



DOI: 10.20514/2226-6704-2025-15-5-336-345

УДК 615.06, 616-006.441, 616.12-008

EDN: GZAQWX



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## МАРКЕРЫ, ОПРЕДЕЛЯЮЩИЕ РИСК РАЗВИТИЯ СЕРДЕЧНО-СОСУДИСТОЙ ТОКСИЧНОСТИ НА ФОНЕ ПРОВОДИМОЙ ПРОТИВООПУХОЛЕВОЙ ИММУНОХИМИОТЕРАПИИ

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## Markers Determining the Risk of Cardiovascular Toxicity Against the Background of Antitumor Immunochemotherapy

### Резюме

**Введение.** Злокачественные новообразования занимают лидирующее место среди причин смертности населения. Несмотря на то, что противоопухолевое лечение способно значительно продлить жизнь пациентам онкологического профиля, оно продолжает оказывать токсический эффект на органы и системы. Не стали исключением пациенты с неходжкинскими лимфомами индолентного типа, получающие антрациклин-содержащие схемы терапии, которые являются ведущими режимами лечения в виду доступности с фармакологической и финансовой стороны на территории Российской Федерации. **Цель исследования.** Выявить клинические, лабораторные и инструментальные показатели, оцениваемые через 3 месяца лечения, определяющие риск развития сердечно-сосудистой токсичности на фоне 6-месячной противоопухолевой иммунохимиотерапии по схеме R-СНОР у пациентов с индолентным типом неходжкинских лимфом. **Материалы и методы.** На базах лечебных учреждений города Самара проводилось наблюдательное исследование «случай-контроль» за пациентами с диагнозом В-клеточная фолликулярная лимфома, которым показано проведение 6 курсов иммунохимиотерапии в режиме R-СНОР. Пациенты были разделены на две группы: основную n=21 (16 (76,2%) мужчин, средний возраст 55,2(9,8) лет) с верифицированной сердечно-сосудистой токсичностью и контрольную n=51 (21 (41,2%) мужчина, средний возраст 53,7(13,6) лет) без нее. В ходе лечения целевые показатели оценивались в 2 этапа: на старте и после 3 курсов терапии. В ходе лечения целевые показатели оценивались в два этапа: на старте и после трех курсов терапии. **Результаты.** На старте исследования пациенты с верифицированной сердечно-сосудистой токсичностью имели большие значения индекса массы тела (ИМТ), конечно-систолического размера (КСР), конечно-диастолического размера (КДР), конечно-систолического объема (КСО), конечно-диастолического объема (КДО), объема левого и правого предсердий, дистального диаметра выносящего тракта по сравнению с контрольной группой ( $p < 0,05$ ). Также у пациентов с кардиоваскулярной токсичностью в процессе лечения статистически значимо удлинялся QTc с 360 (245,0; 411,0) до 412 (279,0; 450,0) мсек.,  $p=0,032$ ; увеличивалась концентрация N-концевой пропептид натрийуретического гормона В-типа (NT-proBNP) с 77 (67,0; 109,0) до 110 (75,0; 222,0) мг/мл,  $p=0,032$ ; а также снижалось значение продольной систолической деформации левого желудочка (ПД ЛЖ) с -21,1 (19,7; 22,4) до -17,7 (15,1; 21,0) %,  $p=0,004$ . **Заключение.** Расширение диагностических протоколов в рамках сердечно-сосудистой токсичности среди пациентов с В-клеточной фолликулярной лимфомой позволяет своевременно оптимизировать тактику ведения пациентов онкогематологического профиля.

**Ключевые слова:** сердечно-сосудистая токсичность, кардиотоксичность, кардиоонкология, лимфомы, индолентные лимфомы

### Конфликт интересов

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

### Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

## Соответствие принципам этики

В настоящем исследовании представлена отселектированная часть данных клинической апробации, одобренной к реализации Министерством здравоохранения Российской Федерации от 2022 года «Метод раннего выявления кардиотоксичности у пациентов с индолентными неходжкинскими лимфомами» (№ 2021-1-3, опубликован 09.04.21, <https://minzdrav.gov.ru/poleznye-resursy/protokoly-klinicheskoy-aprobatsii/realizuemye-protokoly-klinicheskoy-aprobatsii-2021-god-vzroslye/realizuemye-protokoly-klinicheskoy-aprobatsii-2021-god-vzroslye>). Все пациенты, включенные в настоящую работу, подписали информированное добровольное согласие.

Статья получена 16.11.2024 г.

Одобрена рецензентом 20.02.2025 г.

Принята к публикации 05.06.2025 г.

**Для цитирования:** Гимранова Р.Ф., Гиматдинова Г.Р., Данилова О.Е. и др. МАРКЕРЫ, ОПРЕДЕЛЯЮЩИЕ РИСК РАЗВИТИЯ СЕРДЕЧНО-СОСУДИСТОЙ ТОКСИЧНОСТИ НА ФОНЕ ПРОВОДИМОЙ ПРОТИВООПУХОЛЕВОЙ ИММУНОХИМИОТЕРАПИИ. Архивъ внутренней медицины. 2025; 15(5): 336-345. DOI: 10.20514/2226-6704-2025-15-5-336-345. EDN: GZAQWX

## Abstract

**Introduction.** Malignant neoplasms occupy a leading place among the causes of death in the population. Despite the fact that antitumor treatment can significantly prolong the life of cancer patients, it continues to have a toxic effect on organs and systems. Patients with non-Hodgkin's lymphoma of the indolent type receiving anthracycline-containing therapy regimens, which are the leading treatment regimens due to their availability from the pharmacological and financial side in the Russian Federation, are no exception. **The purpose of the study.** To identify clinical, laboratory and instrumental indicators, assessed after 3 months of treatment, determining the risk of developing cardiovascular toxicity against the background of 6-month antitumor immunochemotherapy according to the R-CHOP scheme in patients with indolent type of non-Hodgkin's lymphomas. **Materials and methods.** An observational case-control study was conducted on the bases of medical institutions in Samara for patients diagnosed with B-cell follicular lymphoma, who were shown to undergo 6 courses of immunochemotherapy in the R-CHOP mode. The patients were divided into two groups: the main group n=21 (16 (76.2%) men, average age 55.2(9.8) years) with verified cardiovascular toxicity and the control group n=51 (21 (41.2%) men, average age 53.7(13.6) years) without her. During treatment, the targets were evaluated in two stages: at the start and after three courses of therapy. **Results.** At the start of the study, patients with verified cardiovascular toxicity had higher values of BMI, CDR, CDR, volume of the left and right atria, and distal diameter of the excretory tract compared with the control group ( $p < 0.05$ ). Also, in patients with cardiovascular toxicity, the QTc significantly prolonged during treatment from 360 (245.0; 411.0) to 412 (279.0; 450.0) msec.,  $p=0.032$ ; the concentration of NT-proBNP increased from 77 (67.0; 109.0) to 110 (75.0; 222.0) mg/ml,  $p=0.032$ ; and the value of GLS LV decreased from -21.1 (19.7; 22.4) to -17.7 (15.1; 21.0)%,  $p=0.004$ . **Conclusion.** The expansion of diagnostic protocols within the framework of cardiovascular toxicity among patients with B-cell follicular lymphoma allows timely optimization of management tactics for patients with oncohematological profile.

**Key words:** cardiovascular toxicity, cardiotoxicity, cardioncology, lymphomas, indolent lymphomas

## Conflict of interests

The authors declare no conflict of interests

## Sources of funding

The authors declare no funding for this study

## Conformity with the principles of ethics

This study presents a selected part of the data from a clinical trial approved for implementation by the Ministry of Health of the Russian Federation in 2022 "Method for early detection of cardiotoxicity in patients with indolent non-Hodgkin's lymphomas" (No. 2021-1-3, published on 04/09/21, <https://minzdrav.gov.ru/poleznye-resursy/protokoly-klinicheskoy-aprobatsii/realizuemye-protokoly-klinicheskoy-aprobatsii-2021-god-vzroslye/realizuemye-protokoly-klinicheskoy-aprobatsii-2021-god-vzroslye>). All patients included in this work signed informed voluntary consent.

Article received on 16.11.2024

Reviewer approved 20.02.2025

Accepted for publication on 05.06.2025

**For citation:** Gimranova R.F., Gimatdinova G.R., Danilova O.E. et al. Markers Determining the Risk of Cardiovascular Toxicity Against the Background of Antitumor Immunochemotherapy. The Russian Archives of Internal Medicine. 2025; 15(5):336-345. DOI: 10.20514/2226-6704-2025-15-5-336-345. EDN: GZAQWX

CVT — cardiovascular toxicity; LVEF — left ventricular ejection fraction; LVLS — left ventricular longitudinal systolic deformity; TTE — transthoracic echocardiography; ECG — electrocardiogram; NT-proBNP — N-terminal pro-B-type natriuretic peptide; BMI — body mass index; QTc — corrected QT interval; HR — heart rate; ESD — end-systolic dimension; EDD — end-diastolic dimension; ESV — end-systolic volume; EDV — end-diastolic volume; CPK — creatine phosphokinase

## Introduction

Malignancies and cardiovascular diseases are the two leading causes of death globally. Advancements in treatment methods definitely increase the life expectancy and quality of life of cancer patients. Nevertheless, the rate of validated antineoplastic treatment complications continues to rise significantly. Cardiovascular toxicity (CVT) is

one of the most common adverse effects [1]. This term unites various adverse cardiovascular events that emerge during the main disease treatment [2]. The spectrum of cardiovascular effects of antineoplastic agents is wide and includes heart failure, arrhythmia, hypertension, cardiomyopathy, inflammatory myocardial and valvular lesions, vascular events (arterial thrombosis, venous

thromboembolism), myocardial ischemia (acute coronary syndrome, angina), etc. [3]. CVT is mainly caused by effects not only on neoplastic, but also on normal non-target cells in the cardiovascular system [4].

Molecular mechanisms of adverse cardiovascular events of the drug therapy are variable. The clinical variability directly depends on the specific type of the agent used. The pathogenesis of CVT may be based on oxidative stress, topoisomerase 2- $\beta$  inhibition in cardiomyocytes, inflammation, endothelial dysfunction, apoptosis, impaired  $\text{Ca}^{2+}$  homeostasis, mitochondrial dysfunction, deoxyribonucleic acid (DNA) damage, enhanced levels of various circulating microribonucleic acids, altered function of potential-dependent potassium channels, etc. [3]. Profound knowledge about the basic CVT mechanisms can help with the early detection and management of adverse events [5]. The rate of cardiac complications defines the required thorough monitoring and combined approach of physicians of different specialties to the management of target patients [6]. CVT of antineoplastic treatment methods is one of the main issues to be solved [7].

## Materials and Methods

### *Study Design*

A case-control study was arranged in therapeutic institutions of Samara (Federal State Budget Educational Institution of Higher Education “Samara State Medical University”, Ministry of Health of Russia; Samara Regional Clinical Oncological Dispensary) during the period from January 2022 until September 2023. Clinical, laboratory, and instrumental CVT markers were analyzed during the antineoplastic treatment (R-CHOP protocol) in patients with indolent non-Hodgkin lymphomas. A total of 72 patients (37 (51.4%) males, mean age 54.4 (11.2) years) (21 patients in the main group, mean age 55.2 (9.8) years, 16 (76.2%) males; 51 patients in the control group, mean age 53.7 (13.6) years, 21 (41.2%) males) with the confirmed diagnosis of B-cell follicular non-Hodgkin lymphoma (cytology type 1-2) were included into the study; those patients were administered 6 immunochemotherapy cycles (R-CHOP protocol). The following treatment was administered: Rituximab 375 mg/m<sup>2</sup> IV drip (Day 0 or 1), Doxorubicin 50 mg/m<sup>2</sup> IV drip (Day 1), Cyclophosphamide 750 mg/m<sup>2</sup> IV drip (Day 1), Vincristine 1.4 mg/m<sup>2</sup> for a maximum total dose of 2 mg (Day 1), Prednisolone 100 mg orally (Days 1–5); the treatment was resumed on Day 22.

The duration of patient follow-up was 180 (8) days. The primary endpoint presumed the cardiac toxicity detection. Secondary endpoints included changes in the laboratory (NT-proBNP, troponin) and instrumental (LVEF, GLS) parameters.

Inclusion criteria: patients over 18 years of age; confirmed diagnosis; indications for antineoplastic immunochemotherapy (R-CHOP protocol); no prior history of cardiovascular conditions; negative echocardiographic stress test (stress echo); signed informed consent form.

Non-inclusion criteria: age under 18 years; any concomitant diseases (including cardiovascular ones); positive echocardiographic stress test.

Exclusion criteria: complications which make it impossible to use scheduled therapy (R-CHOP antineoplastic treatment); emergence of conditions and/or diseases which are among non-inclusion criteria; patient refusal to undergo further examination.

**Study objective:** detecting clinical, laboratory, and instrumental parameters evaluated after 3 treatment months that determine the risk of cardiovascular toxicity during the 6-month antineoplastic immunochemotherapy (R-CHOP protocol) in patients with indolent non-Hodgkin lymphomas.

## Materials and Methods

All patients included into the study were divided into 2 groups: 21 patients in the main group (with CVT manifestations), mean age 55.2 (9.8) years, 16 (76.2%) males; and 51 patients in the control group (without CVT), mean age 53.7 (13.6) years, 21 (41.2%) males. Patients were divided into groups based on the following criteria: patients were included into the main follow-up group with the left ventricular ejection fraction (LVEF) decrease > 10% from the baseline level or below 53% in absolute values and/or with the left ventricular longitudinal systolic deformity (LVLS) > 12% from the baseline level according to CVT criteria from the Consensus of Russian Experts on the Prevention, Diagnosis, and Treatment of CVT Resulting from Antineoplastic Treatment, 2021 [8]. Patients without impaired myocardial contractility based on transthoracic echocardiography (TTE) were included into the control group.

*Inclusion criteria:* patients over 18 years of age; confirmed diagnosis; indications for antineoplastic immunochemotherapy (R-CHOP protocol); no prior history of cardiovascular conditions; negative echocardiographic stress test (stress echo); signed informed consent form.

*Non-inclusion criteria:* age under 18 years; any concomitant diseases (including cardiovascular ones); positive echocardiographic stress test.

*Exclusion criteria:* complications which make it impossible to use scheduled therapy (R-CHOP antineoplastic treatment); emergence of conditions and/or diseases which are among non-inclusion criteria; patient refusal to undergo further examination.

**Table 1.** Clinical characteristics of patients depending on the presence of cardiotoxicity

Indicator	Absence of cardiotoxicity (n=51)	The presence of cardiotoxicity (n=21)	p-value
Age, full years, M (SD).	53,7 (13,6) *	55,2 (9,8) *	0,597
BMI, kg/m <sup>2</sup> Me (IQR)	22,1 (20,9;24,4)	24,2 (22,1;27,4)	0,015
Gender, m/w n (%)	21 (41,2%) / 30 (58,8%)	16 (76,2%) / 5 (23,8%)	0,007
Tobacco, n (%)	13 (25,5%) / 38 (74,5%)	10 (47,6%) / 11 (52,4%)	0,095
Arterial hypertension, n (%)	0 (0,0%)	0 (0,0%)	0,999
Coronary artery disease, n (%)	0 (0,0%)	0 (0,0%)	0,999
Lung disease, n (%)	0 (0,0%)	0 (0,0%)	0,999

Abbreviations. BMI is the body mass index

The duration of patient follow-up was 180 (8) days. The primary endpoint presumed the search for factors associated with the risk of cardiotoxicity.

Patients from the main and control group underwent the interrogation for complaints, medical and life history; physical examination; electrocardiography (ECG); TTE with LVEF and LVLS; tests for several biochemical markers (total cholesterol, creatine phosphokinase, myoglobin, troponin T, C-reactive protein, N-terminal pro-B-type natriuretic peptide (NT-proBNP)). The study was arranged in two periods — before starting the treatment and after three antineoplastic immunochemotherapy cycles. The information obtained was recorded in the case report form. During the study, TTE was arranged by the same echocardiography specialist using the Philips EPIQ CVx device (Germany).

See clinical characteristics of patients based on the CVT presence in Table 1.

A selected part of clinically tested data approved by the Ministry of Health of Russia in 2022 (Method of Early Cardiac Toxicity Detection in Patients with Indolent Non-Hodgkin Lymphomas; No. 2021-1-3, published on April 9, 2021, <https://minzdrav.gov.ru/poleznye-resursy/protokoly-klinicheskoy-aprobatsii/realizuemye-protokoly-klinicheskoy-aprobatsii-2021-god-vzroslye/realizuemye-protokoly-klinicheskoy-aprobatsii-2021-god-vzroslye>) is presented in the study. All patients included into the study signed the informed consent.

The results obtained were statistically processed using the SPSS 26 Software Package (USA, IBM SPSS Statistics 26.0.0.0). The distribution normality was assessed using the Shapiro-Wilk test ( $n < 50$ ) or Kolmogorov-Smirnov test ( $n > 50$ ). Data were evaluated using parametric statistical methods (for the normally distributed data) or non-parametric statistics (for those distributed differently than normal). Depending on the distribution, quantitative variables were presented as mean arithmetics and standard deviations (M (SD)), medians (Me), 25th and 75th percentiles (Me(Q1;Q3)) with the distribution different from normal; qualitative parameters were described as an absolute number of patients with proportions (n (%)). Among non-parametric statistic

methods for two unrelated sets, the Student t-test was used for normal distribution of an attribute, the Mann-Whitney U test was used for non-normal distribution, while the Wilcoxon rank sum test was used for related variables in two groups. Significance of differences was assessed using the contingency tables: if the number of observations in any cell of this table was at least 10, chi-square was used; for the number of observations from 5 to 9, Yates correction was applied; if the number of observations was below 5 in any cell, then the Fisher's exact test was used.

The model was constructed using the binary logistic regression, calculating the odds ratio (OR) for the parameters included. ROC-analysis was arranged to calculate the specificity, prognostic value, and diagnostic significance of the model.

Differences were statistically significant at  $p < 0.05$ .

## Results and Discussion

Patients were comparable by age, histological morphology of the disease, treatment administered, and tobacco smoking (Table 1). According to the inclusion/non-inclusion/exclusion criteria, the patients observed did not have concomitant cardiovascular diseases requiring the use of drug products at the start of treatment. According to the follow-up results, patients with the validated CVT had higher body mass indices (BMIs). Females (30 (58.8%) vs. 21 (41.2%),  $p = 0.007$ ) were more common among patients without CVT included into the study.

Laboratory and instrumental investigations were arranged twice — before treatment and after 3 treatment months (which corresponds to three antineoplastic treatment cycles). When comparing electrocardiogram parameters (Table 2) between groups, statistically significant differences were reported for the corrected QT interval (QTc) values. It was longer in patients with CVT after 3 drug therapy cycles ( $p = 0.032$ ). Based on literature data, the experimental study of George M Bodziock et al. (2023) demonstrated that African green monkeys administered doxorubicin (being part of the target antineoplastic therapy in patients analyzed) also had

**Table 2.** *Electrocardiographic characteristics of patients depending on the presence of cardiotoxicity*

Indicator, Me (IQR)	Absence of cardiotoxicity (n=51)	The presence of cardiotoxicity (n=21)	p-value
HR_V <sub>1</sub> , /min	70,0 (59,0;75,0)	75,0 (69,0;84,0)	0,033
HR_V <sub>2</sub> , /min	74,0 (63,0;79,0)	74,0 (71,0;84,0)	0,155
	p=0,431	p=0,750	
PQ_V <sub>1</sub> , msec	147,0 (110,0;190,0)	120,0 (100,0;150,0)	0,087
PQ_V <sub>2</sub> , msec	144,0 (110,0;188,0)	140,0 (100,0;170,0)	0,260
	p=0,952	p=0,155	
QRS_V <sub>1</sub> , msec	90,0 (80,5;100,0)	96,0 (90,0;100,0)	0,288
QRS_V <sub>2</sub> , msec	90,0 (80,0;105,0)	95,0 (87,0;100,0)	0,370
	p=0,888	p=0,604	
QTc_V <sub>1</sub> , msec	333,0(218,0;384,5)	360,0(245,0;411,0)	0,193
QTc_V <sub>2</sub> , msec	342,0(265,5;411,0)	412,0(279,0;450,0)	0,032
	p=0,080	p=0,085	

**Abbreviations.** Heart rate is the heart rate. V1 — before the start of treatment, V2 — after 3 courses of antitumor treatment according to the R-CHOP scheme. QTc is the corrected QT interval

**Table 3.** *Echocardiographic parameters of patients depending on the presence of cardiotoxicity*

Indicator, Me (IQR)	Absence of cardiotoxicity (n=51)	The presence of cardiotoxicity (n=21)	p-value
ESD_V <sub>1</sub> , mm	30,0 (27,0;32,8)	32,1 (32,0;39,0)	0,001
ESD_V <sub>2</sub> , mm	29,0 (26,5;32,0)	35,0 (32,0;39,0)	<0,001
	p=0,581	p=0,669	
EDD_V <sub>1</sub> , mm	45,0 (37,5;48,0)	49,0 (41,0;52,0)	0,028
EDD_V <sub>2</sub> , mm	44,0 (39,0;47,0)	46,0 (40,0;51,0)	0,102
	p=0,012	p=0,131	
LVMi_V <sub>1</sub> , g/m <sup>2</sup>	74,0 (66,0;79,0)	89,0 (77,0;100,0)	<0,001
LVMi_V <sub>2</sub> , g/m <sup>2</sup>	72,0 (65,0;79,0)	81,0 (74,0;102,0)	0,002
	p=0,187	p=0,569	
EDVI_V <sub>1</sub> , ml	86,0 (71,0;97,0)	98,0 (90,0;114,0)	0,013
EDVI_V <sub>2</sub> , ml	84,0 (68,5;97,0)	98,0 (78,0;111,0)	0,052
	p=0,125	p=0,355	
ESV_V <sub>1</sub> , ml	44,0 (31,5;49,0)	59,0 (47,0;71,0)	0,001
ESV_V <sub>2</sub> , ml	44,0 (32,0;49,0)	55,0 (48,0;71,0)	0,001
	p=0,162	p=0,229	
LVEF_V <sub>1</sub> , %	58,0 (53,0;63,0)	55,0 (52,0;63,0)	0,49
LVEF_V <sub>2</sub> , %	57,0 (53,0;61,0)	53,0 (44,0;61,0)	0,133
	p=0,301	p=0,164	
LAV_V <sub>1</sub> , ml/m <sup>2</sup>	29,0 (27,0;32,0)	32,0 (31,0;35,0)	0,002
LAV_V <sub>2</sub> , ml/m <sup>2</sup>	29,0 (26,0;31,0)	32,0 (28,0;34,0)	0,013
	p=0,143	p=0,039	
PDOT BT_V <sub>1</sub> , mm	29,0 (27,0;32,0)	30,0 (29,0;33,0)	0,146
PDOT BT_V <sub>2</sub> , mm	29,0 (27,0;32,0)	31,0 (28,0;33,0)	0,323
	p=0,530	p=0,755	
DDOT BT_V <sub>1</sub> , mm	22,0 (20,0;23,5)	25,0 (22,0;28,0)	0,002
DDOT BT_V <sub>2</sub> , mm	22,0 (20,0;24,0)	24,0 (22,0;28,0)	0,004
	p=0,910	p=0,806	
LAV_V <sub>1</sub> , ml/m <sup>2</sup>	24,0 (21,0;27,0)	29,0 (25,0;32,0)	0,002
LAV_V <sub>2</sub> , ml/m <sup>2</sup>	25,0 (21,0;28,0)	27,0 (24,0;30,0)	0,091
	p=0,169	p=0,637	
PA_V <sub>1</sub> , mmHg	22,0 (17,0;27,0)	25,0 (22,0;28,0)	0,166
PA_V <sub>2</sub> , mmHg.	22,0 (14,5;26,5)	24,0 (21,0;29,0)	0,166
	p=0,514	p=0,702	
GLS LV_V <sub>1</sub> , %	-21,0 (20,5;22,0)	-21,1 (19,7;22,4)	0,921
GLS LV_V <sub>2</sub> , %	-21,5 (19,3;22,1)	-17,7 (15,1;21,0)	<0,001
	p=0,935	p=0,004	

**Note.** GLS LV — global longitudinal strain left ventricle, глобальная продольная систолическая деформация левого желудочка. V1 — before the start of treatment, V2 — after 3 courses of antitumor treatment according to the R-CHOP scheme. ESD — end-systolic dimension, ESV- end-systolic volume, EDVI — end-diastolic volume, EDD — end-diastolic dimension, LVMi — left ventricular mass index, LVEF — left ventricular ejection fraction, LA — left atrium, RA — right atrium, PDOT — proximal diameter outflow tract, DDOT — distal diameter outflow tract, PA — pulmonary artery

statistically significantly prolonged QT ( $p = 0.002$ ) and QTc ( $p = 0.009$ ) intervals with the concomitant absence of significant alterations in the heart rate (HR) or QRS duration ( $p = 0.92$  and  $p = 0.47$ , respectively) [9].

Echocardiography parameters of patients (Table 3) also demonstrated statistically significant discrepancies when comparing parameters between groups. Patients with validated CVT during follow-up had higher values of the left ventricular end-systolic dimension (ESD) ( $p = 0.001$ ), end-diastolic dimension (EDD) ( $p = 0.028$ ), end-systolic volume (ESV) ( $p = 0.001$ ), end-diastolic volume (EDV) ( $p = 0.013$ ), left and right atrial volumes ( $p = 0.002$ ), distal diameter of the left ventricular outflow tract ( $p = 0.002$ ) at the start of treatment. Contractility was not assessed in the LVEF and LVLSD analysis. The latter parametric parameter demonstrated the highest diagnostic significance. LVLSD in the main group patients significantly decreased in accordance with the treatment from  $|21.1 (19.7;22.4)|$  to  $|17.7 (15.1;21.0)|$  ( $p = 0.004$ ), thus confirming CVT.

Similar LVLSD alterations were described in 2023 by Liu Z et al. in the breast cancer patients after 3 months of antineoplastic therapy [10]. Chang H. et al. (2021) analyzed patients with lymphomas administered moderate or low doses of cardiotoxic drug therapy; the study demonstrated decreased myocardial contractility based on TTE speckle-tracking [11].

It is important to note that TTE was the main instrumental investigation which formed the basis for dividing

patients into groups. The targeted imaging assessment of the cardiovascular system function that presumes recording quantitative and qualitative alterations and is supplemented by the GLS LV analysis provides a highly precise diagnosis. With that, the addition of speckle-tracking method to the standard protocol helps the physicians to detect changes in the myocardial function with higher sensitivity than traditional diastolic and systolic functional measurements, including LVEF. It helps to evaluate myocardial deformity as a change in the myocardial segment length relative to its baseline level and the deformity rate (deformity per time unit) in percent. Both parameters can be potentially used in the diagnosis and monitoring of subclinical alterations. Regional and global deformity measurements may independently predict results not only in patients with the confirmed CVT, but also in patients with other clinical conditions.

Laboratory biomarkers that were analyzed twice are reflected in Table 4. Based on the results obtained, patients with the validated CVT at the start of treatment had significantly higher levels of total cholesterol, creatine phosphokinase (CPK), and CPK-MB fraction ( $p = 0.003$ ,  $p = 0.033$ , and  $p < 0.001$ , respectively). After treatment completion, statistically significantly higher myoglobin levels were reported in patients with CVT ( $p = 0.014$ ) vs. patients without CVT. NT-proBNP levels demonstrate active susceptibility to the toxic cardiovascular effects of antineoplastic treatment. This biomarker had a high statistical significance during the whole study.

**Table 4.** Laboratory parameters depending on the presence of cardiotoxicity

Indicator	Absence of cardiotoxicity (n=51)	The presence of cardiotoxicity (n=21)	p-value
TC_V <sub>1</sub> , mmol/l	4,1 (3,41;4,45)	4,7 (4,14;5,2)	0,003
TC_V <sub>2</sub> , mmol/l	4,1 (3,19;4,75)	5,0 (4,14;5,5)	0,008
	p=0,955	p=0,542	
CPK_V <sub>1</sub> , E/l	84,0 (69,0;107,0)	110,0 (97,0;114,0)	0,033
CPK_V <sub>2</sub> , E/l	79,0 (64,0;99,0)	100,0 (71,0;112,0)	0,045
	p=0,076	p=0,339	
CPK(MB)_V <sub>1</sub> , E/l	16,0 (12,0;21,0)	22,0 (21,0;25,0)	<0,001
CPK(MB)_V <sub>2</sub> , E/l	15,0 (11,0;21,0)	21,0 (21,0;27,0)	0,001
	p=0,854	p=0,936	
Myoglobin_V <sub>1</sub> , mkg/l	39,0 (27,0;50,5)	47,0 (37,0;51,0)	0,152
Myoglobin_V <sub>2</sub> , mkg/l	36,0 (23,5;44,5)	49,0 (37,0;59,0)	0,014
	p=0,007	p=0,653	
Troponin_V <sub>1</sub> , pg/ml	10,9 (7,07;14,9)	10,1 (8,7;12,4)	0,771
Troponin_V <sub>2</sub> , pg/ml	11,2 (8,6;14,3)	12,2 (8,3;17,4)	0,295
	p=0,415	p=0,390	
CRP_V <sub>1</sub> , mg/l	3,1 (1,06;5,35)	2,2 (0,5;4,3)	0,111
CRP_V <sub>2</sub> , mg/l	3,0 (2,0;4,3)	1,7 (0,6;4,4)	0,068
	p=0,904	p=0,779	
NT-proBNP_V <sub>1</sub> , mg/ml	74,0 (46,5;100,5)	77,0 (67,0;109,0)	0,301
NT-proBNP_V <sub>2</sub> , mg/ml	57,0 (41,5;74,0)	110,0 (75,0;222,0)	<0,001
	p=0,019	p=0,032	

Note. V1 — before the start of treatment, V2 — after 3 courses of antitumor treatment according to the R-CHOP scheme. OH — total cholesterol, CK — creatine phosphokinase, C-RB — C-reactive protein, NT-proBNP — N-terminal propeptide of the B-type natriuretic hormone

NT-proBNP increased in correlation with the cycles of administered cardiotoxic treatment in the group of patients with CVT from 77.0 (67.0;109.0) mg/mL to 110.0 (75.0;222.0) mg/mL. Fei Fei Gong et al. (2021) described cases of altered NT-proBNP levels in various malignancies [12]. Besides, in the 2024 study of Ehrhardt MJ et al. NT-proBNP is proposed for use in the prediction of the risk of cardiomyopathy associated with anti-neoplastic therapy in children [13].

We have developed a prognostic model for CVT arising during 6 months of therapy (R-CHOP protocol), depending on clinical and diagnostic factors assessed before the therapy using the binary logistic regression method. The observed dependence can be described with the following equation:

$$P = 1 / (1 + e^{-z}) * 100 \%$$

$$z = -7.009 - 0.763 * X_{GLS_{LV}} + 0.204 * X_{ESV} - 0.052 * X_{EDV} + 0.326 * X_{ESS} + 0.012 * X_{NT-proBNP} - 0.034 * X_{troponin} + 0.231 * X_{CPK(MB)}$$

where

- P is the confirmed cardiac toxicity (%),
- $X_{GLS_{LV}}$  is the value of global longitudinal strain, %,
- $X_{ESV}$  is the end-systolic volume value, mL,
- $X_{EDV}$  is the end-diastolic volume value, mL,
- $X_{troponin}$  is the troponin value, pg/mL,
- $X_{CPK(MB)}$  is the creatine phosphokinase MB fraction value, U/L,
- $X_{ESD}$  is the end-systolic diameter value, mm,
- $X_{NT-proBNP}$  is the natriuretic peptide value.

The resulting regression model is statistically significant ( $p < 0.001$ ). Taking into account the Nagelkerke R square, 80.6 % of cardiac toxicity dispersion is due to the factors included into the model. Based on the regression coefficient values, ESV, ESD, NT-proBNP, CPK(MB) values directly correlate with the presence of CVT, while LVLS, EDV, troponin levels inversely correlate with that. Characteristics of each factor are presented in Table 5.

The threshold value of logistic function P was 50 %.

If P was over 50 %, the risk of CVT was considered high.

If P was below 50 %, the risk of CVT was low.

The sensitivity and specificity of the model with the mentioned threshold value were 90.5 % and 98.0 %, respectively. The positive and negative prognostic values were 95.0 % and 96.2 %, respectively.

The area under ROC curve, which corresponded to the relationship between the presence of cardiac toxicity and the value of the logistic regression function, was 0.963 (0.032) with 95 % CI of 0.901–1.0. The resulting model was statistically significant ( $p < 0.001$ ).

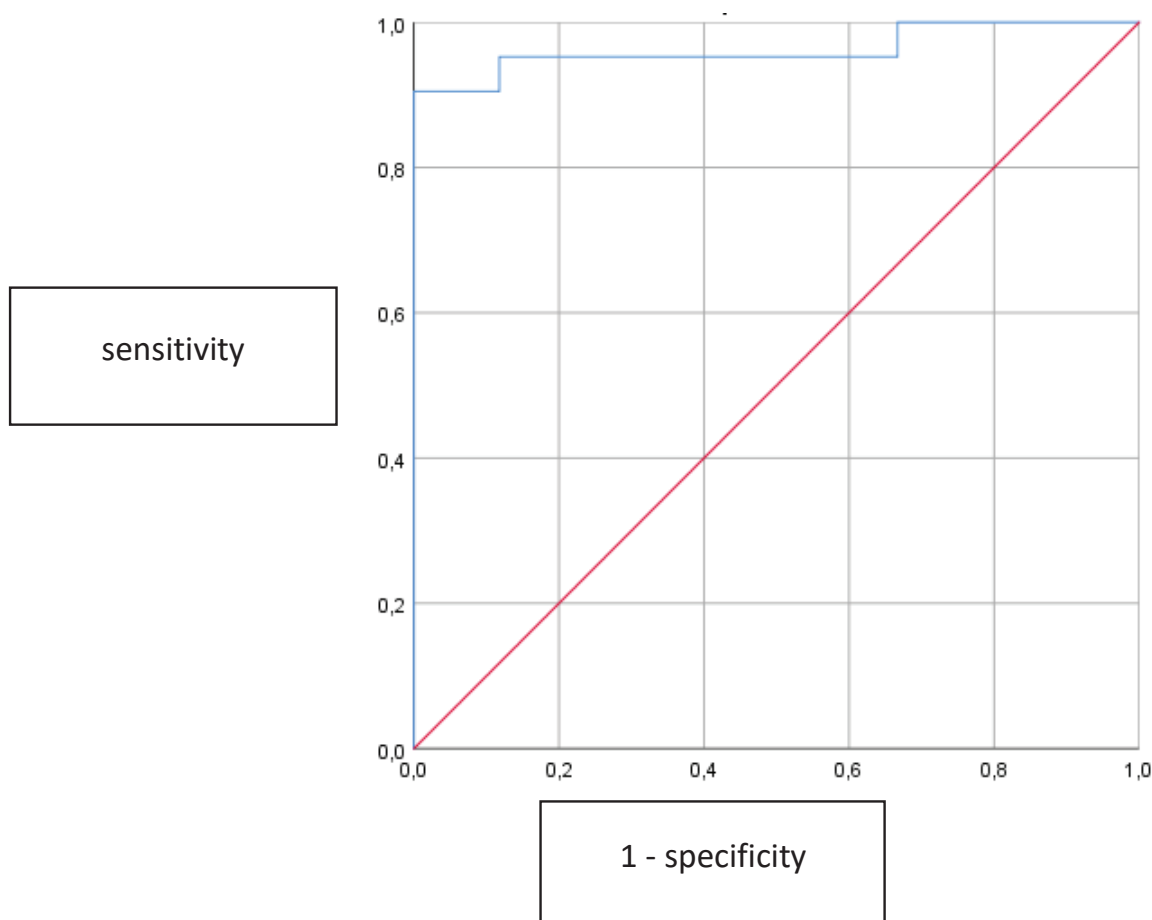
A similar model was presented by us in a 2024 scientific manuscript (Gimatdinova et al.) which described the results of analysis of those patients at the start of treatment and after 6 months of follow-up (the current article describes the assessment after 3 months) [14]. This was a pilot project that demonstrated robust statistical significance.

It is important to note that the majority of patients after the third antineoplastic treatment cycle had CVT phenotypes that did not require active therapy. However,

**Table 5.** Characteristics of the relationship between the predictors of the model, evaluated after 3 months, and the likelihood of cardiotoxicity

Predictors	Single-factor regression analysis		Multivariate regression analysis	
	COR; 95 % CI	p-value	COR; 95 % CI	p-value
Gender m/w	4,57; 1,45-14,4	0,01		
BMI, kg/m <sup>2</sup>	1,14; 1,01-1,29	0,034		
Smoking	2,66; 0,92-7,69	0,072		
OX, mmol/l	1,72; 1,09-2,73	0,02		
CPK, E/l	1,02; 1,003-1,037	0,019		
GLS, %	0,701; 0,573-0,859	0,001	0,466; 0,258-0,842	0,011
ESV, ml	1,078; 1,031-1,128	0,001	1,226; 1,055-1,425	0,008
EDVI, ml	1,025; 1,004-1,046	0,021	0,95; 0,895-1,008	0,088
ESD, mm	1,30; 1,115-1,515	0,001	1,385; 1,084-1,77	0,009
LVMI, g/m <sup>2</sup>	1,065; 1,023-1,11	0,002		
EDD, mm	1,085; 0,995-1,18	0,055		
NT-proBNP, mg/ml	1,016; 1,005-1,027	0,004	1,012; 0,998-1,026	0,081
Troponin, pg/ml	1,021; 0,975-1,068	0,382	0,966; 0,93-1,004	0,079
CPK(MB), E/l	1,147; 1,04-1,265	0,006	1,259; 0,998-1,589	0,052
Myoglobin, mkg/l	1,037; 1,001-1,066	0,01		
HR, /min	1,037; 0,996-1,080	0,08		

**Note.** BMI — body mass index, OH — total cholesterol, CK — creatine phosphokinase, GLS LV — Left Ventricular Global Longitudinal Strain — longitudinal systolic deformity of the left ventricle, ESD — end-systolic dimension, ESV- end-systolic volume, EDVI — end-diastolic volume, EDD — end-diastolic dimension, LVMI — left ventricular mass index, HR — heart rate



**Figure 1.** ROC curve of risk of cardiotoxicity

in line with that, single patients were reported that required the adjustment of the antineoplastic agent doses (50% reduction or switching to monotherapy) due to adverse events from another category (e.g., drug-induced cytopenia, acute kidney injury, secondary immunodeficiency syndrome, etc.). Those alterations could promote statistically less convincing characteristics of the currently developed model compared to the 2024 mathematical model.

## Conclusion

Oncohematological patients administered antineoplastic treatment are vulnerable concerning the emergence of cardiovascular dysfunction. The analysis of LVEF and standard biomarkers does not often help with the timely detection of adverse events during treatment. The expansion of diagnostic protocols in patients with indolent non-Hodgkin lymphomas regarding CVT with the addition of LVLSD and NT-proBNP levels promotes the timely adjustment of antineoplastic agent doses, administration of cardioprotective treatment, and improvement of the patients' quality of life.

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Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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