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Incremental Value of Cardiac Biomarkers in Mid-term Prognosis of Patients with Acute Coronary Syndrome

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Abstract

BACKGROUND: Given the number of prognostic studies, both short- and long-termed, in patients with myocardial infarction (MI), the data on predictors of major adverse cardiac events (MACE) following discharge still remains limited. Assessment of left ventricular (LV) function, combined with the use of cardiac biomarkers, such as NT-proBNP can help in the early identification of patients at risk of developing heart failure and/or other MACE in acute MI (AMI) survivors.

AIM: The aim of the study was to identify early predictors of MACE in MI patients, that underwent primary percutaneous coronary intervention, with special emphasis on cardiac biomarkers.

MATERIALS AND METHODS: We analyzed clinical, LV functional, angiographic variables, as well cardiac troponin (hsTn), a marker of myocardial necrosis, natriuretic peptide (NT-proBNP), a marker of myocardial stress, and white blood cells (WBC), as a marker of inflammation. The study was designed as longitudinal, prospective observational cohort study undertaken on 150 AMI patients hospitalized at University Clinic of Cardiology over the period of September 2018 to March 2019. Inclusion criteria: All incomers hospitalized for AMI over the aforementioned period who were willing to participate in the study and gave signed informed consent. Exclusion criteria: Patients who were not consented to participate in the study, patients who suffered in-hospital mortality over the index hospitalization and those with the previous HF and/or AMI. IBM SPSS statistical software version 22 was used for statistical analysis. Descriptive and comparative statistical methods were applied. Continuous variables were presented as means, while categorical as frequencies and percentages. Comparative statistic tests: Chi-square test, for variables with dichotomous distribution, t-test and one-way ANOVA for continuous variables with two or more categories were applied. Risk ratios with 95% confidence intervals were calculated, and the significance was determined using Cochran and Mantel-Haenszel test (at the level of <0.05). Receiver operator characteristic curves (ROC) were used for prediction capability. Correlations, uni- and multivariate linear, and logistic regression analysis were undertaken to identify significantly associated variables.

RESULTS: The average follow-up period was 31 months. In total, 26 patients suffered from at least one MACE. Multivariate logistic regression analysis identified several independent predictors: NT-proBNP (p = 0.007), number of diseased vessels (p = 0.027), and need for loop diuretic therapy (p = 0.050). ROC curve demonstrated excellent discriminatory function for MACE of NT-proBNP and WBC (area under the curve 0.640, and 0.658, p = 0.025 and 0.011, respectively).

CONCLUSION: The combination of biomarkers for myocardial stress and inflammation improves the prediction of MACE in MI survivors.

Introduction

Acute coronary syndrome (ACS) is the most common cause of admission to the coronary care unit with highest risk of death and adverse outcomes and is accounted for nearly 70% of all admissions in the hospital [1]. ACS patients represent a diverse group in which the seriousness of the underlying coronary artery disease, its prognosis and response to treatment differs greatly. Myocardial infarction (MI) remains one of the most important causes of morbidity and mortality in the world [2].

Current guidelines from the American College of Cardiology and the American Heart Association give practical recommendation for assessing the risk of cardiovascular (CV) events in general population [3] and rough estimation of individual risk [4]. Therefore, great expectations are posited in identification and development of new biomarkers for CV risk prediction and prognostic evaluation [5], [6], especially for short- and long-term clinical outcome.

There are few cardiac biomarkers that are usually used for prediction of CV events. These markers include: Markers for myocardial necrosis – creatinine kinase-myocardial band and troponin, markers for myocardial stress – N-Terminal-pro-brain natriuretic peptide (NT-proBNP), and suppression of tumorigenicity 2 (sST2) and inflammation related procalcitonin (PCT) and C-reactive protein (CRP) [7], [8], [9], [10],

[11], [12]. There are short- and long-term prognostic studies performed on MI patients using either single or combination of these cardiac biomarkers.

At present, as to our knowledge, there are no prognostic studies with multimarker risk stratification in MI survivors in our country and near surrounding. We aimed to identify biomarkers that can help predict major cardiovascular adverse events (MACE) in mid-term perspective in MI survivors treated with successful primary percutaneous coronary intervention (pPCI).

Material and Methods

The idea for designing our study derived from a study of Somuncu *et al*. [13] who analyzed the predicative value of six cardiac biomarkers for MACE in MI survivors.

A longitudinal, prospective observational cohort study was undertaken on 150 patients hospitalized at the University Clinic of Cardiology over the period of September 2018 to March 2019 for acute MI (AMI).

Inclusion criteria

Patients (all incomers) hospitalized for AMI over the aforementioned period who were willing to participate in the study and gave signed informed consent.

Exclusion criteria

Patients who were not consented to participate in the study, patients who suffered in-hospital mortality over the index hospitalization, and patients with previously known heart failure and/or AMI were excluded from the study.

Data were collected on demographics, CV risk factors, co-morbidities, ECG-signs of myocardial injury, biomarkers of myocardial injury, stress and inflammation, left-ventricular function, angiographic distribution of the disease, MI treatment and medications used, and early in-hospital outcome.

At the study entry, to collect variables of interest, every patient underwent: detailed medical history; physical examination; 12-lead ECG recording; blood sampling for: Hemogram, lipid (non-fasting) and glycemic profile, markers of myocardial injury and stress: High sensitivity troponin T/I (hsTn) at admission and brain natriuretic peptide (NT-proBNP) taken between 24 and 48 h after admission, biochemical variables; coronary angiography, and echocardiography (2-D transthoracic echocardiography [2D TTE]).

The study was approved by the ethics committee of the University Clinic of Cardiology and was conducted in accordance with the Helsinki Declaration. Informed consent was obtained from all patients before their inclusion in the study.

Follow up

The total average follow-up was 31 months (mean 27, min 1 month, and max 36 months). First post-hospital evaluation was performed in the time-frame of 3–6 months after the index event. Medical history, physical examination, 12-lead ECG and 2D TTE were undertaken. Patients whose clinical outcomes could not be reached were excluded from the study. Major adverse cardiac events (MACE) were defined as: CV mortality (death due to MI, arrhythmia or heart failure); heart failure (LVEF <40% and presence of Stage 3 symptoms according to the Ney York Heart Association classification despite optimal medical therapy); reinfarction, and stroke occurring after hospital discharge [13].

Statistical analysis

IBM SPSS statistical software version 22 was used for statistical analysis. Descriptive and comparative statistical methods were applied. Continuous variables were presented as means, while categorical as frequencies and percentages. Comparative statistic tests: Chi-square test for variables with dichotomous distribution, t-test and one-way ANOVA for continuous variables with two or more categories defined. Risk ratios with 95% confidence interval were calculated, and the significance was determined using Cochran and Mantel-Haenszel test. Receiver operator characteristic (ROC) curves were used for prediction capability. Correlations, uni- and multivariate linear, and logistic regression analysis were undertaken to identify significantly associated variables. Significance was determined at the level of < 0.05.

Results

A total of 150 MI patients, who underwent successful PCI were included in the study. Their demographic features, angiographic characteristics, laboratory values, and echocardiographic characteristics were compared and shown in Table 1.

All variables were found to be higher in the MACE group; however, statistical significance was reached for biomarkers: NT-proBNP (6380.1 ± 9000.4 vs. 2470.8 ± 3895.9; $p < 0.001$), white blood cells (WBC) (12.8 ± 4.5 vs. 10.9 ± 3.2; $p < 0.016$) and BUN (7.9 ± 5.1 vs. 5.9 ± 2.2; $p < 0.002$); sumSTE (2.8 ± 1.9 vs. 2.0 ± 1.7; $p < 0.030$); and number of diseased vessels (2.2 ± 0.9 vs. 1.8±0.9; $p<0.048$) and LVEF (49.2±10.3 vs

Table 1 : Baseline characteristics of study population according to the presence of major cardiovascular adverse events (MACE)

Variable	Total 150 (100%)	MACE (+) 26 (17,3%)	MACE (-) 124 (82,7%)	Sig	OR (95% CI)
Gender					
Females	45 (30%)	9 (20%)	36 (80%)	0.210	
Males	105 (70%)	17 (17.1%)	88 (82.9%)		
Age (years)	60.9 ± 11.9	63.3 ± 9.6	60.4 ± 12.4	0.108	
BMI	28.2 ± 4.9	27.6 ± 4.7	28.3 ± 5.0	0.781	
Obesity (BMI>30)	29 (19.3%)	2 (7.4%)	27 (22%)	0.077	
HLP	137 (91.3%)	24 (88.9%)	113 (91.9%)	0.399	
Family history	87 (58%)	14 (51.9%)	73 (59.3%)	0.244	
Smoking	98 (65.3%)	16 (59.3%)	82 (66.7%)	0.248	
HTA	133 (88.7%)	23 (85.2%)	110 (89.4%)	0.597	
DM	44 (29.3%)	7 (25.9%)	37 (30.1%)	0.240	
previous MI	22 (14.7%)	3 (11.1%)	19 (15.4%)	0.443	
previous PCI	21 (14%)	2 (7.4%)	19 (15.4%)	0.248	
preexisting LV systolic dysfunction	8 (5.3%)	1 (3.7%)	7 (5.7%)	0.582	
COPD	18 (12%)	2 (7.4%)	16 (13%)	0.360	
anemia	11 (7.3%)	4 (14.8%)	7 (5.7%)	0.292	
Recent bleeding	10 (6.7%)	3 (11.1%)	7 (5.7%)	0.545	
Previous ASA	53 (35.3%)	13 (48.1%)	40 (32.5%)	0.148	
Previous RAAS	100 (66.7%)	15 (55.6%)	85 (69.1%)	0.346	
Previous BB	56 (37.3%)	11 (40.7%)	45 (36.6%)	0.211	
MI characteristics					
MI location					
Anterior	67 (44.7%)	12 (44.4%)	55 (44.7%)	0.688	
Inferior	40 (26.7%)	5 (18.5%)	35 (28.5%)		
Multiple location	43 (28.7%)	10 (37.0%)	33 (26.8%)		
STEMI	100 (66.7%)	20 (20%)	80 (80%)	0.265	
NSTEMI	50 (33.3%)	7 (14%)	43 (86%)		
Q sequel	73 (48.7%)	12 (16.4%)	61 (83.6%)	0.177	
sumSTE (mm)	2.1 ± 1.8	2.8 ± 1.9	2.0 ± 1.7	0.030	
MAW score	2.6 ± 1.0	2.8 ± 1.1	2.6 ± 1.0	0.356	
Biochemical variables					
hsTn (mean)	6769.2 ± 18925.6	9881.6 ± 17535.9	6085.5 ± 12576.1	0.152	
Median	842.1				
NT-proBNP (mean)	3174.5 ± 5369.7	6380.1 ± 9000.4	2470.8 ± 3895.9	0.001	
Median	1201.5				
WBC (Mean)	11.3 ± 3.5	12.8 ± 4.5	10.9 ± 3.2	0.016	
Median (10×10^6)	11.3				
Stress glycemia (mean)	9.3 ± 4.6	10.5 ± 6.3	9.1 ± 4.1	0.084	
Median	8.1				
HbA1c (%)	6.3 ± 1.5	6.1 ± 1.4	6.3 ± 1.5	0.831	
TG (mmol/L)	2.0 ± 1.6	1.8 ± 1.5	2.1 ± 1.6	0.556	
Chol (mmol/L)	5.7 ± 1.3	6.1 ± 1.3	5.6 ± 1.5	0.020	
HDL-C (mmol/L)	1.2 ± 0.3	1.3 ± 0.3	1.2 ± 0.3	0.763	
LDL-C (mmol/L)	3.5 ± 1.1	3.8 ± 1.2	3.4 ± 1.1	0.062	
Er (10×10^9)	4.8 ± 0.6	4.8 ± 0.5	4.7 ± 0.6	0.239	
Hgb (g/L)	141.1 ± 17.8	141.4 ± 17.2	141.0 ± 17.9	0.323	
HTC (%)	41.4 ± 4.5	41.3 ± 4.1	41.4 ± 4.6	0.515	
PLT (10×10^6)	247.1 ± 70.4	240.8 ± 58.8	248.4 ± 72.8	0.372	
BUN (mmol/L)	6.3 ± 3.0	7.9 ± 5.1	5.9 ± 2.2	0.002	
Creatinine (mean)	90.6 ± 37.9	100.1 ± 62.7	88.5 ± 29.9	0.130	
Median (µmol/L)	82.0				
Sodium (mmol/L)	138.3 ± 3.4	138.4 ± 3.6	138.3 ± 3.4	0.552	
Potassium (mmol/L)	4.2 ± 0.5	4.2 ± 0.4	4.2 ± 0.5	0.915	
Angiographic variables					
Number of DV	1.9 ± 0.9	2.2 ± 0.9	1.8 ± 0.9	0.048	
SINTAX score	15.2 ± 7.1	16.8 ± 8.9	14.8 ± 6.6	0.114	
Number of TV	0.99 ± 0.33	1.0 ± 0.5	0.98 ± 0.3	0.820	
Culprit artery					
LMN	4 (2.7%)	1 (3.8%)	3 (2.4%)	0.934	
LAD	70 (46.7%)	12 (46.2%)	58 (46.8%)		
CX	22 (14.7%)	4 (15.4%)	18 (14.5%)		
RCA	54 (36%)	10 (37%)	44 (35.8%)		
LV functional parameters at index event					
LVEDd (mm)	51.8 ± 5.1	52.3 ± 4.4	51.7 ± 5.3	0.269	
LVESd (mm)	36.4 ± 5.7	37.5 ± 5.4	36.2 ± 5.8	0.224	
EF (%)	52.6 ± 9.4	49.2 ± 10.3	53.3 ± 9.0	0.037	
EF<40%	24 (16.1%)	8 (29.6%)	16 (13.1%)	0.242	
Mid-range EF 41–50%	50 (33.6%)	8 (29.6%)	42 (34.4%)		
EF>50%	75 (50.3%)	11 (40.7%)	64 (52.5%)		
Diastolic dysfunction	51 (34%)	10 (37%)	41 (33.3%)	0.271	
Length of hospitalization	5.2 ± 2.3	6.6 ± 3.2	4.9 ± 1.9	<0.001	
In-hospital events	17 (11.3%)	7 (25.9%)	10 (8.1%)	0.016	3.9 (1.3—11.6) p = 0.012
ASA at discharge	143 (97.3%)	24 (100%)	119 (96.7%)	0.476	
P2y12 at discharge	147 (98.6%)	24 (100%)	121 (98.4%)	0.692	
BB at discharge	89 (60.5%)	14 (58.3%)	75 (61%)	0.580	
RAAS at discharge	131 (89.1%)	20 (83.3%)	111 (90.2%)	0.159	
MRA at discharge	38 (25.9%)	8 (33.3%)	30 (24.4%)	0.464	
Loop diuretics at discharge	62 (42.2%)	15 (62.5%)	47 (38.2%)	0.024	2.7 (1.1–6.6) p = 0.031
Follow up period (mean)	27.2	20.6 ± 11.9	28.7 ± 5.8	<0.001	Mean diff. 8.153 (3.181—13.126)
Median	31				

BMI: Body mass index, HTA: Arterial hypertension, DM: Diabetes mellitus, MI: Myocardial infarction, PCI: Percutaneous coronary intervention, CMP isch: Ischemic cardiomyopathy, COPD: Chronic obstructive pulmonary disease, ASA: Acetylsalicylic acid, RAAS: Renin-angiotensin-aldosterone system, BB: Beta blockers, STEMI: ST-segment elevation myocardial infarction, NSTEMI: Non ST-segment elevation myocardial infarction, sumSTE: Sum of ST-segment elevation in all leads, MAW sc: Modified Anderson-Wilkins score, hsTn: High sensitive Troponin, NT-proBNP: N-terminal pro b-type natriuretic peptide, WBC: White blood cells, TG: Triglycerides, Chol: Cholesterol, HDL-C: High density lipoprotein, LDL-C: Low-density lipoproteins, Er: Erythrocytes, Hgb: Hemoglobin, HTC: Hematocrit, PLT: Platelets, BUN: Blood urea nitrogen, DV: Diseased vessels, TV: Treated vessels, LMN: Left main artery, LAD: Left ascending artery, Cx: Circumflex artery, RCA: Right coronary artery, LV: Left ventricle, LVEDd: Left ventricular end diastolic diameter, LVEDd: Left ventricular end sistolic diameter, EF: Ejection fraction, P2y12: Adenosine diphosphate (ADP) receptor antagonists, MRA: Mineralocorticoid receptor antagonists, WBC: White blood cells.

53.3±9.0; p<0.037). Statistical significance was reached for length of hospitalization (6.6 ± 3.2 vs. 4.9 ± 1.9; p ≤ 0.001, in-hospital events (p < 0.016), and the use of diuretics during the course of hospitalization (p < 0.024).

Over the mean follow-up period of 27.2 months

(min 1 - max 36 months) in total 34 MACE were registered in 26 (17.3%) patients. The MACE event rate was calculated to 1 MACE per 17.3 patient years. The cumulative MACEs over the follow-up period were as follows: Nine (6%) cardiac death, 11 patients (7.3%) with UA/re-infarction, 12 (8%) heart failure hospitalizations, and two (1.3%) ischemic strokes (Figure 1).

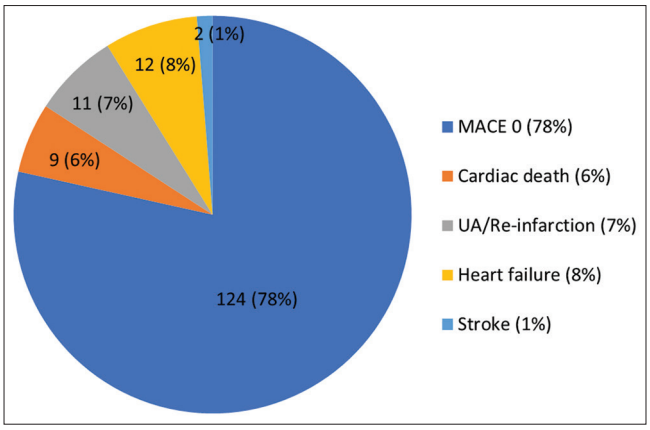

Figure 1: Distribution of MACE subgroups among the study population

Over the follow-up period, all-cause mortality was 16 (10.7%) out of which non-cardiac death were registered in 7 (4.7%) patients: Three COVID-19 related deaths, two tumor related, and one acute kidney failure death. 31 patients (20.7%) underwent scheduled revascularization for non-culprit artery in patients diagnosed with multivessel disease at the index event.

We analyzed correlations between variables found to be statistically significantly different between groups and MACE (Table 2).

Statistically significant correlations were found for sumSTE elevation, angiographic, and biomarker variables; however, LVEF demonstrated no significant correlation with MACE.

We performed ROC analysis to measure the discriminatory function of biomarkers of myocardial injury, strain, and inflammation (hsTn, NTpro-BNP, and WBC) as well as, LVEF for MACE (Figure 2 with Accompanying Table). Only two biomarkers demonstrated statistically significant discriminative function for MACE: NT-proBNP and WBC (area under the curve 0.640, and 0.658, p = 0.025 and p = 0.011, respectively); however, hsTn and left ventricular (LV) function demonstrated no statistical significance.

To identify independent predictors of mid-term outcome in post AMI patients, we performed two-step analysis. For continuous independents, we used linear logistic regression (method enter), while for categorical we applied binary logistic regression (method backword conditional). We identified several statistically significantly associations with MACEs: Number of diseased vessels, hsTn and NT-proBNP, WBC, BUN, and LVEF. Patients with reduced LVEF at the point of index event had OR for MACE 2.9 times higher as compared with patients with preserved LVEF, while OR for MACE was 1.1 for patients with mildly reduced LVEF. In-hospital morbidity, need for diuretic therapy and length of hospitalization were also significant univariate predictors (Table 3).

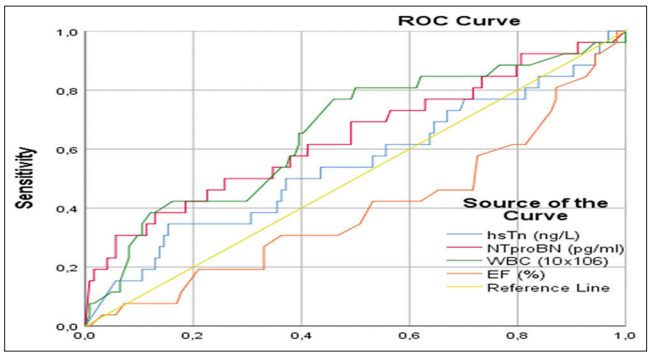

Figure 2: Receiver operating characteristic curves for hsTn, NT-proBNP, WBC, and LVEF in discriminatory function for MACE

Area Under the Curve					
Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	95% Confidence Interval	
				Lower Bound	Upper Bound
hsTn (ng/l)	0.547	0.067	0.449	0.415	0.679
NT-proBNP (pg/ml)	0.640	0.065	0.025	0.512	0.768
WBC (10×10^6)	0.658	0.061	0.011	0.538	0.779
LVEF (%)	0.395	0.064	0.093	0.270	0.520

When included in multivariate logistic regression analysis (backward conditional), at step 5, in a model with Chi-square 23.011, p < 0.001, percent accurate prediction 85.2%, three independent predictors were identified: NT-proBNP, number of diseased vessels, and diuretic treatment over the course of index hospitalization (OR 2.693) (Table 4).

Cardiac biomarkers and MACEs

A special emphasis of this study was on predictive role of cardiac biomarkers on mid-term MACE in post MI patients. There were statistically significant differences in these values among MACE and non-MACE patients (Table 1 and Figure 3).

We performed a multivariate analysis with biomarkers of necrosis, strain, and inflammation, and

Table 2 : Correlation of MACE with variables identified in univariated analysis

Control variables	sumSTE	NO of DV	hsTn	NT-proBNP	WBC	BUN	LVEF	EF <40% EF 40–50% EF >50%	Diuretic at discarge	In-hospital morbidity	Length of hospitalisation
MACE correlation (r)	0.173	0.174	0.201	0.261	0.240	0.244	–0.135	–0.117	0.198	0.190	0.303
Sig. (p)	0.037	0.036	0.015	0.001	0.004	0.003	0.104	0.160	0.017	0.022	0.000

sumSTE: Sum of ST-segment elevation in all leads, hsTn: Highly sensitive troponin, NT-proBNP: N-terminal pro b-type natriuretic peptide, WBC: White blood cells, LVEF: Left ventricular ejection fraction, EF<40%: Reduced LV systolic function, EF 40–50%: Mildly reduced LV systolic function, EF>50%: Preserved LVsystolic function; DV- diseased vessels.

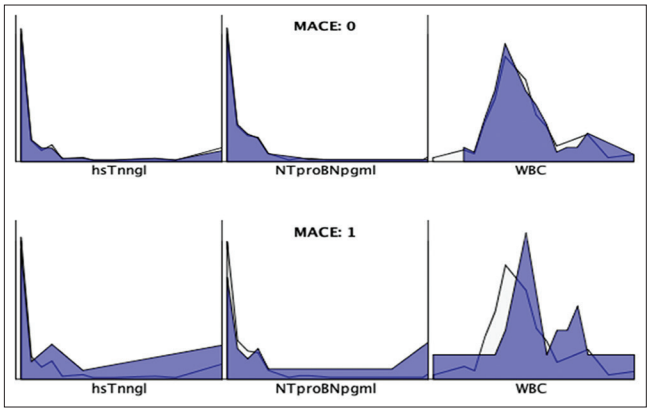

Figure 3: Graphical presentation of cardiac biomarkers distribution among patients with or without MACE

MACE as dependent variable, in an attempt to identify the most important one among them. When included in multivariate logistic regression analysis (backward conditional), in a model with Chi-square 16,143; p = 0.001, two cardiac biomarkers demonstrated statistical significance, and cardiac troponin as a marker of myocardial necrosis failed to be associated with mid-term MACE (Table 5).

Further-on we focused our analysis on biomarker of cardiac stress – NT-proBNP. We divided patients in those with normal (<125 pg/ml) and elevated NT-proBNP (22 vs. 128). Over the follow-up period, two MACEs (9.1%) were registered in this group, as compared with 24 (18.7%) in the group of patients with elevated natriuretic peptide. In the same time, there was no significant difference in the mean follow-up period (33.6 vs. 32.4, overall, 32.8 months, p = ns). Kaplan–Meier hazard function demonstrated good separation of the curves; however, due to small number of registered events in the first group no statistical significance was achieved (Figure 4 and Accompanying Table).

Never the less, as a continuous variable NT-proBNP have an excellent relation with the cumulative hazard ratio (Figure 5).

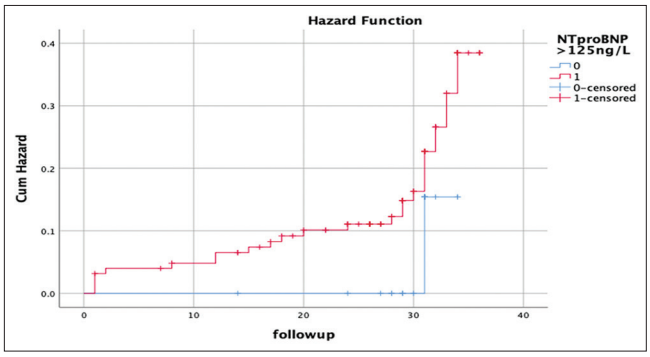

Figure 4: Kaplan–Meier curve for MACE as a function of normal versus elevated NT-proBNP

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	1.307	1	.253
Breslow (Generalized Wilcoxon)	1.819	1	.177
Tarone-Ware	1.571	1	.210

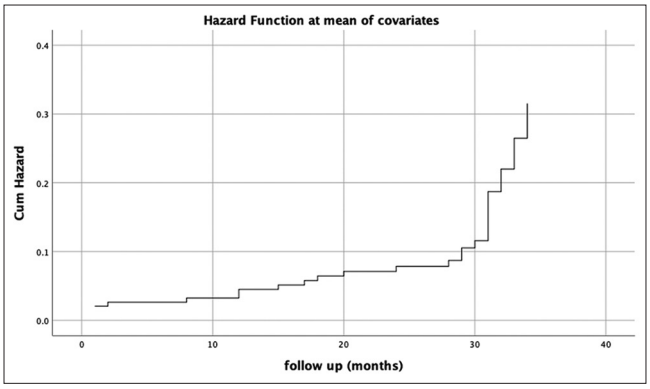

Figure 5: Kaplan–Meier curve for MACE as a function of NT-proBNP

Table 3 : Univariate MACE predictors (linear and binary logistic regression)

Variable	Beta	Sig	OR with 95% CI
sumSTE	0.157	0.055	
NO of diseased vessels	0.162	0.048	
hsTn	0.191	0.019	
NT-proBNP	0.296	0.000	
WBC	0.210	0.010	
BUN	0.249	0.002	
EF (%)	–0.173	0.034	
EF<40%*	–1.068	0.049	2.9 (1.0–8.4)
EF 40–50%*	0.103	0.127	1.1 (0.4–2.9)
Length of hospitalization	0.298	0.000	
In-hospital morbidity	1.375	0.012	3.95 (1.6–11.6)
Loop diuretics	1.077	0.018	2.94 (1.2–7.2)

*As compared with EF >50%. sumSTE: Sum of ST-segment elevation in all leads, hsTn: High sensitive troponin, NTpro-BNP: N-terminal pro b-type natriuretic peptide, WBC: White blood cells, BUN: Blood urea nitrogen, EF: Ejection fraction, EF<40%: Reduced ejection fraction or LV function, EF 40–50%: Mildly reduced ejection fraction or LV function.

LV systolic function/dysfunction and MACE

LV systolic function/dysfunction was found to be asignificant MACE predictor in univariate analysis (Table 3). We found that as compared with patients with preserved LV function, patients with reduced LV function had 2.3 times higher event rate, while patients with mildly reduced LV function had 1.1 higher OR for MACE, however without statistical significance (Figure 6 and Table 6).

Table 4: Multivariate analysis and independent predictors of mid-term MACE

	B	Wald	Sig.	Exp (B)	95% C.I. for EXP (B)	
					Lower	Upper
NT-proBNP (pg/ml)	0.000	7.309	0.007	1.000	1.000	1.000
Loop diuretic at discharge	–0.991	3.657	0.050	2.693	0.976	7.431
sumSTE	0.224	2.911	0.088	1.251	0.967	1.617
Number of diseased vessels	0.597	4.896	0.027	1.816	1.071	3.081
Constant	–3.296	17.463	0.000	0.037		

The same was confirmed with Cox proportional hazard model, finding no statistical significance in the differences between LVEF strata (Figure 7).

Table 5: Multivariate analysis of cardiac biomarkers and MACE

	B	SE	Wald	Sig.	Exp (B)	95.0% CI for Exp (B)	
						Lower	Upper
Step 1							
hsTn (ng/l)	0.000	0.000	0.011	0.915	1.000	1.000	1.000
NT-proBNP (pg/ml)	0.000	0.000	9.662	0.002	1.000	1.000	1.000
WBC (10×10^6)	0.102	0.052	3.901	0.048	1.108	1.001	1.226
Step 2							
NTproBNP (pg/ml)	0.000	0.000	10.012	0.002	1.000	1.000	1.000
WBC (10×10^6)	0.104	0.049	4.399	0.036	1.109	1.007	1.222

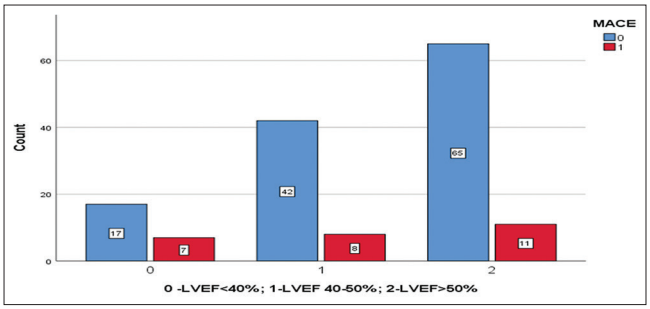

Figure 6: MACE distribution across LVEF strata

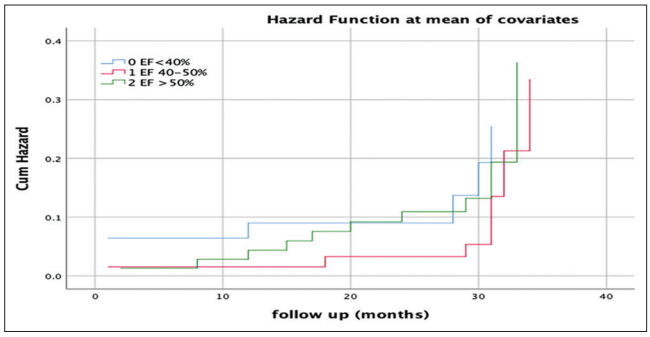

Figure 7: Cox proportional hazard model for MACE as a function of LVEF strata

Cardiac biomarkers in correlation with LV systolic function/dysfunction and MACE

According to the data from the literature stating that LV function is a major predictor of post MI outcome, and our data demonstrating no statistical significance, we undertook an analysis of cardiac biomarkers as spread across patients with reduced, mildly reduced and preserved LV function at the time of index event (Tables 7 and 8).

Biomarker of cardiac injury demonstrated statistically significant differences between the patients with reduced LVEF and mildly reduced and preserved LVEF, but no differences between patients with mildly reduced and preserved LV systolic function.

Biomarker of cardiac strain showed statistically significant difference only between the subgroups of patients with reduced and preserved LV systolic function.

As for biomarkers of inflammation, the registered statistical difference was between patients with reduced and those with mildly reduced and preserved LV systolic function.

For all cardiac biomarkers statistically, significant negative correlations were registered for LV systolic function (Table 7).

In a logistic regression analysis (backward conditional) in the model with Chi-square 10,837; $p < 0.001$; percent of correct prediction 84.7%, only NT-proBNP was identified as an independent predictor ($p < 0.001$) of mid-term MACEs (Table 9).

Discussion

Clinicians are constantly looking for an ideal prognosticator, one that can be measured at the moment of index event (AMI), one that is sensitive enough and easy to obtain, and could identify patients at high risk of MACE over the follow-up period.

Table 6: Univariate analysis of MACE as a function of degree of LV dysfunction

	B	Wald	Sig.	Exp (B)	95% C.I. for EXP (B)	
					Lower	Upper
EF >50% comparator		2.730	0.255			
EF <40%	0.889	2.567	0.109	2.433	0.820	7.220
EF 40–50%	0.118	0.055	0.815	1.126	0.418	3.029
Constant	–1.776	29.691	0.000	0.169		

We investigated the efficacy of biomarkers of myocardial necrosis, myocardial stress and inflammation in predicting MACEs in mid-term follow-up period in patients who survived MI. NT-proBNP as a marker of myocardial stress and WBC as a marker of inflammation were found to be independent predictors of MACEs after AMI. Somuncu *et al*. analyzed the group effect on MACE prediction. They, similarly to our study, found that markers of myocardial injury do not predict MACE; however, myocardial stress and inflammation markers were independent predictors for MACE. Same was confirmed with receiver operating characteristics curve showed highly significant distinguishing ability of CRP, PCT, troponin, creatine kinase-MB, NT-pro B-type natriuretic peptide, and sST2 level for major

Table 7: Cardiac biomarkers in correlation with LVEF strata

Cardiac biomarkers	n	Mean	SD	95% Confidence Interval		ANOVA sig	Tukey *post hoc*
				Lower Bound	Upper Bound		
hsTn (ng/l)							
0 – EF <40%	24	1603.,17	22395.45	6576.41	25489.95	0.001	0 versus 1 0.007
1 - EF 40–50%	50	6037.36	11066.69	2892.24	9182.48		0 versus 2 0.001
2–>50%	76	4325.26	10020.95	2035.38	6615.15		1 versus 2 ns
Total	150	6769.22	13612.27	4573.01	8965.44		
NT-proBNP (pg/ml)							
0 – EF <40%	24	5927.16	7760.22	2650.31	9204.02	0.008	0 versus 1 ns
1 - EF 40–50%	50	3478.30	5225.38	1993.26	4963.34		0 versus 2 0.006
2 - >50%	76	2105.30	4163.15	1153.98	3056.62		1 versus 2 ns
Total	150	3174.46	5369.72	2308.11	4040.82		
WBC (10×10^6)							
0–EF <40%	24	14.15	3.39	12.71	15.58	0.000	0 versus 1 0.001
1-EF 40–50%	50	11.01	3.58	9.99	12.03		0 versus 2 0.000
2 - >50%	76	10.56	3.12	9.85	11.27		1 versus 2 ns
Total	150	11.28	3.54	10.71	11.86		

Table 8: Significant correlation between LV systolic function/ dysfunction and cardiac biomarkers

LVEF strata	hsTn	NT-proBNP	WBC
Correlation	–0.271	–0.248	–0.316
Significance (two-tailed)	0.001	0.002	0.000
df	148	148	148

adverse CV events [13]. In our study, same was found for NT-proBNP and WBC (surrogate marker of inflammation) (area under the curve 0.640, and 0.658, p = 0.025 and 0.011, respectively).

Table 9: Multivariate analysis defining independent predictors of MACE among biochemical and LV systolic functional variables

	B	S.E.	Wald	Sig.	Exp (B)	95% CI for EXP (B)	
						Lower	Upper
Step 1[a]							
hsTn (ng/l)	0.000	0.000	0.092	0.762	1.000	1.000	1.000
NTproBNP (pg/ml)	0.000	0.000	6.363	0.012	1.000	1.000	1.000
WBC (10×10^6)	0.102	0.070	2.115	0.146	1.107	0.965	1.270
EF subgroups			0.224	0.894			
EF>50% versus EF<40%	0.214	0.651	0.109	0.742	1.239	0.346	4.437
EF>50% versus EF 40–50%	–0.099	0.538	0.034	0.854	0.906	0.315	2.601
Constant	–3.111	0.827	14.160	0.000	0.045		
Step 4[a]							
NTproBNP (pg/ml)	0.000	0.000	10.333	0.001	1.000	1.000	1.000
Constant	–2.005	0.272	54.153	0.000	0.135		

There are many clinical scoring and biomarkers that are used to determine the prognosis in post-MI patients. Related studies have been carried out separately for each other marker which was used, in our study, and it has been determined that these markers can provide with valuable prognostic information [13], [14], [15], [16], [17], [18], [19]. In a recently published study on association between NT-proBNP and 12 months MACE in NSTEMI patients, it was concluded that NT-proBNP represents a long-term prognostic biomarker for high-risk MACE in the first 12 months after NSTEMI, especially for older patients and those with reduced LVEF [14]. Khan states that a multibiomarker approach improves cardiac risk prediction, stratification, including MACE after MI [15]. Recently published study, set to determine the relationship between inflammation, natriuretic peptides, and incident HF in older men [16], suggests that increased levels of NT-proBNP are associated with markers of inflammation and the risk of HF. According to Oleynikov *et al*., increased levels of NT-proBNP are prognostic factors for HF progression in patients surviving STEMI [18]. Another study, performed in patients surviving STEMI that underwent pPCI, indicates that natriuretic peptide levels, along with older age (>80 years old), Killip Class >II and BMI are independent predictors for MACE in those patients [19].

When examining the correlations of MACE with variables identified in univariate analyze, we found that there is no significant correlation between MACE and the level of reduction in LVEF function at the index event.

Patients who had LVEF <40% at admission, had 2.9 times higher risk of MACE compared to patients with LVEF >50% (p = 0.049 OR 1.0–8.4). According to Han *et al*., EF <40% has a strong predicative value for MACE in the 1st year of MI [20]. Similar predicative value of LVEF is reported by Prastaro *et al*. [21].

Patients, who had in-hospital morbidity during the acute event had 3.9-times higher probability of MACE (p = 0.012 OR 1.6–11.6) [22], while patients, who needed loop diuretics during their hospital stay had almost 3-times (2.9) higher risk of MACE (p = 0.018 OR 1.2–7.2). According to Kamran *et al*., ischemic stroke combined with cardiac wall motion abnormalities was associated with 1.7-fold higher risks of MACE independent of established risk factors [22]. The use of loop diuretics in patients with suspected coronary artery disease, but without systolic failure or renal failure is associated with all-cause mortality as stated by Schartum-Hansen *et al*. [23].

A multivariate analysis with three biomarkers and MACE as dependent variable showed that hsTn losses its statistical significance, while NT-proBNP and WBC remain as predictors of MACE, with NT-proBNP being the strongest, similar to the review published by Chen *et al*. [24]. The unreliability of hsTn to prognosis in patients with MI survivors may be because patients who had in-hospital fatal events were excluded from our study. Since biomarkers of myocardial necrosis may increase much more in these cases, the removal of these patients from our study may have cause the disappearance of the prognostic features of hsTn [13]. Other possible explanation is that in some of the study subjects we were missing the top values of cardiac troponins, subsequently leading to lower mean levels of hsTn.

A comparative analysis of cardiac biomarkers (hsTn, NT-proBNP and WBC) in patients with different stages of LV dysfunction showed that there is no statistically significant difference between the groups of patients with preserved and mildly reduced LV systolic function. Similar to our results, a study has shown that natriuretic peptides can predict CV and all-cause mortality independent of LVEF [25]. Steen *et al*. state that cTnT has lower performance in estimation of LVEF than NT-proBNP, while having a superior role in infarct mass assessment and relative infarct size, suggesting a multimarker strategy implementation for prognosis work-up [26]. In their study of 1548 patients hospitalized for ACS, Fiechter *et al*. performed analysis of CRP and WBC that revealed a substantial negative correlation with LVEF [27].

Limitations of the study

One of the biggest limitations of this study is the number of study subjects, bearing in mind the prevalence of the disease, which may in some way affect the results that we received.

Furthermore, another limitation of the study is that in some of the patients we missed the top values of hsTn, resulting in mean levels of Tn.

However, this is the first study done with analysis of natriuretic peptides (NTpro-BNP) in a cohort

of patients with acute MI for prognostication purposes. Even though this is a biomarker known for several years it was not widely available in our country, and to the best of our knowledge, this is the first study that analyzes the role of natriuretic peptides in prognostication of MI patients in our country.

Conclusion

We identified several independent predictors of mid-term prognosis of MI survivors treated with pPCI: NT-proBNP, number of diseased coronary arteries and need for loop diuretics over the course of hospitalization.

We confirmed that reduced ejection fraction at the time of index event (LVEF<40%) is a powerful predictor, as in our study, these patients had a three-fold higher MACE as compared with patients with preserved LVEF, however when combined with other covariates, its' significance as independent predictor vanished.

As opposite, cardiac biomarkers, especially biomarkers of myocardial stress bring higher prognostic information especially after adjustment for other covariates.

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