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ДИАГНОСТИЧЕСКОЕ ЗНАЧЕНИЕ УРОВНЯ РАСТВОРИМОГО СТИМУЛИРУЮЩЕГО ФАКТОРА РОСТА У ПАЦИЕНТОВ СО СПОНДИЛОАРТРИТАМИ КАК РАННЕГО МАРКЕРА СЕРДЕЧНО-СОСУДИСТОЙ ПАТОЛОГИИ

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Diagnostic Significance of the Level of Soluble Stimulating Growth Factor in Patients with Spondyloarthritis as an Early Marker of Cardiovascular Pathology

Резюме

Цель — определить клиничко-лабораторные взаимосвязи уровня растворимого стимулирующего фактора роста, экспрессирующегося геном 2 (sST2), с показателями, характеризующими развитие сердечно-сосудистой патологии у пациентов со спондилоартритами (СПА). **Материалы и методы.** Обследовано 46 пациентов со СПА, из них 40 (87 %) с анкилозирующим спондилитом, 6 (13 %) — с псориатическим артритом. Средний возраст пациентов — 39,2±10,2 лет. Среди обследованных 36 (78,3 %) мужчин, 10 (21,7 %) женщин. Из 32 обследованных пациентов у 27 (84,4 %) выявлен HLA-B27. Для оценки активности СПА использовали индексы BASDAI и ASDAS, учитывали значения скорости оседания эритроцитов и С-реактивного белка; определяли уровни фактора некроза опухоли-альфа, N-терминального фрагмента мозгового натрийуретического пептида (NT-proBNP), интерлейкина-6, sST2 в сыворотке крови. Оценивали традиционные факторы сердечно-сосудистого риска, скорость распространения пульсовой волны в аорте (СПВА), результаты стандартной электрокардиографии, трансторакальной эхокар-

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диографии, дуплексного исследования сонных артерий. **Результаты.** Средний уровень sST2 составил $33,34 \pm 11,2$ нг/мл, уровень sST2 выше порогового значения зафиксирован у 19 (41,3 %) пациентов. Значимых взаимосвязей между уровнем sST2 и показателями активности СпА, параметрами эхокардиографии, нарушениями ритма и/или проводимости на электрокардиограммах не обнаружено. У пациентов с уровнем sST2 выше среднего отмечена более высокая СПВА ($p=0,036$); уровень NT-proBNP чаще был повышен у пациентов с высоким уровнем sST2 ($p=0,085$). У пациентов, получающих генно-инженерные биологические препараты в связи с высокой активностью СпА, отмечены более высокие уровни sST2 ($p=0,039$). **Заключение.** У 41,3 % пациентов со СпА установлен уровень sST2 выше порогового значения. Повышение уровня sST2 ассоциируется с увеличением СПВА и повышением уровня NT-proBNP, что может свидетельствовать о начавшихся процессах ремоделирования миокарда, фиброзе миокарда и начальных этапах развития сердечной недостаточности. Полученные новые данные свидетельствуют о целесообразности планирования и выполнения более крупных проспективных исследований пациентов со СпА для раннего выявления доклинических признаков поражения сердечно-сосудистой системы, процессов ремоделирования миокарда, оценки эффективности проводимой терапии.

Ключевые слова: спондилоартриты, анкилозирующий спондилит, уровни sST2, NT-proBNP

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Aim to determine the clinical and laboratory relationships of the level of soluble stimulating growth factor expressed by genome 2 (sST2) with indicators characterizing the development of cardiovascular pathology in patients with spondyloarthritis (SpA). **Materials and methods.** A total of 46 patients aged 39.2 ± 10.2 years with SpA (including 40 (87 %) with ankylosing spondylitis, 6 (13 %) with psoriatic arthritis) were examined. There were 36 (78.3 %) males, 10 (21.7 %) females among the enrolled patients. 27 (84.4 %) of 32 examined patients had HLA-B27. To assess the disease activity the BASDAI and ASDAS scores were used, the erythrocyte sedimentation rate and C-reactive protein values were measured; the levels of tumor necrosis factor-alpha (TNF-alpha), N-terminal fragment of brain natriuretic peptide (NT-proBNP), interleukin-6 (IL-6), sST2 in blood serum were evaluated. Traditional cardiovascular risk factors, aortic pulse wave velocity (PWVAo), the results of standard electrocardiography, transthoracic echocardiography, carotid duplex ultrasonography were assessed. **Results.** The mean sST2 level was 33.34 ± 11.2 ng/ml, an sST2 concentration above the threshold value was found in 19 (41.3 %) patients. No significant relationships between serum sST2 level and disease activity indicators, echocardiographic parameters, rhythm and/or conduction disturbances on electrocardiograms were found. A higher PWVAo was noted in patients with sST2 level above the average ($p=0.036$); the level of NT-proBNP was more often increased in patients with high levels of sST2 ($p=0.085$). Higher sST2 concentrations were found in patients treated with biological disease-modifying antirheumatic drugs due to the high disease activity ($p=0.039$). **Conclusion.** An increase in sST2 levels was found in 41.3 % of patients with SpA. An increase in serum sST2 concentration is associated with an elevated PWVAo and an increase in the level of NT-proBNP, which may indicate incipient cardiac remodeling, cardiac fibrosis, and the initial stages of the development of heart failure. The new data obtained indicate the advisability of planning and performing larger prospective studies of patients with SpA for the early detection of preclinical signs of damage to the cardiovascular system, cardiac remodeling, and assessment of the effectiveness of therapy.

Key words: spondyloarthritis, ankylosing spondylitis, sST2, NT-proBNP

Conflict of interests

The authors declare no conflict of interests

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aPWV — aortic pulse wave velocity, AS — ankylosing spondylitis, ASDAS — Ankylosing Spondylitis Disease Activity Score, BASDAI — Bath Ankylosing Spondylitis Disease Activity Index, CRP — C-reactive protein, CVD — cardiovascular disease, CVR — cardiovascular risk, DMARDs — basic disease-modifying antirheumatic drugs, ECG — electrocardiography, EchoCG — echocardiography, ESR — erythrocyte sedimentation rate, GEBDs — genetically engineered biological drugs, HLA-B27 — human leukocyte antigen-B27, IL-6 — interleukin-6, IMT — intima-media thickness, NSAIDs — non-steroidal anti-inflammatory drugs, NT-proBNP — N-terminal fragment of brain natriuretic peptide, PsA — psoriatic arthritis, SpA — spondyloarthritis, sST2 — soluble stimulating growth factor expressed by genome 2, ST2 — stimulating growth factor expressed by genome 2, TNF- α — tumor necrosis factor-alpha

Introduction

The medical and social significance of spondyloarthritis (SpA) is determined not only by deterioration of quality of life but also by its short duration, primarily due to damage to the cardiovascular system [1]. It has been shown that the incidence of cardiovascular diseases (CVD) in patients with SpA is higher than in the overall population [1]. This may be due to a higher prevalence of standard CVD risk factors associated with active systemic inflammation and endothelial dysfunction [2–4], hypercoagulability due to chronic systemic inflammation [3], and participation of several pro-inflammatory cytokines (tumor necrosis factor- α (TNF α) and interleukins (IL) -1, -6) in atherogenesis [2, 5, 6]. The development of CVD can also be influenced by ongoing treatment: TNF α inhibitors and long-term use of non-steroidal anti-inflammatory drugs (NSAIDs), which reduce the risk of CVD due to their anti-inflammatory activity [7, 8]. In ankylosing spondylitis (AS), the most common disease of the SpA group, the aortic valve and aortic bulb are often affected, rhythm and conduction disorders develop, as well as myocardial infarction, diastolic dysfunction and decreased reserve of coronary blood flow [9].

In this regard, the pathology of the cardiovascular system should be identified as soon as possible. The well-studied N-terminal fragment of the brain natriuretic peptide (NT-proBNP) is a marker of “hemodynamic” myocardial stress, while the stimulating growth factor expressed by gene 2 (ST2) can be considered a marker of “mechanical” myocardial stress [10]. ST2 protein belongs to the IL-1 family and has four isoforms; soluble ST2 (sST2) is of particular interest [11]. It competitively binds to IL-33, which is released from damaged or necrotic cells and prevents the development of the cardioprotective effect [11]. Vascular endothelial cells were found to be the main source of sST2 [11, 12]. There are also studies that confirm the involvement of sST2 in the pathogenesis of many inflammatory diseases. Patients with AS have higher levels of sST2 than patients of the control group, and an association with the parameters of disease activity was found [13, 14]. In psoriatic arthritis (PsA), patients with atherosclerotic plaques in carotid arteries have higher levels of sST2 [15]. Soluble sST2 can be considered one of the “bridges” between inflammation and fibrosis in AS [14]. In this regard, the role of sST2 in the early diagnosis of the pathology of the cardiovascular system in patients with SpA is of particular interest.

The objective is to determine clinical and laboratory relationships between the level of soluble stimulating growth factor expressed by gene 2 (sST2) and the parameters characterizing the development of cardiovascular pathology in patients with spondyloarthritis (SpA).

Materials and methods

Forty-six patients with SpA were examined, including 40 (87 %) patients with AS who met the international

New York criteria (1984), six (13 %) patients with PsA who met the CASPAR criteria (2006). The mean age of the patients was 39.2 ± 10.2 years. There were 36 (78.3 %) male and 10 (21.7 %) female patients. Twenty-seven (84.4 %) of the 32 examined patients had human leukocyte antigen-B27 (HLA-B27).

BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) and ASDAS (Ankylosing Spondylitis Disease Activity Score) scales were used to assess the disease activity. Sacroiliitis (SI) stage was assessed according to Kellgren (1966). Peripheral joint arthritis and coxitis, dactylitis, enthesitis, current or past uveitis, family history of SpA, and age of disease onset were considered. Serum levels of TNF α , NT-proBNP, IL-6, and sST2 were analyzed.

The investigated parameters in patients were determined by enzyme immunoassay using commercial reagent kits. To determine NT-proBNP, we used the NTproBNP-IFA-BEST reagent kit (ZAO Vektor-Best, Novosibirsk, Russia), for IL-6 — Interleukin-6-IFA-BEST kit (ZAO Vektor-Best, Novosibirsk, Russia), for TNF- α — Alpha-FNO-IFA-BEST kit (ZAO Vektor-Best, Novosibirsk, Russia), for sST2 — Presage[®] ST2 Assay kit (ZAO BioKhimMak, Moscow, Russia). The level of NT-proBNP ≤ 125 pg/mL was considered normal, the threshold value for sST2 was ≤ 35 ng/mL [10].

The following conventional cardiovascular risk factors (CVRs) were considered: age, smoking, overweight/obesity, hypercholesterolemia, family history; arterial hypertension; cardiovascular risk (CVR) was defined using QRISK3. Results of standard electrocardiography (ECG) and transthoracic echocardiography (EchoCG) were evaluated. Aortic pulse wave velocity (aPWV) was determined via the oscillographic method using the TensioClinic arteriograph (Tensiomed, Hungary).

The thickness of the intima-media complex (IMT) was determined with duplex ultrasound of carotid arteries using the Acuson 128 XP/100 ultrasound system equipped with a 7 MHz phased array linear transducer. IMT was measured in carotid arteries at three points: in the area of bifurcation of the common carotid artery, in the common carotid and internal carotid arteries (10 mm proximal and distal to the bifurcation); the structure of the wall and the diameter of the vessel lumen were assessed. Mean IMT was calculated (the sum of IMT values at three points in both carotid arteries/6), and the presence of atherosclerotic plaques was detected.

The nature of the quantitative trait distribution was evaluated using the Shapiro-Wilk test; distribution at $p > 0.05$ was considered normal. Quantitative traits with normal distribution were described with the indication of the arithmetic mean (M) and standard deviation (SD). Quantitative traits with non-normal distribution were described with the median value (Me) and upper and lower quartiles [Q1; Q3]. Comparison of two independent groups of quantitative traits with normal distribution was carried out using Student's t-test. Comparison of two independent groups of quantitative traits with non-normal distribution was carried out using the

Mann-Whitney test. Pearson's χ^2 test or Fisher's exact test were used to assess differences in the frequency of the trait in two independent groups. Relationships between two qualitative traits with normal distribution were analyzed by calculating the Pearson correlation coefficient. Relationships between two qualitative traits with non-normal distribution were analyzed by calculating the non-parametric Spearman coefficient. Differences and relationships were considered statistically significant at $p < 0.05$; $p < 0.1$ was considered as a trend towards a significant difference or relationship between parameters.

Results

Most of the examined patients were middle-aged male individuals, the average duration of the disease was 15.9 ± 7.5 years, 35 (76.1 %) patients demonstrated high and very high activity of the disease. The description of SpA in the examined patients is presented in Table 1.

Among the conventional factors of cardiovascular risk in the examined patients were the high prevalence of overweight, smoking, hypercholesterolemia and arterial hypertension (Table 2). All patients had no signs of coronary heart disease or heart failure. Results of ECG demonstrate rhythm disorders in 10 (21.7 %) patients, and conduction disorders in 7 (15.2 %) patients. Three (6.5 %) patients had left ventricular hypertrophy.

Relationships between the level of NT-proBNP and laboratory parameters of disease activity were revealed: ESR ($R = 0.432$, $p = 0.003$), CRP ($R = 0.343$, $p = 0.024$), TNF α ($R = 0.451$, $p = 0.011$), and ASDAS score ($R = 0.330$, $p = 0.025$); relationships were found between the levels of IL-6 and CRP ($R = 0.536$, $p = 0.003$), the level of TNF- α ($R = 0.458$, $p = 0.01$).

The mean value of sST-2 level was 33.34 ± 11.2 ng/mL; sST-2 level above the threshold value of 35 ng/mL was found in 19 (41.3 %) patients. No significant relationships between the sST2 level and SpA activity parameters,

Table 1. Characteristics of spondyloarthritis in the examined patients

Characteristics	All patients (n=46) M±SD / Me [Q1;Q3] / n (%)	sST-2 > 35 ng/ml (n=19) M±SD / Me [Q1;Q3] / n (%)	sST-2 ≤ 35 ng/ml (n=27) M±SD / Me [Q1;Q3] / n (%)	P
Age, years	39,2±10,2	41,7±11,2	37,4±9,2	0,159
Men	36 (78,3 %)	16 (84,2 %)	20 (74,1 %)	0,328
Women	10 (21,7 %)	3 (15,8 %)	7 (25,9 %)	
Age of debut, years	21 [17;28]	21 [20;31]	21,5±9,1	0,240
Debut at the age of 18 and younger				
Yes	14 (30,4 %)	4 (21,1 %)	10 (37,0 %)	0,246
No	32 (69,6 %)	15 (78,9 %)	17 (63,0 %)	
Arthritis				
Yes	35 (76,1 %)	15 (78,9 %)	20 (74,1 %)	0,492
No	11 (23,9 %)	4 (21,1 %)	7 (25,9 %)	
Dactylitis				
Yes	10 (21,7 %)	4 (21,1 %)	6 (22,2 %)	0,610
No	36 (78,3 %)	15 (78,9 %)	21 (77,8 %)	
Enthesitis				
Yes	16 (34,8 %)	6 (31,6 %)	10 (37,0 %)	0,702
No	30 (65,2 %)	13 (68,4 %)	17 (63,0 %)	
Uveitis				
Yes	15 (32,6 %)	7 (36,8 %)	8 (29,6 %)	0,607
No	31 (67,4 %)	12 (63,2 %)	19 (70,4 %)	
Family history of the spondyloarthritis				
Yes	8 (17,4 %)	2 (10,5 %)	6 (22,2 %)	0,267
No	38 (82,6 %)	17 (89,5 %)	21 (77,8 %)	
Sacroiliitis				
1 stage	2 (4,3 %)	0 (0,0 %)	2 (7,4 %)	-
2 stage	10 (21,7 %)	7 (36,8 %)	3 (11,1 %)	
3 stage	15 (32,6 %)	6 (31,6 %)	9 (33,3 %)	
4 stage	19 (41,3 %)	6 (31,6 %)	13 (48,2 %)	
ASDAS	3,5 [3,0;4,0]	3,7 [2,4;4,0]	3,5±1,0	0,973
BASDAI	5,5±2,2	5,4±2,5	5,5±2,0	0,769
ESR, mm/h	15,5 [8,0;26,0]	19,7±13,7	16,4±9,6	0,383
CRP, mg/ml	11,2 [23,0]	18,0±13,9	11,0 [3,95;20,75]	0,301
TNF- α , pg/ml (n=31, n=15, n=16)	3,2 [2,4;6,3]	3,3 [2,4;7,0]	3,15 [2,5;4,9]	0,740
IL-6, pg/ml (n=31, n=15, n=16)	4,4 [2,0;11,7]	2,9 [1,7;12,6]	6,35 [2,3;10,48]	0,599

Notes: sST2 — soluble stimulating growth factor expressed by gene 2, ASDAS — Ankylosing Spondylitis Disease Activity Score, BASDAI — Bath Ankylosing Spondylitis Disease Activity Index, ESR — the erythrocyte sedimentation rate, CRP — C-reactive protein, TNF- α — tumor necrosis factor-alpha, IL-6 — interleukin-6

cardiovascular risk factors (except for age), EchoCG parameters, rhythm and/or conduction disorders on ECG were found. Patients with an above-average sST2 level had higher aPWV ($p=0.036$).

Groups of patients with sST2 levels above 35 ng/mL ($n = 19$) and below 35 ng/mL ($n = 27$) were identified. The average age of patients with sST2 levels above 35 ng/mL was 41.7 ± 11.2 years; this group included 16 (84.2%) men and 3 (15.8%) women; 17 (89.5%) patients with AS and 2 (10.5%) with PsA. Eleven (84.6%) of the 13 examined patients were found to be carriers of HLA-B27. The

average age of patients with sST2 levels below the threshold value was 37.4 ± 9.2 years. This group included 20 (74.1%) men and 7 (25.9%) women; 23 (85.2%) patients with AS and 4 (14.8%) with PsA. Sixteen (84.2%) of the 19 examined patients were found to be carriers of HLA-B27. The description of SpA in the examined patients of the two groups is presented in Table 1, assessment of the cardiovascular risk and state of the cardiovascular system — in Table 2. When comparing the studied parameters, no significant differences were found. However, in patients with sST-2 levels above the threshold

Table 2. Traditional factors of cardiovascular risk, echocardiography parameters, the average thickness of the intima-media complex and aortic pulse wave velocity in the examined patients with spondyloarthritis

Характеристики / Characteristics	Все пациенты / All patients (n=46) M±SD / Me [Q1;Q3] / n (%)	sST-2 > 35 нг/мл / sST-2 > 35 ng/ml (n=19) M±SD / Me [Q1;Q3] / n (%)	sST-2 ≤ 35 нг/мл / sST-2 ≤ 35 ng/ml (n=27) M±SD / Me [Q1;Q3] / n (%)	p
Family history of early development of coronary heart disease				
Yes	10 (21,7%)	3 (15,8%)	7 (25,9%)	0,233
No	36 (78,3%)	36 (84,2%)	36 (74,1%)	
Overweight/obesity				
Yes	18 (39,1%)	6 (31,6%)	12 (44,4%)	0,379
No	28 (60,9%)	13 (68,4%)	15 (55,6%)	
Smoking				
Yes	15 (32,6%)	3 (15,8%)	12 (44,4%)	0,101
No	27 (58,7%)	14 (73,7%)	13 (48,2%)	
In the anamnesis	4 (8,7%)	2 (10,5%)	2 (7,4%)	
Arterial hypertension				
Yes	18 (39,1%)	7 (36,8%)	11 (40,7%)	0,912
No	28 (60,9%)	12 (63,2%)	16 (59,3%)	
Total cholesterol, mmol/l	4,9±1,0	4,6±1,1	4,6±0,9	0,954
Hypercholesterolemia				
Yes	17 (37%)	7 (36,8%)	10 (37,0%)	0,912
No	29 (63%)	12 (63,2%)	17 (63,0%)	
QRISK3	2,1 [0,75;8,5]	2,1 [0,7;11,6]	2,4 [0,68;6,68]	0,605
NT-proBNP, pg/ml	2,75 [0,0;52,7]	25,7 [0,0;86,2]	0,0 [0,0;43,2]	0,242
NT-proBNP level above the normal level	5 (10,9%)	4 (21,1%)	1 (3,7%)	
Normal level of NT-proBNP	41 (89,1%)	15 (78,9%)	26 (96,3%)	0,085*
sST-2, ng/ml	33,34±11,2	43,6 [38,5;46,4]	25,6±5,5	0,0001**
Average thickness of the intima-media complex, mm	0,717 [0,633;0,833] (n=39)	0,667 [0,621;0,796] (n=16)	0,764±0,149 (n=23)	0,263
Atherosclerotic plaque	n=39	n=16	n=23	
Yes	8 (20,5%)	4 (25,0%)	4 (17,4%)	0,425
No	31 (79,5%)	12 (75,0%)	19 (82,6%)	
Aortic pulse wave velocity, m/s	7,14 [6,73;8,74] (n=37)	7,61 [7,01;9,83] (n=14)	7,0 [6,68;8,62] (n=23)	0,077*
Diastolic function	n=33	n=10	n=23	
Yes, broken by the relaxation type	16 (48,5%)	5 (50,0%)	11 (47,8%)	0,603
No	17 (51,5%)	5 (50,0%)	12 (52,2%)	
Ejection fraction, %	63,5±3,8 (n=33)	64,0±3,6 (n=10)	64,0 [61,425;65,75] (n=23)	0,867
Left ventricular hypertrophy (n=33)	n=33	n=10	n=23	
Yes	7 (21,2%)	3 (30,0%)	4 (16,7%)	0,330
No	26 (78,8%)	7 (70,0%)	20 (83,3%)	
Condition of the aortic valve flaps	n=33	n=10	n=23	
Normal	10 (30,3%)	2 (20,0%)	8 (34,8%)	0,339
Compacted	23 (69,7%)	8 (80,0%)	15 (65,2%)	
Condition of the aortic walls	n=33	n=10	n=23	
Normal	7 (21,2%)	2 (20,0%)	5 (21,7%)	0,648
Compacted	26 (78,8%)	8 (80,0%)	18 (78,3%)	

Notes: NT-proBNP — N-terminal fragment of brain natriuretic peptide. * — $p<0,1$, ** — $p<0,05$

value, there was a tendency towards a more frequent high level of NT-proBNP and higher aortic pulse wave velocity ($p = 0.085$ and $p = 0.077$, respectively). The level of sST2 above the threshold value probably indicates early preclinical changes in the myocardium and vascular wall, i.e., remodeling processes.

All patients with sST2 levels above the threshold were taking NSAIDs, 14 (73.7%) of them additionally received synthetic DMARDs, 9 (47.4%) — genetically engineered biological drugs (GEBDs), while 7 (36.8%) patients required a combination of DMARDs and GEBDs to control disease activity, 11 (57.9%) patients required additional oral glucocorticoids (GCs). Among patients with sST2 levels below the threshold, 26 (96.3%) were taking NSAIDs, 15 (55.6%) were taking DMARDs, and 7 (25.9%) were taking GEBDs. The combination of DMARDs and GEBDs was prescribed to 3 (11.1%) patients, oral GCs — to 12 (44.4%) patients. Patients with high disease activity and unable to achieve remission at the previous stages of treatment and, therefore, receiving GEBDs, demonstrated higher levels of sST2 ($p = 0.039$), which may also indicate the processes of myocardial remodeling and fibrosis that have already started.

Discussion

One of the tasks facing modern medicine is the detection of developing pathology as early as possible. Therefore, there is a constant search for laboratory markers that would be as informative as possible. The choice of the optimal method for diagnosing damage to the cardiovascular system and myocardium in comorbid patients is a huge challenge.

The role of several markers for diagnosing myocardial stress is discussed. NT-proBNP is a more labile parameter and, according to our results, it depends on the activity of systemic inflammation at a given point in time. Changes in the cardiovascular system in patients with AS develop quite early, even before clinical manifestations; therefore, it is advisable to search for the markers of this early damage to the heart and vascular wall [14]. There is insufficient data in literature sources on the role of sST2 in the pathogenesis of cardiovascular pathology in SpA. In our study, sST2 levels above the threshold value were found in 41.3% of patients with no history of CVD, which may indicate changes in the cardiovascular system. However, sST2 level is not associated with laboratory parameters of the activity of systemic inflammation at a given point in time, which differs from the available literature data, as in the case of studying patients with AS [13]. Information about sST2 levels in rheumatoid arthritis is also contradictory: despite the absence of a clear relationship between sST2 levels and parameters of disease activity, according to some studies, there are lower levels of sST2 in patients with a good response to basic treatment [16]. A number of large studies (CORONA, PHFS) demonstrated the prognostic value of sST2 level [10]. Therefore, a more complete assessment of the value of sST2 level in patients with SpA

requires further follow-up, with the allocation of patients with an elevated level of this marker to a high-risk group.

Conclusion

The sST2 level was above the threshold value in 41.3% of patients with SpA. An increase in the sST2 level is associated with increased aortic pulse wave velocity and increased NT-proBNP level, which may indicate the onset of myocardial remodeling, myocardial fibrosis, and the initial stages of heart failure. The new results obtained suggest there is a need to plan and conduct larger prospective studies on patients with SpA for the early detection of preclinical signs of damage to the cardiovascular system, myocardial remodeling processes, and evaluation of the effectiveness of ongoing therapy.

Limitations

The study was conducted on a small sample of patients, with follow-up starting at different stages of the disease, with different duration and different treatment. Extrapolating the results of this study to all patients with SpA should be done with caution.

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Список литературы / References:

1. Braun J., Krüger K., Manger B., et al. Cardiovascular Comorbidity in Inflammatory Rheumatological Conditions. *Dtsch Arztebl Int.* 2017; 114(12): 197-203. doi: 10.3238/arztebl.2017.0197.

2. Tournadre A., Mathieu S., Soubrier M. Managing cardiovascular risk in patients with inflammatory arthritis: practical considerations. *Ther Adv Musculoskelet Dis.* 2016; 8(5): 180-191. doi: 10.1177/1759720X16664306.
3. Ungprasert P., Srivali N., Kittanamongkolchai W. Risk of coronary artery disease in patients with ankylosing spondylitis: a systematic review and meta-analysis. *Ann Transl Med.* 2015; 3(4): 51. doi: 10.3978/j.issn.2305-5839.2015.02.05.
4. Ter Maaten J.M., Damman K., Verhaar M.C., et al. Connecting heart failure with preserved ejection fraction and renal dysfunction: the role of endothelial dysfunction and inflammation. *Eur J Heart Fail.* 2016; 8(6): 588-598. doi: 10.1002/ehf.497.
5. Mozos I., Malainer C., Horbańczuk J., et al. Inflammatory Markers for Arterial Stiffness in Cardiovascular Diseases. *Front Immunol.* 2017; 8: 1058. doi: 10.3389/fimmu.2017.01058.
6. Heslinga S.C., Van Sijl A.M., De Boer K., et al. Tumor necrosis factor blocking therapy and congestive heart failure in patients with inflammatory rheumatic disorders: a systematic review. *Curr Med Chem.* 2015; 22(16): 1892-902. doi: 10.2174/0929867322666150209160701.
7. Tsai W.C., Ou T.T., Yen J.H., et al. Long-term frequent use of non-steroidal anti-inflammatory drugs might protect patients with ankylosing spondylitis from cardiovascular diseases: a nationwide case-control study. *PLoS One.* 2015; 10(5): e0126347. doi: 10.1371/journal.pone.0126347.
8. Lee J.L., Sinnathurai P., Buchbinder R., et al. Biologics and cardiovascular events in inflammatory arthritis: a prospective national cohort study. *Arthritis Res Ther.* 2018; 20(1): 171. doi: 10.1186/s13075-018-1669-x.
9. Amin A., Chitsazan M., Navid H. Left ventricular systolic dysfunction in two patients with ankylosing spondylitis: What is the role of corticosteroids? *Eur J Rheumatol.* 2016; 3(4): 179-181. doi: 10.5152/eurjrheum.2016.15069.
10. Камардинов Д. Х., Сонгуров Р. Н., Иошина В. И. и др. Растворимый ST2 — как биомаркер, инструмент стратификации риска и терапевтическая мишень у пациентов с хронической сердечной недостаточностью. *Кардиология.* 2020; 60(2): 111–121. <https://doi.org/10.18087/cardio.2020.2.n816> Kamardinov D.K., Songurov R.N., Ioshina V.I., et al. Soluble ST2 — as a biomarker, a tool for risk stratification and therapeutic target in patients with chronic heart failure. *Kardiologiya.* 2020; 60(2): 111–121. <https://doi.org/10.18087/cardio.2020.2.n816> [In Russian]
11. Dudek M., Kałużna-Oleksy M., Migaj J., et al. Clinical value of soluble ST2 in cardiology. *Adv Clin Exp Med.* 2020; 29(10): 1205–1210. doi:10.17219/acem/126049.
12. Bartunek J., Delrue L., Van Durme F, et al. Nonmyocardial production of ST2 protein in human hypertrophy and failure is related to diastolic load. *J Am Coll Cardiol.* 2008; 52(25): 2166–2174. doi:10.1016/j.jacc.2008.09.027.
13. Li X.L., Lin T.T., Qi C.Y., et al. Elevated serum level of IL-33 and sST2 in patients with ankylosing spondylitis: associated with disease activity and vascular endothelial growth factor. *J Investig Med.* 2013; 61(5): 848-51. doi: 10.2310/JIM.0b013e31828deed2.
14. Ozkaramanli Gur D., Ozaltun D.N., Guzel S., et al. Novel Imaging Modalities in Detection of Cardiovascular Involvement in Ankylosing Spondylitis. *Scandinavian Cardiovascular Journal.* 2018; 52(6): 320-327. doi: 10.1080/14017431.2018.1551564
15. Shen J., Shang Q., Wong C.K., et al. Carotid plaque and bone density and microarchitecture in psoriatic arthritis: the correlation with soluble ST2. *Sci Rep.* 2016; 6: 32116. doi: 10.1038/srep32116.
16. Shi L.J., Liu C., Li J.H., et al. Elevated Levels of Soluble ST2 were Associated with Rheumatoid Arthritis Disease Activity and Ameliorated Inflammation in Synovial Fibroblasts. *Chin Med J.* 2018; 131: 316-322. doi: 10.4103/0366-6999.223847.