm, or over 5 cycles if the patient was in atrial fibrillation, and then the mean value was calculated.

Left ventricular ejection fraction (LVEF) was calculated using the Teicholtz method (14) in M-mode or the Simpson method (14) in case of regional abnormalities in kinetics. LVEF was calculated as end-diastolic volume minus end-systolic volume divided by end-diastolic volume. The kinetics of the left ventricular walls were determined, where hypokinesia indicated reduced systolic thickening and contraction, akinesia indicated complete absence of systolic thickening and contraction, and dyskinesia indicated aneurysm formation. Assessment of the valvular apparatus was also performed, regarding the presence of stenosis or regurgitation graded as mild/moderate/severe. Diastolic dysfunction was assessed based on mitral flow and the ratio of peak early filling velocities (E wave) and late filling velocities due to atrial contraction (A wave), the so-called E/A ratio, and the deceleration time of the E wave (DCT).

Statistical analysis

The collected data were condensed and subjected to descriptive statistical analysis. For normally distributed data, frequencies and percentages were employed, accompanied by the presentation of mean and standard deviation (mean±SD). Non-normally distributed data were represented by the median and interquartile range (25^{th}, 75^{th} percentile). To explore associations between various variables and specific phenomena, independent samples t-test, Mann-Whitney U test, or $\chi 2$ test, as deemed suitable, were performed. A logistic regression analysis was conducted to assess the influence of various biochemical, haematological, and echocardiographic parameters on the risk of MACE occurrence in participants after ACS. The model including 6 predictor variables: serum creatinine levels, RDW, MPV, platelet count (PLT), left atrial size (LA), and LVEF at discharge. The statistical significance threshold was set at $p<0.05$ (two-sided).

RESULTS

During the period from January 2019 to December 2021, a total of 121 patients after ACS who were followed up were included in the study (15 patients were excluded due to the exclusion criteria). The majority of patients were male, 102 (84.3%), with a mean age of 60.83±12.61 years. Out of 121 patients, 94 (77.7%) had hypertension, 84 (69.4%) dyslipidaemia, 91 (75.2%) diabetes mellitus, 67 (55.4%) were active smokers, and 81 (66.9%) had a positive family history of cardiovascular diseases. The MACE occurred in 33 (27.3%) patients since the initial ACS; those patients were significantly older compared to those who did not experience MACE (mean age of 65.48±12.65 and 59.08±12.21 years), respectively ($p=0.012$).

The patients who experienced MACE post-hospitalization had a significantly higher level of creatinine ($p<0.001$) during hospitalization, while there was no significant difference in the values of other biochemical and haematological parameters.

No significant difference in RDW values between patients with and without MACE after discharge was found. Also, no significant difference in the PLR during hospitalization between patients with and without MACE: 23.35 (18.89-29.3) and 23.38 (20.3-31.51), respectively after discharge ($p=0.675$). No significant difference was found in the maximum serum troponin values between patients with and those without MACE: 2065.00 (629.5-3777.5) and 1120 (384.5-3984.5) ng/m L), respectively, after discharge ($p=0.350$). Patients who experienced MACE after discharge had significantly higher serum creatinine values during hospitalization compared to patients who did not experience MACE, 117 (85.5-159.5) and 84.5 (72.8-101.0) µmol/L, respectively ($p<0.001$) (Table 1).

Out of 121 patients after ACS, 57 (47.1%) had mildly reduced systolic function, and 50 (41.3%) had reduced systolic function. Severe mitral insufficiency was found in five (4.13%). Eight patients (7%) experienced rhythm disturbance in the form of atrial fibrillation. The patients who experienced MACE after discharge had a significantly lower LVEF ($p<0.001$). The patients who experienced MACE had a significantly larger left atrial diameter ($p=0.032$) (Table 1).

A logistic regression analysis including 6 predictor variables showed statistical significance ($p<0.001$). The model as a whole explains between 22.7% and 32% of the variance in the occurrence of MACE in patients after ACS and accurately classifies 72.3% of cases. Two variables showed a statistically significant contribution to

Table 1. Haematological and biochemical parameters during hospitalization in patients with and without major adverse cardiac events (MACE) since the initial acute coronary syndrome (ACS)

Laboratory parameters	Reference values	Patients without MACE (N=88)	Patients with MACE (N=33)	Total (N=121)	p
Leukocytes (median; 25th, 75th percentile) (x10^9)/L	4-10	12.0 (10.2-15.1)	12.7 (10.7-15.7)	12.0 (10.2-15.1)	0.571
Erythrocytes L (mean±SD) (x10^{12})/	4.3-5.7	4.7±0.6	4.6±0.7	4.7±0.6	0.557
Platelets (median; 25th, 75th percentile) (x 10^9)/L	150-400	246.5 (209.2-290.0)	224.0 (205.0-276.0)	243.0 (207.0-288.0)	0.707
Haemoglobin (mean±SD) (g/L)	138-175	140.5±17.9	137.6±24.4	139.7±19.9	0.540
Haematocrit (mean±SD) (%)	41-53	41.9±5.4	40.9±7.3	41.6±5.9	0.535
MPV (fL) (mean±SD) (%)	7.4-10.4	8.1±1.8	8.3±1.5	8.2±1.8	0.312
RDW (median (25th, 75th percentile) (%)	11.5-15.5	12.4 (11.6-13.6)	12.1 (11.6-14.3)	12.4 (11.6-14.1)	0.582
Platelet/lymphocyte ratio (median; 25th, 75th percentile)	36.6-149.1	23.4 (20.3-31.5)	23.3 (18.9-29.3)	23.3 (20.2-30.9)	0.675
Troponin (median; 25th, 75th percentile) (ng/L)	0-14	2065.0 (629.5-3777.5)	1120.0 (384.5-3984.5)	1854.0 (556.0-3766.0)	0.350
CKMB) (median; 25th, 75th percentile) (U/L	<25	152.0 (67.7-337.5)	120.0 (61.0-222.0)	126.0 (68.0-319.0)	0.359
Uric acid (mean±SD) (µmol/L)	154-357	341.8±88.2	361.1±74.0	348.4±84.4	0.670
Creatinine) (median; (25th, 75th percentile) (µmol/L	45-90	84.5 (72.7-101.0)	117.0 (85.5-159.5)	89.0 (75.0-113.0)	<0.001
Cholesterol (median; 25th, 75th percentile) (mmol/L)	3.1-5.2	5.1 (4.1-6.1)	5.1 (4.3-6.0)	5.1 (4.2-6.1)	0.516
LDL (mmol/L) (median (25th, 75th percentile) (mmol/L)	2.0-4.3	2.9 (2.1-3.8)	2.9 (2.6-3.9)	2.9 (2.3-3.8)	0.798
HDL (median; 25th, 75th percentile) (mmol/L)	1.04-1.50	1.0 (0.8-1.2)	1.0 (0.8-1.1)	1.0 (0.8-1.2)	0.344
Triglycerides (median; 25th, 75th percentile) (mmol/L)	0.11-1.70	1.7 (1.5-2.5)	1.9 (1.2-2.7)	1.7 (1.3-2.5)	0.765
Albumin (median; 25th, 75th percentile) (g/L)	35-50	37.0 (34.0-39.0)	36.0 (33.0-40.0)	37.0 (34.0-39.0)	0.976
Sodium (median; 25th, 75th percentile) (mmol/L)	136-145	139.0 (138.0-141.0)	139.0 (138.0-140.0)	139.0 (138.0-140.0)	0.200

MACE, major adverse cardiac events; MPV, mean platelet volume; RDW, red cell distribution width, CKMB, creatine kinase myoglobin binding; LDL, low density lipoprotein cholesterol; HDL, high density lipoprotein cholesterol

the model, namely LVEF at discharge and serum creatinine level. The strongest predictor of MACE was LVEF, with OR=0.92, indicating that with 1% increase in LVEF, the probability of MACE occurrence decreases by 8% (Table 2).

DISCUSSION

During the period from 2019 to 2021, there was a notable prevalence of MACE among patients diagnosed with ACS. The majority patients were male, older and with prevalent cardiovascular risk factors. The patients who experienced MACE were older, exhibited elevated level of creatinine, lower LVEF and larger LA at discharge compared to those who did not experience MACE. Logistic regression analysis underscored the significance of serum creatinine level and LVEF as key predictors of MACE. The findings of our study highlight the importance of age, creatinine levels, and echocardiographic parameters, particularly LVEF and LA, in predicting adverse cardiovascular events post-ACS.

In terms of gender, the results of our study showed a significantly higher representation of males compared to

females, and these results correlate with similar studies (16). The demonstrated gender differences in coronary artery disease, with higher prevalence of males are confirmed by other studies too (17–19).

Table 2. Logistic regression model for predicting the likelihood of major adverse cardiac events (MACE) occurrence in patients after ACS

Variable	B	p	Odds ratio (95% CI)
Creatinine	0.014	0.017	1.014 (1.003-1.026)
LVEF	-0.079	0.013	0.924 (0.869-0.984)
LA	-0.171	0.749	0.843 (0.295-2.409)
RDW	0.097	0.122	1.102 (0.974-1.246)
PLT	-0.006	0.065	0.994 (0.987-1.000)
MPV	-0.018	0.892	0.982 (0.456-1.276)
Constant	1.583	0.643	4.869

B, the estimated coefficient; CI, confidence interval; LVEF, left ventricular ejection fraction; LA, left atrium; RDW, red cell distribution width; PLT, -platelets; MPV, mean platelet volume

Our study revealed 27.3% of patients encountered MACE following discharge from hospital. It is slightly lower compared to the findings from a Finish study (20), which found 34.4% MACE within the first year, and 48.4% within three years. This suggests that factors such as regional differences or patient demographics may influence MACE rates post-ACS. Moreover, disparities in post-ACS cardiologist follow-up may also contribute to variations in our data, as many patients are inconsistent with regular checkups.

Through the analysis of haematological and biochemical parameters, significantly higher levels of creatinine were found in the group of patients who experienced MACE after hospitalization. Although creatinine is not given much prognostic significance in existing literature for patients diagnosed with ACS, it has proven to be more significant than cardiac necrosis markers in ACS (3). Granger et al. (4) found that an increase in creatinine by 1 mg/dL causes a 1.2 times higher risk of mortality. What arises as a question is whether creatinine as an unfavourable survival predictor was a result of renal damage due to comorbidities such as diabetes and hypertension, or if the reduction in LVEF after ACS led to decreased stroke volume and reduced renal perfusion (cardiorenal syndrome type 1).

We found that patients who experienced MACE at discharge had a significantly lower LVEF compared to patients who did not, which could be attributed to the fact that patients with lower LVEF had a more extensive infarction and a greater propensity for heart failure and mortality (4,5,20). The outcomes align with similar studies (21), showing that patients with mid-range preserved LVEF have a 1.6-fold higher mortality risk, while those with reduced LVEF face a threefold increased risk of death and recurrent hospitalizations. This may be due to a higher likelihood of heart failure exacerbations and malignant arrhythmias in these patients (22).

Through analysis of left atrial size, a significant difference in left atrial dimensions was observed between patients who experienced MACE. In some studies (23) it was demonstrated that an increase in LA is significantly associated with MACE in patients within one-year post-discharge. LA dilation may serve as a marker of prolonged exposure to cardiovascular risk factors such as hypertension or obesity, or it may indicate overall structural heart disease in patients with ACS, mitral valve stenosis, or left ventricular dysfunction (24).

One of the significant drawbacks of our study is the relatively small sample size, limiting the generalizability of the results to the entire population of patients with ACS. Since this is a retrospective cohort study, all data used were obtained from hospital registries, discharge letters, hospital information systems, and similar sources. Therefore, additional limitations of this study include the lack of historical data on the duration and treatment of the risk factors, as well as a more detailed analysis of previous therapy. Further prospective and retrospective studies with a larger number of participants are needed to further elucidate the relationship between risk factors in ACS and predictors of worse disease outcomes, aiming for more successful prevention and treatment strategies.

In conclusion, our investigation identified critical factors linked to MACE following ACS. Age was a significant predictor, with older patients more prone to MACE. Elevated creatinine level and lower LVEF values were independently associated with MACE, indicating the importance of assessing both cardiac and renal functions following ACS. Haematological parameters did not predict MACE within 12 months. Larger left atrial dimensions were also notable in patients with MACE. These findings highlight the need for comprehensive risk evaluations to improve outcomes for ACS patients and suggest further research to enhance preventive and therapeutic strategies.

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TRANSPARENCY DECLARATION

Conflict of interests: None to declare.

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