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Prognostic value of humoral markers in patients with anthracycline-related cardiac dysfunction

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ABSTRACT

Aim. To carry out a 12-month study on the prognostic role of humoral markers responsible for the main mechanisms of initiation of cardiotoxic myocardial damage (endothelin-1, soluble Fas-L, N-terminal pro-brain natriuretic peptide (NT-proBNP), tumor necrosis factor-α, interleukin (IL)-1β, matrix metalloproteinase (MMP)-2 and MMP-9, soluble form of the ST2 protein (sST2), a tissue inhibitor of metalloproteinase-1, and tetranectin) in assessing the risk of progression of anthracycline-related left ventricular dysfunction.

Materials and methods. The study included a total of 114 women aged 48.0 (46.0; 52.0) years without concomitant cardiovascular diseases and risk factors who received chemotherapy with anthracyclines in the past. The levels of serum biomarkers were determined using the enzyme immunoassay. Transthoracic echocardiography was performed at baseline and at 12 months of follow-up.

Results. After 12 months of follow-up, all patients were retrospectively divided into 2 groups: group 1 (n = 54) included patients with an unfavorable course of anthracycline-related cardiac dysfunction (ARCD), group 2 (n = 60) encompassed patients with a favorable course of the disease. According to the ROC analysis, MMP-2 ≥ 338.8 pg / ml (sensitivity 57%, specificity 78%; AUC = 0.629; p = 0.025), MMP-9 ≥ 22.18 pg / ml (sensitivity 89%, specificity 87%; AUC = 0.886; p < 0.001), sST2 ≥ 32.4 ng / ml (sensitivity 64%, specificity 70.5%; AUC = 0.691; p = 0.002), and tetranectin ≤ 15.4 pg / ml (sensitivity 69%, specificity 72%; AUC = 0.764; p < 0.001) were identified as predictors of an adverse course of ARCD. When comparing ROC curves, it was found that the concentration of MMP-9 (p = 0.002) was the most significant predictor of the progression of ARCD.

Conclusion. MMP-2 and -9, soluble ST2, and tetranectin can be considered as non-invasive markers for assessing the risk of ARCD progression. At the same time, an increased level of MMP-9 is the most significant predictor of ARCD progression.

Keywords: left ventricular dysfunction, anthracyclines, humoral markers, prognosis

Conflict of interest. The authors declare the absence of obvious or potential conflict of interest related to the publication of this article.

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Conformity with the principles of ethics. All patients signed an informed consent to participate in the study. The study was approved by the local ethics Committee at the Cardiology Research Institute of Tomsk NRMC (Protocol No. 177 of 30.10.2018).

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Прогностическая роль гуморальных маркеров у больных с дисфункций левого желудочка, индуцированной приемом антрациклинов

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РЕЗЮМЕ

Цель. В ходе 12-месячного исследования изучить прогностическую роль гуморальных маркеров, ответственных за основные механизмы инициирования кардиотоксического повреждения миокарда (эндотелин-1, растворимый Fas-L, NT-proBNP, фактор некроза опухоли альфа, интерлейкин-1β, матриксные металлопротеиназы-2 (ММП-2) и -9 (ММП-9), растворимая форма белка ST2 (sST2), тканевой ингибитор металлопротеиназы-1 и тетранектин), в оценке риска прогрессирования дисфункции левого желудочка (ЛЖ), индуцированной приемом антрациклинов.

Материалы и методы. Обследованы 114 женщин в возрасте 48,0 (46,0; 52,0) лет без сопутствующих сердечно-сосудистых заболеваний и факторов риска, получавших в анамнезе химиотерапевтическое лечение антрациклинами. Уровни биомаркеров в сыворотке крови определяли с помощью иммуноферментного анализа. Трансторакальная эхокардиография была выполнена исходно и через 12 мес наблюдения.

Результаты. Через 12 мес все пациентки были ретроспективно разделены на две группы: 1-ю группу (n = 54) составили больные с неблагоприятным течением дисфункции ЛЖ, индуцированной приемом антрациклинами, 2-ю группу (n = 60) – с благоприятным. По данным ROC-анализа, концентрации ММП-2 ≥ 338,8 пг/мл (чувствительность 57%, специфичность 78%; AUC = 0,629; p = 0,025), ММП-9 ≥ ≥ 22,18 пг/мл (чувствительность 89%, специфичность 87%; AUC = 0,886; p < 0,001), растворимой формы белка ST2 ≥ 32,4 нг/мл (чувствительность 64%, специфичность 70,5%; AUC = 0,691; p = 0,002) и тетранектина ≤ 15,4 пг/мл (чувствительность 69%, специфичность 72%; AUC = 0,764; p < 0,001) были идентифицированы как предикторы неблагоприятного течения дисфункции ЛЖ. При сравнении ROC-кривых установлено, что концентрация ММП-9 (p = 0,002) была наиболее значимым предиктором.

Заключение. Матриксные ММП-2 и -9, растворимый ST2 и тетранектин могут быть рассмотрены как неинвазивные маркеры для оценки риска прогрессирования дисфункции ЛЖ, индуцированной приемом антрациклинов. При этом повышенный уровень матриксной ММП-9 является наиболее значимым предиктором прогрессирования дисфункции ЛЖ, индуцированной приемом антрациклинов.

Ключевые слова: дисфункция левого желудочка, антрациклины, гуморальные маркеры, прогноз

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INTRODUCTION

Currently, several anticancer drugs are most commonly used to treat neoplasms. These drugs are highly effective, but at the same time have a potentially high risk of developing cardiotoxicity: cyclophosphamide, doxorubicin, trastuzumab, fluorouracil, cisplatin, and immunosuppressive drugs (that block cytotoxic T-lymphocyte-associated protein 4, programmed cell death protein-1, and programmed cell death receptor ligand) [1]. At the same time, anthracyclines are some of the main components in treatment regimens for patients with breast cancer (BC), leukemia, lymphoma, and sarcoma, however, anthracycline-induced cardiac dysfunction remains a common clinical problem, jeopardizing the effectiveness of anticancer therapy [2].

Subclinical damage to myocardial cells exerted by anthracyclines can manifest itself by asymptomatic anthracycline-related cardiac dysfunction (ARCD), as well as by symptomatic heart failure [2]. It has been established that the risk of developing ARCD increases with an increase in the administered cumulative dose of anthracyclines, the age of patients, previous or concomitant radiation therapy, and the presence of cardiovascular pathology or risk factors [3, 4]. Cardiomyocytes are considered as the main cellular target of the toxic effect of anthracyclines on the heart due to the effect of doxorubicin on the mitochondrial redox cycle, which leads to their death and progression of cardiac dysfunction [5].

Recently, other cell types, such as cardiovascular progenitor cells, cardiac fibroblasts, and endothelial cells, have been identified as potential cellular targets, creating a more complex and intriguing scenario in the pathogenesis of ARCD [6]. It is discussed that the mechanisms of this pathology are implemented through mitochondrial dysfunction (mitochondrial NADH dehydrogenase), changes in iron homeostasis, generation of oxidative stress with the help of NRF2 and reactive oxygen species (ROS) by nitric oxide mediated by neuronal NO synthase, development of endothelial dysfunction, stimulation of apoptosis (induction of p53 protein), pyroptosis (activation of proinflammatory molecules), and various caspases, as well as through induction of the signaling pathway influencing interstitial and perivascular fibrosis with the participation of matrix metalloproteinases (MMPs) and transforming growth factor-β [1, 6–10]. However, the role of these factors in further progression of ARCD has not yet been determined.

The aim of this research was to carry out a comprehensive study on the prognostic role of humoral markers responsible for the main mechanisms of initiation of cardiotoxic myocardial damage (endothelin-1, soluble Fas-L, N-terminal pro-brain natriuretic peptide (NT-proBNP), tumor necrosis factor-α, interleukin (IL)-1β, MMP-2 and MMP-9, soluble form of the ST2 protein (sST2), a tissue inhibitor of metalloproteinase-1 (TIMP-1), and tetranectin) in assessing the risk of ARCD progression during a 12-month follow-up.

MATERIALS AND METHODS

The study was approved by the local Ethics Committee at Cardiology Research Institute of Tomsk NRMC (Protocol No. 177 of 30.10.2018). All patients signed an informed consent to participate in the study.

It was a prospective, observational, single center study. From December 2020 to September 2021,

114 women aged 48.0 (46.0; 52.0) years who met the inclusion / exclusion criteria were consecutively included in the study.

Inclusion criteria: 1) women with BC without cardiovascular disease in the medical history; 2) previous polychemotherapy to treat BC: a combination of doxorubicin and cyclophosphamide (AC regimen), or a combination of doxorubicin, cyclophosphamide, and docetaxel (TAS regimen); 3) cancer in remission; 4) newly diagnosed ARCD (symptomatic or asymptomatic); 5) a signed informed consent.

Exclusion criteria: 1) type 1 and type 2 diabetes; 2) coronary artery disease; 3) arterial hypertension; 4) valvular defects and cardiomyopathy of any etiology; 5) heart failure with an alternative cause of manifestation; 6) glomerular filtration rate (CKD-EPI) < 50 ml / min / m^2; 7) Child – Pugh class C liver failure; 8) hemoglobin level < 100 g / l; 9) chronic alcohol abuse or mental disorders; 10) previous pulmonary embolism with pulmonary hypertension (systolic pressure in the right ventricle ≥ 45 mm Hg); 11) severe form of bronchial asthma and chronic obstructive pulmonary disease; 12) pathology of the thyroid gland; 13) pathology of the reproductive system.

The cumulative dose of doxorubicin was 300–360 mg / m^2, and all patients underwent radiation therapy. All patients underwent a 6-minute walk test to assess the functional class (FC) of heart failure. ARCD was diagnosed in accordance with the European guidelines on cardio-oncology (2022) [11]. According to the criteria, 36 patients had symptomatic ARCD or FC I–III heart failure, and 78 patients had asymptomatic ARCD.

Echocardiography. The Philips Affiniti 70 enhanced imaging ultrasound machine was used to perform two-dimensional (2D, B-real time) transthoracic echocardiography. All studies were performed by one highly qualified specialist at baseline and at 12 months of follow-up. In the analysis of echocardiography parameters, linear dimensions of the heart were assessed (measurements at the basal, middle, and apical levels): thickness of the interventricular septum (IVS); posterior wall thickness (PWT) of the left ventricle (LV); end-systolic dimension (ESD), and end-diastolic dimension (EDD) of the LV. Left ventricular ejection fraction (LVEF) was calculated using the Simpson's rule.

Biochemistry test. Blood sampling was performed by venipuncture, and serum samples obtained after centrifugation were stored at –24 °C with one freeze – thaw cycle. Serum biomarker levels were determined using the enzyme immunoassay – NT-proBNP (Biomedica immunoassays, Austria), MMP-2 and MMP-9 (eBioscience, USA), TIMP-1 (Biomedica immunoassays, Austria), sST2 (Presage® ST2 assay, Critical Diagnostics, USA), tetranectin (eBioscience, USA), endothelin-1 (BG Medicine, Waltham, USA), soluble Fas-L (Human ELISA Kit, USA), IL-1β (Boster Biological Technology, USA), and tumor necrosis factor (TNF)α (TNFSF1A Immunoassay, Minneapolis, USA).

Adverse cardiovascular events and follow-up. Adverse cardiovascular events were hospitalizations due to progression of symptoms of heart failure, a decrease in the functional class of heart failure by 1 or more (according to NYHA), an asymptomatic decrease in LVEF by 10 or more absolute units (%), emergence of symptoms / signs of heart failure. After detection of LV dysfunction and inclusion in the study, all patients were prescribed optimal drug therapy. After adjustment of treatment, follow-up began. At 12 months of follow-up, following a patients' visit to the clinic, we collected and analyzed data on the presence of adverse events and the time of their onset, changes in drug therapy over this period, and the clinical status of patients. Echocardiography was performed to assess the asymptomatic decrease in LVEF.

Statistical analysis. Statistical processing of the study results was carried out using the STATISTICA 10.0 and MedCalc 11.5.0.0 software packages. The data were presented as the median and the interquartile range *Me* ($Q_{25;}$ Q_{75}). To test statistical hypotheses when comparing two independent samples, the Mann – Whitney *U*-test was used. The Wilcoxon signed rank test was used to compare two dependent samples. For qualitative variables, contingency tables were analyzed using the Pearson's $\chi 2$ test. To identify predictors of an unfavorable course of the disease, the ROC analysis was used with the construction of characteristic curves and the calculation of area under the curve (AUC). The univariate regression analysis with the calculation of odds ratio (OR) and 95% confidence interval (CI) was used to evaluate the effect of biomarker levels on the risk of developing adverse cardiovascular events. The critical significance level *p* for all statistical procedures was taken equal to 0.05.

RESULTS

Initially, we examined 114 women aged 48.0 (46.0; 52.0) years without concomitant cardiovascular diseases and risk factors who previously received chemotherapy with anthracyclines. After 12 months of follow-up, all patients were retrospectively divided into 2 groups: group 1 (n = 54) included patients with an unfavorable course of ARCD, group 2 (n = 51) encompassed individuals with a favorable course of the disease. Baseline clinical and demographic characteristics of patients did not differ between the groups, except for the levels of MMP-2, MMP-9, sST2, and tetranectin (Table 1). In patients in group 1, MMP-2 concentrations were higher by 8% (p = 0.017), MMP-9 – by 15.7% (p < 0.001), sST2 – by 26.9% (p < 0.001), while tetranectin was lower by 24.5% (p < 0.001).

Table 1

Baseline clinical and demographic characteristics, *Me* (Q_{25}; Q_{75})

Parameter	Group 1, n = 54	Group 2, n = 60	p
Age, years	48 (46; 50)	50 (48; 52)	0.918
CD of doxorubicin, mg / m^2	360 (300; 360)	360 (300; 360)	0.817
Body mass index, kg / m^2	24.7 (21.8; 25.8)	23.0 (21.1; 25.6)	0.781
Polychemotherapy regimen, n (%): – AC; – TAC	 29 (53.7) 25 (46.3)	 36 (60.0) 24 (40.0)	 0.747 0.516
Stage of breast cancer, n (%): – 2A–2B; – 3A–3B	 34 (62.9) 20 (37.1)	 39 (65.0) 21 (35.0)	 0.712 0.716
Heart rate, beats / min	75 (68; 83)	72 (69; 81)	0.615
Systolic blood pressure, mm Hg	115 (112; 124)	115 (110; 120)	0.981
Diastolic blood pressure, mm Hg	70 (68; 79)	72 (69; 80)	0.761
Smoking, n (%)	7 (12.9)	9 (15.0)	0.153
COPD, n (%)	4 (7.4)	5 (8.3)	0.614
Menopause, n (%)	40 (74.1)	43 (71.1)	0.515
GFR, ml / min / m^2	89 (78; 96)	88 (76; 98)	0.192
6MWT, m	554 (451; 574)	558 (461; 598)	0.291
Total cholesterol, mmol / l	5.2 (4.85; 5.7)	5.25 (4.8; 5.7)	0.616
Potassium, mmol / l	4.2 (3.9; 4.7)	4.3 (3.96; 4.56)	0.761
Hemoglobin, g / l	109.5 (100; 117)	108.5 (101; 117.5)	0.173
NT-proBNP, pg / ml	324.7 (263.05; 378.2)	316.6 (260.1; 377.7)	0.832
MMP-2, ng / ml	376.8 (329.5; 426.7)	348.1 (295.3; 381.7)	0.017
MMP-9, ng / ml	23.6 (21.4; 24.6)	19.9 (19.4; 20.7)	< 0.001
TIMP-1, ng / ml	1,191 (998.3; 1,651.1)	1,087 (912; 1,429.1)	0.412
Soluble ST2, ng / ml	41.2 (32.1; 47.6)	30.1 (27.3; 34.9)	< 0.001
Tetranectin, ng / ml	13.9 (12.7; 16.8)	18.4 (16.9; 20.7)	< 0.001
Endothelin-1, ng / ml	6.96 (5.34; 7.61)	6.32 (4.79; 7.03)	0.756
Soluble Fas-L, ng / ml	117.9 (103; 137.5)	109.1 (99.7; 128.3)	0.376
Interleukin-1β, ng / ml	5.4 (4.7; 6.3)	5.9 (4.9; 6.1)	0.541
Tumor necrosis factor-α, ng / ml	5.3 (4.9; 6.2)	5.6 (4.8; 6.7)	0.172

Note: AC-regimen – a combination of doxorubicin and cyclophosphamide; TAC-regimen – a combination of doxorubicin, cyclophosphamide, and docetaxel; CD – cumulative dose; MMP – matrix metalloproteinase; GFR – glomerular filtration rate (according to the CKD-EPI equation); TIMP-1 – tissue inhibitor of metalloproteinase-1; 6MWT – 6-minute walk test; COPD – chronic obstructive pulmonary disease.

Baseline echocardiography parameters were also comparable in both groups. However, after 12 months of follow-up, in group 1, LVEF significantly (p < 0.001) decreased by 8% from 50 (48; 51) to 46 (39; 49.5)%; ESD increased by 3.0% (p = 0.037), EDD rose by 4.0% (p = 0.001), the size of the left atrium increased by 3.1% (0.049), the 6-minute walk test distance decreased (p = 0.045) by 5.1%. In group 2, LVEF significantly (p = 0.005) increased by 7.4% from 50 (47; 53) to 54 (51; 55)%.

Table 2

Dynamics of echocardiography parameters and 6-minute walk test distance, *Me* (Q_{25}; Q_{75})

Parameter	Baseline		*p*	At 12 months		*p*
	Group 1, *n* = 54	Group 2, *n* = 60		Group 1, *n* = 54	Group 2, *n* = 60	
LVEF, %	50 (48; 51)	50 (47; 53)	0.699	46 (39; 49.5)	54 (51; 55)	<0.001
LA, mm	31 (30; 35)	30 (29; 33.3)	<0.001	32 (31; 37)	31 (29.5; 34)	<0.001
EDD, mm	50 (48; 51.0)	48 (45; 50.5)	0.079	52 (48; 54)	48 (45; 49)	<0.001
ESD, mm	36 (34; 38)	36 (33; 38.5)	0.889	37 (36; 39)	34 (32; 36)	<0.001
IVS, mm	10.5 (10; 11)	10.5 (10; 11)	0.783	11 (10; 11)	10.5 (10; 11)	0.041
PWS, mm	11 (10; 12)	11 (10; 12)	0.076	11 (10; 12)	11 (10; 12)	0.008
GLS, %	–16.1 (–14.8; –18.3)	–15.9 (–13.6; –17.8)	0.162	–14.5 (–13.1; –17.2)	–15.1 (–13.3; –17.9)	<0.001
6MWT, m	412 (364; 466)	429 (356; 470)	0.617	391 (332; 412)	476 (400; 517)	<0.001

Note: GLS - global longitudinal strain of the left ventricle; EDD – end-diastolic dimension; ESD – end-systolic dimension; LA – left atrium; IVS – interventricular septum; PWS – posterior wall thickness of the left ventricle; 6MWT – 6-minute walk test; LVEF – left ventricular ejection fraction.

Following the ROC analysis, the concentrations of MMP-2 ≥ 338.8 pg / ml (sensitivity 57%, specificity 78%; AUC = 0.629; $p = 0.025$), MMP-9 ≥ 22.18 pg / ml (sensitivity 89%, specificity 87%; AUC = 0.886; $p < 0.001$), sST2 ≥ 32.4 ng / ml (sensitivity 64%, specificity 70.5%; AUC = 0.691; $p = 0.002$), and tetranectin ≤ 15.4 ng / ml (sensitivity 69%, specificity 72%; AUC = 0.764; $p < 0.001$) were identified as predictors of an adverse course of ARCD during 12 months of follow-up (Fig. 1). When comparing the ROC curves, it was found that the level of MMP-9 ($p = 0.002$) was a more significant predictor (Fig. 2).

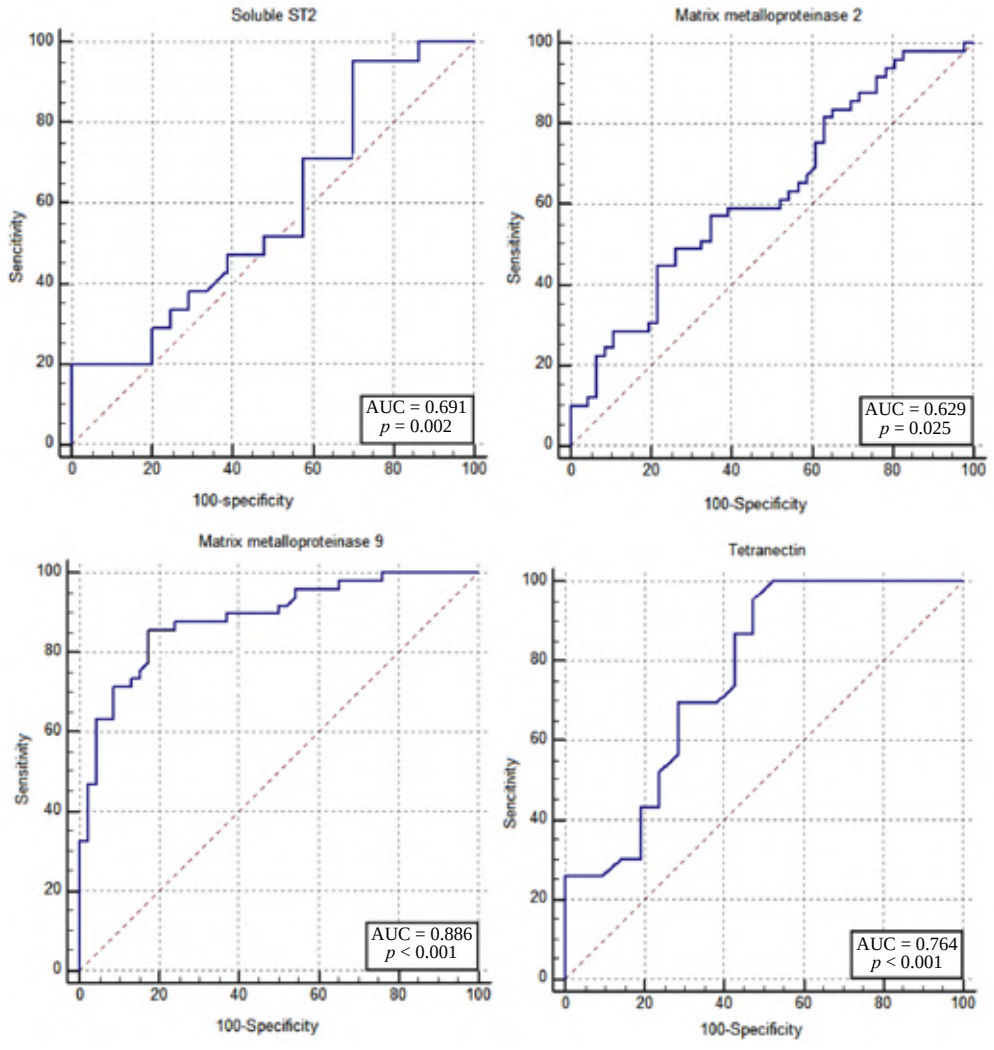

Fig. 1. Sensitivity and specificity of sST2, MMP-2, MMP-9, and tetranectin levels in the risk stratification for an adverse course of ARCD during 12-month follow-up

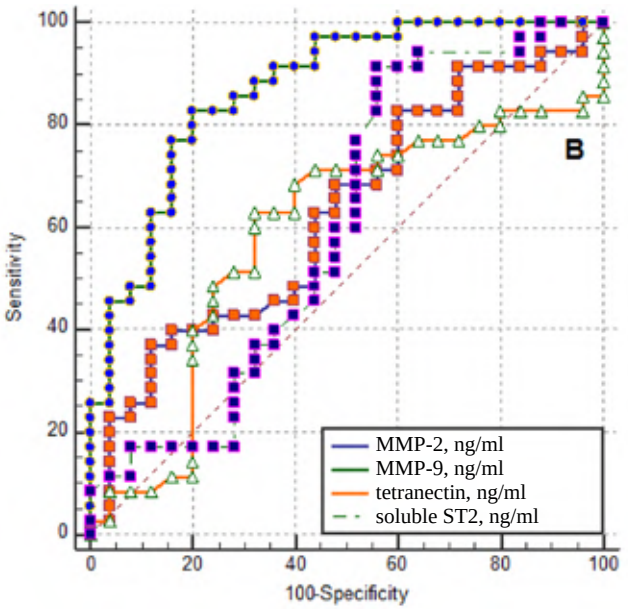

Fig. 2. Comparison of the ROC curves for concentrations of humoral markers in assessing the risk of ARCD progression during 12-month follow-up

Based on the univariate regression analysis, it was found that MMP-2 overexpression ≥ 338.8 ng / ml (OR 1.92; 95% CI 1.09–3.93; $p = 0.003$), MMP-9 ≥ 22.18 ng / ml (OR 4.76; 95% CI 2.98–14.54; $p < 0.0001$), sST2 ≥ 32.4 ng / ml (OR 2.01; 95% CI 1.54–4.18; $p = 0.012$), and a decrease in tetranectin expression ≤ 15.4 ng / ml (OR 2.98; 95% CI 1.23–4.97; $p = 0.001$) were associated with the progression of ARCD during the 12-month follow-up (Table 3).

Table 3

Results of the univariate regression analysis

Variable	OR	95% CI	*p*
MMP-2 (<338.8 / ≥ 338.8 ng / ml)	1.92	1.09–3.93	0.003
MMP-9 (<22.18/ ≥ 22.18 ng /ml)	4.76	2.98–14.54	<0.0001
sST2 (<32.4/ ≥ 32.4 ng /ml)	2.01	1.54–4.18	0.012
Tetranectin (>15.4/ ≤ 15.4 ng / ml)	2.98	1.23–4.97	0.001

DISCUSSION

Doxorubicin, first isolated in the early 1960s, remains one of the most effective anthracycline antibiotics with antitumor activity against BC [2]. However, its use has dose-dependent cardiovascular toxic effects, which lead to changes in cardiomyocytes, vessels, and endothelium, which can potentially lead to the development of severe and irreversible LV dysfunction [2–4, 11]. Some of the triggers for the formation of anthracycline-induced damage to the myocardium are generation of ROS, development of endothelial dysfunction, and inhibition of topoisomerase 2β in cardiomyocytes. Inhibition of topoisomerase 2β by doxorubicin in cardiomyocytes leads to damage to mitochondria and activation of the internal p53-mediated and external Fas-L pathways of apoptosis [12].

In contrast to the triggers of ARCD initiation, triggers of its further progression are myocardial fibrosis and tissue hypoxia, which is most likely provoked by endothelial dysfunction, development of perivascular fibrosis, and induction of apoptosis of cardiomyocytes [13]. It has been proven that myocytolysis, focal myocardial necrosis, focal myocardial fibrosis, and diffuse interstitial pulmonary fibrosis are significantly associated with the use of anthracyclines [14]. Myocardial fibrosis, previously considered as a non-specific sign, is now a major component of anthracycline-induced cardiac remodeling, even after low cumulative doses [15]. Ultimately, direct death of cardiomyocytes and subsequent fibrosis contribute to cardiac dysfunction and a decreased cellular response to hypoxia [16]. In our study, we found that biomarkers of fibrosis, such as sST2, MMP-2, MMP-9, and tetranectin, were involved in further progression of ARCD.

MMPs are present in a healthy heart in an inactive form. MMP activation in patients with heart failure, especially activation of gelatinases MMP-2 and MMP-9, is associated with adverse LV remodeling and dilatation [17]. MMP-2 and MMP-9 are secreted by cardiac fibroblasts, cardiomyocytes, and endothelial and immune cells [18], and their expression can be increased during oxidative stress, endothelial dysfunction, and inflammation [19–21]. Doxorubicin causes a significant increase in the generation of ROS and a rapid rise in the expression and activation of MMPs, which explains the presence and activity of MMP-2 and MMP-9 in ARCD [20]. MMP-2 and probably also MMP-9 are stimulated by oxidative stress at both transcriptional and post-translational levels.

First, oxidative stress enhances MMP-2 transcription, including *de novo* expression of intracellular N-terminal truncated MMP-2, through an alternative promoter in the first intron [22]. Second, intracellular MMP-2 is directly activated by peroxynitrite via S-glutathiolation, opening its catalytic site [23]. MMP-2 is best known not only for proteolyzing extracellular matrix proteins, but it is also active inside cardiomyocytes, where it cleaves sarcomeric proteins [23, 24].

Changes in the extracellular matrix and pronounced transcriptional activation of some specific MMPs in ARCD have been demonstrated in several animal models [14, 25]. In rats, the effects of doxorubicin were associated with stimulation of plasma MMP-2 and MMP-9 activity and tissue expression of MMP-2, which was associated with stimulation of AKT1 activation, superoxide dismutase inhibition, increased superoxide levels, induction of iNOS expression, and caspase-3 activation. [25]. In a model of non-ischemic anthracycline-induced chronic cardiomyopathy in rabbits, the immunohistochemical analysis revealed increased MMP-2 expression in both cardiomyocytes and fibroblasts [14]. An increase in MMP-2, MMP-7, and MMP-9 and a rise in the levels of TIMP-3 and TIMP-4 were noted in the group of children receiving high doses of anthracycline [26].

Our study demonstrated that patients with an unfavorable course of ARCD had higher MMP-2 and MMP-9 levels than patients with favorable outcomes. According to the ROC analysis, concentrations of MMP-2 $\geq$ 338.8 pg / ml (AUC = 0.629; p = 0.025) and MMP-9 $\geq$ 22.18 pg / ml (AUC = 0.886; $p < 0.001$) were identified as predictors of an unfavorable course of ARCD. At the same time, it was found that the concentrations of MMP-9 (p = 0.002) were more significant predictors. These data prove that MMPs are undoubtedly involved in the pathogenesis of ARCD.

Tetranectin, a potential new biomarker for heart failure, is expressed in the myocardium and is associated with cardiac fibrosis. It is suggested that tetranectin is involved in tissue remodeling due to its ability to stimulate plasminogen activation and expression in developing tissues, such as bones and muscles [27]. It was also found in endothelial and epithelial tissues, especially in cells with a high storage function, such as parietal cells and absorptive cells of surface epithelium in the small intestine, exocrine gland ducts, and pseudostratified columnar epithelium in the airways. Mesenchymal cells also exhibit a positive staining reaction for tetranectin, which is most prominent in mast cells, but is also present in some lymphocytes, plasma cells, macrophages, granulocytes, striated and smooth muscle cells, and fibroblasts [28, 29].

For many years, this biomarker has been evaluated in cancer patients and found to be present in the extracellular matrix in some human carcinomas (tumors of the breast, colon, and ovaries), whereas low plasma tetranectin levels have been associated with an increased risk of cancer progression and mortality [30]. In the case of ovarian cancer, a decrease in plasma tetranectin was a stronger predictor of a poor prognosis than a cancer stage [28]. It was shown that serum tetranectin concentrations decrease not only in cancer, but also in non-cardiovascular conditions (sepsis, inflammatory diseases) [31]. Recently, tetranectin has been found to be a potential new diagnostic biomarker for heart failure that accumulates in the myocardium and is associated with cardiac fibrosis. The results of the study showed significant expression of tetranectin in the human myocardium and its correlation with the degree of tissue fibrosis, possibly due to its role in extracellular matrix remodeling [32].

K. McDonald et al. were the first to put forward and prove the hypothesis that a decrease in the level of circulating tetranectin indicates its accumulation in the myocardium to combat myocardial interstitial fibrosis. Therefore, it is possible that a decrease in circulating tetranectin may predispose to the development of heart failure [32]. In another study, higher plasma tetranectin levels were inversely correlated with the risk of atherosclerosis [33]. Y. Chen et al. reported lower serum tetranectin levels in patients with coronary artery disease compared to healthy subjects and hypothesized that atherosclerosis-associated endothelial injury may lead to accumulation of tetranectin in the intima in complexes of atherosclerotic plaques with lipoprotein (a) and / or fibrin, thus reducing its serum levels [34]. We demonstrated that circulating tetranectin levels were reduced to a greater extent in patients with an unfavorable course of ARCD compared to patients with a favorable course of the disease ($p < 0.001$); and its decrease $\leq$ 15.4 ng / ml (AUC = 0.764; $p < 0.001$) was identified as a predictor of an adverse course of ARCD during the 12-month follow-up.

One of the main biomarkers that signals the presence and severity of adverse cardiac remodeling and tissue fibrosis that occur with myocardial infarction, acute coronary syndrome, or progression of chronic heart failure is sST2 [35]. In patients with ARCD, sST2 levels most likely reflect periarteriolar fibrosis, which may result from endothelial dysfunction. ROS generation, apoptosis, and endothelial dysfunction may contribute to periarteriolar fibrosis and microvascular rarefaction, leading to sST2 overexpression [36]. Following the ROC analysis, the concentration of sST2 $\geq$ 32.4 ng / ml (AUC = 0.691; p = 0.002) was also identified as a predictor of an unfavorable course of ARCD during 12 months of follow-up.

The best option for predicting the development of LV dysfunction from the point of view of a cardiologist is to develop multi-biomarker panels, which would be used in specially designed system algorithms [37].

CONCLUSION

Thus, it was found that overexpression of MMP-2, MMP-9, and sST2 and hypoexpression of tetranectin can be considered as non-invasive markers for assessing the risk of ARCD progression. The levels of MMP-9 are the most significant predictors of ARCD progression ($p = 0.002$).

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Grakova E.V. – conception and design of the study, coordination of the research, drafting of the article, final approval of the manuscript for publication. Kopeva K.V. – statistical processing of the data, critical revision of the manuscript for important intellectual content, final approval of the manuscript for publication. Shilov S.N. – compilation of the database, critical revision of the manuscript for important intellectual content, final approval of the manuscript for publication. Bobyleva E.T. – review of the literature, acquisition and interpretation of the clinical data, compilation of the database, final approval of the manuscript for publication. Berezikova E.N – acquisition and interpretation of the clinical data, compilation of the database, final approval of the manuscript for publication. Kalyuzhin V.V. – review of the literature, interpretation of the data, drafting of the article, final approval of the manuscript for publication. Teplyakov A.T. – coordination of the research, drafting of the article, final approval of the manuscript for publication

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