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Old markers, new approach to assessment of risk in heart failure

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Abstract

Background: Heart transplantation (HTx) is still the optimal treatment for refractory heart failure (HF). However, there is great disproportion between the number of donors and potential recipients. Several parameters are used in patient evaluation before HTx, but the qualification process still requires improvement. High-sensitivity C-reactive protein (hsCRP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) possess high prognostic value for patients with advanced HF.

Aim: To assess the prognostic significance of NT-proBNP and hsCRP separately, as well as in combination, in a group of patients with advanced HF, considered for HTx.

Methods: Registry — 632 patients referred for HTx in Poland (2003–2007). Following proper treatment correction and routine clinical evaluation (i.e. mean New York Heart Association [NYHA] classification 3.2 ± 0.6, heart rate 77 ± 15 bpm, systolic/diastolic blood pressure [SBP/DBP] 103/67 ± 15/11 mm Hg, left ventricular ejection fraction [LVEF] 22 ± 8%, serum Na^+ 136 ± 4 mmol/L, NT-proBNP 3942 ± 5637 pg/mL, hsCRP 9 ± 22 mg/L levels, HFSS according to Aaronson 8 ± 1, etc.) patients were qualified for HTx. Based on ROC analysis (cut-off points for NT-proBNP 2435 pg/mL and hsCRP 2.4 mg/L) subjects were stratified into four subgroups: (1) non-elevated hsCRP (–)/NT-proBNP (–) (n = 179); (2) non-elevated hsCRP (–)/ /elevated NT-proBNP (+) (n = 92); (3) elevated hsCRP (+)/non-elevated NT-proBNP (–) (n = 159); and (4) elevated hsCRP (+)/ /NT-proBNP (+) (n = 202). The end point was defined as death/urgent HTx. The mean follow-up period was 601 days.

Results: In univariate regression analysis we confirmed that classical risk factors were independent predictors of end point: NYHA (HR = 2.311; p < 0.0001), heart rate (HR = 1.016; p = 0.0009), SBP (HR = 0.984; p = 0.0111), LVEF (HR = 0.951; p < 0.0001), serum Na^+ (HR = 0.901; p < 0.0001), NT-proBNP (HR = 1.004; p = 0.0159), and hsCRP (HR = 1.010; p = 0.0002); HFSS (HR = 0.557; p < 0.0001). Frequency-of-events analysis revealed that patients in the hsCRP (–)/ /NT-proBNP (–) subgroup presented with the best prognosis (13% of patients reached end point) followed by the hsCRP (–)/ /NT-proBNP (+) subgroup, in which 24% of patients reached end point (Kaplan-Meier χ^2 = 8.5319; p = 0.0035) and the hsCRP (+)/NT-proBNP (+) subgroup (χ^2 = 42.0413; p < 0.0001), which was associated with the worst prognosis (39% of patients reached end point).

Conclusions: The classical risk factors: NYHA class, heart rate, SBP, LVEF, HFSS, serum Na^+, NT-proBNP, and hsCRP concentrations, proved to be valuable in the assessment of risk in advanced HF patients. However, concomitant evaluation of old markers: hsCRP and NT-proBNP, may become a good prognostic tool for identification of highest-risk patients among all referred for HTx. Such a new approach to risk stratification before HTx seems promising but requires further investigation.

Key words: heart failure, C-reactive protein, B-type natriuretic peptide, transplantation

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INTRODUCTION

Chronic heart failure (HF) affects about 0.4–2% of the population, which amounts to 6.5–10 million people in Europe alone. In Poland the number of patients with HF is estimated at 0.6–0.7 million [1]. As the average lifespan increases with improvement of health care, the incidence and prevalence of HF increase as well. Despite great progress in treatment, introduction of new drugs (angiotensin-converting enzyme inhibitors [ACE-I], beta-blockers, etc.) and implantable devices

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(ICD, CRT), the disease is associated with particularly poor prognosis [2]. Mortality in the population of patients with most severe disease (III and IV class according to New York Heart Association [NYHA]) is high. Prognosis of patients with NYHA IV class is the poorest — the probability of surviving one year is only 50%.

Heart transplantation (HTx) remains one of the key methods of treatment for refractory HF. However, there is a great disproportion between the number of donors (with a steady decrease over the past decade) and the number of people awaiting HTx. Left ventricular (LV) assist devices can be used as a bridge to transplantation and, in rare cases, as a curative method, but access to such treatment is limited. Despite a careful process of qualification for HTx, taking into account rigorous indications and contraindications, the final decision is often difficult and its outcome uncertain. There are misgivings as to the exact moment at which a patient referred for elective HTx should be transplanted. There is also the question of which patients awaiting transplantation have the most urgent indications for the procedure. Therefore, there is a need for simple, reliable, and easily accessible tests that would allow us to select the group of patients awaiting elective transplantation with the worst prognosis, who should be offered this radical and invasive treatment first. We looked at parameters that have been available in clinical practice for years that could be used for new purposes. There is evidence in the literature that high-sensitivity C-reactive protein (hsCRP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) have high prognostic value in patients with HF [3, 4]. NT-proBNP is associated with volume overload, haemodynamic stress, and stretching of the myocardial ventricular wall, whereas raised hsCRP level is a marker of inflammation, which plays a role in the pathophysiology of HF. Despite correlations between levels of each marker and HF prognosis, there is only a slight association between both biomarkers. As HF is heterogeneous in its aetiology, it is possible that weak association between hsCRP and NT-proBNP reflects this heterogeneity. Therefore, each marker may have a different significance depending on the type of underlying pathology. The aim of this study was to evaluate prognostic significance of NT-proBNP and hsCRP separately, as well as in combination, in the population of patients with severe HF referred for HTx included in the POLCARD-HF registry [2], and to find a means of selecting patients with the worst prognosis, who carry the highest risk of death, using easily available parameters.

METHODS

Study population

POLCARD-HF multicentre registry [2] included a group of patients referred for HTx between 2003 and 2007. Following a detailed evaluation and appropriate treatment at one of four transplantation centres in Poland, 658 patients were qualified for HTx and were included in the register.

Study protocol

Informed consent was obtained from each patient participating in the study according to the protocol approved by the Local Ethics Committee. The investigation conformed to the principles outlined in the Declaration of Helsinki.

All patients were stratified according to the NYHA classification and underwent a clinical assessment that included: rest electrocardiogram (ECG), chest radiography, echocardiography, right heart catheterisation, and exercise testing (6-minute walk test [6MWT] and peak maximal oxygen consumption [peak VO_2]). Venous blood samples were obtained from each subject at the time of inclusion into the study. Blood samples for NT-proBNP, and hsCRP levels were acquired at the same time as for the remaining blood workup. All examinations were performed at the same time period.

Statistical analysis

Means and standard deviations were used for presenting the results. A comparison of analysed continuous parameters was conducted using the analysis of variance (Shapiro-Wilk test verified for normal distribution) and non-parametrical Mann-Whitney-Wilcoxon test (non-normal distribution) or Kruskal-Wallis test. Prediction values of analysed variables in terms of end point occurrence were analysed using the logistic regression method with single-variable and size of the area under receiver operating characteristic (ROC) curve (Fig. 1). The entire studied group was divided into four subgroups depending on hsCRP and NT-proBNP levels: (1) non-elevated hsCRP and NT-proBNP; (2) non-elevated hsCRP, elevated NT-proBNP; (3) elevated hsCRP, non-elevated NT-proBNP, and (4) elevated hsCRP and NT-proBNP. Composite endpoint was defined as death or urgent transplantation. For evaluation of survival rates, Kaplan-Meier curves were used, together with log-rank test for verification of a hypothesis on homogeneity of survival rate curves. For identification of independent predic-

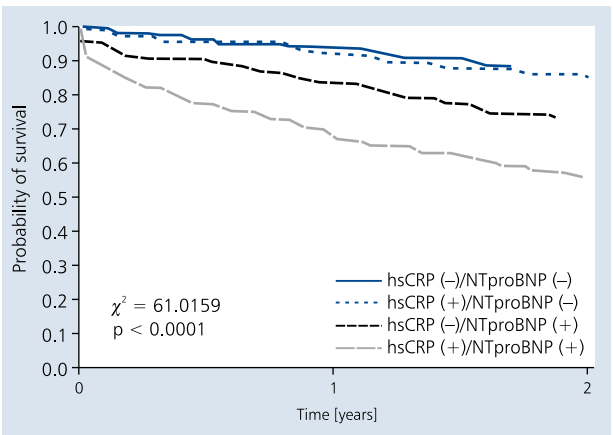

Figure 1. Kaplan-Meier survival curves in various subgroups ($p < 0.0001$). Description of subgroups — see abbreviations under Table 1

tors of the end point occurrence in subgroups, a multifactor logistic regression model was built with the stepwise variable selection method, based on single variable regression.

RESULTS

Study group

The entire study population included in the register consisted of 658 HF patients referred for HTx. Both hsCRP and NT-proBNP levels were measured in 632 patients, and those subjects were included in our study. Between 2003 and 2007, of the 632 patients 152 (24%) reached the end point (death or urgent HTx): 128 (20%) died and 24 (9%) underwent urgent transplantation. A total of 325 (49%) patients underwent transplantation during the observation period.

The average age of the referred patients was 49.9 ± ± 10.7 years. Mean heart rate (HR) was 77.4 ± 15.2 bpm. The entire group exhibited severe impairment of LV ejection fraction (LVEF) (mean 22.4 ± 7.9%) together with increased LV systolic/diastolic diameter (61.1 ± 11.6 mm and 72.3 ± 9.8 mm, respectively). Patients demonstrated significant neurohumoral (NT-proBNP 3942.4 ± 5637.2 pg/mL) and proinflammatory (hsCRP 9.0 ± 22.1 mg/dL) activation. Mean serum sodium concentration was 136.2 ± 4.4 mmol/L. The average HF survival score HFSS was 7.8 ± 0.9, indicating moderate risk of death. The average observation period was 601 days. More detailed characteristics of the entire study group were described in previous publications of the POLCARD-HF group [1, 2].

Despite optimal pharmacological therapy, consisting of ACE-I/angiotensin II receptor blockers (99.4%), aldosterone antagonists (6.8%), beta-blockers (99.8%), and diuretics (100%), the patients remained symptomatic and were referred for heart transplantation. All participants had HF symptoms and were classified according to NYHA functional classes II, III, and IV. Patients in II NYHA class were referred for cardiac transplantation mainly due to reasons other than HF, such as ischaemic heart disease refractory to treatment or life-threatening arrhythmias.

Depending on aetiology, our patient population was divided into three subgroups: (1) ischaemic cardiomyopathy, (2) dilated cardiomyopathy, or (3) other or unknown aetiology. Patients with ischaemic cardiomyopathy comprised 43% of the entire studied group (n = 272), with dilated cardiomyopathy comprising 51% (n = 321) and other aetiologies 6% (n = 39).

Comparison of parameters depending on the subgroup

Cut-off values for hsCRP and NT-proBNP were established (2.364 mg/L and 2435.474 pg/mL, respectively) based on ROC analysis. Sensitivity and specificity values for the tests were 65.7% and 58.9% for NT-proBNP and 70.8% and 46.5% for hsCRP, respectively. The entire studied group was divided into four subgroups depending on hsCRP and NT-proBNP levels: (1) non-elevated hsCRP and NT-proBNP (n = 179); (2) non-elevated hsCRP, elevated NT-proBNP (n = 92); (3) elevated hsCRP, non-elevated NT-proBNP (n = 159); and (4) elevated hsCRP and NT-proBNP (n = 202).

A Tukey range test for multiple comparisons used in combination with ANOVA demonstrated that the subgroups differed significantly from each other with regard to almost all variables except for age (Table 1). Analysis revealed that the hsCRP (+)/NT-proBNP (–) group was characterised by the highest body mass index (BMI), and the difference was statistically significant. Both groups presenting with NT-proBNP elevation demonstrated significantly reduced ejection fraction compared to the remaining groups regardless of CRP levels. Groups 1 and 2 differed with regard to all variables except for age and hsCRP concentration. No significant differences were noted between groups 1 and 3 with respect to almost all parameters except for age, diastolic blood pressure (DBP), maximal oxygen uptake and, naturally, level of CRP. Groups 1 and 4 differed significantly regarding all parameters with the exception of the following: age, DBP, and LV end-diastolic diameter. Groups 2 and 3 were alike with respect to age, HR, NYHA classification, sodium concentration, and VO_2max, while all other parameters demonstrated statistically significant differences. Groups 2 and 4 differed with respect to NYHA classification and serum sodium levels as well as NT-proBNP concentration and, as expected, level of hsCRP. Besides age, HR, LV end-systolic, and end-diastolic diameters, groups 3 and 4 did not show significant differences (Tables 1–3).

Kaplan-Meier survival curves in various subgroups

Analysis of Kaplan-Meier survival curves (Fig. 1) revealed statistically significant differences between all four subgroups ($p = 0.0001$). Comparison between subgroups using Kaplan-Meier curves revealed that the group of patients presenting with elevation of both hsCRP and NT-proBNP above the cut-off values established in ROC analysis was exposed to a significantly greater risk of death/urgent transplantation than a population without concomitant elevation of both markers ($p < 0.0001$). The prognosis of patients presenting with isolated NT-proBNP elevation was also less favourable in comparison to the hsCRP/NT-proBNP-negative group, statistical significance being demonstrated by a p-value of 0.0035. On the other hand, isolated elevation of hsCRP was not associated with significantly greater probability of end point occurrence compared to the group without elevation of either marker, as evidenced by a p-value of 0.5243, indicating that hsCRP alone is not a good predictor of outcome in the population of patients with severe HF referred for cardiac transplantation. There was a statistically significant difference in survival without necessity of urgent HTx between the hsCRP (+)/NT-proBNP (–) group and the hsCRP (+)/NT-proBNP (+) group ($p < 0.0001$). However, there were also statistical differences in survival between populations of patients with isolated NT-proBNP or

Table 1. Comparison of parameters varying between subgroups divided according to hsCRP and NT-proBNP levels (ANOVA)

	1. hsCRP (–)/ /NT-proBNP (–) (n = 179)	2. hsCRP (–)/ /NT-proBNP (+) (n = 92)	3. hsCRP (+)/ /NT-proBNP (–) (n = 159)	4. hsCRP (+)/ /NT-proBNP (+) (n = 202)	P
Age [years]	50.5 ± 10.1	48.4 ± 11.2	51.3 ± 8.7	48.9 ± 12.3	0.0724
BMI [kg/m^2][a]	26.2 ± 4.2	24.5 ± 4.5	28.3 ± 4.6	25.3 ± 4.4	< 0.0001
Ejection fraction [%][b]	23.9 ± 8.1	18.7 ± 6.1	25.3 ± 7.9	20.5 ± 7.3	< 0.0001
LVEDD [mm][c]	70.6 ± 8.8	75.6 ± 10.8	72.0 ± 9.2	72.5 ± 10.3	< 0.0013
LVESD [mm][d]	58.5 ± 11.4	65.2 ± 11.9	60.1 ± 11.4	62.2 ± 11.2	< 0.0001
Heart rate [bpm][e]	73.5 ± 14.5	79.8 ± 15.1	77.1 ± 14.7	80.1 ± 15.7	0.0001
Systolic BP [mm Hg][f]	105.0 ± 13.3	99.7 ± 15.3	106.3 ± 16.2	98.8 ± 15.4	< 0.0001
Diastolic BP [mm Hg][g]	68.0 ± 10.6	64.6 ± 12.1	69.3 ± 11.5	64.7 ± 11.4	0.0002
PASP [mm Hg][h]	40.6 ± 16.9	48.3 ± 16.0	40.4 ± 17.2	48.4 ± 16.1	< 0.0001
mPCWP [mm Hg][i]	18.6 ± 9.8	22.6 ± 7.9	17.6 ± 9.4	23.3 ± 9.1	< 0.0001
hsCRP [mg/dL] (median)[j]	1.03 (0.03; 2.3)	1.0 (0.05; 2.2)	5.0 (2.4; 196.8)	7.85 (2.37; 347)	< 0.0001
NT-proBNP [pg/mL] (median)[k]	1065 (77; 2376)	4280.5 (2443; 29590)	1420 (28; 2434)	5240.5 (2436; 46128)	< 0.0001
HFSS[l]	8.2 ± 0.9	7.5 ± 0.9	8.07 ± 0.9	7.3 ± 0.9	< 0.0001
NYHA class[m]	2.7 ± 0.6	2.9 ± 0.6	2.8 ± 0.6	3.2 ± 0.7	< 0.0001
Na^+ [mmol/L][n]	137.6 ± 3.3	136.2 ± 3.8	137.1 ± 4.1	134.3 ± 5.1	< 0.0001
VO_2max [mL/kg mc./min][o]	15.2 ± 4.8	13.0 ± 4.4	13.7 ± 4.2	11.5 ± 3.9	0.0008

BMI — body mass index; LVEDD — left ventricular end-diastolic diameter; LVESD — left ventricular end-systolic diameter; BP — blood pressure; PASP — pulmonary artery systolic pressure; mPCWP — mean pulmonary capillary wedge pressure; hsCRP — level of C-reactive protein measured with a high-sensitivity test, NT-proBNP — level of N-terminal pro-B-type natriuretic factor; HFSS — heart failure survival score; NYHA class — classification according to the New York Heart Association; Na^+ — sodium concentration; VO_2max — maximal oxygen consumption

Description of subgroups: hsCRP (–) — level of hsCRP below the cut-off value determined using ROC analysis for assessing the influence of those parameters on mortality (2.3645 mg/L); hsCRP (+) — level of hsCRP above the cut-off value determined by ROC analysis; NT-proBNP (–) — level of NT-proBNP below the cut-off value determined using ROC analysis for assessing the influence of those parameters on mortality (2435.474 pg/mL); NT-proBNP (+) — level of NT-proBNP above the cut-off value determined by ROC analysis

[a]Differences between all subgroups were statistically significant ($p < 0.05$) except for comparisons between subgroups 1 vs. 4 and 2 vs. 4; [b]differences between all subgroups were statistically significant ($p < 0.05$) except for comparisons between subgroups 1 vs. 3 and 2 vs. 4; [c]differences were statistically significant ($p < 0.05$) for comparisons between subgroups 2 vs. 3 and 1 vs. 2; [d]differences were statistically significant ($p < 0.05$) for comparisons between subgroups 2 vs. 3, 1 vs. 2 and 1 vs. 4; [e]differences were statistically significant ($p < 0.05$) for comparisons between subgroups 1 vs. 2 and 1 vs. 4; [f]differences between all subgroups were statistically significant ($p < 0.05$) except for comparisons between subgroups 1 vs. 3 and 2 vs. 4; [g]differences were statistically significant ($p < 0.05$) for comparisons between subgroups 1 vs. 2, 1 vs. 3 and 2 vs. 3; [h]differences between all subgroups were statistically significant ($p < 0.05$) except for comparisons between subgroups 1 vs. 3 and 2 vs. 4; [i]differences between all subgroups were statistically significant ($p<0.05$) except for comparisons between subgroups 1 vs. 3 and 2 vs. 4; [j]differences between all subgroups were statistically significant ($p < 0.05$) except for comparisons between subgroups 1 vs. 2; [k]differences between all subgroups were statistically significant ($p < 0.05$) except for comparisons between subgroups 1 vs. 3; [l]differences between all subgroups were statistically significant ($p < 0.05$) except for comparisons between subgroups 1 vs. 3 and 2 vs. 4; [m]differences between all subgroups were statistically significant ($p < 0.05$) except for comparisons between subgroups 1 vs. 3 and 2 vs. 3; [n]differences between all subgroups were statistically significant ($p < 0.05$) except for comparisons between subgroups 1 vs. 3 and 2 vs. 3; [o]differences between all subgroups were statistically significant ($p < 0.05$) except for comparisons between subgroups 2 vs. 3 and 2 vs. 4

Table 2. Univariate Cox regression analysis of factors influencing survival without death or urgent heart transplantation in the whole group

Parameter	Hazard ratio estimates (univariate)			
	Point estimate	95% confidence interval		P
		Lower	Upper	
Ejection fraction [%]	0.951	0.928	0.975	< 0.0001
Heart rate [bpm]	1.016	1.007	1.026	0.0009
Systolic blood pressure [mm Hg]	0.984	0.973	0.996	0.0111
Heart failure survival score	0.557	0.468	0.663	< 0.0001
NYHA class	2.311	1.800	2.967	< 0.0001
Na^+ [mmol/L]	0.901	0.873	0.930	< 0.0001

NYHA class — classification according to the New York Heart Association; Na^+ — sodium concentration

Table 3. Univariate and multivariate Cox regression analyses of factors influencing survival without death or urgent heart transplantation in subgroups divided depending high-sensitivity C-reactive protein (hsCRP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels

Parameters	Subgroups							
	1. hsCRP (–)/NT-proBNP (–)		2. hsCRP (–)/NT-proBNP (+)		3. hsCRP (+)/NTproBNP (–)		4. hsCRP (+)/NT-proBNP (+)	
	Univariate OR (95% CI)	Multivariate OR (95% CI)	Univariate OR (95% CI)	Multivariate OR (95% CI)	Univariate OR (95% CI)	Multivariate OR (95% CI)	Univariate OR (95% CI)	Multivariate OR (95% CI)
Age [years]	1.006 (0.964–1.049)	–	0.969 (0.937–1.002)	–	0.996 (0.958–1.035)	–	0.984 (0.966–1.003)	–
Weight [kg]	1.018 (0.989–1.047)	–	0.996 (0.969–1.024)	–	1.016 (0.992–1.040)	–	0.991 (0.975–1.006)	–
BMI [kg/m^2]	1.046 (0.953–1.147)	–	0.959 (0.871–1.057)	0.728 (0.587–0.904)	1.017 (0.940–1.100)	–	0.962 (0.911–1.015)	–
Ejection fraction [%]	0.958 (0.899–1.021)	–	0.982 (0.917–1.051)	–	0.957 (0.904–1.012)	–	0.975 (0.943–1.007)	–
LVEDD [mm]	1.035 (0.985–1.087)	–	1.034 (0.992–1.077)	1.147 (1.052–1.250)	1.042 (0.996–1.089)	1.087 (1.009–1.172)	1.025 (1.002–1.049)	–
LVESD [mm]	1.011 (0.971–1.052)	–	1.018 (0.982–1.055)	–	1.021 (0.986–1.057)	–	1.024 (1.003–1.046)	–
Heart rate [bpm]	1.006 (0.979–1.035)	–	0.994– (0.968–1.022)	–	0.994 (0.969–1.020)	–	1.032 (1.018–1.046)	–
Systolic BP [mm Hg]	0.979 (0.946–1.013)	–	0.992 (0.958–1.027)	–	0.999 (0.976–1.023)	–	0.994 (0.678–1.010)	–
Diastolic BP [mm Hg]	0.999 (0.958–1.042)	–	1.001 (0.966–1.038)	–	1.017 (0.985–1.050)	–	0.993 (0.973–1.014)	–
PASP [mm Hg]	1.020 (0.985–1.056)	–	1.033 (1.003–1.064)	–	1.012 (0.984–1.040)	–	0.985 (0.970–1.000)	0.974 (0.955–0.992)
mPCWP [mm Hg]	1.003 (0.945–1.065)	–	1.055 (0.993–1.121)	–	1.024 (0.975–1.076)	–	1.007 (0.981–1.034)	–
hsCRP [mg/dL]	0.646 (0.327–1.277)	–	0.983 (0.518–1.867)	–	0.996 (0.965–1.027)	–	1.005 (1.000–1.011)	–
NT-proBNP [pg/mL]	1.001 (1.000–1.001)	–	1.000 (1.000–1.000)	–	1.000 (0.999–1.000)	–	1.000 (1.000–1.000)	–
HFSS	0.645 (0.398–1.044)	–	0.787 (0.484–1.227)	–	0.791 (0.515–1.215)	–	0.621 (0.479–0.805)	–
NYHA class	1.149 (0.540–2.445)	–	1.368 (0.668–2.803)	–	1.016 (0.586–1.763)	–	3.020 (2.088–4.367)	–
Na^+ [mmol/L]	1.017 (0.893–1.158)	–	0.867 (0.777–0.967)	–	0.947 (0.868–1.033)	–	0.931 (0.893–0.969)	0.904 (0.843–0.970)
VO_2max [mL/kg mc./min]	0.952 (0.866–1.047)	–	0.959 (0.849–1.083)	0.766 (0.615–0.954)	0.894 (0.794–1.006)	–	0.984 (0.911–1.064)	–

OR — odds ratio; CI — confidence interval; rest abbreviation as in Table 1

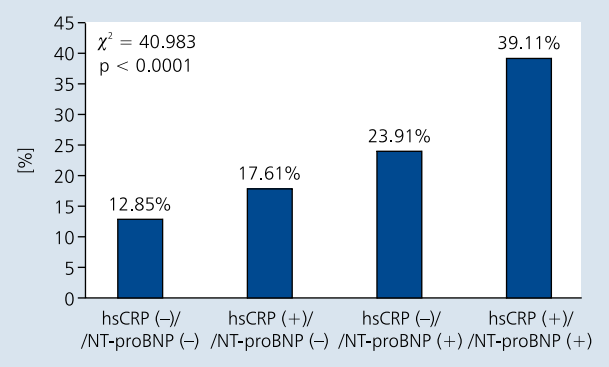

Figure 2. Frequency of composite end point occurrence in particular subgroups divided according to high-sensitivity C-reactive protein (hsCRP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels (χ^2 test). Description of subgroups — see abbreviations under Table 1

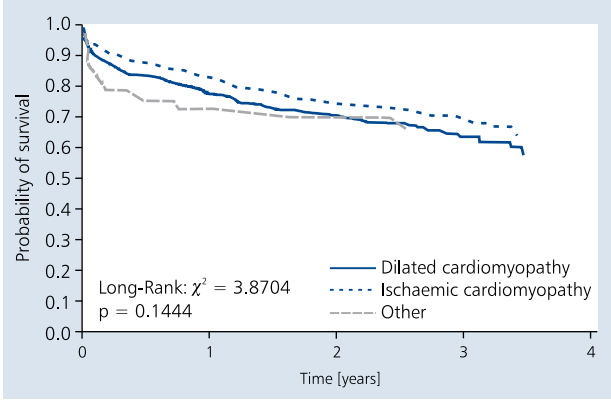

Figure 3. Kaplan-Meier curves comparing survival of patients depending on aetiology (p = 0.1444)

hsCRP elevation (p = 0.0223), the latter being associated with better prognosis (Fig. 1).

Frequency of composite end-point occurrence in all subgroups was also assessed using the χ^2 test. The greatest percentage of patients reached the end point in the hsCRP (+)/NT-proBNP (+) group (39.11%), while the hsCRP (–)/ /NT-proBNP (–) group was associated with the lowest probability of death/urgent HTx (12.85%) (Fig. 2).

Factors influencing outcome in the entire group — Cox analysis

In univariate regression analysis, out of all parameters, six significant predictor factors affecting the outcome (death or urgent HTx) were identified in the entire group: ejection fraction (p < 0.0001), HR (p = 0.0009), systolic blood pressure (SBP; p = 0.0111), HFSS according to Aaronson (p < 0.0001), functional class according to NYHA (p < 0.0001), and sodium concentration (p < 0.0001) (Table 2).

Following univariate analysis, all parameters were used for building a multivariate Cox regression model with stepwise variable selection in order to identify the characteristics that influence the occurrence of end-point events and can be considered independent predictors of death/urgent transplantation in particular subgroups (Table 3). The following factors were found to affect the outcome in particular subgroups: pulmonary artery systolic pressure (PASP) and sodium concentration predicted outcome in the hsCRP (+)/NT-proBNP (+) group, BMI, LV end-diastolic diameter, and maximal oxygen uptake influenced endpoints in the hsCRP (–)/NT-proBNP (+) population, while LV end-diastolic diameter was an independent predictor of death/urgent transplantation in the hsCRP (+)/ /NT-proBNP (–) group. No additional factors were found to have an impact on mortality/necessity of urgent HTx in the remaining groups.

Aetiology

There were no statistical differences between subgroups (χ^2 test) with regard to the aetiology of HF (p = 0.3576), as shown in Table 4.

Analysis of Kaplan-Meier curves showed no differences between aetiological groups (dilated cardiomyopathy, ischaemic cardiomyopathy, other) with regard to the frequency of end point occurrence (p = 0.1444) (Fig. 3).

DISCUSSION

The continuing increase in the morbidity of HF and limited access to HTx resulting from a shrinking number of donors forces us to search for new parameters that would allow better assessment of prognosis in patients referred for HTx, and would help in choosing the appropriate time for final qualification to the procedure. Despite a number of tests performed in the course of qualification process, there is still a great need to find additional prognostic factors in this group of most severely ill, optimally treated patients, for whom we have no options other than organ transplantation. As HTx is a high-risk procedure and the organ pool is sparse, it is important to select patients from this group, who present the greatest risk of death and would benefit most from this kind of treatment.

Inflammation plays a role in the pathophysiology of HF itself and one of the most commonly used markers of inflammation, hsCRP, is associated with poor prognosis in HF [3]. Some authors imply that it contributes to the progression of the disease. Cachexia and haemodynamic instability, which contribute to the overall clinical picture of HF, are connected with the presence of proinflammatory cytokines (interleukin-6 and -18, tumour necrosis factor-alpha [TNFα]) [5, 6]. According to the Val-HeFT study, in patients with HF, raised hsCRP levels were associated with more severe disease, as reflected by clinical status and BNP levels [7]. Moreover, inflammation is strongly associated with the pathophysiology of atherosclerosis and ischaemic heart disease — the most common cause of HF.

Table 4. Aetiology of heart failure — percentage distribution in each subgroup (test $\chi^2 = 6.6180$)

	hsCRP (–)/ /NT-proBNP (–)	hsCRP (–)/ /NT-proBNP (+)	hsCRP (+)/ /NT-proBNP (–)	hsCRP (+)/ /NT-proBNP (+)
Dilated cardiomyopathy	47.49	57.61	47.17	53.47
Ischaemic cardiomyopathy	48.04	35.87	46.54	39.11
Other	4.47	6.52	6.29	7.43

Abbreviations as in Table 1.

There are numerous studies showing a correlation between elevated CRP levels in the first days following acute myocardial infarction and development of HF and death [8]. According to the study by Sabatine et al. [9], combining hsCRP, BNP (B-type natriuretic factor), and troponin I measurements adds to the predictive value of CRP itself in a population of patients with non-ST elevation myocardial infarction. The question remains: whether there are differences in hsCRP levels between populations with ischaemic vs. non-ischaemic HF. Our study showed no significant differences in mortality between subgroups as far as aetiologies were concerned, corroborating the results of other studies [7]. As is known from the PRAISE (Prospective Randomized Amlodipine Survival Evaluation) and SOLVD (Studies Of left Ventricular Dysfunction) trials, increased concentrations of inflammatory cytokines, such as TNFα, IL-6, and their receptors, are associated with poor short-term and long-term prognosis in HF [10–12]. They are not, however, routinely assessed in a hospital setting. Cachexia, closely associated with immunological activation, is also an independent predictor of poor outcome in HF. Therefore, it seems logical that CRP, a long-known indicator of inflammation and a mediator of endothelial dysfunction [13], commonly assessed during hospitalisation, has the potential to become an excellent prognostic marker. Elevated level of CRP detected using high-sensitivity tests is a strong predictor of myocardial infarction, stroke, peripheral artery disease, and death from vascular causes.

According to several population studies, hsCRP is a predictor of HF development [10]. A cohort study by Hamer et al. [14] has shown that significantly elevated CRP levels (> 10 ng/mL) are associated with an increased risk of all cardiovascular events and all-cause mortality. This risk is particularly apparent in the population of patients with coronary artery disease [15] because chronic inflammation plays a role in the pathogenesis of atherosclerosis. In the PROVE IT-TIMI 22 study, which included 4162 patients after acute coronary syndrome, hsCRP and NT-proBNP levels were measured 30 days after inclusion into the study [16]. Hospitalisations due to HF or cardiovascular death occurring after that time were followed up for a mean of 24 months. In their analysis, Sirica et al. [8] found a weak but significant correlation between hsCRP and BNP levels at 30 days after inclusion. Both elevated hsCRP and BNP concentrations were independently correlated with the occurrence of symptoms of HF and with cardiovascular death or HF. Studies by Alonso-Martinez et al. [17] confirmed that an inflammatory response is present in a failing heart and increased CRP levels correlate with higher NYHA class and are related to higher rates of readmission and mortality in an entire population with HF.

A study by Anand et al. [7] from 2005 stated that in a population of patients with HF elevated CRP is an indicator of more severe disease and that it affects mortality and morbidity. Anand et al. [7] also found that CRP and BNP are equally good indicators of prognosis and that there is an additive effect when BNP and CRP measurements are used together to assess prognosis, which is in accordance with the results of our investigation. They also stated that there was no difference in CRP levels in disease states of ischaemic and non-ischaemic aetiology (although assessment of aetiology in his study was clinical and not based on angiographic findings), which is consistent with our findings.

In our study, we focused on a group of most severely ill, optimally treated patients who had been qualified for HTx in the absence of other therapeutic options. We assessed the value of hsCRP and NT-proBNP as prognostic factors separately as well as jointly. Based on the Kaplan-Meier survival curves, we may conclude that the combined prognostic value of hsCRP and NT-proBNP taken together is greater than each of these markers taken separately. Our study also showed that, while NT-proBNP is an independent factor predicting mortality in this group of patients, increased levels of hsCRP alone do not significantly affect survival. This stands in contradiction to previous studies by other authors, but may be related to the fact that our studied group was carefully selected from patients on optimal HF treatment, including adequate doses of ACE-I (or angiotensin receptor blockers), beta-blockers, and statins, which may affect hsCRP levels. We have also identified risk factors within the subgroups that could help us set apart individuals with highest risk of death in the group of patients referred for heart transplantation. In the group characterised by highest risk, where both hsCRP and NT-proBNP were above the cut-off values, PASP and sodium concentration influenced the outcome (Table 3). This is not a surprising finding because low sodium concentration and elevated PASP are indicators of cardiovascular decompensation and/or inadequate diuretic therapy. The influence of the remaining parameters of circula-

tory instability (i.e. HR, blood pressure) may be obscured by the administration of pharmacotherapy typical for HF (i.e. beta-blockers, vasopressors).

Our study showed that there are also differences in other parameters among groups of patients depending on concentrations of hsCRP and NT-proBNP. Group 3 was characterised by the highest BMI, and the difference was statistically significant. Since it is known that excess fat tissue is related to elevated inflammatory markers, it is not surprising that the group with increased hsCRP and non-elevated NT-proBNP presented with higher BMI values. Both groups with elevated NT-proBNP levels (2 and 4) were characterised by reduced ejection fraction and LV end-systolic diameters. With regard to HR, there were statistically significant differences between groups 1 and 2 and 1 and 4. This might be related to the fact that NT-proBNP is a laboratory marker of HF decompensation, and individuals with elevated concentrations of this hormone were also characterised by higher HRs, indicating either inadequate beta-blocker therapy or a state of circulatory instability. Haemodynamic markers of disease severity — PASP and mean pulmonary capillary wedge pressure — were also increased in both groups characterised by NT-proBNP elevation, compared to other groups, and these differences were statistically significant. Group 4 was characterised by the lowest sodium concentration, and it differed significantly from other groups in that regard. It is in accordance with other findings of our study, elevated hsCRP and NT-proBNP levels are associated with a higher probability of end point occurrence, as shown by our Kaplan-Meier curves, and reduced serum sodium level is also associated with higher risk of death/urgent transplantation in this group of patients.

Univariate Cox regression analysis of factors influencing survival without death or urgent HTx in the entire group revealed that the following characteristics influence end points: ejection fraction, HR, SBP, Aaronson score, NYHA class, and sodium concentration. These factors have previously been shown to be markers of poor prognosis, and our study stands in agreement with these findings.

Analysis of Kaplan-Meier survival curves for various aetiologies of HF (ischaemic vs. dilated cardiomyopathy vs. other) showed no statistically significant differences between those groups ($p = 0.1444$). We may therefore conclude that the aetiology of HF does not significantly influence the risk of death/urgent transplantation in the group of most severely ill patients who qualify for cardiac transplantation.

Limitations to the study

One must keep in mind that NT-proBNP measurements were obtained at the time of inclusion into the study; therefore, it is likely that patients presented different haemodynamic statuses at that time, as reflected by natriuretic peptide levels. It poses a possible limitation to our study. The same is true for the remaining examinations: imaging studies, and biochemical and functional tests. It also is worth noting that the treatment of HF has changed over the years and is constantly evolving. Treatment guidelines and availability of various types of treatment (i.e. electrotherapy) have changed since the time of the study. Patients recruited during years 2003–2007 received the optimal therapy that was available at the time, as presented in the 'results' section of this publication.

CONCLUSIONS

In conclusion, routinely measured parameters such as NT-proBNP and hsCRP are valuable for prediction of poor outcome among patients with advanced HF referred for transplantation. Moreover, their predictive value becomes even more pronounced when they are considered in combination.

Conflict of interest: *none declared*

References

1. Rywik TM, Kołodziej P, Targoński R et al. Characteristics of the heart failure population in Poland: ZOPAN, a multicentre national programme. Kardiol Pol, 2011; 69: 24–31.
2. Korewicki J, Browarek A, Zembala et al. Ogólnopolski rejestr chorych z ciężką niewydolnością serca, zakwalifikowanych do przeszczepu serca — POLKARD-HF 2003–2007. Folia Cardiol Excrepta, 2008; 3: 403–421.
3. Kozdag G, Ertas G, Kilic T et al. Elevated level of high-sensitivity C-reactive protein is important in determining prognosis in heart failure. Med Sci Monit, 2010; 16: 156–161.
4. Miller VM, Redfield M, McConnell JP. Use of BNP and CRP as biomarkers in assessing cardiovascular disease: diagnosis versus risk. Curr Vascular Pharmacol, 2007; 5: 15–25.
5. Anker S, von Haeling S. Inflammatory mediators in heart failure: an overwiew. Heart, 2004; 90: 464–470.
6. Rauchhaus M, Doehner W, Francis D et al. Plasma cytokine parameters and mortality in patients with chronić heart failure. Circulation, 2000; 102: 3060–3067.
7. Anand IS, Latini R, Florea VG et al. C-reactive protein in heart failure: prognostic value and the effect of valsartan. Circulation, 2005; 112: 1428–1434.
8. Sirica BM, Cannon CP, Sabatine MS et al. Concentrations of C-reactive protein and B-type natriuretic peptide 30 days after acute coronary syndromes independently predict hospitalization for heart failure and cardiovascular death. Clin Chem, 2009; 55: 265–273.
9. Sabatine MS, Morrow DA, de Lemos JA et al. Multimarker aproach to risk stratification in non-ST elevation acute coronary syndromes: simultaneous assessment of troponin I, C-reactive protein and B-type natriuretic peptide. Circulation, 2002; 105: 1760–1763.
10. Choi EY, Yan RT, Fernandes VRS et al. High-sensitivity C-reactive protein as an independent predictor of progressive myocardial functional deterioration. Am Heart J, 2012; 164: 251–258.
11. Mohler ER, Sorensen LC, Ghali J et al. Role of cytokines in the mechanism of action of amlodipine: the PRAISE heart failure trial. J Am Coll Cardiol, 1997; 30: 35–41.
12. Torre-Amione G, Kapadia S, Benedict C et al. Proinflammatory cytokine levels in patients with depressed left ventricular ejection fraction: a report from teh studies of left ventricular dysfunction (SOLVD). J Am Coll Cardiol, 1996; 27: 1201–1206.
13. Szmitko PE, Wang CH, Weisel R et al. New markers of inflammation and endothelial cel activation. Circulation, 2003; 108: 1917–1923.
14. Hamer M, Chida Y, Stamatakis E. Association of very highly elevated C-reactive protein concentration with cardiovascular events and all-cause mortality. Clin Chem, 2010; 56: 132–135.
15. Janoskuti L, Forhecz Z, Hosszufalusi N et al. High levels of C-reactive protein with low total cholesterol concentrations additively predict all-cause mortality in patients with coronary artery disease. Eur J Clin Investigation, 2005; 35: 104–111.
16. Ridker P, Cannon C, Morrow D et al. C-reactive protein levels and outcomes after statin therapy. N Engl J Med, 2005; 352: 20–28.
17. Alonso-Martinez JL, Llorente-Diez B, Echegaray-Agara M et al. C-reactive protein as a predictor of improvement and readmission in heart failure. Eur J Heart Failure, 2002; 4: 331–336.

Zastosowanie ogólnie dostępnych markerów w ocenie ryzyka w zaawansowanej niewydolności serca

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Streszczenie

Wstęp: Przeszczep serca (HTx) pozostaje optymalną metodą leczenia zaawansowanej niewydolności serca (HF). Jednak mamy do czynienia z istotną dysproporcją między liczbą dawców a potencjalnych biorców, w związku z czym proces oceny i kwalifikacji pacjentów do HTx wymaga udoskonalenia. Stężenie białka C-reaktywnego oceniane testem o wysokiej czułości (hsCRP) i stężenie N-końcowego fragmentu peptydu natriuretycznego typu B (NT-proBNP) cechuje wysoka wartość prognostyczna wśród osób z zaawansowaną HF.

Cel: Celem pracy była ocena wartości prognostycznej NT-proBNP i hsCRP samodzielnie i w skojarzeniu, w grupie pacjentów z zaawansowaną niewydolnością serca, kwalifikowanych do HTx.

Metody: Badanie dotyczyło rejestru 632 pacjentów kwalifikowanych do HTx w Polsce w latach 2003–2007. Po optymalizacji leczenia i rutynowej ocenie klinicznej [m.in. średnia klasa wg *New York Heart Association* (NYHA) 3,2 ± 0,6; rytm serca 77 ± 15 uderzeń/min, ciśnienie skurczowe i rozkurczowe (SBP/DBP) 103/67 ± 15/11 mm Hg, frakcja wyrzutowa lewej komory (LVEF) 22 ± 8%, stężenie Na^+ w surowicy 136 ± 4 mmol/l, stężenie NT-proBNP 3942 ± 5637 pg/ml i hsCRP 9 ± 22 mg/l, HFSS 8 ± 1] pacjenci zostali zakwalifikowani do HTx. Na podstawie analizy krzywych ROC (punkt odcięcia dla NT-proBNP 2435 pg/ml, dla hsCRP 2,4 mg/l) każdego pacjenta przydzielono do jednej z czterech grup: (1) niepodwyższone hsCRP (–)/ /NT-proBNP (–) (n = 179); (2) niepodwyższone hsCRP (–)/podwyższone NT-proBNP (+) (n = 92); (3) podwyższone hsCRP (+)/ /niepodwyższone NT-proBNP (–) (n = 159); (4) podwyższone hsCRP (+)/NT-proBNP (+)(n = 202). Punkt końcowy zdefiniowano jako zgon/konieczność transplantacji w trybie pilnym. Średni czas obserwacji wynosił 601 dni.

Wyniki: Jednoczynnikowa analiza regresji potwierdziła wartość klasycznych czynników ryzyka w HF: NYHA (HR = 2,311; p < 0,0001), rytm serca (HR = 1,016; p = 0,0009), SBP (HR = 0,984; p = 0,0111), LVEF (HR = 0,951; p < 0,0001), stężenie Na^+ (HR = 0,901; p < 0,0001), NT-proBNP (HR = 1,004; p = 0,0159), hsCRP (HR = 1,010; p = 0,0002); HFSS (HR = 0,557; p < 0,0001). Analiza częstości zdarzeń wykazała, że najlepsze rokowanie cechuje pacjentów z podgrupy hsCRP (–)/NT-proBNP (–) (13% pacjentów osiągnęło punkt końcowy) i podgrupy hsCRP (–)/NT-proBNP (+), w której 24% pacjentów osiągnęło punkt końcowy (analiza Kaplana-Meiera: χ^2 = 8,5319; p = 0,0035), podczas gdy podgrupa hsCRP (+)/NT-proBNP (+) charakteryzowała się najgorszym rokowaniem (χ^2 = 42,0413; p < 0,0001) — 39% pacjentów osiągnęło punkt końcowy.

Wnioski: Potwierdzono wartość prognostyczną klasycznych czynników ryzyka w HF: klasa NYHA, rytm serca, SBP, LVEF, HFSS, osoczowe stężenie Na^+, wartość NT-proBNP i hsCRP. Jednak ocena hsCRP w połączeniu z NT-proBNP może stanowić znakomite narzędzie prognostyczne w identyfikacji pacjentów najwyższego ryzyka pośród tych kwalifikowanych do HTx. Tego rodzaju nowe podejście do stratyfikacji ryzyka przed HTx budzi nadzieje, lecz wymaga dalszej oceny.

Słowa kluczowe: niewydolność serca, białko C-reaktywne, peptyd natriuretyczny typu B, transplantacja serca

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