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Prognostic value of low and moderately elevated C-reactive protein in acute coronary syndrome: A 2-year follow-up study

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Background: The main goal of this study was to improve diagnostic and predictive value of low and moderately elevated C-reactive protein (CRP) in patients with acute coronary syndrome (ACS), related to noninvasive clinical parameters, in order to improve and prolong patient life with low or no additional costs.

Material/Methods: A prospective, open clinical study was conducted at the University Hospital Split, Croatia with 112 patients with ACS and low or moderately elevated CRP (<3.0 mg/L). After diagnosing ACS, data on physical activity, alcohol consumption, and functional status were recorded. Anthropometric measurements were made. Blood and urine samples were taken for analyses. Electrocardiographic, ergometric, and echocardiographic testing was performed. A total of 72 parameters were monitored at the time of hospital admission in ACS patients to analyze which ones could predict disease outcome at the end of follow-up in patients with low or moderately elevated CRP. Patients were followed up for 2 years.

Results: The variables that were predictive of major adverse cardiac events (MACE) within 2 years of ACS hospitalization were hemoglobin, fibrinogen, antithrombin III, cholesterol levels, brain natriuretic peptide, and microalbuminuria. ACS patients with CRP <3.0 mg/L had significantly higher risk of developing MACE within 2 years if ≥50% of the 8 key parameters were outside the reference values.

Conclusions: Major adverse cardiac events can be predicted in patients with acute coronary syndrome whose CRP values are low or moderately elevated.

Key words: acute coronary syndrome • C reactive protein • prognosis

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Background

Acute coronary syndrome (ACS) is a broad term encompassing a number of clinical conditions with the clinical signs and symptoms of myocardial ischemia, including unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI) [1–5]. Patients with ACS are frequently seen in emergency departments and are often admitted for in-hospital care [6,7].

C-reactive protein (CRP) is an acute phase reactant synthesized by the liver [8]. CRP production increases in response to a variety of systemic events such as infection, trauma, or autoimmune inflammatory diseases. As a sensitive, nonspecific marker for ongoing chronic inflammation, the role of CRP is significant because inflammation plays a role in the pathogenesis of ACS [9,10]. CRP has consistently been shown to be a useful prognostic indicator in ACS and is a strong predictor of future coronary events in apparently healthy individuals. Additionally, CRP can identify individuals with normal lipid levels who are at increased risk for future coronary events [11–13]. Prognostic relevance of CRP levels was also found in initially healthy middle-aged men. Lowering of C-reactive protein is associated with reduced cardiovascular disease risk. This observation has lead to the conclusion that CRP is no longer merely a marker, but is increasingly considered a mediator of cardiovascular disease [14].

High CRP levels are associated with major adverse cardiac events (MACE) and higher mortality [15–17]. However, there are ACS patients with low or moderately elevated CRP (<3.0 mg/L) who also experience MACE. Therefore, it would be beneficial to study prognostic value of low and moderately elevated CRP levels for patients with ACS, to help physicians identify patients at risk of future adverse cardiac events and to choose appropriate therapy. Therefore, new risk-based diagnostic protocols are necessary in those patients to improve overall outcome and reduce future cardiac events.

The main goal of this study was to improve the diagnostic and predictive value of low and moderately elevated CRP in patients with ACS, related to noninvasive clinical parameters, in order to improve and prolong patient life with low or no additional costs.

Material and Methods

Study design and setting

A prospective, open clinical study was conducted at the Coronary Unit, Department of Internal Medicine, University Hospital Split from February 2005 to October 2011. Convenience sampling was used.

Study participants

During the study, 589 patients with ACS diagnosed according to the European Society of Cardiology (ESC) guidelines were assessed for inclusion in the study. Out of 589 patients with ACS, 112 (19%) patients meeting the inclusion criteria were considered eligible and were enrolled in the study in a prospective manner.

Inclusion criteria

Patients aged 18–85 years, with clear clinical signs of ACS and with CRP values <3.0 mg/L, were included in the study. ACS comprised unstable angina pectoris, acute myocardial infarction with elevated ST-segment elevation (STEMI), and acute myocardial infarction without ST-segment elevation (NSTEMI).

Unstable angina pectoris was diagnosed in patients with acute chest pain and prolonged (>20 min) anginal pain at rest, new onset (*de novo*) angina (Class II or III of the Classification of the Canadian Cardiovascular Society), with recent destabilization of previously stable angina with at least Canadian Cardiovascular Society Class III angina characteristics (crescendo angina), or those with post-myocardial infarction angina with changes of ST segment typical for myocardial ischaemia and without rise of troponin activity in several consecutive measurements [18].

STEMI was diagnosed in patients with acute chest pain and persistent (>20 min) ST-segment elevation in 2 concomitant leads, accompanied by typical rise of cardiac biomarkers in several consecutive measurements, especially troponin and creatine kinase. This generally reflects an acute total coronary occlusion [19,20].

NSTEMI was diagnosed in patients with acute chest pain, prolonged over 20 minutes, but without persistent ST-segment elevation. These patients have rather persistent or transient ST-segment depression or T-wave inversion, flat T waves, pseudo normalization of T waves, or no ECG changes at presentation, accompanied by typical rise of cardiac biomarkers, especially troponin and creatine kinase, in several consecutive measurements [18].

Exclusion criteria

To avoid variables that could influence CRP serum levels, we excluded patients with liver diseases (bilirubin >30 µmol/L, γGT >75 U/L), chronic kidney lesions (creatinine >200 µmol/L), coagulopathies, hemorrhagic diathesis, neoplasms, gastrointestinal hemorrhage, collagenoses, hypokalemia (<3.5 mmol/L), obesity, gout, uricemia (>536 µmol/L), and insulin-dependent diabetes. We excluded patients who were immunocompromised, with insulin-dependent diabetes, history of alcohol or

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substance abuse, women who had recently given birth, patients who participated in another clinical study within 3 months, and those treated with corticosteroids, NSAIDs, neuroleptics, and antidepressives.

Study protocol

Diagnosis of ACS was established after taking patient history, clinical examination, ECG, and measuring standard biomarkers. A structured questionnaire was used for collecting patient data. Data on physical activity, alcohol consumption, and functional status were recorded. Anthropometric measurements were made. Blood and urine samples were taken for analyses. Electrocardiographic, ergometric, and echocardiographic tests were performed.

Patients were followed up for 2 years after hospital discharge. Follow-up visits with a cardiologist were scheduled 1 month after discharge and then every 3 months until the end of the study. During follow-up, patients were monitored for major adverse cardiac events (MACE), including acute myocardial infarction, ischaemic stroke, coronary arterial occlusion, death), which were considered as end-points. Otherwise, measurements were obtained at the end of the study. Standard treatment methods according to the current guidelines were utilized. After completing data collection in all patients, we studied an association between the variables collected on admission and patient outcome after 2 years.

Variables

At the time of hospital admission, 72 parameters were monitored in ACS patients, to analyze which ones could predict disease outcome at the end of follow-up in patients with low or moderately elevated CRP. The parameters were divided into 8 groups: inflammatory, traditional, coagulation/hyperviscosity, biomarkers, anthropometric, electrocardiographic, ergometric, and echocardiographic.

Inflammatory variables were erythrocyte sedimentation rate, white blood cell (WBC) count, anti-cardiolipin antibodies IgG and IgM, and microalbuminuria. Traditional variables were family history of ACS, personal history of ACS, hypertension, diabetes mellitus, hyperlipidemia, dyslipidemia, smoking, physical activity, alcohol consumption, and total number of traditional risk factors. Coagulation/hyperviscosity variables were fibrinogen, antithrombin III, homocysteine, plasminogen activator inhibitor – 1 (PAI-1), D-dimer, platelets, and hemoglobin. Analyzed biomarkers were aspartate-transaminase (AST), alanine- transaminase (ALT), creatine kinase (CK), MB fraction of creatine kinase (MB-CK), lactate dehydrogenase (LDH), troponin T, precursor of brain natriuretic peptide (pro-BNP), and brain natriuretic peptide (BNP). Anthropometric indicators were age, sex, systolic blood pressure, diastolic blood pressure, basal heart rate, body mass index, adiposity measured with hip and waist circumference, and functional status according to the New York Heart Association (NYHA) classification.

Electrocardiographic (ECG) indicators that were analyzed included: location of changes, type of ST segment changes, basal heart rate, heart frequency, therapy with beta-blockers, signs of left ventricular hypertrophy in ECG, conduction disturbances in ECG, duration of QRS complex, early ventricular ectopic activity, late ventricular ectopic activity, heart rate variability parameters, average RR interval, standard deviation of RR intervals of non-ectopic impulses, standard deviation of the average normal RR intervals for all 5-minute segments of the 24-hour recordings, square root of the mean squared differences of successive RR intervals, percent of heart beats where difference between new R-R interval and previous RR interval is greater than 50 ms, and recorded ischemia.

Analyzed ergometric parameters were: test of coronary flow reserve, assessment of workload measured by metabolic equivalents, maximum heart rate during treadmill testing, ectopic ventricular activity, recovery of the heart rate, and NYHA classification. Echocardiographic parameters were systolic and diastolic dysfunction, left ventricular ejection fraction, dimensions of heart chambers, wall motion score index, and heart valve function.

Blood sampling laboratory investigations were conducted upon hospital admission, as well as analysis of urine. Some of the cardiac biomarkers (AST, CK, MB, and troponin T) were sampled several times, and for the purpose of this study the highest values were used.

Hs-CRP was measured in each patient on admission. A native value, unrelated to possible medical interaction, was mandatory for this study. The classical acute phase reactant CRP, described by Tillett and Francis in 1930 [8], appears in markedly elevated concentration in the sera of individuals undergoing reactions of acute inflammation. The traditional CRP test uses immunoassay methods that are sensitive to concentrations of 5–20 mg/L. The hs-CRP test, with its increased sensitivity, is able to detect C-reactive protein at lower levels (0.5–10.0 mg/L). In 2002, the AHA and CDC recommended measurement of hs-CRP as an aid in the diagnosis and treatment of CVD [21]. At low levels it can detect persons at risk for cardiac heart disease. At high levels in those with no history of heart disease, it indicates high risk for AMI, stroke, or peripheral vascular disease. For patients with ACS or stable coronary disease, hs-CRP is used to predict future coronary events. Ranges of hs-CRP in prediction of risk for CVD are: <1.0 mg/L for low CVD risk, 1.0–3.0 mg/L for average risk for CVD, and >3.0 mg/L for high risk for future CVD. Results >10.0 mg/L are considered for an acute or active chronic inflammatory condition due to

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Table 1. Value of the 8 key variables in study participants on admission.

Variable*	Patients with MACE	Patients without MACE	*P*
Hb (g/L)	118.54±22.43	137.73±14.88	<0.000
FI (mg/L)	5.70±1.45	4.18±1.55	0.045
ATIII (%)	97.61±13.79	142.81±21.91	<0.000
TC (mmol/L)	6.09±1.26	4.93±1.39	<0.000
LDL (mmol/L)	4.61±1.18	3.41±1.28	<0.000
CH/HDL	5.34±2.04	3.88±1.73	<0.000
pro-BNP (pg/mL)	715.97±446.68	226.53±87.54	<0.000
MAU (µg/mL)	70.63±30.59	34.99±23.02	<0.000

* Hb – hemoglobin; FI – fibrinogen; ATIII – antithrombin III; TC – total cholesterol; LDL – low-density lipoprotein; CH/HDL – ratio of total cholesterol and high-density lipoprotein; BNP – brain natriuretic peptide; MAU – microalbuminuria.

non-cardiovascular cause (eg, active arthritis, lupus, infection) and do not necessarily implicate cardiovascular risk. Values of this parameter are indicated as hs-CRP throughout this article.

Standard 12-lead ECG was performed on a 3-channel Electrocardiograph Cardiostat 31S® (Siemens, Germany) and a 6-channel digital Electrocardiograph MAC® 1200 ST (General Electric Medical Systems, USA).

Exercise testing was performed pre-discharge on a treadmill (Siemens Megacart v. 4.8 Burdick T600, Siemens Elema AB, Sweden). A standard exercise test was conducted according to the Bruce protocol, with progressive increase of the workload.

Echocardiography was performed using a Mark® 8 (Advanced Technology Laboratories Inc., USA) and a Sonotron® Vingmed CFM 800 (Vingmed, Finland).

Data analysis

Patient data were entered into spreadsheets and analyzed using Statistical Package for the Social Sciences software (SPSS v. 16.0, IBM, Armonk, NY, United States). Descriptive statistics was calculated for each variable, and their differences were tested using Student's t-test and the χ^2 test. For calculating contribution of all variables to disease outcome, regression analysis was performed. For calculating contribution of individual variables to disease outcome, hierarchical and stepwise regression analyses were conducted. Correlations were calculated using Spearman's rho correlation coefficient. Statistical significance was set at $P<0.05$.

Ethics

The study was approved by the Ethics Committee of University Hospital Split.

Results

Among 112 patients included in the study, there were 81 men (72%) and 31 women (28%). The average age of the study participants was 68.53±7.68 years.

During the 2-year follow-up, 39 (34.8%) study participants with low or moderately elevated CRP at hospital admission had experienced MACE, and their average age was 68.26±7.26 years. Among patients experiencing MACE, there were 24 (61.5%) men and 15 (38.5%) women. The average ages of men and women with MACE were 67.8±7.15 years and 68.53±7.68 years, respectively.

A series of correlation analyses was conducted to analyze association of 72 traditional, inflammatory, coagulation/hyperviscosity, biomarkers, anthropometric, electrocardiographic, ergometric, and echocardiographic variables with CRP. Among them, the 8 variables that were significantly associated with CRP values on admission were: hemoglobin (r=–0.202; $P<0.001$), fibrinogen (r=0.255; $P=0.002$), antithrombin III (r=–0.036; $P<0.0001$), total cholesterol (r=0.258; $P=0.002$), total cholesterol/LDL ratio (r=0.174; $P=0.025$), pro BNP (r=0.618; $P<0.001$), BNP (r=0.317; $P<0.001$), and microalbuminuria (r=0.388; $P<0.001$). These 8 variables were then studied in detail to assess their predictive value for patient outcome within 2 years of hospitalization for ACS.

Patients experiencing MACE during follow-up had significantly higher CRP at the tie of hospital admission compared to patients without MACE (2.128±0.61 mg/l *vs.* 1.84±0.72 mg/l, $P=0.044$). Values of all the 8 key variables recorded on admission were significantly different between these 2 patient groups (Table 1). Logistic regression revealed that all 8 variables were significantly associated with MACE during follow-up (Table 2).

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Table 2. Logistic regression analysis of 8 variables in 112 patients with MACE and low or moderately elevated CRP.

Variable*	Score	df	*P*
Hb	23.584	1	<0.001
FI	4.021	1	0.045
ATIII	62.030	1	<0.001
TC	16.263	1	<0.001
LDL	19.552	1	<0.001
CH/HDL	53.228	1	<0.001
pro-BNP	39.484	1	<0.001
MAU	34.175	1	<0.001

* DF – degrees of freedom; Hb – hemoglobin; FI – fibrinogen; ATIII – antithrombin III; TC – total cholesterol; LDL – low density lipoprotein; CH/HDL – ratio of total cholesterol and high density lipoprotein; BNP – brain natriuretic peptide, MAU – microalbuminuria.

Table 3. Spearman's rho correlation coefficients between variables.

Variable	CRP	Hb (g/L)	FI (mg/L)	AT III (%)	CH (mmol/L)	LDL (mmol/L)	CH/HDL	pro-BNP (pg/mL)	Microalb (mg/mL)	Outcome at 2 years
CRP		–0.212*	0.149	–0.150	0.306**	0.342**	0.153	0.209*	0.251**	–0.187*
Hb	–0.212*		–0.319**	0.353**	–0.377**	–0.398**	–0.366**	–0.383**	–0.279**	0.421**
FI	0.149	–0.319**		–0.532**	0.368**	0.388**	0.427**	0.407**	0.419**	–0.571**
AT III	–0.150	0.353**	–0.532**		–0.328**	–0.394**	–0.556**	–0.400**	–0.426**	0.761**
TC	0.306**	–0.377**	0.368**	–0.328**		0.902**	0.510**	0.418**	0.374**	–0.408**
LDL	0.342**	–0.398**	0.388**	–0.394**	0.902**		0.633**	0.467**	0.451**	–0.436**
CH/HDL	0.153	–0.366**	0.427**	–0.556**	0.510**	0.633**		0.488**	0.472**	–0.671**
pro-BNP	0.209*	–0.383**	0.407**	–0.400**	0.418**	0.467**	0.488**		0.453**	–0.626**
MAU	0.251**	–0.279**	0.419**	–0.426**	0.374**	0.451**	0.472**	0.453**		–0.531**

* Statistical significance at $P<0.05$; ** statistical significance at $P<0.01$; Hb – hemoglobin; FI – fibrinogen; ATIII – antithrombin III; TC – total cholesterol; LDL – low density lipoprotein; CH/HDL – ratio of total cholesterol and high density lipoprotein; BNP – brain natriuretic peptide, MAU – microalbuminuria.

Correlation analyses between the 8 key variables revealed that CRP on admission was significantly associated with hemoglobin, total cholesterol, LDL cholesterol, pro-BNP or BNP, microalbuminuria, and disease outcome at 2-year follow-up (Table 3). Disease outcome at 2-year follow-up was significantly associated with all 8 key variables. MACE during follow-up was significantly associated with lower values of hemoglobin and antithrombin III, and with higher values of CRP, fibrinogen, total cholesterol, LDL, total cholesterol/HDL ratio, pro BNP, and microalbuminuria (Table 3).

Patients were then categorized according to the number of the 8 variables that were outside of the reference values into those with <4 and those with ≥4 variables outside the reference range. A significant difference in MACE during 2-year follow-up was found in the group of patients that had ≥50% of the 8 key variables outside of the reference range (χ^2=71.559; DF=1; $P<0.001$) (Table 4).

A hierarchical regression analysis was conducted to examine the influence of the 8 key variables on disease outcome within 2-year follow-up. The analysis revealed that 6 variables explain 71.4% of variance of the criterion variable 'disease outcome', with a significant contribution, including antithrombin III, total cholesterol, LDL, total cholesterol/HDL ratio, pro BNP, and microalbuminuria (Table 5).

Stepwise regression analysis was conducted to determine the best predictors of MACE within 2 years of hospitalization for

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Table 4. Frequency of variables outside of reference range in patients with our without MACE during 2-year follow-up.

Patient group	Variables outside of reference range, N (%)		*P*
	<4	≥4	
Patients with MACE	2 (3)	37 (80.4)	<0.001
Patients without MACE	64 (97)	9 (19.6)	

MACE – major adverse cardiac events.

Table 5. Hierarchical regression analysis of the 8 key variables.

Variable	*B*	*SE B*	β	t	*P*
Constant	1.494	0.381		3.917	0.000
Hb	0.003	0.002	0.094	1.489	0.139
FI	0.006	0.009	0.035	0.650	0.517
ATIII	0.010	0.001	0.455	6.837	0.000
TC	–0.120	0.054	–0.278	–2.218	0.029
LDL	0.137	0.060	0.301	2.274	0.025
CH/HDL	–0.022	0.007	–0.201	–3.028	0.003
pro-BNP	0.000	0.000	–0.283	–4.300	0.000
MAU	–0.003	0.001	–0.133	–2.068	0.041

Hb – hemoglobin; FI – fibrinogen; ATIII – antithrombin III; TC – total cholesterol; LDL – low density lipoprotein; CH/HDL – ratio of total cholesterol and high density lipoprotein; BNP – brain natriuretic peptide; MAU – microalbuminuria.

Table 6. Stepwise regression analysis predicting MACE within 2 years of hospitalization for ACS.

Model	R	R2	Corr R2	SE	ΔR^2	F	df1	df2	*P*
1	0.484	0.234	0.227	0.54891	0.234	33.633	1	110	0.000
2	0.493	0.243	0.229	0.54819	0.009	1.287	1	109	0.259
3	0.751	0.564	0.551	0.41822	0.320	79.275	1	108	0.000
4	0.759	0.577	0.561	0.41383	0.013	3.306	1	107	0.072
5	0.761	0.580	0.560	0.41434	0.003	0.737	1	106	0.392
6	0.803	0.644	0.624	0.38298	0.065	19.065	1	105	0.000
7	0.838	0.702	0.682	0.35234	0.058	20.056	1	104	0.000
8	0.845	0.714	0.691	0.34692	0.012	4.278	1	103	0.041

R – correlation coefficient; Corr R2 – corrected R2; SE – standard error; ΔR^2 – change of R; F – F-statistics; DF – degrees of freedom.

ACS (Table 6). Variables were entered in the same order as in the first version of the regression analysis. The contribution of predictors changes when they were entered individually; after each input in the regression equation a portion of variance was calculated. The stepwise regression analysis confirmed the significant contribution of all variables except hemoglobin and LDL cholesterol. Hemoglobin explains 23.4% of variance in the criterion variable (disease outcome/MACE), and contribution of this variable subsequently decreased as the other variables were entered into the equation. When hemoglobin was entered as the last variable, its contribution was not significant. The variable 'antithrombin III' explained 32% of the variance.

After the variable 'hemoglobin' was excluded from the stepwise regression analysis, contribution of the remaining variables

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Table 7. Stepwise regression analysis predicting MACE within 2 years of hospitalization for ACS, without variable hemoglobin in the analysis.

Model	R	R2	Corr R2	SE	ΔR^2	F	df1	df2	*P*
FI	0.158	0.025	0.016	0.61938	0.025	2.809	1	110	0.097
ATIII	0.717	0.514	0.505	0.43927	0.489	109.697	1	109	0.000
TC	0.739	0.545	0.533	0.42681	0.031	7.457	1	108	0.007
LDL	0.740	0.547	0.530	0.42803	0.002	0.386	1	107	0.536
CH/HDL	0.789	0.622	0.605	0.39259	0.075	21.186	1	106	0.000
pro-BNP	0.834	0.696	0.679	0.35401	0.073	25.366	1	105	0.000
MAU	0.841	0.707	0.688	0.34894	0.011	4.070	1	104	0.046

Hb – hemoglobin; FI – fibrinogen; ATIII – antithrombin III; TC – total cholesterol; LDL – low density lipoprotein; CH/HDL – ratio of total cholesterol and high density lipoprotein; BNP – brain natriuretic peptide; MAU – microalbuminuria; R – correlation coefficient; Corr R2 – corrected R2; SE – standard error; ΔR^2 – change of R; F – F-statistics; DF – degrees of freedom.

increased, with antithrombin III explaining 48.9% of the variance in this analysis (Table 7).

Discussion

The main finding of this study is that major adverse cardiac events can be predicted in patients with acute coronary syndrome whose CRP values are low or moderately elevated. The main hypothesis of this study was that patients with CRP <3.0 mg/L are at risk of MACE. This hypothesis was confirmed: the 8 key variables that help predict MACE within 2 years of ACS hospitalization were hemoglobin, fibrinogen, antithrombin III, total cholesterol, total cholesterol/LDL ratio, pro BNP, BNP, and microalbuminuria. Furthermore, ACS patients with CRP <3.0 mg/l had significantly higher risk of developing MACE within 2 years if ≥50% of the 8 key parameters are outside the reference values.

Patients with acute chest pain are frequently seen in emergency departments. After initial assessment, including ECG and chest radiograph, a quarter of patients will be left with no clear diagnosis [22]. Undiagnosed patients present a difficult challenge for healthcare professionals. Most of them will have a benign cause of their pain; however, discharging them to home bears the risk of inadvertently discharging patients with ACS [23].

ACS covers the whole spectrum of clinical conditions; ACS patients are a heterogenous population with varying degrees of risk of MACE in short-term and long-term follow-up. Among patients without myocardial necrosis, a mild elevation of troponins and elevated CRP level without systemic inflammatory disease may reflect widespread activation of inflammatory cells and coronary disease activity [24].On the other end of the ACS spectrum are patients with myocardial damage where CRP predominantly reflects the extent of inflammatory response to myocardial necrosis [25]. Since CRP is a sensitive but nonspecific marker that can reveal underlying inflammation, in this study we excluded patients with acute or chronic inflammatory diseases so that those conditions would not confound the interpretation of study results.

Damage to the coronary vessels by atherosclerosis is usually reflected in the clinical course of ACS. As an inflammatory disease, atherosclerosis is associated with more intense expression of inflammatory markers. Therefore, higher titers of CRP at the time of hospital admission of a patient with ACS may be associated with a greater risk of poor outcomes. A higher level of inflammatory markers may indicate which patients have greater risk of future adverse events [26].

Clinical trials published to date have clearly shown an association between the clinical course of coronary disease and CRP values [27,28]. Although there are still uncertainties about the clinical utility of continued CRP measurements in patients with ACS, an examination of the predictive validity of CRP revealed that the future occurrence of death is associated with higher CRP values at admission and at 1 month after hospital discharge [26].

Data from the literature regarding ACS and sex indicate that ACS is more common among men [29]. In most of the clinical studies on ACS, women account for fewer than 40% of participants [30]. In large clinical trials, differences related to sex were noted in clinical presentation of ischemic heart disease, as well as in the patient outcomes [31–33]. In our study there were more men than women affected with ACS and more men

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experienced MACE compared to women (62% *vs.* 38%), thus our sex-related findings on ACS and its adverse events are in accordance with the available literature.

In patients with ACS, anemia can worsen myocardial ischemia, but data relating to hemoglobin and clinical outcomes of ACS remain limited [34]. In this study we found a significant negative correlation of hemoglobin values with CRP on admission. However, we did not find an association between hemoglobin values at the time of admission to the hospital with patient outcomes after 2-year follow-up. In an earlier study of 39 922 patients enrolled in clinical trials of ACS, an association between baseline hemoglobin values and MACE through 30 days was analyzed and found that anemia is a powerful and independent predictor of MACE in patients across the spectrum of ACS [34]. Anemia negatively influences myocardial ischemia in ACS syndromes because it decreases oxygen content of the blood supplied to the damaged myocardium [35] and increases oxygen demand through higher cardiac output, which is necessary to maintain appropriate systemic oxygen supply [36].

Fibrinogen is commonly cited in the literature as a potential risk factor for cardiovascular disease [37]. Fibrinogen is a protein essential for blood clotting; it is a precursor of fibrin and one of the main factors determining blood viscosity and platelet aggregation. In conditions with increased endothelial inflammation (e.g., ACS), coagulation process is activated [38]. Fibrinogen, like CRP, is also an acute-phase reactant produced by the liver during inflammation. An increased level of fibrinogen is considered an indirect marker of tissue activity. In clinical settings, high levels of coagulation activity markers can identify patients who could respond to anticoagulant therapy [39]. We found that baseline fibrinogen CRP levels were associated, as well as positive correlation between higher fibrinogen values and MACE at the end of 2-year follow-up. However, in the regression analysis fibrinogen was not found to be a predictor of negative patient outcome.

Antithrombin III is an endogenous coagulation inhibitor. It was previously found that the level of antithrombin III is significantly lower in patients with ACS compared to patients with stable angina [40]. In our study as well, lower antithrombin III values were associated with CRP values at baseline, and lower antithrombin III values were significantly correlated with adverse ACS patient outcomes after 2 years. Antithrombin III was also a significant predictor of an adverse outcome in regression analyses.

We found that total cholesterol, LDL cholesterol, and total cholesterol/LDL ratio at the time of ACS patient presentation were significant predictors of patient outcome after 2 years. Abnormal lipids are a risk factor for developing cardiovascular disease [41]. Current clinical guidelines for managing patients with ACS recommend measuring serum lipids within 24 hours of admission, as well as lipid-lowering therapy as a secondary prevention [42]. Authors of the SPACE ROCKET study even recommend that serum lipids should be measured within the first hours after a patient presents with ACS [43]. However, many physicians do not measure serum lipid early after admission of an ACS patient, which can negatively impact the potential of lipid-lowering therapy [44]. Data from 26 studies from 1963 to 2008 show that total cholesterol falls for the first 2 weeks after ACS and takes 1–3 months to recover [43]. These data are in contrast with findings of Pitt et al that lipid variables do not significantly change after ACS [45], indicating that more studies are needed to fully determine the extent of lipid changes after ACS presentation. Findings of our study support the current guidelines and views that lipid variables should be tested early after ACS presentation.

BNP was significantly associated with CRP levels on admission and it was also a significant predictor of MACE 2 years after ACS presentation in this study. BNP is an indicator of long-term mortality in ACS patients [46]. However, the prognostic value of BNP in ACS has not been well established, although it has been repeatedly assessed. According to current understanding, baseline BNP measurement in ACS patients is an important risk stratification tool [47]; the findings of our study support this notion.

Microalbuminuria was also confirmed in our study as significantly associated with CRP levels on admission and a significant predictor of the patient outcomes after 2 years. Microalbuminuria is a novel biochemical marker of ACS. When present in patients without diabetes, microalbuminuria signals that kidney vasculature, especially the endothelium, is functionally failing [48].

Out of 72 analyzed parameters, the 8 key variables showed predictive value for ACS patients after 2-year follow-up. These simple measurements can help clinicians perform appropriate risk stratification in patients with low and moderately elevated CRP, who are traditionally considered to beat lower risk of adverse cardiac events compared to patients with high CRP. Better risk stratification enables better selection of therapy and optimal use of invasive procedures by identifying the target patients [49].

Conclusions

This study analyzed various parameters, obtained during patient work-up upon hospitalization for ACS, to find a new methodology that can help predict negative outcomes when patients have low or moderately elevated CRP. Early risk stratification of patients with ACS characterized with low or moderately elevated CRP is possible by measuring 8 key variables

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on admission: hemoglobin, fibrinogen, antithrombin III, total cholesterol, total cholesterol/LDL ratio, pro BNP, BNP, and microalbuminuria. If more than half of these variables are outside of their reference range, ACS patients with low or moderately elevated CRP are at increased risk of major cardiac adverse events after 2 years.

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