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Prognostic value of biomarkers and co-morbidities in patients with acute heart failure: one-year follow-up study
Прогностички значај биомаркера и комобирдитета код пацијената са акутном срчаном инсуфицијенцијом: студија једногодишњег праћења

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SUMMARY

Introduction/Objective Clinical risk stratification of patients hospitalized due to acute heart failure (AHF) applying the following biochemical markers: B-type natriuretic peptide (BNP), troponin I (TnI) and high-sensitivity C-reactive protein (hsCRP) can contribute to early diagnosis of AHF and lower mortality rates.

The aim of the this study was to is to investigate the prognostic significance of biomarkers (BNP, TnI i hsCRP) and co-morbidity concerning one-year mortality in patients with AHF.

Methods Clinical group consisted of 124 consecutive unselected patients, age 60–80 years, treated in the Coronary Care Unit. The patients were monitored for one year after the discharge. During the first 24 hours after admission, BNP, TnI and hsCRP were measured in fasting serum.

Results Total one-year mortality was 29.8%. The levels of serum BNP were significantly higher in the group of non-survivors compared to the group of survivors (1353.8±507.8 vs 718.4±387.6 pg/mL, p<0.001). Independent predictors of one-year mortality were: BNP, TnI, depression, hypotension, chronic renal failure (CRF), ejection fraction, and right-ventricle systolic pressure.

Conclusion The presence of both biomarkers including BNP,TnI and even more co-morbidities such as depression or chronic renal failure have significant influence of one-year mortality in patients with AHF.

Key Words: biochemical marker, cardiac failure, trial.

САЖЕТАК

Увод/Циљ Стратификација клиничког ризика код пацијената хоспитализованих због акутне срчане инсуфицијенције (АСИ) коришћењем биомаркера: натриуретик-пептид Б-типа (БНП), тропонин I (Тн I) и високо осетљиви Ц-реактивни протеин (ЦРП), може допринети раном постављању дијагнозе и нижим стопама смртности.

Циљ ове студије био је да се испита прогностички значај биомаркера (БНП, Тн I и ЦРП) и комобирдитета на једногодишњи морталитет код пацијената са АСИ.

Методе Клиничка група обухватила је 124 узастопна неселектована болесника старости 60–80 година лечених и Коронарној јединици. Пацијенти су праћени годину дана након отпуста. Током прва 24 часа након пријема, БНП, Тн I и ЦРП мерени су у серуму на таште.

Резултати Свеукупни једногодишњи морталитет износио је 29,8%. Нивои серумског БНП-а били су знатно виши у групи нболесника који су преминули у односу на групу који су преживели (1353.8±507.8 тј. 718.4±387.6 pg/mL, p<0,001). Независни предиктори једногодишњег мортаитета били су: БНП, Тн I, депресија, хипотензија, хронична бубрежна инсуфицијенција (ХБИ), ејекциона фракција, систолни притисак у десној преткомори.

Закључак Присуство оба биомаркера, БНП, ТнI, чак и више коморбидитета, као што су депресија или ХБИ има значајан утицај на једногодишњу смртност пацијената са АСИ.

Кључне речи: биохемијски маркер, срчана слабост, студија.

INTRODUCTION

Acute heart failure (AHF) is the leading cause of hospitalizations within the age group over-65-year-olds and it represents a significant economic burden [1]. One of the challenging areas in management of patients with AHF is the involvement of multiple organs and presence of multiple co-morbidities. The care of patients with AHF is complex, involving clinical assessment and prediction as integral parts of daily clinical practice. AHF is associated with a very high mortality rate, and clinical risk stratification after hospitalization due to AHF remains a relevant challenge. In recent years, a growing attention has been paid to new blood-based biomarkers for their ability to risk-stratify patients with AHF. Over the past several years, B-type natriuretic peptide (BNP) and its N-terminal precursor fragment (NT-proBNP) have become the biomarker "gold standards" for

predicting risk, with studies demonstrating the value of each test for risk stratification of AHF [2]. Additionally, a decrease in natriuretic peptide levels with proven HF therapy and parallel improvement in prognosis have led to the concept of biomarker-"guided" HF management, with promising results. New biomarkers for HF evaluation include soluble ST2 (sST2), growth differentiation factor (GDF)-15, and highly-sensitive troponinT (hsTnT). Each has a growing set of data supporting its use, and sST2 and troponin measurements were included in the American College of Cardiology/American Heart Association guidelines for the evaluation of HF [3].

However, the value of any biomarker for risk prediction in AHF, should clearly depend on the degree to which it adds to the prognostic information provided by standard risk factors, co-morbidities and other available markers.

Several demographic and clinical factors, co-morbidities, and biochemical variables are associated with short and mid-term mortality in AHF, including measures of renal function, blood pressure and other relevant predictors [2,4,5,6].

OBJECTIVE

Tha aim of this study was to investigate the prognostic significance of biomarkers (BNP, TnI and hsCRP) and the influence of co-morbidities on one-year mortality in patients with AHF.

METHODS

This prospective study included 124 consecutive patients within the unselected population, who were admitted to the Coronary Care Unit of the Cardiology Department of the Institute of Niska Banja during the period from 1st July 2010 to 1st July 2013, with signs and symptoms of AHF. AHF was diagnosed at the admission to the hospital according to the ESC guidelines for ACH [7] and at discharge from the hospital, the same diagnosis (AHF) had to be confirmed. Immediately after admission to the hospital anthropometric measurements were carried out and existing diseases were registered along with the causes of acute heart failure, precipitating factors, clinical presentation of the patients, as well as 12-lead electrocardiogram (ECG). During the first 24 hours after admission, both standard laboratory analysis and analysis of specific biomarkers (BNP, TnI and hsCRP) were performed. Blood samples were taken in the morning, on an empty stomach, after a night's rest and 8-hour-fasting. Creatinine clearance (CrCl) was determined according to the Cockcroft-Gault formula. Brain natriuretic peptide (BNP) (its fragment) (8-29) was determined on the appliance (*Elysis Uno, Human, Wiesbaden, Germany*).

We used ELISA method with the quantitative determination of BNP fragments in biological fluids, with a set of reagents and manufacturers (*Biomedica Gruppe, Wien, Austria*) and the reference values ranged from 0-2400 pg/ml. Measurement of hsCRP was performed on the analyzer (*HumaStar 180 System, Human, Wiesbeden, Germany*). We used ELISA method, "sandwich" type. Troponin I

was determined ELISA method. During the first 48 hours of hospitalization, all patients underwent echocardiography. End-diastolic and systolic volumes of the left ventricle (LV) and ejection fraction (EF) were measured by Simpson's "*biplane*" method.

During hospitalization, all the patients underwent 24-hour Holter monitoring using the appliance *Del Mar*, as well as the analyses of the frequency and complexity of ventricular arrhythmias. After discharged from the hospital, mortality of patients were being monitored for the following 12 months.

Statistical Analysis

To assess the significance of the differences, we used chi-square (χ^2)-test, Student's *t*-test, McNamara-test and Mann-Whitney *U*-test. Univariable and multivariable regression analysis were performed to identify the predictors of one-year mortality. The analysis of survival among the study groups was performed using the Kaplan-Meier's method, as well as Log-rank test to compare survival rates. The correlations between certain parameters were determined by Spearman's correlation coefficient. Testing of the biomarkers (BNP, troponin and CRP) as predictors of mortality was estimated using ROC curves by calculating the area under the AUROC curve (*Area Under Receive Operating Characteristic Curve*) and by determining the statistical significance of difference of 0.5. The limit value (*cut-off*), was determined as the value of the product of optimal sensitivity and specificity.

Statistical analyses were performed using the statistical SPSS program, version 20.0. for the level of statistical significance of $p < 0.05$.

RESULTS

The study included 124 patients, 76 males (61.3%) and 48 females (38.7%), average age 60-80 years. The most frequent causes of AHF within the observed population were: coronary heart disease (55%), valvular diseases (19%) and dilatation cardiomyopathy of unknown etiology (19%). The 12-month all-cause mortality was 29.8%.

The levels of serum BNP (Table 1) were significantly higher in the group of non-survivors compared to the group of survivors (1353.8±507.8 vs 718.4±387.6 pg/mL, p<0.001). TnI and hsCRP values were higher in the group of deceased patients, with no statistical significance. The mean value of systolic blood pressure (SBP) diastolic blood pressure (DBP) at the admission were most significant investigated variables in survivors (p<0.001). The presence of chronic renal failure (CRF), peripheral artery disease (PAD), and depression were significantly more frequent among deceased patients compared to the patients who survived (p = 0.001 and p=0.045, p=0.012, respectively). Myocardial infarction and angina pectoris were more frequent in the group of deceased patients, with no statistical significance. In other general investigated biochemical parameters and clinical characteristics there were no statistically significant plural related to death (Table 1).

**Table 1. Clinical characteristics and biochemical parameters of the study patients
and comparison between one-year survivors and non-survivors**

VARIABLES	All n=124	Survivors n=87	Non-survivors n=37	*p*-value
Age (years)	70.7±9.8	70.9±10.0	70.1±9.3	0.660
Sex (M/W)	76/48	52/35	24/13	0.740
Number of previous hospitalizations	1.8±1.8	1.8±1.7	1.9±2.1	0.807
BMI (kg/m^2)	27.4±4.9	27.2±4.7	27.9±5.4	0.479
Hemoglobin (g/l)	128.6±19.6	128.5±19.5	128.7±20.2	0.962
Hematocrit	0.37±0.07	0.37±0.07	0.36±0.07	0.864
Urea (mmol/l)	8.6±4.7	7.9±4.4	8.9±4.8	0.254
Creatinine (μmol/l)	118.3±53.9	111.6±36.8	121.2±59.7	0.276
GFR (ml/min/1.73 m^2)	60.9±28.3	64.3±27.4	59.4±28.7	0.373
Glycemia (mmol/l)	7.6±3.4	7.7±3.5	7.3±2.9	0.445
Na (mmol/l)	141.5±4.6	141.4±4.6	141.7±4.9	0.712
TC (mmol/l)	4.6±1.4	4.7±1.4	4.6±1.2	0.702
LDL-C (mmol/l)	3.0±1.1	3.0±1.2	2.9±0.9	0.465
HDL-C (mmol/l)	1.1±0.4	1.1±0.3	1.1±0.4	0.519
TG (mmol/l)	1.4±0.9	1.4±0.9	1.4±0.6	0.807
CRF	42 (33.9)	21 (24.1)	21 (56.8)	0.001
CVI	19 (15.3)	13 (14.9)	6 (16.2)	0.857
IM	58 (46.8)	40 (46.0)	18 (48.6)	0.845
AP	58 (46.8)	39 (44.8)	19 (51.4)	0.558
HT	95 (76.6)	66 (75.9)	29 (78.4)	0.821
PAD	46 (37.1)	28 (32.2)	18 (48.6)	0.045
DM	49 (39.5)	36 (41.4)	13 (35.1)	0.553
COPD	37 (29.8)	25 (28.7)	12 (32.4)	0.674
Ventricular arrhythmias	43 (34.7)	32 (36.8)	11 (29.7)	0.538
Hypotension	18(15)	2(11)	16(89)	0.043
Depression	33 (26.6)	22 (25.3)	11 (29.7)	0.012
BNP (pg/ml)	908.0±515.5	718.4±387.6	1353.8±507.8	<0.001
TnI (ng/ml)	1.7±6.9	1.1±2.7	3.3±11.9	0.402
hsCRP (mg/l)	13.6±15.2	13.0±16.0	15.1±13.2	0.140
SBP (mmHg)	135.9±31.5	144.2±28.5	116.6±30.1	<0.001
DBP (mmHg)	81.9±17.4	85.6±15.9	73.1±17.9	<0.001
HR (beats/min)	95.9±25.8	98.2±25.8	90.5±25.5	0.132

BMI=body mass index, GFR=Glomerular filtration rate, CRF=Chronic renal failure, Na=sodium, TC=total cholesterol, LDL low-density lipoprotein cholesterol, HDL-C high-density lipoproteins cholesterol TG= triglyceride, CVI=Cerebrovascular insult, IM infarctus myocardii, AP=Angina pectoris, HT=hypertension, PAD=peripheral arterial disease, DM=Diabetes mellitus, COPD=Chronic obstructive pulmonary disease, BNP=B-type Natriuretic Peptide, TnI=Troponin-l, hs-CRP=high-sensitivity C-reactive protein SBP=systolic blood pressure DBP=diastolic blood pressure, HR=heart rate.

The most important predictors of mortality (p<0.001) were: concentration of BNP, hypotension at admission, left bundle branch block (LBBB), presence of CRF, SBP at admission, DBP at admission, EF, right ventricular systolic pressure (RVSP) and size of left atrial (LA). Also, statistically more significant predictors of mortality were: TnI, ventricular arrhythmia, depression, left ventricular end-systolic (and end-diastolic) diameter and the presence of diastolic dysfunction (Tables 2).

According to univariate Cox analysis two multivariate models were formed. In model 1, the used parameters were all biomarkers (BNP, TnI, hsCRP) as well as parameter of renal function (the presence of CRF, GFR) and LVEF. In the second model, the presence of the following co-morbidities

Table 2. Predictors of one-year death outcome-univariate Cox regression analysis

VARIABLES	HR	95%CI	*p*
Age	0.999	0.967-1.033	0.961
Sex	0.788	0.394-1.577	0.501
BNP	1.166	1.034-1.311	<0.001
TnI	1.042	1.011-1.074	0.007
hsCRP	1.008	0.991-1.024	0.375
Systolic blood pressure (SBP)	0.967	0.953-0.981	<0.001
Diastolic blood pressure (DBP)	0.948	0.924-0.973	<0.001
CRF	3.780	1.943-7.356	<0.001
Ventricular arrhythmias	2.115	1.099-4.071	0.025
Depression	2.602	1.346-5.029	0.004
EF	0.925	0.889-0.962	<0.001
EDDLV	1.056	1.022-1.091	0.001
ESDLV	1.050	1.021-1.081	0.001
RVSP	1.066	1.043-1.089	<0.001
LA	1.052	1.025-1.081	<0.001
LBBB	5.708	2.746-11.863	<0.001
Diastolic dysfunction	2.946	1.048-8.383	0.041
Hypotension at admission	7.226	3.692-14.143	<0.001

BNP=B-type Natriuretic Peptide, TnI=Troponin-l, hs-CRP=High-sensitivity high-sensitivity C-reactive protein, CRF=Chronic renal failure, EF=Ejection fraction, EDDLV=End-diastolic diameter, ESDLV=End-systolic diameter, RVSP=Right ventricular systolic pressure, LA=Left atrial, LBBB=Left bundle branch block.

Table 3. Cox multivariate analysis of mortality predictors - model 1.

VARIABLES	HR	95%CI	*p*
BNP	1.166	1.034-1.311	<0.001
TnI	1.041	1.002-1.082	0.039
hsCRP	1.001	0.970-1.033	0.956
Presence of CRF	1.723	0.821-3.617	0.151
GFR	0.996	0.983-1.009	0.519
EF	0.960	0.923-0.998	0.040

HR=hazard ratio, 95%CI (confidence interval), BNP=B-type Natriuretic Peptide, TnI=Troponin-l, hs-CRP=High-sensitivity C-reactive protein, CRF=Chronic renal failure, GFR=Glomerular filtration rate, EF=Ejection fraction.

Table 4. Cox multivariate analysis of mortality predictors - model 2

VARIABLES	HR	95%CI	*p*
Presence of CRF	3.300	1.662-6.550	0.001
Presence of DM	1.124	0.562-2.248	0.741
Presence of CVI	0.957	0.389-2.353	0.924
Presence of depression	2.050	1.021-4.117	0.043
Presence of COPD	0.972	0.473-1.999	0.939

HR=hazard ratio, 95%CI (confidence interval), CRF=Chronic renal failure, DM=Diabetes mellitus, CVI=Cerebrovascular insult, COPD=Chronic obstructive pulmonary disease

was tested: CRF, diabetes mellitus (DM), cerebrovascular insult (CVI), depression and chronic obstructive pulmonary disease (COPD) (Table 3, 4).

In the first multivariate model (Table 3) a significant predictor of mortality were BNP, TnI, and EF. Other data are in the Table 3.

In the second multivariate model (Table 4), as the strongest predictor of mortality, adjusted for other tested variables in the model, the presence of CRF and the presence of depression were distinguished.

The presence of CRF increases of risk of death for 3.3 times (HR 3.300, p=0.001), and the presence of depression - 2 times (HR 2.050, p=0.043).

In the investigated population, there was a statistically significant positive correlation between BNP and TnI (ρ=0.217, p=0.015). Both between BNP and hsCRP and between CRP and TnI, there was no statistically significant correlation. EF had significantly negative correlation with BNP (ρ =-0.396, p<0.001).

Between BNP and GFR there was a negative correlation, close to statistical significance (p=0.065).

In the studied population, serum concentrations of brain BNP could represent a mortality marker of hospitalized patients with heart failure (AUC 0.840, p<0.001).

In our study the limit value (cut-off) was 905.7 pg/ml with a sensitivity of 83.8% and specificity of 77%. The other two markers (TnI and hsCRP) had no statistically significant

Table 5. Parameters in analysis of ROC curve for BNP, TnI and hsCRP.

PREDICTOR	Cut off	Sensitivity	Specificity	AUC	SE	95%CI	p
BNP	905.7	83.80%	77.0%	0.840	0.039	0.765-0.915	**<0.001**
TnI	0.04	51.40%	59.8%	0.546	0.058	0.432-0.659	0.422
hsCRP	8.97	59.50%	60.9	0.584	0.058	0.469-0.699	0.140

BNP=B-type Natriuretic Peptide, TnI= Troponin-l, hs-CRP=High-sensitivity CRP.

discriminant value (p>0.05). The value of BNP≥905.7 pg/ml was associated with a higher risk of mortality in patients with AHF (Table 5).

DISCUSSION

The total one-year mortality in the study group was 29.8%. Slightly higher than found in previous studies of similar design [4,8-10] which included a higher number of respondents. The high mortality rate in patients with AHF, shown in all previous studies, is a sign of challenging and limited therapeutic options in the treatment.

In our study, the following indicators are shown as strong predictors of mortality in patients hospitalized with AHF in the univariate model: increased concentrations of BNP, hypotension at admission, the presence of CRF, reduced value of EF, systolic and diastolic blood pressure at admission, LBBB, RVSP and the size of LA. Statistically more significant predictors of mortality are: troponin I, ventricular arrhythmia, depression, diastolic and systolic left ventricular diameter and diastolic dysfunction.

Concerning the complexity of the immune /inflammatory/ proliferative ethiopathogenesis of HF, as well as generalized nature and progressive course of the disease, it is important to monitor the level and change in the level of specific biomarkers (BNP, TnI, hsCRP), because the value of BNP can reflect the progression of the disease, prognosis and therapeutic approach.

In patients hospitalized due to decompensated HF, high levels of BNP are associated with a worse prognosis. Results similar to our study were presented in a recent pilot study, on a study sample of 187 subjects and it showed that BNP was an independent predictor of adverse events in patients with acute worsening of chronic HF [11].

In the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) trial [12], the discharge (rather than admission) log-transformed BNP was the most important predictor of one-year mortality (HR of 1.34) and one-year death or re-hospitalization (HR 1.15).

In other studies[10], the value of BNP and NTproBNP at admission has not been shown as a predictor of one-year mortality in patients with AHF. Other authors have shown that serial measurement of BNP during hospitalization, as well as the measurement of BNP immediately before discharge of patients from hospital, have greater prognostic value than the measurement of BNP

immediately after admission to the hospital [13]. Values of BNP were taken once on admission in this study.

In recent years, the cut-off value of BNP>100 pg/mL has been standardized for diagnosing acute HF with high accuracy at 85% and strong prediction of HF, outperforming the clinical criteria. In our study of cases, the cut-off value for BNP or its fragment (8-29), was 905.7 pg/ml with a sensitivity of 83.8% and specificity of 77%.

In univariate Cox regression analysis, the concentration of BNP was distinguished as the strongest predictor of mortality in our population. Statistically more significant predictor of mortality was troponin I. The weaker statistical significance of troponin can be explained by the fact that ischemia (or myocardial necrosis) is not the cause of all HF; in fact, it appears in only 55% of patients, which has also influenced our results. Our research has shown that there is a direct correlation between BNP and TnI.

The slight increase of troponin is often seen in serious HF or during the episodes of decompensation of HF in the absence of acute coronary syndrome or even significant coronary disease [14].

There is clear evidence that even low levels of measurable TnI in patients with HF have important prognostic implications related to mortality and morbidity. In patients who showed clinical improvement after admission, the level of TnI became undetectable after a few days. However, in patients with refractory HF who died in the hospital, detectable levels of TnI persisted during the observation period [15].

In a recent study we investigated the role of TnI in predicting unfavorable outcomes in 238 patients with advanced HF who were suggested cardiac transplantation [15].

Patients with detectable levels of cTnI (from 0.04 ng/ml or more) had higher levels of BNP, hemodynamic compromise and increased mortality rate. The researchers from "Acute decompensated Heart Failure National Registry" (ADHERE) study the correlation between the levels of cardiac TnI and unfavorable events in 84.872 patients with acute decompensated HF [16]. The patients with positive levels of TnI (6.2%) had lower blood pressure (BP) at admission, lower EF and a higher rate of in-hospital mortality than those with undetectable TnI levels (8% vs 2.7%, p<0.001). The study confirmed a strong prognostic benefit of increased levels of TnI in predicting mortality in patients hospitalized due to decompensated HF [17].

Prognostic implications of hsCRP in patients with CHF have been tested in metaanalysis in 6600 patients [18]. There was a significant association between the increased hsCRP levels and more unfavorable cardiovascular outcomes, including mortality in patients with ischemic and non-ischemic etiology of HF. Unlike some recent studies [4,19], the results of the *Banovic et al.* study (10) as well as the results of our study, have not shown that hsCRP is a predictor of mortality.

The reasons are not clear enough, because it is not certain yet whether the increased CRP in AHF reflects only the weakening of the heart muscle or it is the result of associated infections. It should be noted that all three specific biomarker (BNP, TnI, hsCRP) were higher in the group of deceased patients with AHF. With an increasing number of responders, hsCRP would probably show statistical significance as a predictor of mortality.

The combination of two biomarkers (eg, BNP and TnI or CRP and BNP) showed better risk stratification than that achieved by using a single biomarker [20]. Better risk stratification allows optimization of therapy or application of more aggressive therapy for the patients with higher predictive risk.

Prognostic value of worsening renal function in discharge patiens with chronic heart failure was based mostly on serum creatinine and estimated glomerular filtration rate [21,22,23]. In our study, the presence of renal failure was significantly more frequent in the group of deceased patients with AHF, while the value rates of creatinine, urea and glomerular filtration did not differ significantly between the deceased and surviving patients with AHF, although they were slightly increased in the group of deceased patients. Multivariate analysis revealed that the presence of CRF increases the risk of death 3.3 times.

The prevalence rates of depression in CHF samples ranged from 24%–42% [24].

In our study, depression was present in 19.50% of surviving patients with AHF compared to 43.20% of deceased patients with AHF, which was statistically significant.

A larger number of studies have shown that depression is a graded, independent risk factor for readmission to the hospital, functional decline, and mortality in patients with congestive heart failure [25,26]. The patients with HF and depression were found to have the increased concentration of circulating catecholamines, proinflammatory and anti-inflammatory cytokines [27], which can be a cause of poor prognosis.

We need new clinical studies that will involve multi-factorial etiology of this syndrome.

CONCLUSION

High rate of one-year mortality in patients with AHF (29.8%), shown not only in our study, is a clear sign of our complexity in treating this syndrome. The most common cause of AHF in the observed population is coronary heart disease, followed by valvular heart disease, and dilatation cardiomyopathy of unknown etiology.

The following mortality predictors were distinguished as strong evaluated parameters: the concentration of BNP, TnI, reduced value of EF, hypotension at admission, presence of CRF and depression. However, renal failure and BNP are common and strong predictors of one-year mortality in hospitalized patients with heart failure, independent of other factors.

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