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[1]Clinic for Heart and Vessel Disease and Rheumatism, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina

[2]Polyclinic „Dr. Nabil", Sarajevo, Bosnia and Herzegovina

[3]Clinic for Nephrology, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina

Corresponding author: Azra Durak-Nalbantic, MD, PhD. Clinic for Heart and Vessel Disease and Rheumatism, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina. ORCID ID: thhtp://www.orcid.org: 0000-0002-5175-8941. Tel: +387 33 297 500, fax: +387 33 297 805. E-mail: azradurak@yahoo.com

Predictors of Hospitalization for Heart Failure Decompensation in 18-months Follow-up After Index Hospitalization for Acute Heart Failure

Azra Durak-Nalbantic[1], Alen Dzubur[1], Naser Nabil[2], Aida Hamzic-Mehmedbasic[3], Faris Zvizdic[1], Enisa Hodzic[1], Nerma Resic[1]

ABSTRACT

Introduction: Heart failure (HF) has very high rate of repeat hospitalizations due to HF decompensation (HHFD), sometimes very shortly after discharge for acute HF. Aim: The aim of this paper is to investigate rate of HHFD and to identify their possible predictors. Patients and Methods: Total amount of 222 patients hospitalized at Clinic for heart and vessel disease and rheumatism in acute HF were followed for next 18 months for occurrence of HHFD. During hospitalization were collected demographic data, risk factors, routine laboratory tests and admission BNP (brain natriuretic peptide), discharge BNP, percentage change of BNP during hospitalization, high sensitive troponin I, CA125 (cancer antigen125) and cystatin C. Results: In next 18 months 129 patients (58.11%) reached end-point HHFD- mean time of its occurrence was 2.2 (95% CI=1.67-2.7) months. Patients with HHFD had more often arterial hypertension (HTA) (p=0.006), had higher BMI (p=0.035) and had higher values of bilirubin, admission BNP (p=0.031), discharge BNP (p <0.001), CA125 (p=0.023) and cystatin C (p=0.028). There was no difference in troponin values (p=0.095), while % reduction of BNP during hospitalization was lower (p<0.001) in group with HHFD. In univariate Cox hazard analysis HTA was positively and BMI negatively correlated with HHFD, while in multivariate Cox hazard analysis independent predictors were HTA (HR 1.6; 95% CI=1.1-2.2; p=0.018) and BMI<25 (HR 1.6; 95% CI=1.1-2.3; p=0.007). In univariate Cox hazard analysis admission BNP, discharge BNP, rise of BNP during hospitalization, CA125 and bilirubin were positively correlated, while sodium was negatively correlated with HHFD. In multivariate Cox hazard analysis there was only one independent predictor of HHFD - discharge BNP (HR 6.05; 95% CI=1.89-19.4; p=0.002). Conclusion: Arterial hypertension, BMI>25 and discharge BNP are independent predictors of HHFD. This could help us to identify high-risk patients for readmission who should be monitored more frequently and treated with sophisticated drug and device therapy.

Keywords: heart failure, BNP, predictors of decompensation.

1. INTRODUCTION

Treatment with modern drug and device therapy, as well as wider availability of invasive treatment lead to better survival in cardiology. It seems that heart failure is an exception due to rising incidence and its bed survival. Mortality in heart failure (HF) is very high and worse then in most common carcinoma (1). Another problem is very high decompensation rate with a need of hospitalization, often very shortly after discharge–25% patients are readmitted within 1 month (2). Mesquita et al. (3) reported that patients admitted with HF have a high event rate (>50%) with a mortality rate between 10 and 15% and a rehospitalization rate within 6 months after discharge of 30 to 40%. Cardiologists are trying to find initiatives to stop this negative trends. One possible solution could be identification of strong and independent predictors of decompensation and early recognition of high-risk population. Among biomarkers, natriuretic peptides are most often use for diagnostic, but recently also for prognostic purpose. Measurement of BNP or NT-proBNP is useful for establishing disease severity in chronic HF, but also for prognosis estimation (4).

2. AIM

Aim of this study is to observe a rate of hospitalizations due to HF decompensation (HHFD) in 18-months period after index hospitalization for acute HF and to identify predictors of decompensation among demo-

graphic data, risk factors, routine laboratory tests and biomarkers.

3. PATIENTS AND METHODS

We collected data from 222 patients hospitalized at Clinic for heart and vessel disease and rheumatism in acute HF between 1 April 2014 and 1 January 2016. The patients were followed for next 18 months for occurrence of hospitalization due to HF decompensation (HHFD). During index hospitalization were collected demographic data, risk factors and it were collected blood samples for routine laboratory tests. Additionally, it were collected samples for the following biomarkers: BNP at admission, BNP at discharge, percentage change of BNP during hospitalization, high sensitive troponin I, CA125 and cystatin C. BNP values were determined by AxSYM® BNP (Abbott Laboratories) enzyme immunoassay. The upper normal limit is 100 pg/ml (5). Serum levels of CA125 were determined using tumor marker CA125 AxSYM assay (Abbott Laboratories). CA125 assay values are defined by using the OC125 monoclonal antibody who is reactive with repeating OC125-reactive determinants expressed by nonmucinous and epithelial ovarian carcinomas, tissue of pleura, pericardium, and peritoneum. The upper normal limit of CA125 in serum is 35 U/mL (6). ARCHITECT STAT High Sensitive Troponin-I assay (Abbott Diagnostics, Abbott Park, Il, USA) was used for determination of serum troponin on Abbott ARCHITECT i2000SR analyzer (7). 99-th percentile taken as a cut-off is 28 pg/ml. Cystatin C was quantitatively determined by N Latex Cystatin C test (particle enhanced nephelometric immunoassay) on BNII nephelometer (Siemens Healthcare Diagnostics, Marburg, Germany, ex-Dade-Behring) and referent values are 0.53-0.95 mg/l (8).

Research was conducted according to the Declaration of Helsinki, as well as the International Medical Research, revision 2008. Study had got approval from Ethic committee of University Clinical Center Sarajevo and Ethical Committee of Medical faculty University of Sarajevo. If normally distributed continuous variables are presented as mean +/-SD, or if non-normally distributed as median-interquartile range. Kolmogorov-Smirnov test was used for determination of variables distribution. Comparison of mean value was done by Student-test for independent samples if the variables were continuous (normal distribution) and Mann-Whitney test for a non-normally distributed variables. Kaplan-Meier curve of survival was used to estimate the survival function from lifetime data. Cox regression analysis was used to determine hazard ratio for every single parameter. Variables that met statistical significance on univariate analysis at p<0.05 were included in the multivariate Cox hazard analysis to prove independent predictors of HHFD. A p value <0.05 was

considered statistically significant. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software version 13.0 for Windows.

4. RESULTS

There was 138 patients with reduced ejection fraction (REF) (62.16%) and 74 (37.84%) with preserved EF (PEF) (p <0.001) (cut-off value for EF was 45%). In next 18 months of follow up 1 patient suffered ischaemic stroke, 1 patient myocardial infarction, 1 patient dissection of aorta, 1 patient pulmonary thromboembolism, in 1 patient was implanted ICD and in 2 patients was implanted mechanical valve in aortic position. Mean time of follow up was 3.5 (1.4-7.6) months. Time to occurrence of HHFD endpoint was 2.2 (95% CI=1.67-2.7) months.

In the next 18 months 129 patients (58.11%) were hospitalized due to decompensation. When we did reanalysis by months, we found that 31(13.96%) patients were hospitalized due to decompensation in first 1 month after discharge, 74 (33.33%) patients were rehospitalized in 1-6 months period, 105 (47.30%) patients in 0-6 months period, 18 (8.11%) patients in 6-12 months period, 123 (55.40%) patients in 0-12 months and 6 (2.7 %) in 12-18 months period. We followed up patients up to 24 months, but there was no new HHFD in period of 18-24 months.

Parameter	With end-point HHFD n= 129	No end-point HHFD n=93	p value
Age	69.3±13.4	72.0±10.4	0.1
Male sex	60 (46.51%)	53 (56.99%)	0.16
Atrial fibrillation	68 (52.71%)	46 (49.46%)	0.73
Arterial hypertension	75 (58.14%)	72 (77.42%)	0.004
Diabetes mellitus type 2	49 (37.98%)	45 (48.39%)	0.16
BMI (body mass index)	27.1±5.1	25.5±5.9	0.035
COPD	36 (27.90%)	21 (22.58%)	0.46
Sodium (mmol/l)	139.7±3.6	138.8±5.1	0.12
Hemoglobine (mg/dl)	130.8±22.5	133.0±19.4	0.46
Iron (µmol/l)	9.6±5.1	9.4±4.7	0.84
Creatinine (µmol/l)	106.3±39.4	109.4±40.6	0.57
eGFR(mL/min/1.73m²)	62.6±24.9	62.7±23.3	0.98
Uric acid (µmol/l)	535.8±164.2	497.1±152.8	0.154
Total cholesterol mmol/l	3.9±1.1	4.1±1.2	0.118
LDL-cholesterol (mmol/l)	2.4±0.83	2.4±0.96	0.85
Triglycerides(mmol/l)	1.3±0.6	1.37±0.7	0.44
Bilirubin (µmol/l)	23.4±17.7	17.9±12.2	0.021
Albumins (g/l)	34.03±4.1	34.4±5.0	0.57
Admission BNP (pg/ml)	1023.7 (525.2-1791.9)	790.5 (325.1-1481.5)	0.031
Discharge BNP (pg/ml)	685.0 (269.3-1480.4)	272.4 (134.2-601.8)	<0.001
% reduction of BNP (%)	-25.2(-58.9-1.2)	-54.2(-72.0-28.4)	<0.001
CA125 (IU/ml)	116.0(54.4-223.5)	68.7 (23.5-195.9)	0.023
hs troponin I (pg/ml)	53.7 (33.5-139.9)	50.6 (22.6-110.9)	0.095
Cystatin C (mg/l)	1.58 (1.22-1.96)	1.32 (1.1-1.73)	0.028

Table 1. Demographic data, risk factors, laboratory results and biomarkers in patients with and without end point HHFD (hospitalisation for heart failure decompensation). Abbrev.: HHFD–hospitalisation for heart failure decompensation; COPD–Chronic obstructive pulmonary disease; eGFR–estimated glomerular filtration rate; LDL-cholesterol: low density lipoprotein cholesterol; BNP: brain natriuretic peptide; CA125–cancer antigen 125.

Demographic	Univariate analysis				Multivariate analysis			
	B	p	HR	95% CI for HR	B	p	HR	95% CI for HR
Age	0.011	0.15	1.01	1.0-1.03				
Sex	0.21	0.24	1.23	0.87-1.74				
Arterial hypertension	0.55	0.003	1.73	1.2-2.5	0.44	0.018	1.6	1.1-2.2
Diabetes mellitus type 2	0.28	0.12	1.3	0.9-1.9				
Atrial fibrillation	0.1	0.59	1.1	0.8-1.6				
COPD	0.2	0.33	1.2	0.8-1.8				
BMI<25	-0.046	0.01	0.96	0.92-0.99	0.49	0.007	1.6	1.1-2.3

Table 2. Univariate Cox regression hazard analysis of prediction of HHFD after AHF. Abbrev. HHFD—hospitalisation for heart failure decompensation; COPD—chronic obstructive pulmonary disease; BMI—body mass index, B—beta factor; HR—hazard ratio, CI—confidence interval.

Laboratory value	Univariate analysis				Multivariate analysis			
	B	p	HR	95% CI for HR	B	p	HR	95% CI for HR
Creatinine	-0.002	0.4	1	1.0-1.003				
eGFR	0.001	0.75	1,0	1.0-1.008				
Uric acid	0,001	0,085	1.001	1-1.002				
Admission BNP	0.5	0.02	1.65	1.08-2.5				
Discharge BNP	0.96	0.0001	2.6	1.8-3.8	1.8	0.002	6.05	1.89-19.4
% change of BNP	0.003	0.004	1.003	1.001-1.005				
Troponin I	0.26	0.11	1.3	0.94-1.8				
Cystatin C	0.74	0.14	2.1	0.78-5.6				
CA125	0.53	0.003	1.7	1.19-2.4				
Hemoglobin	-0.004	0.37	1	1-1.004				
CRP	-0.09	0.71	0.9	0.6-1.4				
Albumins	-0.01	0.6	1	0.95-1.03				
Bilirubin	0.02	0.005	1.02	1.005-1.03				
Sodium	-0.04	0.032	0.96	0.92-0.997				

Table 3. Univariate and multivariate Cox regression hazard analysisof predictors of HHFD (hospitalization for heart failure decompensation). Abbrev.: HHFD—hospitalisation for heart failure decompensation, B—beta factor; HR—hazard ratio; CI—confidence interval, BNP—brain natriuretic peptide; CRP—C reactive protein.

Patients with end-point HHFD were younger, more often male, they have more often atrial fibrillation and diabetes, but difference was not significant (Table 1). Patient with HHFD suffered significantly more from arterial hypertension (p= 0.006) and have higher BMI (p=0.035). Among routine laboratory test results only serum bilirubin was statistically higher in patient with HHFD (p=0.021) (Table 1). In patients with end-point HHFD were found higher values of admission BNP (p=0.031), discharge BNP (p <0.001), CA125 (p=0.023) and cystatin C (p=0.028), while percentage reduction of BNP during hospitalization was lower (p<0.001). There was no significant difference in the troponin I values in patients with and without end-point (Table 1).

Analyzing ECG characteristics, there was no difference in presence of sinus rhythm (p=0.25), AF (p=0.91), QRS duration (more or less than 0.12 sec, p=0.1), heart rate (p=0.9) and Q wave (p=0.6) in group with and without HHFD.

4.1. Demographic data, risk factors and biomarkers as a predictors of decompensation

We did univariate and multivariate Cox regression analysis of demographic data, risk factors, laboratory tests and biomarkers to identify possible predictors of decompensation. Demographic variables that met statistical significance on univariate analysis at p<0.05 (HTA+ BMI> 25) were included in the multivariate Cox hazard analysis to prove independent predictors of HHFD. Arterial hypertension (HR 1.6; 95% CI=1.1-2.2; p=0.018) and BMI<25 (HR 1.6; 95% CI=1.1-2.3; p=0.007) kept their independent predictor role for HHFD (Table 2).

Analyzing laboratory tests and biomarkers in univariate Cox hazard analysis, we found that admission BNP, discharge BNP, rise of BNP during hospitalization, CA125 and bilirubin were positively correlated, while serum sodium was negatively correlated with end-point HHFD. Variables correlated with HHFD in univariate analysis were included again in multivariate Cox hazard analysis with an aim of identifying independent predictors of HHFD. Only single independent predictor of HHFD was discharge BNP (HR 6.05; 95% CI=1.89-19.4; p=0.002 (Table 3).

5. DISCUSSION

In our study we found very high rate of HHFD–in 18 months period after discharge for AHF (index hospitalization) more than a half of patients were rehospitalized and the most of rehospitalization happened in first 6 months after discharge. Cardiologists are trying to reduce these negative trends and to identify strong predictors of repeat admission. LVEF as a conventional predictor has its limitation due to fact that many patients with HF have preserved EF (HFPEF). Today there are many biomarkers in HF and most of them are used only in experimental

studies. What we wanted to do was to identify predictive biomarkers among biomarkers widely available in clinical practice. In univariate analysis the highest HR for readmission had discharge BNP and in multivariate analysis only parameter which kept its independent predictive value was again discharge BNP. Another important conclusion from our results is that is not enough to measure BNP only once during hospitalization. Recent recommendations are to measure at least 2 times–at admission and discharge. Although some studies are reporting percentage change of BNP as an independent predictor, in our study we could not prove it. Magalhães and al. (9) also identified discharge NT-proBNP as independent predictor of combined end-point cardiovascular death with rehospitalization for decompensated HF in 60 days. The area under the curve of NT-proBNP absolute variation for 60 day-events was 0.65 (p = 0.04; 95% CI = 0.51–0.79) and the area under the curve for NT-BNP at discharge was 0.69 (p = 0.03; 95%CI = 0.58–0.80). In the multivariate analysis, pre-discharge NT-proBNP was a predictor of the primary outcome, independently of the NT-proBNP at admission and other risk factors. Abnormal levels of circulating cardiac troponin are commonly found in patients with acute decompensated HF, often without obvious myocardial ischemia or underlying coronary artery disease (CAD), and this is associated with worse clinical outcomes and higher risk of death. Huynh et al. (10) reported that troponin could be used as a predictor of rehospitalization or death among HF patients. In our study we found elevated troponin in AHF, but not significantly higher in group with HHFD compared to group without HHFD and in univariate Cox regression hazard analysis of the troponin was not predictor of HHFD. In our study we identified BMI<25 as an independent predictor of decompensation–that confirmed so called "obesity paradox" in HF. Although overweight and obesity are risk factor for cardiovascular disease, it seems that adipose patients in HF have better survival than do their leaner counterparts (11). A systematic review of 6 studies (12) demonstrated that the risk for hospitalization and total and CVD mortality was higher in underweight patients with chronic HF, compared to the risk for CVD mortality and hospitalization in overweight subjects, implicating a protective role of increased body weight. Obesity paradox in HF is multi-factorial and complex. Obese patients have more often hypertension and may better tolerate ACE inhibitors. HF is a catabolic state and obese patients have more metabolic reserve and, therefore, a more favorable prognosis, while muscle wasting in leaner patients leads to poorer outcomes (13). Endotoxin/lipid hypothesis suggests that lipids in circulatory blood bind to endotoxins and inhibit their harmful effects. Increased levels of cholesterol and lipids or hyperlipidemia provide more molecules for binding to endotoxins and remove them from circulation and prevent the subsequent inflammatory response (14). Another possible explanation of better survival of obese patients in HF is a fact that the expression of circulating natriuretic peptides is reduced in overweight and obese patients (15), compared to normal weight patients. One another interesting thing came out from our study results: although there was no significant difference in serum creatine and eGFR, cystatin C were significantly higher in patients with hospitalization due to decompensation – 1.58 (1.22-1.96) vs.1.32 (1.1-1.73) mg/l, p=0.028. We hypothesized that cystatin C could be elevated in HF not due to renal dysfunction, but other mechanism such as interstitial fibrosis and rigid, stiff left ventricle could be involved. Xie et al. (16) reported elevation of cystatin C in doxorubicin induced mice cardiomyopathy correlated with an inhibition of cathepsin B (CTB), accumulation of collagen I, collagen III, and fibronectin in the ischemic area of the myocardium. They reported also over expression of cystatin C gene or treating fibroblasts with purified cystatin C protein could finally lead to inhibition of CTB activity and accumulation of the extra-cellular matrix protein (ECM). Conclusion is that cystatin C participated in the progression of chronic HF by regulating the degradation or accumulation of the ECM proteins. Breidthardt and al. (17) found that plasma cystatin C levels do not adequately predict acute kidney injury (AKI) in patients with AHF. However, in multivariate regression analysis cystatin C predicted mortality in AHF after the adjustment for baseline renal function, AKI, BNP levels and heart failure risk factors.

6. CONCLUSION

Discharge BNP is a strong and an independent predictor of repeat decompensation after AHF in univariate and multivariate analysis, as well as arterial hypertension and BMI < 25. These predictors help us to properly identify high-risk patients for hospital readmission in whom we should apply more intensive treatment- more frequent control, telephone contact, advanced drug and device therapy. All of these initiatives could lead to decreased rate of decompensation and lower mortality in HF.

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