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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Soluble ST2 protein in the short-term prognosis after hospitalisation in chronic systolic heart failure

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Abstract

Background: The prognosis in patients with chronic heart failure (CHF) is poor. ST2 protein is a promising prognostic biomarker for CHF. ST2 belongs to the cardioprotective signalling pathway involving interleukin-33 and its concentration in the serum depends on the biomechanical stress of cardiomyocytes (biomechanical strain).

Aim: To determine the prognostic value of ST2 in short term follow-up after hospitalisation among patients with CHF.

Methods: The study included 167 patients (mean age 62 years, 83% men) in stable NYHA class I–III with left ventricular ejection fraction (LVEF) of ≤ 45% (average 29.65%, ranges 13–45%). We analysed 58 variables including: demographics, co-morbidities, resting ECG, echocardiographic and coronary arteriography data, basic laboratory tests including N-terminal prohormone B-type natriuretic peptide (NT-proBNP), serum concentration of soluble form of ST2 (sST2) using quantitative ELISA test ST2 Kit (Medical and Biological Laboratories; Japan) and adverse cardiovascular events during a one year observation. In the study, the primary endpoint (death) and the composite endpoint (hospitalisation for HF worsening, worsening in NYHA functional class, the need to increase the dose of diuretics, and/or death in a one year observation) were determined.

Results: Patients who died (n = 24; 14.55%) were in more advanced NYHA class, had prolonged QRS duration, higher levels of sST2, NT-proBNP, and lower estimated glomerular filtration rate. From multivariate analysis, the independent variable for the primary endpoint was NT-proBNP (OR = 1.00012; 95% CI 1.00002–1.00022; p = 0.018). 93 (56%) patients reached the composite endpoint. Multivariate analysis revealed that fasting glucose (OR = 1.343; 95% CI 1.041–1.732; p = 0.023) and sST2 (OR = 3.593; 95% CI 1.427–9.05; p = 0.007) independently enhanced the risk of composite endpoint occurrence in a one year observation.

Conclusions: In patients with CHF with LVEF ≤ 45%, the prognostic value of sST2 protein in a short-term observation of one year was confirmed. sST2 protein was an independent variable for the composite endpoint, which consisted of worsening NYHA functional class, hospitalisation for worsening of HF, the need to increase the dose of diuretics, and/or death.

Key words: sST2 protein, chronic heart failure, prognosis

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INTRODUCTION

Hospitalisations due to decompensation of heart failure (HF) and the need to increase doses of diuretics are often seen in patients suffering from chronic HF (CHF). Despite ongoing research, there are no optimal prognostic tools for identifying patients who are at increased risk of exacerbations in CHF. Accurate assessment of prognosis is essential to intensify treatment and delay the progression of HF, as well as to reduce the cost associated with the maintenance of HF patients. The use of biomarkers can help to achieve this goal. However, concentrations of commonly used natriuretic peptides are dependent on some demographic and clinical features such as age, sex, weight or comorbidities, for example chronic kidney disease [1, 2].

ST2 protein is an interleukin-33 (IL-33) receptor. IL-33 and its receptor are part of the cardioprotective system which helps to prevent fibrosis, hypertrophy and apoptosis of cardiomyocytes [3–5]. The soluble form of ST2 (sST2) binds to IL-33 and inhibits its beneficial effects. sST2 is produced by cardiomyocytes and cardiac fibroblasts due to

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mechanical stress, which is called biomechanical strain. sST2, as a mediator of HF progression and therefore a marker of poor prognosis, seems to be useful in the risk stratification of worsening HF [6–8].

sST2 protein prognostic utility was fairly well documented in acute HF [6–14], but there are only a few studies in CHF [15–17]. The aim of this study was to determine the prognostic value of sST2 protein in patients with CHF in a short term one-year observation after hospitalisation.

METHODS

The study included 167 consecutive patients in stable New York Heart Association (NYHA) class I–III, of left ventricular ejection fraction (LVEF) below or equal to 45%, with optimal treatment of HF according to the guidelines of the European Society of Cardiology (ESC). Patients were admitted to the hospital in order to determine the aetiology of HF and to establish its management. The exclusion criteria were: NYHA class IV, acute HF, acute coronary syndrome, inflammatory states and thyroid dysfunction.

The patient's clinical history and basic laboratory results were assessed at hospital entry as well as standard 12-lead electrocardiography (ECG). The results of echocardiography and coronary arteriography were obtained according to the ASE/EAE and ESC recommendations.

The following 58 parameters were analysed in this study, including:

- clinical features such as NYHA class, age, body mass index, arterial blood pressure, smoking status, coincidence of arterial hypertension, diabetes mellitus (DM), stroke, myocardial infarction, peripheral arterial disease or chronic lung diseases;
- selected laboratory results such as morphology, sodium, creatinine, estimated glomerular filtration rate (eGFR), serum lipid concentrations, C-reactive protein, high-sensitivity troponin T and N-terminal prohormone B-type natriuretic peptide (NT-proBNP);
- ECG variables: heart rhythm (sinus rhythm or atrial arrhythmias), heart rate, left bundle branch block, QRS duration, QTc;
- selected echocardiographic results (M-mode, two-dimensional and Doppler echocardiographic examinations): left atrial diameter, left ventricular end-systolic and end-diastolic dimensions, left ventricular end-systolic and end-diastolic volume, and LVEF;
- coronary arteriography results (stenosis ≥ 50% of left main coronary artery, ≥ 75% of other coronary arteries; analysed as 1-, 2-, or 3-vessel disease) to determine the aetiology of HF (ischaemic vs. non-ischaemic). Coronary arteriography was performed with radial or femoral approach with visual quantification of sclerotic alteration.

Blood samples (5 mL) for sST2 serum measurements were collected from the haemodynamically stable and fasting patients on admission to hospital using standard collection techniques into vacuum tubes containing clot activator. After the formation of a clot, the samples were centrifuged for 5 min at 3,000 rpm. Centrifugation and separation of the serum from the cellular components occurred as soon as possible after collection. The supernatant (serum) was immediately separated and frozen at –76°C. Then after thawing of serum, the sST2 level was measured by quantitative assay using a sandwich ELISA kit (Medical and Biological Laboratories, Japan). The ST2 assay is validated for use with human serum. The assay of sandwich ELISA kit uses two monoclonal antibodies against two different epitopes of human sST2. Serum samples were incubated in microwells coated with the first antihuman sST2 monoclonal antibody. After the washing stage, the second incubation with the peroxidase conjugated anti-human sST2 monoclonal antibody was conducted. After further washing, the peroxidase substrate was added into each well and the optical density was measured at 450 nm using a microplate reader.

In all patients, a telephone interview was conducted by the cardiologist 12 months after hospitalisation. Information about the NYHA functional class, hospitalisations due to decompensated HF, the need to increase doses of diuretics and incidents of death were collected. The cause of death was established during interview based on medical records or post mortem chart if available, or interview with family member in cases where the patient died outside the hospital.

The primary endpoint (death in one year observation) and the composite endpoint (worsening in NYHA functional class, need to increase the dose of diuretics, hospitalisation for CHF exacerbation, and/or death) were determined.

This study was approved by the Bioethics Committee at the Medical University in Lodz (Nr RNN/79/10/KE) and all patients signed informed consent to participate.

Statistical analysis

The calculations were performed using the statistical package STATISTICA PL 9.0 (StatSoft, Inc. 2009), STATISTICA (data analysis software system, version 9, Tulsa, OK, USA) and SPSS 19.0 (IBM SPSS Statistics, version 19, USA).

For measurable variables, basic descriptive characteristics: mean, median, maximum and minimum value, interquartile range (IQR, Q25–Q75) and standard deviation (SD) were provided. For qualitative variables, the number of observations (N) and the corresponding percentage (%) were indicated. Normality was tested using the Shapiro-Wilk test of normality.

For comparison of two independent groups of quantitative variables, Student's t-test (in the case of a normal distribution in both groups) or nonparametric Mann-Whitney U test (in the absence of normal distribution) was used. For the comparison of more than two independent groups of quantitative variables, the test of variance analysis ANOVA (in the case of normal in all groups) or non-parametric ANOVA

Kruskal-Wallis test (in the absence of normal distribution) was used. To verify the relationship between qualitative variables, an independence χ^2 test or an independence χ^2 test with Yates' correction (in lower numbers) was used.

To study the correlation between the variables measured on at least ordinal scale, Spearman's rank correlation coefficient was used.

For statistically significant quantitative variables, receiver operating characteristics (ROC) curves were drawn and the optimal cut-off points were determined. The sensitivity, specificity, positive and negative predictive value (PPV and NPV), odds ratio (OR) and a 95% confidence interval (95% CI) were also assigned.

In order to determine the factors related to primary and composite endpoints, univariate and multivariate forward stepwise regression analysis was performed. Variables which reached in univariate analysis $p < 0.1$ were used in the stepwise logistic regression models. For the primary and the composite endpoint, survival curves were set using the Kaplan-Meier method. Based on the Kaplan-Meier method and ROC curves, predictive tests were built for the primary endpoint and the composite endpoint. Results were considered statistically significant at $p < 0.05$.

Patients were analysed according to primary and composite endpoints.

Tables present only variables which differ or are selected in the context of the article.

RESULTS

The study included patients with a mean age of 62.92 ± 11.58 years. Most patients were men (83%), mostly in NYHA class III (72%), and 49.1% of them had LVEF lower than 30% (mean LVEF 29.65 ± 7.83%, ranges 13–45%). Ischaemic aetiology of CHF occurred in 54% of patients, 53% had hypertension, 22% chronic kidney disease, 12% chronic lung disease, and 37% had DM. Mean sST2 level was 0.65 ± 0.7 ng/mL (median 0.35 ng/mL), and NT-proBNP was 3,677.69 ± 5,188.1 mg/dL (median 1,970 mg/dL).

Patients who died (n = 24; 14.55%) were in more advanced NYHA class, had prolonged QRS duration, higher levels of sST2, NT-proBNP, and lower eGFR (Table 1). From multivariate analysis, the only significant independent variable for the primary endpoint was NT-proBNP (Table 2).

Using ROC analysis, the cut-off point value for NT-proBNP ≥ 2,556 mg/dL was determined (AUC [95% CI] = 0.749 [0.605–0.893]; p = 0.001) with sensitivity of 75%, specificity of 63.72%, low PPV of 22.64% and high NPV 94.74%. Finally, for the primary endpoint, survival curves were determined using the Kaplan-Meier method (Fig. 1). High concentrations of the studied biomarkers NT-proBNP and sST2 above the thresholds of the ROC curves (≥ 2,556 mg/dL and ≥ 0.3848 ng/mL, respectively), indicated a significantly worse prognosis (p = 0.0032), with the probability of survival for one year decreasing from 95% to 65%. However, statistical analysis showed that the addition of sST2 to NT-proBNP did not improve the predictive ability of the short term model for the primary endpoint (from 0.739 to 0.75, $p > 0.05$).

Patients who reached the composite endpoint (n = 93, 56%) had a higher incidence of diabetes and higher levels of sST2 (Table 3). Multivariate forward stepwise regression analysis revealed that glucose and sST2 are independently associated with the occurrence of the composite endpoint in a short observation of one year (Table 2). sST2 was included in the multivariate analysis as a quantitative variable. If sST2 protein concentration increased by one unit, the risk of the composite endpoint increased by more than 3.5-fold. On the other hand, if the concentration of serum fasting glucose increased by one unit, the risk of the composite endpoint increased by 34.3%. Using ROC analysis, a cut-off point value for sST2 ≥ 0.3389 ng/mL was determined (AUC [95% CI] = 0.68 [0.599–0.762]; p = 0.000) with a sensitivity of 64.52%, specificity 62.50%, PPV and NPV of 68.97% and 57.69%.

For composite endpoint in one year observation, survival curves were determined using the Kaplan-Meier method (Fig. 2). Low levels of sST2 < 0.3389 ng/mL, below the threshold from ROC curve, compared to the high concentrations of sST2 ≥ 0.3389 ng/mL, indicated a better prognosis (p = 0.0001), and the probability of non-occurrence of the composite endpoint increased from 0.3 to 0.58.

DISCUSSION

Our work documented the prognostic value of sST2 protein as an independent variable for the poor prognosis in short term observation after hospitalisation among patients with CHF and LVEF ≤ 45%. We determined the composite endpoint to be worsening in NYHA functional class, a need to increase the dose of diuretics, hospitalisation for CHF exacerbation, and/or death. To the best of our knowledge, no reports have examined the relationship between such a broad spectrum of exacerbations in CHF and sST2. Moreover, this is the first work describing the sST2 protein in the Polish population suffering from CHF.

The largest previously published study on the prognostic value of sST2 protein in CHF was carried out by Ky et al. [15] in a population of 1,141 patients (mean LVEF 32 ± 17%; mean age 56 ± 14 years and 67% male). Patients in this study were followed for nearly three years. Researchers discovered that patients with elevated levels of sST2 in the highest tertile (sST2 > 36.3 ng/mL) had a significantly higher risk of death or heart transplantation (OR = 3.2; 95% CI 2.2–4.7; p < 0.0001) compared to patients in the lowest tertile (sST2 < 22.3 ng/mL). In the present work, we revealed the relationship between higher concentrations of sST2 protein (sST2 ≥ 0.3848 ng/mL) and the occurrence of death in a one year observation (p = 0.0176). However, sST2 was not an independent va-

Table 1. Patient characteristics depending on primary endpoint

Variables	Without primary endpoint (n = 146)		Primary endpoint (n = 21)		P
	N or mean ± SD (range)	% or median (IQR)	N or mean ± SD (range)	% or median (IQR)	
Demographic and clinical variables					
Male	120	85.11	17	70.83	0.08507
Age [years]	63.06 ± 11.57 (24–87)*	64 (57–71)	62.25 ± 12.31 (30–83)*	62 (59–71.5)	0.8059
Body mass index [kg/m^2]	26.72 ± 3.85 (16.6–39.26)	26.42 (23.9–29.39)	26.28 ± 4.93 (16.46–37.1)	26.95 (23.62–29.7)	0.6918
NYHA class:					
I	6	4.26	0	0.00	
II	37	26.24	1	4.17	**0.02600**
III	98	69.50	23	95.83	
Ischaemic HF	81	57.45	9	37.50	0.06965
Former or current smoking	80	65.04	12	54.55	0.34647
Arterial hypertension	74	54.41	9	40.91	0.23932
Diabetes mellitus	50	36.76	10	45.45	0.43588
Peripheral sclerosis	18	13.14	3	13.04	0.74810
Myocardial infarction	77	54.61	9	37.50	0.12088
Chronic lung disease	14	10.29	5	21.74	0.11759
Systolic BP [mm Hg]	120.39 ± 17.93 (85–190)*	120 (110–130)	112.08 ± 16.93 (90–140)*	110 (100–130)	0.0635
Diastolic BP [mm Hg]	73.29 ± 10.05 (55–100)*	70 (70–80)	71.09 ± 10 (55–90)*	70 (60–75)	0.3227
Electrocardiography results					
Atrial fibrillation	32	23.19	9	39.13	0.10423
LBBB	38	27.94	10	43.48	0.13332
Heart rate [bpm]	77.84 ± 18.37 (53–170)*	75 (65–85)	83.65 ± 18.93 (53–130)	83 (68–90)	0.0925
QRS duration [ms]	112.39 ± 28.86 (60–200)*	102 (100–130)	125.33 ± 30.62 (80–220)*	120 (110–140)	**0.0359**
QTc [ms]	390.93 ± 49.82 (260–520)	383 (360–420)	398.2 ± 54.5 (260–500)	400 (362–420)	0.5799
Echocardiography results					
LVEF [%]	29.8 ± 7.6 (13–45)	30 (24–35)	28.17 ± 9.21 (15–45)	27.5 (20–34.5)	0.4172
LVESD [cm]	5.44 ± 0.89 (3.4–8)	5.4 (4.8–6.05)	5.89 ± 1.43 (3.9–9.3)	5.6 (4.8–6.7)	0.1586
LVEDD [cm]	6.73 ± 0.85 (4.7–9.2)	6.7 (6.1–7.3)	6.99 ± 1.28 (4.6–10.1)	7.1 (5.9–8)	0.3697
LVESV [mL]	142.76 ± 62.03* (34–364)	133 (99–175)	147.19 ± 90.95* (41–418)	117 (89–165)	0.7065
LVEDV [mL]	199.88 ± 75.2* (55–477)	190 (146–236)	197.52 ± 99.45* (66–490)	185 (124–209)	0.6703
LA [cm]	5.96 ± 0.91 (3.5–8.6)	5.9 (5.4–6.55)	6.28 ± 1.15 (3.7–8.4)	6 (5.6–7.5)	0.2200

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Table 1. (cont.) Patient characteristics depending on primary endpoint

Variables	Without primary endpoint (n = 146)		Primary endpoint (n = 21)		P
	N or mean ± SD (range)	% or median (IQR)	N or mean ± SD (range)	% or median (IQR)	
Coronary arteriography (extent of CAD)					
1 vessel	23	23.71	3	18.75	
2 vessels	26	26.8	2	12.5	0.40110
3 vessels	14	14.43	2	12.5	
Biochemical results					
sST2 [ng/mL]	0.62 ± 0.68 (0.19–4.3)*	0.34 (0.28–0.61)	0.85 ± 0.79 (0.27–3.43)*	0.48 (0.33–1.04)	**0.0176**
NT-proBNP [mg/dL]	3,020 ± 4,091 (197–35,000)*	1,886 (857–3,421)	8,486 ± 8,836 (199–35,000)*	5,739 (2,508–11,101)	**0.0010**
hsTnT [mg/L]	0.044 ± 0.059 (0.004–0.36)*	0.025 (0.014–0.049)	0.043 ± 0.034 (0.021–0.11)*	0.032 (0.025–0.04)	0.3269
hsCRP [mg/L]	6.87 ± 12.68* (0.2–97)	3.1 (0.8–6.7)	10.29 ± 15.36* (0.3–63.5)	5.2 (1.6–9.7)	0.2006
Creatinine [mg/L]	89.57 ± 23.82* (49–194.66)	88.48 (70.78 – 97.33)	101.32 ± 29.4 (44.24–159.26)	106 (79.63–115.02)	0.0511
eGFR [mL/min/1.73 m^2]	87.87 ± 32.45* (27–223.5)	85.51 (67.1–111)	75.95 ± 40.35* (31.54–185)	59.21 (52–100)	**0.0294**
Sodium [mmol/L]	136.99 ± 3.14* (127–144)	137 (135–139)	135.59 ± 4.23 (129–144)	135.5 (132–139)	0.1555
Glucose [mmol/L]	6.26 ± 1.75* (2.63–16.2)	5.94 (5.32–6.5)	6.83 ± 2.79* (4.37–16.24)	5.99 (5.1–7.39)	0.8076

*Variables with non-parametric distribution; IQR — interquartile range; CAD — coronary artery disease; BP — blood pressure; eGFR — estimated glomerular filtration rate; hsCRP — high-sensitivity C-reactive protein; hsTnT — high-sensitivity troponin T; HF — heart failure; LBBB — left bundle branch block; LA — left atrial diameter, LVESD — left ventricular end-systolic dimension; LVEDD — left ventricular end-diastolic dimension; LVESV — left ventricular end-systolic volume; LVEDV — left ventricular end-diastolic volume; LVEF — left ventricular ejection fraction; NT-proBNP — N-terminal prohormone B-type natriuretic peptide; SST2 — soluble ST2 protein

Table 2. Results of multivariate stepwise logistic regression analysis

Variables	B–parameter estimation	Standard error	P	Exp(B)–OR	95% CI for OR	
Primary endpoint						
NT-proBNP	0.00012	0.00005	0.018	1.00012	1.00002	1.00022
Composite endpoint						
sST2	1.279	0.471	0.007	3.593	1.427	9.050
Glucose	0.295	0.130	0.023	1.343	1.041	1.732

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

riable for annual mortality in our study. Our results differ from those obtained by Ky et al. [15], probably due to the smaller studied population and the shorter follow-up. Moreover Ky et al. [15] used a highly sensitive test for the detection of sST2.

In turn Weinberg et al. [16] evaluated 181 patients with CHF (mean age 62 years, mean LVEF 22% and 73% male) and documented that the increase of sST2 concentration of 0.1 ng/mL in two weeks after first measurement was associated with the risk of death or heart transplantation in 47 patients (25.9%, p = 0.048). On the other hand, Pascual-Figal et al. [17] conducted a case-control study which included 36 patients after sudden cardiac death (SCD) (mean age 66 years, mean LVEF 29% and 83% male) and 63 patients in control, matched for age, sex and LVEF. All patients were observed

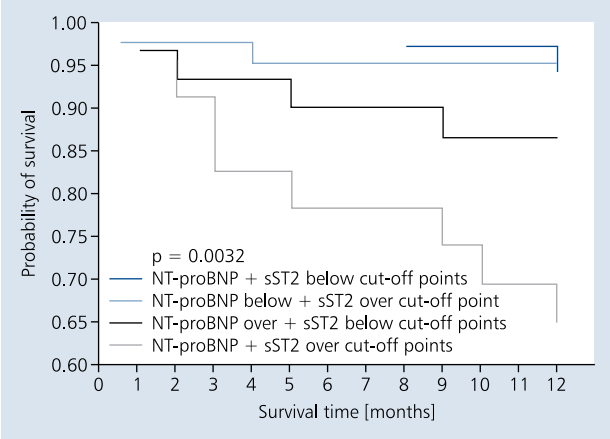

Figure 1. Kaplan-Meier survival curves based on sST2 and N-terminal prohormone B-type natriuretic peptide (NT-proBNP) concentrations

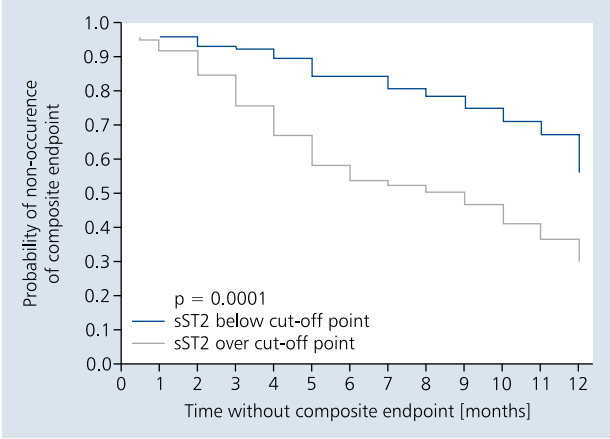

Figure 2. Kaplan-Meier curves for composite endpoint based on sST2 concentrations

Table 3. Patient characteristics depending on composite endpoint

Variables	Without composite endpoint (n = 74)		Composite endpoint (n = 93)		P
	N or mean ± SD (range)	% or median (IQR)	N or mean ± SD (range)	% or median (IQR)	
Demographic and clinical variables					
Male	57	79.17	80	86.02	0.24469
Age [years]	62.33 ± 12.49 (24–85)	64 (54.5–72)	63.41 ± 10.99 (30–87)*	63 (58–71)	0.7436
Body mass index [kg/m^2]	26.5 ± 3.86 (16.6–34.7)	26.5 (23.67–29.07)	26.77 ± 4.13 (16.46–39.26)	26.4 (23.9–29.41)	0.6833
NYHA class:					
I	0	0.00	6	6.45	
II	18	25.00	20	21.51	0.08592
III	54	75.00	67	72.04	
Ischaemic HF	38	52.78	52	55.91	0.68825
Former or current smoking	39	61.90	53	64.63	0.73514
Arterial hypertension	33	47.14	50	56.82	0.22636
Diabetes mellitus	19	27.14	41	46.59	**0.01235**
Peripheral sclerosis	6	8.57	15	16.67	0.13250
Myocardial infarction	35	48.61	51	54.84	0.42710
Chronic lung disease	8	11.59	11	12.22	0.90369
Systolic BP [mm Hg]	119.3 ± 16.74 (90–160)	120 (110–130)	119.08 ± 18.96 (85–190)*	120 (105–130)	0.7776
Diastolic BP [mm Hg]	72.07 ± 9.11 (55–90)*	70 (70–80)	73.66 ± 10.69 (55–100)*	70 (67.5–80)	0.4176
Electrocardiography results					
Atrial fibrillation	17	24.64	24	26.09	0.83454
LBBB	18	26.09	30	33.33	0.32391
Heart rate [bpm]	78.34 ± 21.3 (54–170)*	70 (65–83.5)	78.92 ± 16.25 (53–130)*	80 (65–86)	0.2683

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Table 3. (cont.) Patient characteristics depending on composite endpoint

Variables	Without composite endpoint (n = 74)		Composite endpoint (n = 93)		P
	N or mean ± SD (range)	% or median (IQR)	N or mean ± SD (range)	% or median (IQR)	
QRS duration [ms]	109.79 ± 29.32 (60–180)*	100 (80–120)	117.67 ± 29.09 (60–220)*	120 (100–133)	0.0805
QTc [ms]	109.79 ± 29.32 (60–180)*	100 (80–120)	117.67 ± 29.09 (60–220)*	120 (100–133)	0.0805
Echocardiography results					
LVEF [%]	29.86 ± 7.62 (13–43)	30 (24–36)	29.33 ± 8.04 (14–45)	29 (24–35)	0.6694
LVESD [cm]	5.41 ± 0.9 (3.5–8)	5.4 (4.9–6)	5.6 ± 1.08 (3.4–9.3)	5.6 (4.8–6.2)	0.2591
LVEDD [cm]	6.66 ± 0.82 (5–9.2)	6.5 (6–7.2)	6.86 ± 1 (4.6–10.1)	6.9 (6.1–7.5)	0.1942
LVESV [mL]	136.24 ± 57.86* (46–343)	120 (92–170)	148.68 ± 72.16* (34–418)	137 (105–180)	0.3151
LVEDV [mL]	192.14 ± 70.78* (87–477)	176 (140–230)	205.04 ± 84.07* (55–490)	190 (156–242)	0.3180
LA [cm]	5.91 ± 0.95* (3.6–8.6)	5.7 (5.4–6.4)	6.08 ± 0.95 (3.5–8.4)	6 (5.55–6.7)	0.1035
Coronary arteriography (extent of CAD)					
1 vessel	11	22.92	15	23.08	
2 vessels	11	22.92	17	26.15	0.64715
3 vessels	5	10.42	11	16.92	
Biochemical results					
sST2 [ng/mL]	0.44 ± 0.3 (0.19–1.65)*	0.3 (0.27–0.41)	0.82 ± 0.86 (0.25–4.3)*	0.41 (0.3–0.9)	**0.0001**
NT-proBNP [mg/dL]	2,940 ± 3,125 (197–13,863)*	1,951 (837.9–3,323)	4,261 ± 6,284 (199–35,000)*	2,145 (1,032–4,462)	0.3719
hsTnT [mg/L]	0.045 ± 0.072 (0.007–0.36)*	0.025 (0.014–0.053)	0.043 ± 0.045 (0.004–0.21)*	0.028 (0.016–0.044)	0.4922
hsCRP [mg/L]	7.41 ± 15.27 (0.2–97)	3.1 (0.8–6.7)	7.39 ± 11.41* (0.3–63.5)	3.4 (1–7.8)	0.6607
Creatinine [mg/L]	87.77 ± 20.64* (49–168.11)	88.48 (70.78 – 97.33)	93.79 ± 27.54* (44.24 – 194.66)	88.48 (73–109.09)	0.2828
eGFR [mL/min/1.73 m^2]	85.99 ± 28.3* (27–156.32)	82 (67.5–109.35)	86.51 ± 37.57* (27.9–223.5)	80.91 (59.1–109)	0.6081
Sodium [mmol/L]	137.15 ± 3.11* (127–143)	138 (136–139)	136.52 ± 3.48* (129–144)	137 (134–139)	0.3228
Glucose [mmol/L]	5.89 ± 0.93* (4.37–9.3)	5.82 (5.26–6.13)	6.89 ± 2.49* (2.63–16.2)	6.05 (5.63–7.39)	**0.0095**

*Variables with non-parametric distribution; abbreviations as in Table 1

earlier for three years in the MUSIC registry (MUerte Súbita en Insuficiencia Cardiaca) [18]. In the SCD group, the researchers documented higher concentrations of sST2 protein compared to the control group (0.23 ng/mL [IR 0.16–0.43 ng/mL] vs. 0.12 ng/mL [IR 0.06–0.23 ng/mL], p = 0.001). However, the Pascual-Figal et al. [17] study was not prospectively followed up, and patients who experienced SCD were taken to comparative analysis and matched with a control group retrospectively.

Moreover, Bayes-Genis et al. [19] in a population of 891 patients with CHF (mean age 70.2 years, mean LVEF 34% and 71.6% male) found that sST2 protein (OR = 1.04; 95% CI 1.029–1.051; p = 0.001) and NT-proBNP (OR = 1.632; 95% CI 1.484–1.795; p = 0.001) were independent risk factors for mortality of 244 (27%) patients in a prospective observation (median 33.4 months). The authors also demonstrated the complementary role of both markers in the prediction of mortality. In our study, we did not reveal the benefit of adding sST2 protein to NT-proBNP in the prediction of short term mortality.

In our work, the second independent variable associated with the composite endpoint was glucose (OR = 1.343; p = 0.023). It is evident that diabetes and high concentrations of glucose are associated with worse prognosis of patients with CHF [20, 21]. Also in the study of Miller et al. [22], sST2 levels were associated strongly with glucose (effect estimate) per 1 SD increase in sST2: 1.02 [1.00, 1.03], and recently Fousteris et al. [23] revealed a correlation between sST2 and DM (p < 0.001) in patients with left ventricular diastolic dysfunction.

The relationship between the two biomarkers of prognosis in CHF: NT-proBNP and sST2 is interesting. In contrast to our initial study on a smaller group of patients [24], and the results of other researchers into CHF [15–17], the present study did not report a relationship between the concentrations of sST2 and NT-proBNP. Ky et al. [15] showed on the basis of the multivariable linear regression model for log-transformed ST2 that NT-proBNP is an independent factor influencing the concentration of sST2 (percent difference in ST2: 7.9%; 95% CI 5.8–10.0%; p < 0.0001 for NT-proBNP multiplicative difference of 2). In turn, Weir et al. [25] found no correlation between sST2 and NT-proBNP in patients after myocardial infarction. Mechanisms of release of both biomarkers are different, and the clinical conditions that induce their secretion are similar. There is a need for further research on a larger group of patients to ultimately determine or exclude the existence of this relationship.

Recently, some researchers have described the benefits of complementary use of biomarkers in CHF. Lupon et al. [26] documented in a group of 876 outpatients with CHF that a strategy based on combined use of high sensitivity sST2 and high-sensitivity troponin T gives good measurements of performance (C statistic 0.789). Adding NT-proBNP to that model did not bring significant benefits. Also Ky et al. [15] investigated the role of sST2 in stratifying the risk of patients with CHF. They compared Seattle Heart Failure Model alone and combined with NT-proBNP and sST2. Adding these two biomarkers, 14.9% of patients were reclassified into more appropriate risk categories (p = 0.017). It seems that a multimarker approach including sST2 might become a standard procedure in CHF patients.

Limitations of the study

Our study has some limitations. A functional assessment such as cardiopulmonary exercise test or six minute walk test was not carried out. However, functional assessment was not the purpose of this work. Our desire was to see whether sST2 protein in a single measurement has predictive value for patients with CHF with LVEF ≤ 45% without the need for additional tests, including functional assessment.

Lack of objective assessment of the cause of one outside the hospital death is another limitation (arrhythmic vs. CHF progression or non-cardiogenic cause), because the follow up was performed on the basis of interview with a family member.

In addition, a control group was not created. However, the determined prognostic threshold of sST2 is similar to that reported by other authors, who also did not create control groups.

Finally, we assessed only a few echocardiographic parameters of the left ventricular functions. The reason for not analysing variables such as dyssynchrony and concomitant mitral regurgitation was the small number of sub-populations with these irregularities. Another limitation was the lack of assessment of strain rate in our centre.

Use of the older, less sensitive generation of test for the determination of sST2 is also an important issue.

CONCLUSIONS

In patients with CHF and LVEF ≤ 45%, the prognostic value of sST2 in a short-term observation of one year was documented in this study. sST2 protein was an independent variable for the composite endpoint, which included worsening NYHA functional class, hospitalisation for exacerbation of CHF, the need to increase the dose of diuretics, and/or death.

At the present stage of knowledge, it seems that the sST2 protein might be useful in the short-term prognosis of CHF.

Conflict of interest: *none declared*

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Białko sST2 w krótkoterminowym rokowaniu po hospitalizacji u chorych z przewlekłą skurczową niewydolnością serca

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Streszczenie

Wstęp: Rokowanie u pacjentów z przewlekłą niewydolnością serca (CHF) jest niepomyślne. Białko sST2 należące razem z interleukiną 33 do szlaku kardioprotekcyjnego jest obiecującym markerem w CHF. Stężenie białka sST2 w surowicy wzrasta w przypadku mechanicznego odkształcenia kardiomiocytów.

Cel: Celem pracy było określenie wartości prognostycznej sST2 w krótkoterminowej obserwacji po hospitalizacji wśród pacjentów z CHF.

Metody: Do badania włączono 167 osób (średnia wieku 62 lata, 83% mężczyzn) w I–III klasie wg NYHA, z frakcją wyrzutową lewej komory ≤ 45% (średnio 30%, 13–45%). Przeanalizowano 58 zmiennych, m.in.: dane demograficzne, elektrokardiograficzne, echokardiograficzne, choroby współistniejące, wyniki koronarografii, podstawowe badania laboratoryjne, w tym N-końcowy propeptyd natriuretyczny typu B (NT-proBNP), stężenie sST2 (ilościowy test ELISA ST2 Kit), wystąpienie niekorzystnych zdarzeń sercowo-naczyniowych w ciągu rocznej obserwacji. W badaniu wyznaczono pierwszorzędowy punkt końcowy (zgon w obserwacji rocznej) oraz złożony punkt końcowy (łącznie hospitalizacja z powodu pogorszenia HF, nasilenie klasy NYHA, konieczność zwiększenia dawki leków moczopędnych lub zgon w obserwacji rocznej).

Wyniki: U chorych, którzy zmarli (n = 24; 14,55%), występowała bardziej zaawansowana klasa NYHA, wydłużony czas trwania zespołu QRS, wyższe stężenie sST2, NT-proBNP i niższa wartość estymowanego wskaźnika filtracji kłębuszkowej. Z analizy wielowymiarowej jedyną zmienną niezależną dla pierwszorzędowego punktu końcowego było NT-proBNP (OR = 1,00012; 95% CI 1,00002–1,00022; p = 0,018). Złożony punkt końcowy wystąpił u 93 (56%) pacjentów. Analiza wieloczynnikowa wykazała, że stężenie glukozy (OR = 1,343; 95% CI 1,041–1,732; p = 0,023) i sST2 (OR = 3,593; 95% CI 1,427–9,05; p = 0,007) są niezależnymi czynnikami związanymi z ryzykiem wystąpienia złożonego punktu końcowego w rocznej obserwacji.

Wnioski: U chorych z CHF z frakcją wyrzutową lewej komory ≤ 45% potwierdzono wartość prognostyczną białka sST2 w obserwacji krótkoterminowej. Białko sST2 było niezależną zmienną dla złożonego punktu końcowego, na który składały się: pogorszenie w zakresie klasy wg NYHA, hospitalizacja z powodu pogorszenia HF, konieczność zwiększenia dawki leków moczopędnych i zgon w obserwacji rocznej.

Słowa kluczowe: sST2, przewlekła niewydolność serca, rokowanie

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