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Heart failure with preserved left ventricular ejection fraction in patients with obstructive sleep apnea syndrome: prognostic value of biomarkers

Aim — To study the role of soluble ST_2 (sST_2), N-terminal pro-brain natriuretic peptide (NT-proBNP), and C-reactive protein (CRP) in patients with chronic heart failure and preserved left ventricular ejection fraction (CHF with pLVEF) and syndrome of obstructive sleep apnea (SOSA) in stratification of the risk for development of cardiovascular complications (CVC) during one month of a prospective observation.

Material and methods — The study included 71 men with SOSA with an apnea/hypopnea index (AHI) >15 per hour, abdominal obesity, and arterial hypertension. Polysomnographic study and echocardiography according to a standard protocol with additional evaluation of left ventricular myocardial fractional changes and work index were performed for all patients at baseline and after 12 months of observation. Serum concentrations of sST_2, NT-proBNP, and CRP were measured at baseline by enzyme-linked immunoassay (ELISA).

Results — The ROC analysis showed that the cutoff point characterizing the development of CVC were sST_2 concentrations ≥29.67 ng/l (area under the curve, AUC, 0.773, sensitivity 65.71%, specificity 86.11%; p<0.0001) while concentrations of NT-proBNP (AUC 0.619; p=0.081) and CRP (AUC 0.511; p=0.869) were not prognostic markers for the risk of CVC. According to data of the ROC analysis, all patients were divided into 2 groups based on the sST_2 cutoff point: group 1 included 29 patients with ST_2 ≥29.67 ng/l and group 2 included 42 patients with ST_2 <29.67 ng/l. The Kaplan-Meyer analysis showed that the incidence of CVC was higher in group 1 than in group 2 (79.3 and 28.6%, respectively, p<0.001). The regression analysis showed that adding values of AHI and left ventricular myocardial mass index (LVMMI) to sST_2 in the model increased the analysis predictive significance.

Conclusion — Measuring sST_2 concentration may be used as a noninvasive marker for assessment of the risk of CVC development in patients with CHF with pLVEF and SOSA within 12 months of observation. Adding AHI and LVMMI values to the model increases the predictive significance of the analysis.

Keywords — Chronic heart failure; syndrome of obstructive sleep apnea; cardiovascular complications; soluble ST_2; brain natriuretic peptide

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Chronic heart failure (CHF) is a natural stage of progression of most clinically significant cardiovascular diseases (CVDs): coronary artery disease, arterial hypertension (AH), valvular heart disease, etc. As the mean age of the population increases, the role of comorbidities becomes more important in such patients. According to the European Society of Cardiology, more than 70% of patients with CHF have at least one comorbidity [1].

Patients with obstructive sleep apnea syndrome (OSAS) have been of particular interest in recent years in terms of comorbidities and CHF. This is due to the high prevalence of OSAS with a clear trend towards the increase with age [2] and several pathogenetic links similar to CVDs.

OSAS is associated with AH, heart rate and conduction disorders, increased risk of sudden cardiac death at night [3–5]. The main pathogenetic links of

OSAS are the formation of pulmonary hypertension associated with nocturnal intermittent hypoxia with subsequent hyperactivation of the sympathetic and renin-angiotensin-aldosterone systems and the development of endothelial dysfunction [6, 7]. OSAS-associated cyclic hypoxia-reoxygenation processes trigger oxidative stress and free-radical oxidation. More and more data on the important role of inflammation processes in the OSAS pathogenesis have been published in recent years [8]. Some papers discuss increased levels of several pro-inflammatory cytokines in OSAS: C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) [9]. The pathogenetic role of inflammatory mechanisms grows as cardiovascular comorbidity and CHF develop.

Researchers have paid close attention in recent years to the role of the interleukin-1 (IL-1) family in the processes of endothelial dysfunction and cardiovascular remodeling [10]. The significant protective role of the cytokine chain of the IL-33 family in these processes was demonstrated [11]. At the same time, the role of another cytokine from this family, soluble isoform of suppression of tumorigenesis 2 (ST_2), which is an IL-33 antagonist in a certain sense, is very promising in terms of evaluating the prognostic value. According to most researchers, the serum levels of ST_2 are associated with adverse clinical outcomes in CHF with reduced left ventricular ejection fraction (HFrEF), acute myocardial infarction, chronic bronchopulmonary disease [12]. ST_2 is therefore considered as a promising independent biomarker in CHF. The authors point out several potential advantages of ST_2 over conventional biomarkers of CHF, such as N-terminal pro-brain natriuretic peptide (NT-proBNP), unlike which the levels of ST_2 is less dependent on age, sex, weight, CHF origin, and comorbidities [13]. According to Aimo et al. (2017), ST_2 levels have the strongest correlations with CHF of non-ischemic origin [14]. Thus, the American College of Cardiology and the American Heart Association included ST_2 as an additional risk stratification factor in the 2013 Guideline for the Management of Heart Failure [15]. Individual studies revealed significant correlations of the ST_2 levels with echocardiographic markers of left ventricular (LV) diastolic dysfunction, which may indirectly indicate an active involvement of this cytokine in the pathogenesis of CHF with preserved LVEF (HFpEF) [16].

Of note, the scientific literature provides data on the ST_2 prognostic value in both HFrEF and HFpEF [17]. However, the role of the cytokine of interest was much less studied in HFpEF, and the available data for this category of patients are scarce and contradictory. The findings of the studies of the combined estimation of the prognostic value of ST_2 and the conventional biomarker of CHF NT-proBNP are of particular interest [18]. The authors provide data on a substantial growth of the prognostic role when these biomarkers are evaluated in combination compared to separate estimation.

There is even less data on the participation of the IL-1 cytokines, including the role of IL-33 and ST_2, in the pathogenesis of OSAS. Single papers on this topic mention the increased levels of IL-33 in patients with OSAS compared to the control group of healthy individuals [19]. However, there is much more information in the literature on the active participation of IL-33, ST_2, and other cytokines of the IL-1 family in chronic inflammatory processes associated with chronic obstructive pulmonary disease (COPD), bronchial asthma, and abdominal obesity [20]. Given the close association of these diseases with obstructive sleep respiratory disorder and common individual links of the pathogenesis, it can be suggested that the investigation of the activity of these biomarkers in patients with HFpEF and OSAS could open the way for treatment strategy personification.

Objective

Examine the role of soluble ST_2, NT-proBNP, and CRP in patients with HFpEF and OSAS in the stratification of risk of developing cardiovascular events during the 12-month prospective follow-up.

Material and methods

The study protocol was approved by the Biomedical Ethical Committee of the Research Institute for Cardiology of Tomsk National Research Medical Center, minutes No. 177 dated 30.10.2018

All patients signed the informed consent to be included in the study. The screening was conducted among locomotive crew members at risk of developing OSAS, as part of the routine annual physical examination. Patients at risk (body mass index (BMI) ≥30 kg/m^2, snoring, AH) were referred to the somnological center for the examination. A total of 327 employees were examined. A total of 71 patients met the inclusion criteria; the included patients were prospectively followed up over the next 12 months.

Inclusion criteria

LVEF ≥50% according to echocardiography; moderate to severe OSAS (apnea/hypopnea index (AHI)>15 episodes per hour); AH, including patients with blood pressure (BP) stabilized with hypotensive drug therapy; abdominal obesity (waist circumference (WC)≥92 cm, BMI≥30 kg/m^2); male patients.

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Table 1. Baseline characteristics of the patients (n=71)

Parameter	Value
Age, years	47 [37; 55]
Weight, kg	111 [96; 124]
Height, sm	178 [174; 182]
BMI, kg/m2	34 [30.7; 39.0]
AHI	31.5 [22; 36]
mSpO2	94.3 [93.5; 96.0]
DI, episodes per hour	30.2 [22.0; 38.0]
Duration of AH, years	7 [4; 14]
COPD, n (%)	19 (26.5)
Smoking, n (%)	22 (31.3)
Dyslipidemia, n (%)	33 (46.5)
Diabetes mellitus, n (%)	14 (19.7)
VPB (Lown grade II-III), n (%)	17 (24.4)
Paroxysmal atrial fibrillation, n (%)	13 (18.6)
LVEF, %	59 [52; 71]
CHF FC, n (%)	
CHF FC I (NYHA)	47 (66.2)
CHF FC II (NYHA)	20 (28.2)
CHF FC III (NYHA)	4 (5.6)
6MWD, m	494.2 [378.0; 615.0]
NT-proBNP, pg/mL	299.5 [101.1; 997.3]
ST2, ng/mL	30.5 [20.64; 50.99]

The data are presented as the median and interquartile range (Me [25th percentile; 75thpercentile]) or the absolute and relative values (n (%)). BMI, body mass index; AHI, apnea/hypopnea index; mSpO2, mean saturation; DI, desaturation index; AH, arterial hypertension; COPD, chronic obstructive pulmonary disease; VPB, ventricular premature beat; LVEF, left ventricular ejection fraction; CHF, chronic heart failure; FC, functional class; 6MWD, 6 minute walk distance; NT-proBNP, N-terminal pro-brain natriuretic peptide. ST2 is a soluble stimulating growth factor.

Exclusion criteria

Primary pulmonary hypertension; history of pulmonary thromboembolism with high pulmonary hypertension (right ventricular systolic pressure≥45 mm Hg); severe bronchial asthma, COPD; valvular heart disease (mitral, tricuspid, or aortic valve failure grade≥II); hypertrophic and dilation cardiomyopathy; coronary artery disease; persistent atrial fibrillation; thyroid pathology; severe renal insufficiency (glomerular filtration rate (CKD-EPI)<30 mL/min/1.73 m^2) and hepatic insufficiency; administration of drugs that contribute to oropharynx muscle weakness (sleep aids, narcotic analgesics, testosterone), alcohol; neurological diseases causing oropharynx muscle weakness; refusal to sign the informed consent.

The study included male patients with moderate to severe OSAS (AHI >15 episodes per hour), the median age of 47 [37.0; 55.0] years (Table 1). All included patients had abdominal obesity (WC>92 cm), BMI>30 kg/m^2, AH, but they had target BP levels at the time of inclusion due to the best-possible hypotensive drug treatment. CHF NYHA functional class (FC) I, II, and III was diagnosed in 47 (66.2%), 20 (28.2%), and 4 (5.6%) patients, respectively. NT-proBNP levels were above the reference values (>125 pg/mL) in all the included patients.

The analysis of the data obtained according to the predetermined criteria showed that 35 (49.3%) patients had a favorable clinical course of the disease (Group A), and 36 (50.7%) patients had an unfavorable clinical course (Group B) (Figure 1). The criteria of unfavorable course of CHF were the progression of CHF as assessed by 6-minute walking distance (6MWD) test, transition to higher NYHA FC, hospitalization due to CVDs, paroxysmal atrial fibrillation or ventricular arrhythmias of high grades (grades III–V, Lown, 1975), or death. There was one fatality caused by hemorrhagic stroke, and there were no other drop-outs.

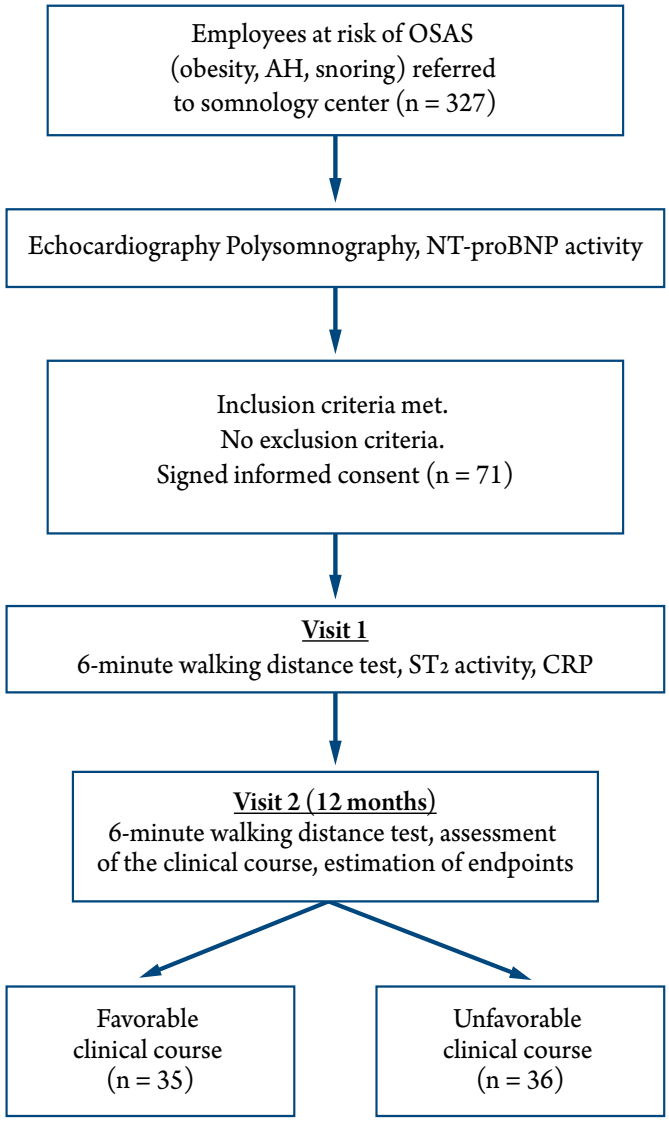
Drug treatment AH and CHF received by patients at the time of inclusion and during the 12-month follow-up corresponded to current guidelines (Table 2).

OSAS was diagnosed in all patients by night sleep polysomnography using the Somnolab^{2}PSG diagnostic system (Weinemann, Germany). The severity of obstructive sleep respiratory disorders was assessed by AHI. The study included patients with moderate (14<AHI <30 episodes per hour) and severe (AHI ≥30 episodes per hour) OSAS. Moreover, polysomnography findings were used to assess mean night saturation ($mSpO_2$ mean), desaturation index, and night-time cardiac arrhythmias. All patients underwent a 6MWD test immediately after the inclusion.

Echocardiography was carried out under the standard protocol [21] using an EPIQ device. The following parameters were evaluated: left and right chamber dimensions, LVEF by Simpson's method, left ventricular mass index (LVMI), interventricular septal thickness, left and right ventricular wall thickness, pulmonary artery systolic pressure (calculated by the degree of tricuspid regurgitation using the continuous wave method). The right ventricular (RV) global systolic dysfunction was also assessed by analyzing the right ventricular (RV) fractional area (ΔSRV) and RV myocardial performance index (RVMPI). ΔSRV was calculated using the formula:

$$\Delta SRV = 100 \times (RVEDA - RVESA / RVEDA),$$

Figure 1. Study design



where RVEDA is RV end-diastolic area, and RVESA is RV end-systolic area. RVMPI (Tay index) was calculated as the ratio of the sum of isovolumic relaxation time (IVR) and isovolumetric contraction time (IVCT) to the ejection time:

RVMPI=(IVR+IVCT) / ET (normally 0.28±0.04).

All patients underwent 24-hour BP monitoring at baseline under the standard protocol using a Shiller system. NT-proBNP, CRP, and ST_2 were evaluated, which were tested on the same blood sample taken after the inclusion. Blood samples were collected by vein puncture from 08:00 and 09:00 in the morning, and the corresponding serum samples were stored at -24°C after centrifugation and a single freeze-thaw cycle. sST_2 was measured in serum samples using a highly sensitive sandwich monoclonal immunoassay (Presage ST_2). NT-proBNP was estimated using a sandwich immunoassay (Biomedica immunoassays). Serum levels of CRP were determined by immunoturbidimetry using a Konelab Prime 60 device (Thermo Scientific).

After 12 months of prospective follow-up, 6MWD test and 24-hour BP monitoring (Shiller HTV) were repeated in all patients.

The data obtained were processed using the Statistica 10.0 and Medcalc 11.5.0.0 software suites. The nature of variable distribution was assessed using the Kolmogorov-Smirnov/Lilliefors test, the Shapiro-Wilk test and visually by constructing histograms. The homogeneity of general dispersion was evaluated by the Levene test. The Mann – Whitney test was used when comparing two independent groups to test statistical hypotheses in the analysis of quantitative indicators. The qualitative analysis used contingency tables, Pearson's chi-square test, Fischer's exact test or Yates' correction for continuity. The data are presented as the median and interquartile range (Me [25th percentile; 75th percentile]) or the absolute and relative values (n (%)). Correlation analysis and the calculation of Spearman rank correlation coefficients were used to find the correlations between the variables. Survival analysis was performed in the groups using the Kaplan–Meier method, and two curves were compared using a

Table 2. Drug therapy in patients with different clinical courses of CHF, n (%)

Drugs	Group A			Group B		
	baseline (n=35)	in 12 months (n=35)	p	baseline (n=36)	in 12 months (n=35)	p
ACE inhibitors	17 (49)	18 (51)	0.153	19 (53)	18 (51)	0.132
Beta-blockers	13 (37)	12 (34)	0.232	12 (33)	12 (34)	0.193
Diuretics	17 (49)	17 (49)	0.918	17 (47)	16 (46)	0.871
Calcium channel blockers	15 (43)	13 (37)	0.121	15 (42)	12 (34)	0.091
Angiotensin II receptor blockers	18 (51)	17 (49)	0.153	17 (47)	17 (49)	0.139

CHF, chronic heart failure; ACE, angiotensin-converting enzyme.

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log-rank test. Logistic regression was used to identify predictors of adverse outcomes (endpoints). The odds ratios (OR) and 95% confidence intervals (CI) were calculated to identify factors having a significant impact on the course and prognosis of the disease. ROC analysis and the construction of characteristic curves with the AUC calculation were used to identify predictors of adverse endpoints. The area under the ROC curve>0.70 was considered significant. The critical significance value for all the statistical analysis procedures used was p=0.05.

Results

The ROC analysis showed that ST_2 could be considered as a biomarker that allows predicting cardiovascular events in patients with HFpEF and OSAS with a high degree of probability (Figure 2).

The level of $sST_2 \geq 29.67$ ng/L is the cut-off for the development of cardiovascular events with a sensitivity of 65.71% and a specificity of 86.11% (AUC 0.773; p<0.0001). NT-proBNP (AUC 0.619; p=0.081) and CRP (AUC=0.511; p=0.869) were not predictive markers for the risk of adverse events.

Based on the ROC analysis results, all patients were divided into two groups depending on the ST_2 levels: Group 1 included 29 patients with $ST_2 \geq 29.67$ ng/L, and Group 2 included 42 patients with $ST_2 < 29.67$ ng/L. The clinical and demographic characteristics of patients are provided in Table 3.

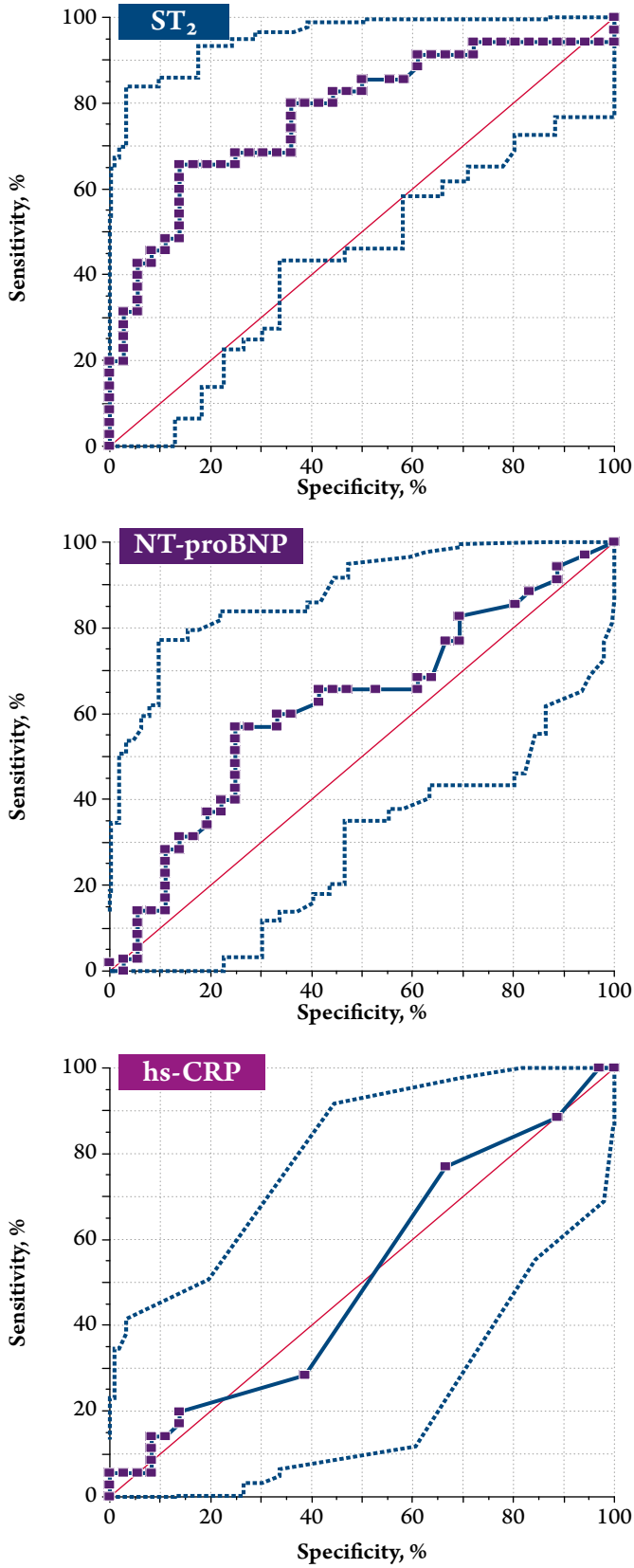
Patients with ST2 hyperexpression (≥29.67 ng/L) had higher AHI (p=0.049), lower ΔSRV (p=0.027) and greater LVMI (p=0.013) at the time of inclusion. The remaining clinical and demographic characteristics were comparable between the groups.

AHI was significantly correlated with BMI (r=0.362), left atrial volume (r=0.570), RV fractional area (r=–0.527), RVMPI (r=–0.377), NT-proBNP (r=0.611), 6MWD (r=–0.511), RV anterior wall thickness (r=0.472), and ST_2 were significantly correlated with the LV remodeling parameters: LVEF (r=–0.301), LV end-systolic volume (LVESV) (r=0.453), LV end-diastolic volume (LVEDV) (r=0.396), LV end systolic dimension (LVESD) (r=0.373), LV end-diastolic dimention (LVEDD) (r=0.288).

According to the Kaplan–Meier analysis results, the incidence of cardiovascular events differed in the groups (p<0.001; Figure 3). Cardiovascular events developed significantly more often during 12 months in Group 1 than in Group 2 (23 (79.3%) versus 12 (28.6%); Table 4).

Additional ROC-analysis of the combined effect of ST_2 and NT-proBNP on the prognosis of HFpEF course

Figure 2. ROC-curves of sensitivity and specificity of ST2, NT-proBNP, and CRP in the estimation of unfavorable course of HFpEF in patients with OSAS



NT-proBNP, N-terminal pro-brain natriuretic peptide; hsCRP, high sensitivity C-reactive protein; HFpEF, chronic heart failure with preserved left ventricular ejection fraction; OSAS, obstructive sleep apnea syndrome.

Table 3. Clinical and instrumental indicators depending on the level of ST_2 activity

Parameter	$ST_2 \geq 29.67$ ng/mL (n=29)	$ST_2 < 29.67$ ng/mL (n=42)	p
Age, years	48 [38; 57]	46 [37; 55]	0.405
Weight, kg	112 [107; 124]	101 [96; 112]	0.052
Height, sm	178 [174; 181]	178 [174; 182]	0.875
BMI, kg/m2	35.83 [32.7; 39.0]	33.1 [30.7; 36.1]	0.126
AHI	30.6 [26.0; 36.5]	28 [22; 32]	0.049
mSpO2	94.0 [93.5; 95.5]	94.5 [93.5; 96.0]	0.331
DI, episodes per hour	32.0 [26.0; 38.0]	26.25 [22.0; 32.0]	0.091
LVEF, %	60.0 [52; 71]	60 [54; 68]	0.425
mSBP 24-h BP, mm Hg	120.0 [114; 137]	131.5 [119; 141]	0.189
LA volume/BSA, mL/m2	37.6 [32.0; 44.2]	34.6 [33.2; 38.2]	0.578
LVEDD, cm	5.7 [5.3; 6.2]	5.7 [5.0; 6.2]	0.740
IVC, cm	1.2 [1.0; 1.2]	1.1 [0.9; 1.2]	0.432
LVPW, cm	1.1 [1.0; 1.2]	1.05 [0.9; 1.2]	0.136
Area of the right atrium, cm2	20.8 [18.0; 22.7]	18.2 [16.0; 21.2]	0.056
ΔSRV, %	37.0 [34.0; 40.0]	40.0 [36.0; 44.0]	0.027
RVMPI	0.24 [0.24; 0.26]	0.24 [0.22; 0.26]	0.671
LVMI, g/m2	122.2 [98.0; 134.6]	97.6 [85.0; 119.0]	0.013
RVAWT, cm	4.0 [4.0; 5.0]	4.0 [4.0; 5.0]	0.697
CHF FC, n (%)			
I	20 (69.0)	27 (64.3)	0.554
II	8 (27.6)	12 (28.6)	0.320
III	1 (3.4)	3 (7.1)	0.596
6MWD, m	411.0 [378.0; 512.0]	566.0 [456.0; 615.0]	0.189
RVSBP, mm Hg	30.0 [19.0; 42.0]	23.0 [19.0; 34.0]	0.549
RVEDD, cm	2.8 [2.4; 3.1]	2.4 [2.2; 2.7]	0.740
CI	1.2 [1.1; 1.24]	1.21 [1.17; 1.22]	0.432
NT-proBNP, pg/mL	220.8 [101.1; 997.3]	221.2 [102.7; 847.8]	0.732
CRP, mg/L	4.0 [4.0; 5.0]	4.0 [3.0; 5.0]	0.439
ST2, ng/mL	41.39 [33.31; 50.99]	22.18 [20.64; 25.5]	< 0.000001
DD type 1, n (%)	11 (37.9)	23 (54.8)	0.596
DD type 2, n (%)	18 (62.1)	19 (45.2)	0.232
PAH FC, n (%)	28 (96.6%)	38 (90.5)	0.589
I	22 (75.9)	28 (66.7)	0.234
II	5 (17.3)	10 (23.8)	0.495
III	1 (3.4)	0	0.932
Number of patients receiving PAP therapy, n (%)	3 (10.3)	5 (11.9)	0.786

BMI, body mass index; AHI, apnea/hypopnea index; mSpO2, mean saturation; DI, desaturation index; LVEF, left ventricular ejection fraction; mSBP 24-h BP, mean systolic blood pressure according to 24-hour blood pressure monitoring; LA, left atrium; LA volume/BSA, left atrial volume index; LVEDD, left ventricular end-diastolic dimension; IVC, interventricular septum; LVPW, left ventricular posterior wall; ΔSRV, right ventricular are fractional change; RVMPI, right ventricular myocardial performance index; LVMI, left ventricular mass index; RVAWT, right ventricular anterior wall thickness; CHF, chronic heart failure; FC, functional class; 6MWD, 6-minute walking distance; RVSBP, right ventricular systolic blood pressure; CI, circadian index; NT-proBNP, N-terminal pro-brain natriuretic peptide; CRP, C-reactive protein; DD, diastolic dysfunction; PAH FC, pulmonary arterial hypertension functional class.

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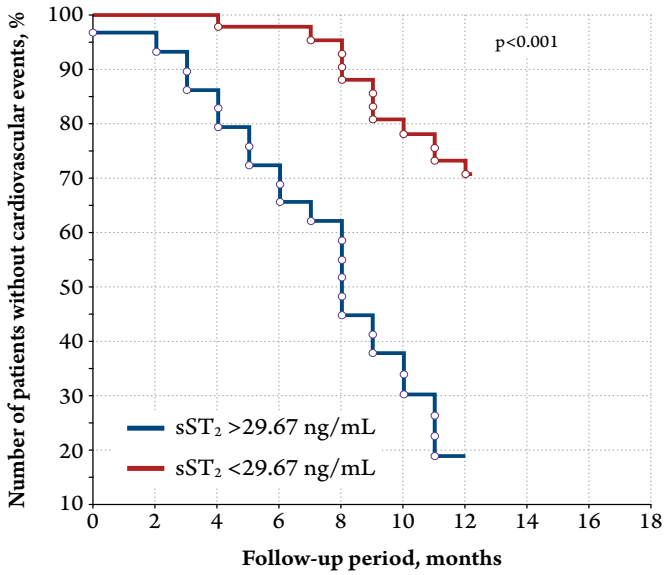
Figure 3. Role of ST2 in the assessment of the risk of cardiovascular events

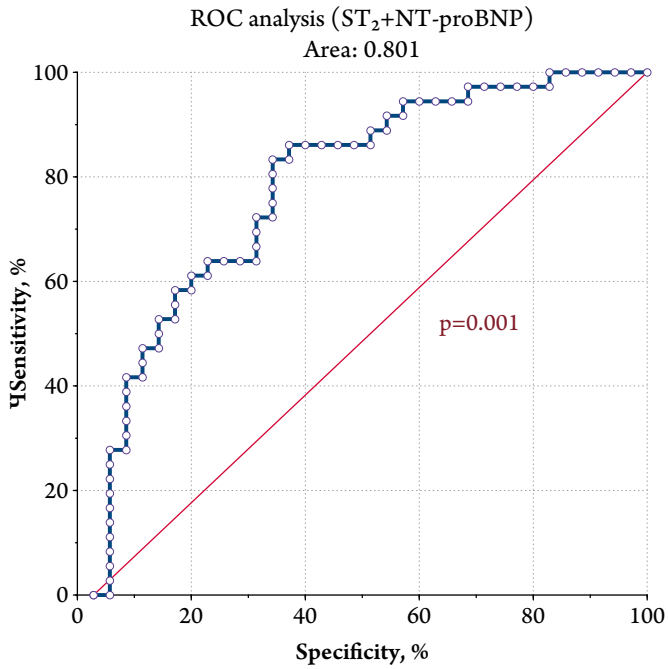


in patients with OSAS was performed. The addition of NT-proBNP did not significantly affect prognostic significance compared with the determination of only ST_2 (Figure 4).

Given the baseline intergroup differences of AHI, ΔSRV, and LVMI, a ROC-analysis was carried out to assess the prognostic significance of these parameters. According to this ROC analysis, all three parameters (AHI, ΔSRV, and LVMI) can be considered in patients with HFpEF and OSAS as instrumental parameters that allow predicting the adverse course of the disease with high probability (Figure 5).

For example, AHI≥29.4 per hour (sensitivity 77.14%, specificity 88.89%, AUC 0.862; p<0.0001), ΔSRV (frSRV) ≤35.0 (sensitivity 42.86%, specificity 91.67%, AUC 0.662; p=0.0150) and LVMI≥96.4 g/m² (sensitivity 88.57%, specificity 66.67%, AUC 0.796;

Figure 4. Sensitivity and specificity of sST2 and NT-proBNP in the assessment of the adverse course of CHF in patients with OSAS (ROC analysis)



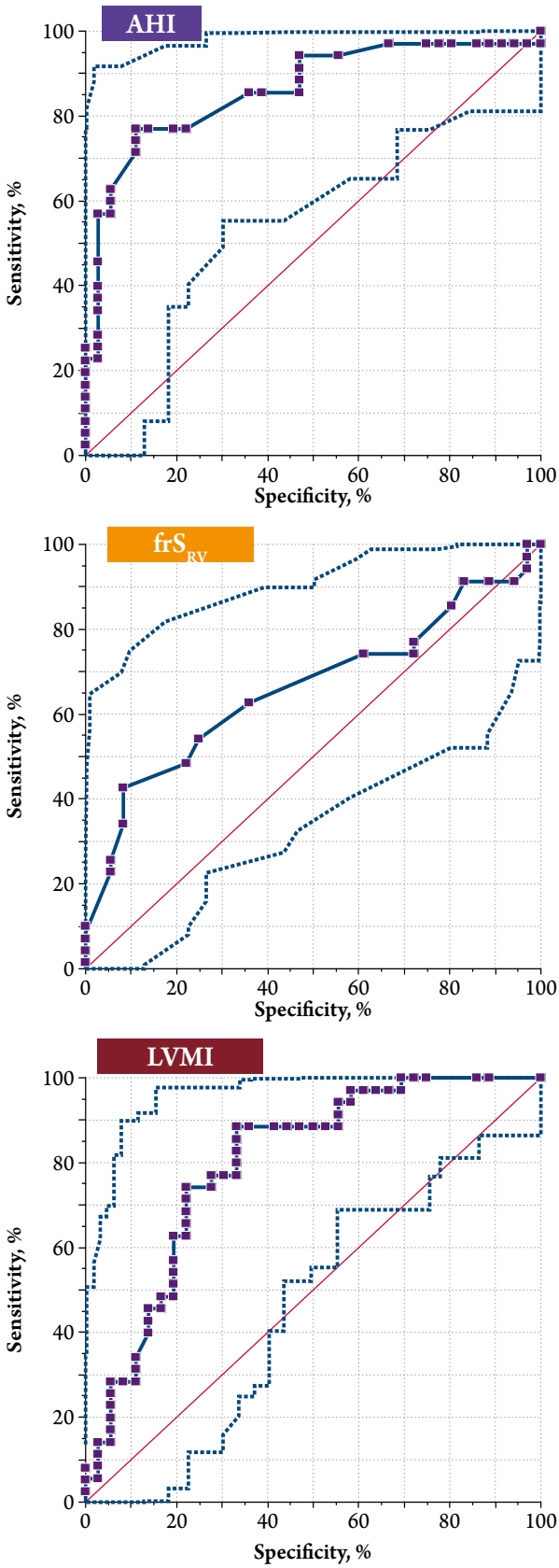
NT-proBNP, N-terminal pro-brain natriuretic peptide; HFpEF, chronic heart failure with preserved left ventricular ejection fraction; OSAS, obstructive sleep apnea syndrome.

Table 4. Number of cardiovascular events during the 12-month follow-up depending on ST2 level

Cardiovascular events	ST_2≥29.67 ng/mL (n=29)	ST_2<29.67 ng/mL (n=42)
Total	23 (79.3)	12 (28.6)
Progression of CHF (based on 6MWD)	20 (68.9)	12 (28.6)
Development of AF	10 (34.5)	6 (14.4)
APB	5 (17.2)	7 (16.7)
VPB	7 (24.1)	7 (16.7)
Repeated hospitalizations	6 (20.7)	4 (9.5)
PE	1 (3.4)	0
ACS	2 (6.9)	0
CVA	1 (3.4)	0
Death	1 (3.4)	0

The data are expressed as the absolute and relative values (n (%)). 6MWD, 6 minute walking distance; AF, atrial fibrillation; APB, atrial premature beats; VPB, ventricular premature beats; PE, pulmonary embolism; ACS, acute coronary syndrome; CVA, cerebrovascular accident.

Figure 5. ROC-curves of sensitivity and specificity of echocardiographic and respiration parameters in the assessment of the unfavorable course of HFpEF in patients with OSAS



HFpEF, chronic heart failure with preserved left ventricular ejection fraction; OSAS – obstructive sleep apnea syndrome; LVMI, left ventricular myocardial mass index.

p<0.0001) allow predicting a high risk of developing cardiovascular events.

The regression analysis identified parameters that were included in the prognostic model: ST_2 (OR 2.25; 95% CI 2.06–3.29; p=0.036), AHI (OR 3.28; 95% CI 3.09–4.49; p=0.012), LVMI (OR 2.14; 95% CI 2.01–3.07; p=0.021):

$Y = -17.01 + 0.16 \times sST_2$ (ng/mL) + 0.25 × AHI (episodes per hour) + 0.042 × LVMI (g/m^2).

Then the following formula was applied:

$$p = \frac{e^y}{1+e^y},$$

where p is the estimated probability of the development of cardiovascular events; e is the Euler number=2.718281828459045.

If the calculated result is≥0.65, the risk of cardiovascular events is high, and when it is<0.65, the risk is low.

Our findings clearly demonstrated that the adverse course of HFpEF in patients with OSAS was associated with the presence of markers of adverse cardiovascular events: increased $sST_{2activity}$, increased LVMI (echocardiography), and increased AHI (night-sleep polysomnography). Personalized consideration of these factors followed by mathematical processing using the proposed formula allows stratifying the risk of developing adverse cardiovascular events within 12 months in this category of patients, identifying the priority patient group for regular medical checkups, and organizing personalized targeted measures for the prevention of complications and high early mortality in these patients.

Discussion

The study established that ST_2 had the strongest correlations with the adverse clinical course of CHF in patients with OSAS. This marker had significant associations with the influence on all outcomes of interest and intermediate cut-off points (repeated hospitalizations, development of paroxysmal atrial fibrillation, development of cardiovascular events). ST_2 was also significantly correlated with echocardiographic parameters of right and left heart remodeling and AHI, which is a key indicator of OSAS severity, as well as with the adverse course.

The associations of the other two biomarkers of interest, NT-proBNP and CRP, with the adverse course of CHF were less weighty. In the absence of statistically significant correlations with the adverse clinical

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course, NT-proBNP had quite natural associations with echocardiographic parameters of remodeling, which is consistent with the published data [22]. The combination of the two biomarkers, NT-proBNP and sST_2, did not improve the prognostic significance of the analysis for the adverse course of HFpEF in patients with OSAS compared to the separate assessment of sST_2, which does not agree much with the published data [18]. The most likely cause of this discrepancy is that the study included patients with HFrEF with other pathogenetic links playing a leading role in the progression of the disease [1, 11].

High sensitivity CRP was not a prognostic marker, as it had no significant associations with the clinical course of the disease or the echocardiographic parameters. This may be due to a relatively short period of follow-up [23].

Attention is drawn to the correlations of several biomarkers of interest with the echocardiographic parameters of the right and left chamber remodeling. And being a criterion for OSAS severity, AHI is correlated with the parameters mainly of the right heart (ΔSRV, RVMPI, RV anterior wall thickness) and left atrial volume. This regularity is consistently explained by the peculiarities of OSAS pathogenesis: persistent elevation of intrathoracic and intraperitoneal pressure in apnea gradual formation of chronic pulmonary hypertension, which was described in other studies [24]. The molecular biomarker sST_2 correlated on the contrast mainly with echocardiographic criteria of LV remodeling: LVEF, LVESV, LVEDV, LVESD, LVEDD. This may be due to a certain extent to the larger LV mass and possibly longer period necessary for LV remodeling processes. Thus, it seems that the adverse course of CHF flow and the development of arrhythmias in patients with OSAS of the study group was to some extent associated with the baseline structural myocardial remodeling correlated with the activity of serum ST_2 and the peculiarities of pulmonary hemodynamic changes in this disease.

The absence of significant differences in the drug treatments and adherence between the groups with different clinical courses detected by retrospective analysis indicates that this factor does not have a significant effect on the clinical outcomes of interest. It seems interesting to study the effects of positive airway pressure (PAP) therapy as the most effective method of correcting respiratory disorders on the clinical course of CHF in OSAS and the levels of ST_2. However, the small number of patients (n=8) receiving regular PAP-therapy did not allow performing a reliable estimation.

Multiple identified significant associations of sST_2 with both clinical pattern and echocardiographic and functional parameters may indicate that the cytokine of interest plays a significant pathogenetic role in this combined pathology. The results of the studies published recently in broadsheet journals indicate the significant role of sST_2 in the progression of HFpEF due to its hyperexpression in the myocardium, on the one hand, and its non-cardiac origin and active participation, particularly in the development of chronic bronchopulmonary pathology, on the other hand [20]. According to the published data, sST_2, being a functionally significant representative of the IL-33 family, plays a significant role in the formation of fibrosis and remodeling of pulmonary tissue in patients with COPD and bronchial asthma [25]. Such multisystemic nature of sST_2 may be of particular significance in the pathogenesis of CHF in OSAS, since pathogenetic cardiopulmonary relationships in patients of this category are exceptionally closely correlated and develop almost simultaneously as in abdominal obesity [26, 27].

Closer association of sST_2 with clinical course compared to NT-proBNP and the fact that the correction for NT-proBNP levels did not change the statistical parameters for sST_2 may be indicative of higher sensitivity and specificity of sST_2 in the prognosis of the disease course compared to NT-proBNP in patients with HFpEF. This hypothesis should undoubtedly be verified in larger studies.

The active participation of sST_2 in the formation of myocardial and pulmonary fibrosis [28] and its significant role in the structural cardiopulmonary remodeling processes, in general, may indicate the significant predictive role of this biomarker for patients with OSAS and HFpEF [29]. There is good reason to believe that sST_2 may manifest these properties in the earliest stages of the disease. sST_2 has the potential to become a promising early biomarker of structural remodeling and adverse clinical course and personalized therapy control in patients with OSAS when these hypotheses are confirmed in larger studies in this cohort of patients.

Conclusion

Our findings suggest that sST_2 may be used in patients with chronic heart failure with preserved left ventricular ejection fraction combined with obstructive sleep apnea syndrome as a non-invasive marker for the assessment of the risk of developing cardiovascular events with the 12-month follow-up and the additional use of apnea/hypopnea index and left ventricular mass index in the model increases the predictive value of the analysis.

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The data obtained allow evaluating ST_2 activity as an independent predictor of the adverse clinical course of the disease and using it for the risk stratification and decision making on treatment strategies in this category of patients.

This study was limited by the number of included patients, specificity of the sample (the study included patients with predefined clinical and demographic demographics), and a relatively short period of follow-up.

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