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Prognostic value of biomarkers and co-morbidities in patients with acute heart failure – A one-year follow-up study

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SUMMARY

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

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

Methods Clinical group comprised 124 consecutive unselected patients, age 60–80 years, treated at the Coronary Care Unit of the Niška Banja Institute, Niš. 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, $p < 0.001$). We identified several clinical and biochemical prognostic risk factors by univariate and multivariate analysis. Independent predictors of one-year mortality were the following: BNP, TnI, depression, hypotension, chronic renal failure, ejection fraction, and right-ventricle systolic pressure.

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

Keywords: biochemical marker; cardiac failure; trial

INTRODUCTION

Acute heart failure (AHF) is the leading cause of hospitalization within the age group of 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. Care for 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-15 (GDF-15), and highly-sensitive troponinT (hsTnT). Each has a growing set of data supporting its use, and sST2 and troponin measurements have been 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 pertaining to 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].

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

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of the Cardiology Department of the Niška Banja Institute during the period from July 1, 2010 to July 1, 2013, with signs and symptoms of AHF. AHF was diagnosed at the admission to the hospital according to the European Society of Cardiology guidelines for ACH, and the same diagnosis (AHF) had to be confirmed at discharge from the hospital [7]. Immediately after admission to the hospital, anthropometric measurements were carried out and existing diseases were registered along with the causes of AHF, precipitating factors, clinical presentation of the patients, as well as 12-lead electrocardiogram. 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 eight-hour fasting. Creatinine clearance was determined according to the Cockcroft–Gault formula. A BNP fragment (8-29) was determined using Elisys Uno device (Human Diagnostics, 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, Vienna, Austria) and the reference values were in the 0–2,400 pg/ml range. Measurement of hsCRP was performed on HumaStar 180 analyzer (Human Diagnostics). We used the "sandwich" type ELISA method. Troponin I was determined by ELISA method. During the first 48 hours of hospitalization, all the 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 a Del Mar device, as well as the analyses of the frequency and complexity of ventricular arrhythmias. After discharged from the hospital, mortality of the patients was being monitored for the following 12 months.

Statistical analysis

To assess the significance of the differences, we used the 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 method, as well as log-rank test to compare survival rates. The correlations between certain parameters were determined by Spearman's rank correlation coefficient. Testing of the biomarkers (BNP, TnI, and hsCRP) as predictors of mortality was estimated using ROC (receiver operating characteristic) curves by calculating the AUROC (the area under the receiver operating characteristic) curve and by determining the statistical significance of difference of 0.5. The limit value (cut-off point) was determined as the value of the product of optimal sensitivity and specificity.

Statistical analyses were performed using SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA) 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%), with the average age being 60–80 years. The most frequent causes of AHF within the observed population were as follows: 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

Table 1. Clinical characteristics and biochemical parameters of the patients studied 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/m²)	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 (l/l)	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 m²)	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 I; hsCRP – high-sensitivity C-reactive protein; SBP – systolic blood pressure DBP – diastolic blood pressure; HR – heart rate

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

Variables	HR	95% CI	p-value
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
SBP	0.967	0.953–0.981	< 0.001
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

HR – hazard ratio; CI – confidence interval; BNP – B-type natriuretic peptide; TnI – troponin I; hsCRP – high-sensitivity C-reactive protein; SBP – systolic blood pressure; DBP – diastolic blood pressure; CRF – chronic renal failure; EF – ejection fraction; EDDLV – end-diastolic diameter; ESDLV – end-systolic diameter; RVSP – right ventricular systolic pressure; LA – left atrium; LBBB – left bundle branch block

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

Variables	HR	95% CI	p-value
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; CI – confidence interval; BNP – B-type natriuretic peptide; TnI – troponin I; hsCRP – 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-value
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; CI – confidence interval; CRF – chronic renal failure; DM – diabetes mellitus; CVI – cerebrovascular insult; COPD – chronic obstructive pulmonary disease

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 values of systolic and diastolic blood pressures on admission were the most significant investigated variables in survivors (p < 0.001). The presence of chronic renal failure (CRF), peripheral arterial disease, and depression were significantly more frequent among deceased patients compared to patients who survived (p = 0.001, p = 0.045, and p = 0.012, respectively). Myocardial infarction and angina pectoris were more frequent in the group of de-

ceased patients, with no statistical significance. In other general investigated biochemical parameters and clinical characteristics there were no statistically significant factors related to death (Table 1).

The most important predictors of mortality (p < 0.001) were the following: concentration of BNP, hypotension at admission, left bundle branch block (LBBB), presence of CRF, systolic and diastolic blood pressures at admission, EF, right ventricular systolic pressure (RVSP) and the size of the left atrium (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 (Table 2).

According to univariate Cox analysis, two multivariate models were formed. In model 1, the used parameters were all biomarkers (BNP, TnI, and hsCRP) as well as the parameter of renal function (the presence of CRF, GFR) and LVEF. In the second model, the presence of the following co-morbidities was tested: CRF, diabetes mellitus, cerebrovascular insult, depression, and chronic obstructive pulmonary disease (Tables 3 and 4).

In the first multivariate model (Table 3), significant predictors of mortality were BNP, TnI, and EF.

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 risk of death due to the presence of CRF is 3.3 times higher [hazard ratio (HR) 3.300, p = 0.001], and the presence of depression represents a twofold increase in the risk (HR 2.050, p = 0.043).

In the investigated population, there was a statistically significant positive correlation between BNP and TnI (p = 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 (p = -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 [area under the curve (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 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, Figure 1).

DISCUSSION

The total one-year mortality in the study group was 29.8% – slightly higher than found in previous studies of similar design which included a higher number of respondents [4, 8, 9, 10]. High mortality rate in patients with AHF, shown in all previous studies, is a sign of challenging and limited therapeutic options in the treatment.

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

Predictor	Cut-off	Sensitivity	Specificity	AUC	SE	95% CI	p-value
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

ROC – receiver operating characteristic; AUC – area under curve; SE – standard error; CI – confidence interval; BNP – B-type natriuretic peptide; TnI – troponin I; hsCRP – high-sensitivity CRP
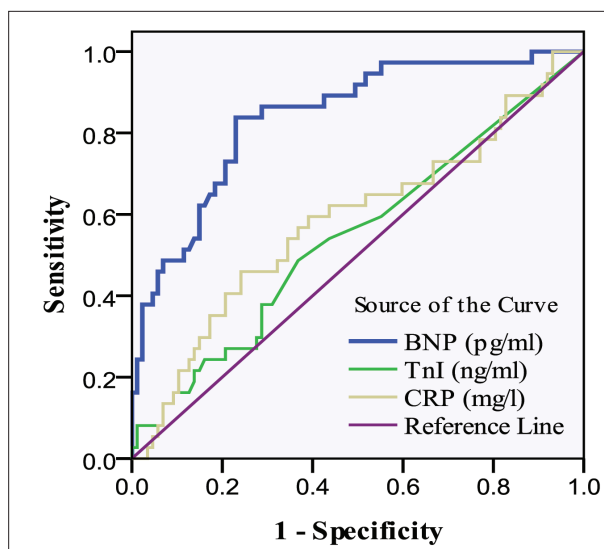

Figure 1. Analysis of receiver operating characteristic curve for BNP (B-type natriuretic peptide), TnI (troponin I), and hsCRP (high-sensitivity CRP)

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 etiopathogenesis 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 poorer 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 (OPTI-MIZE-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 values of BNP and NTproBNP at admission have not been shown as predictors of one-year mortality in patients with AHF. Other authors have shown that serial measurements of BNP during hospitalization, as well as measurements of BNP immediately before discharge of patients from hospital, have greater prognostic value than the measurements of BNP immediately after admission to the hospital [13]. In this study, values of BNP were taken once on admission.

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 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) studied 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 a meta-analysis in 6,600 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 Banović 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 biomarkers (BNP, TnI, and 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 (e.g. 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 patients with higher predictive risk.

Prognostic value of worsening renal function in discharged patients with CHF 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 were in the 24–42% range [24].

In our study, depression was present in 19.5% of surviving patients with AHF, compared to 43.2% 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 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: concentrations of BNP and 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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Прогностички значај биомаркера и комобирдитета код пацијената са акутном срчаном инсуфицијенцијом – студија једногодишњег праћења

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Увод/Циљ Стратификација клиничког ризика код пацијената хоспитализованих због акутне срчане инсуфицијенције (АСИ) коришћењем биомаркера натриуретик-пептида Б-типа (БНП), тропонина I (Тн I) и високоосетљивог Ц-реактивног протеина (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 у Коронарној јединици. Пацијенти су праћени годину дана након отпуста. Током прва 24 часа након пријема, БНП, Тн I и ЦРП мерени су у серуму наташте.

Резултати Свеукупни једногодишњи морталитет износио је 29,8%. Нивои серумског БНП-а били су знатно виши у групи болесника који су преминули у односу на групу пацијената који су преживели (1353.8 ± 507.8 тј. 718.4 ± 387.6 pg/mL, $p < 0,001$). Независни предиктори једногодишњег морталитета били су: БНП, Тн I, депресија, хипотензија, хронична бубрежна инсуфицијенција (ХБИ), ејекциона фракција, систолни притисак у десној преткомори.
Закључак Присуство оба биомаркера, БНП и Тн I, чак и више коморбидитета, као што су депресија или ХБИ имају значајан утицај на једногодишњу смртност пацијената са АСИ.

Кључне речи: биохемијски маркер; срчана слабост; студија