Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Differential Genetic and Morphofunctional Patterns of Anthracycline-Induced Cardiotoxicity in Breast Cancer Patients with Pre-existing Hypertension

Irina A. Karputs
Grodno State Medical University
Victor A. Snezhitskiy
Grodno State Medical University
Mikhail N. Kurbat
Grodno State Medical University
Volga A. Harustovich
Grodno State Medical University
Alexander Y. Rubinskij
Grodno University Clinic
Dmitry A. Zinovkin
Gomel State Medical University
Zahidul I. Pranjol
University of Sussex
Andrei S. Babenka
labmdbt@gmail.com

Republican Scientific and Practical Centre “Cardiology”

Research Article

Keywords: Breast cancer, Anthracyclines, Cardiotoxicity, Arterial hypertension, Echocardiography, GLS

Posted Date: May 19th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9616662/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background.

Current HFA-ICOS guidelines do not mandate intensive monitoring for patients at low or moderate risk. However, pre-existing arterial hypertension (AH) before chemotherapy (CTx) may qualitatively alter myocardial sensitivity to anthracyclines, necessitating the classification of these patients into a distinct surveillance group.

Objective.

To conduct a comparative analysis of echocardiographic (ECHO) parameters, cardiac biomarkers, and a genetic profile of 15 polymorphisms to identify predictors of early cancer therapy-related cardiac dysfunction (CTRCD) in breast cancer (BC) patients at low/moderate risk (HFA-ICOS) based on pre-existing AH.

Methods.

This prospective study included 100 females with Stage I–III BC (AH + n = 33; AH– n = 67) receiving doxorubicin (cumulative dose 240 mg/m²). All patients were initially categorized as low/moderate risk. Pre- and post-CTx, patients underwent ECHO with assessment of LVEF and global longitudinal strain (GLS), measurement of hs-cTnI, hs-cTnT, and NT-proBNP levels, and genotyping of 15 polymorphisms (including *CBR3, ABCC2, GSTP1, CELF4, MMPs, HAS3*).

Results.

The incidence of early CTRCD was comparable between groups; however, injury mechanisms differed fundamentally. AH+ patients exhibited a “diastolic scenario” (E/e’ increased by 12.1%, p = 0.029; LAVI increased, p = 0.006) and “biochemical CTRCD” (hs-cTnI and hs-cTnT increased by 29.4% and 21.2%, respectively, within the normal range). The genetic architecture in the AH+ group was associated with transport/metabolism loci (*CBR3, ABCC2, CELF4*) and matrix remodeling genes (*MMPs, HAS3*), whereas in the AH– group, *GSTP1* was the predominant predictor.

Conclusions.

Pre-existing AH fundamentally modifies the morphofunctional, biochemical, and genetic landscape of CTRCD. This heterogeneity justifies classifying AH patients into a separate risk group and emphasizes the need for a differentiated monitoring approach to shorten the diagnostic window for cardioprotective therapy.

INTRODUCTION

Currently, improvements in comprehensive treatment approaches for breast cancer (BC) have significantly increased the five-year survival rate of patients. Doxorubicin remains a key component of most chemotherapy (CTx) regimens. Despite its high efficacy, its use is limited by dose-dependent anthracycline cardiotoxicity or cancer therapy-related cardiac dysfunction (CTRCD), which can cause irreversible myocardial damage. The most severe manifestation of CTox is chronic heart failure (CHF), which frequently becomes a cause of mortality unrelated to the primary oncological disease [1–3].

Among clinical risk factors for CTRCD, arterial hypertension (AH) is of particular importance. More than 30% of patients with BC have concomitant AH, and this figure grows along with the average age of the population [4]. In AH, the myocardium is initially "primed" by pressure overload and structural remodeling. The combination of this background with the oxidative stress induced by doxorubicin sharply increases the probability of cardiovascular system decompensation [5].

According to the guidelines (HFA-ICOS), left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS) are used for the diagnosis of CTRCD. However, standard risk stratification algorithms often classify controlled AH as "low" or "moderate" risk. As a result, 60–80% of patients with BC do not receive preventive cardioprotective therapy (CPT) and lack clear monitoring standards. At the same time, the absolute number of CHF cases in these groups is comparable to those in high-risk groups [6, 7]. This indicates a clear underestimation of AH as an independent modifier of the toxic effect. In particular, the presence of AH can increase the risk of developing cardiotoxicity even with strict blood pressure control, reaching an odds ratio of 27.1 (95% CI 7.51–97.76; $p < 0.001$) [8].

Despite the growing interest in the search for biological markers, the potential of individual genetic predisposition in current CTRCD risk stratification models has not been fully revealed and has not yet found wide daily application. Inter-individual variability in response to CTx suggests that it is genomic variants that modulate myocardial sensitivity to anthracyclines.

A number of modern studies have already confirmed the significance of genetic testing. Thus, current consensus documents and guidelines (including HFA-ICOS) include polymorphisms with the strongest evidence base: the nucleoside transporter gene (SLC28A3 rs7853758), the retinoic acid receptor (RARG rs2229774), and the RNA splicing regulator (CELF4 rs1786814) [6].

Nevertheless, to form a complete picture of individual myocardial vulnerability, especially in patients with a comorbid background, an assessment of a wider spectrum of genetic markers is required. In our study, we expanded this panel, categorizing the analyzed polymorphisms by their functional roles: transport, metabolism, and accumulation. In addition to the aforementioned SLC28A3, this group included the transporter ABCC2 (rs8187710) [9] and carbonyl reductase CBR3 (rs1056892) [10], which is associated with the conversion of doxorubicin into its toxic derivative, doxorubicinol. Antioxidant defense and detoxification: variants of the SOD2 (rs4880) and GSTP1 (rs1695) genes [11] determine the myocardium's ability to neutralize free radicals and withstand oxidative stress. Matrix integrity and

remodeling: a wide panel of matrix metalloproteinase genes MMP2 (rs243865, rs243866), MMP3 (rs35068180, rs522616, rs679620), MMP9 (rs17576, rs3918242), and hyaluronan synthase HAS3 (rs2232228) [10] allows for the assessment of genetic predisposition to fibrosis and structural heart remodeling [12–17].

In this regard, the presence of AH should be considered not merely as a concomitant disease, but as a pathophysiological "platform." In combination with an unfavorable genetic profile, AH predestines the individual scenario of myocardial injury. This necessitates the classification of patients with AH into a special attention group, with the development of personalized monitoring protocols both during CTx and in the long-term period, even when using low cumulative doses of doxorubicin.

The aim of the study: to conduct a comparative analysis of echocardiography (ECHO) parameters and the genetic profile of 15 polymorphisms to identify predictors of early CTRCD in patients with BC at low and moderate risk (HFA-ICOS), depending on the presence of AH.

We hypothesize that the presence of AH prior to treatment forms a structural and functional "platform" that modifies the pathophysiological myocardial response to chemotherapy. In this model, the patient's genetic profile (including both standard HFA-ICOS markers and an expanded panel of metabolism and matrix genes) acts as a determinant of a specific CTRCD scenario. Integrating ECHO and genotyping data may reveal hidden vulnerabilities in low- and moderate-risk patients, justifying the need for individualized monitoring protocols and early cardioprotection.

MATERIALS AND METHODS

Study Design and Ethical Approval

Population Characteristics and Inclusion Criteria

The study included 100 women with a verified diagnosis of Stage I–III BC. Inclusion criteria were developed in accordance with national and international guidelines for the diagnosis and treatment of malignant neoplasms and cardiovascular diseases. These included primary resectable Stage I–III BC of the following molecular subtypes: Luminal A, Luminal B (HER2-negative), and Triple-negative breast cancer. Participants were aged between 25 and 70 years and had a low or moderate baseline cardiovascular risk according to the HFA-ICOS stratification.

Exclusion Criteria

To ensure an accurate assessment of the toxic effects of anthracyclines, patients with the following conditions were excluded from the study. Cardiovascular pathology: heart failure of any functional class, cardiomyopathies, significant valvular heart disease (stenosis Grade I–III, regurgitation Grade II–III), ischemic heart disease (history of myocardial infarction, revascularization, stable angina), and a baseline

LVEF < 50%. Arrhythmias and conduction disorders: atrial fibrillation or flutter, ventricular premature beats (> 5% of total beats or > 1000/day), ventricular tachycardia, Grade II or higher AV block, and complete bundle branch blocks. Comorbidities: Type 1 and Type 2 diabetes mellitus, thyroid pathology (hyper- and hypothyroidism), chronic kidney disease (GFR < 60 ml/min/1.73 m^2), and Grade 2–3 hypertension. Oncological and other factors: advanced stages of BC, neoadjuvant chemoradiotherapy, primary multiple tumors, severe somatic pathology with a life expectancy < 1 year, and active inflammatory processes of any etiology.

Chemotherapy Protocol

Chemotherapy Protocol
All patients were indicated for anthracycline-based adjuvant CTx. To minimize the influence of other potentially cardiotoxic agents, the AC combination therapy regimen (doxorubicin + cyclophosphamide) was selected: doxorubicin at a dose of 60 mg/m^2 and cyclophosphamide at a dose of 600 mg/m^2. The treatment course included 4 or 6 cycles (ACx4 and ACx6). The total cumulative dose of doxorubicin was 240 mg/m^2 (for the ACx4 regimen). A portion of the patients subsequently received taxane therapy and/or adjuvant radiotherapy according to BC treatment protocols.

Examination and Monitoring Protocol

Baseline cardiovascular risk assessment before starting anthracycline therapy was conducted according to the HFA-ICOS scale. All patients underwent a comprehensive diagnostic evaluation before the initiation and after the completion of doxorubicin chemotherapy. Instrumental diagnostics included transthoracic ECHO with mandatory assessment of global longitudinal strain (GLS), standard ECG, and 24-hour Holter monitoring. Laboratory monitoring included the measurement of high-sensitivity troponins (I and T), brain natriuretic peptide (BNP), and N-terminal pro-brain natriuretic peptide (NT-proBNP). In accordance with consensus criteria (ESC 2021, ESMO [18, 19]), the toxic effects of doxorubicin (CTRCD) were classified as follows. Overt CTRCD: a decrease in LVEF by more than 10% from baseline to values below 50%. Subclinical CTRCD: a decrease in GLS by more than 15% (or > 12% according to the used threshold values) from baseline while maintaining LVEF above 50%.

Instrumental and Laboratory Methods

Transthoracic ECHO was performed on a GE Vivid E95 expert-class ultrasound system (GE Healthcare, Norway) using an M5Sc transducer by the same qualified specialist. The study was conducted in 2D and M-modes in accordance with ASE/EACVI recommendations. Assessment of left ventricular GLS was carried out using the 2D Speckle Tracking Echocardiography method based on gray-scale B-mode analysis. Image analysis was performed using EchoPAC standalone software at a frame rate of 60–90 fps. Resting ECG registration was performed on a 12-channel digital electrocardiograph Intecard 3 (Cardian, Belarus). For the detection of arrhythmias and conduction disorders, 24-hour monitoring was

used on the Cardian KR 01 system. Levels of cardiac-specific biomarkers (troponins, NT-proBNP) were determined by enzyme-linked immunosorbent assay (ELISA) on a SUNRISE analyzer (Tecan, Austria). Commercial FineTest reagent kits (China) were used.

Concomitant Therapy

Patients with concomitant Grade 1 hypertension at the time of inclusion received standard antihypertensive therapy (ACE inhibitor — lisinopril 5 mg/day). This therapy was considered baseline blood pressure control and was not a specialized primary cardioprotection strategy for the prevention of CTRCD. No cases of de novo hypertension were recorded during the chemotherapy process.

Genotyping

Genomic DNA extraction was performed from EDTA-stabilized peripheral venous blood samples using the sorbent method with "Nucleosorb" reagent kits (Set B, Primetech, Belarus). The concentration and purity of the isolated DNA were assessed spectrophotometrically using a NanoDrop microvolume spectrophotometer (Thermo Scientific, USA). To evaluate individual myocardial sensitivity to anthracyclines, a panel of 15 polymorphisms was established, divided into functional groups: transport/metabolism, antioxidant defense, and matrix remodeling (Fig. 2). Genotyping of 15 single nucleotide polymorphisms (SNPs): MMP9_rs17576, ABCC2_rs8187710, HAS3_rs2232228, MMP2_rs243865, MMP3_rs35068180, MMP3_rs522616, CBR3_rs1056892, GSTP1_rs1695, MMP2_rs243866, MMP3_rs679620, MMP9_rs3918242, SLC28A3_rs7853758, RARG_rs2229774, CELF4_rs1786814, and SOD2_rs4880 was carried out using real-time polymerase chain reaction. Specific custom-designed test systems (primers and TaqMan probes), validated by Primetech (Minsk, Belarus), were used. Amplification and signal detection were performed on CFX96 Touch and CFX Connect thermal cyclers (Bio-Rad, USA). To ensure genotyping quality, 5% of randomly selected samples were re-analyzed; the concordance rate of the results was 100%.

The compliance of genotype frequency distribution with the Hardy-Weinberg equilibrium (HWE) was assessed using the chi-square test. In the group of patients with arterial hypertension (AH+), the genotype distribution for most loci corresponded to population expectations (Table S10). In the group of patients without arterial hypertension (AH–), HWE compliance was also confirmed for most of the studied SNPs (Table S11). Isolated deviations from the HWE recorded for some loci (specifically within the MMP and HAS3 systems) were considered acceptable given the specifics of the clinical sample and the exploratory nature of the study. Significance levels for genetic associations were interpreted as nominal ($p < 0.05$) within the framework of hypothesis generation for further validation.

Statistical Analysis

Statistical data processing was performed using IBM SPSS Statistics v.27.0.1. The distribution of quantitative data was tested for normality using the Shapiro-Wilk test. Since the distribution of all quantitative variables deviated from normal, the Mann-Whitney U-test was used for comparing independent groups, and the Wilcoxon signed-rank test was used for dependent samples (before/after dynamics). Data are presented as medians and interquartile ranges (Me [Q1; Q3]). To minimize Type I errors during multiple comparisons (12 ECHO parameters), the Bonferroni correction was applied; consequently, the critical significance level for these parameters was set at $p < 0.0042$. To assess associations between genetic polymorphisms and the development of CTRCD, Fisher's exact test was used. Given the exploratory and pilot nature of the genetic phase of the study and the limited sample size in the CTRCD+ subgroups, the results of the association analysis were interpreted as exploratory. The significance level was set at $p < 0.05$ without a rigid correction for multiple comparisons, with the aim of identifying potential biological trends that require further validation in larger cohorts.

RESULTS

Baseline Clinical Data

At the initial stage, a comparative analysis of the baseline clinical, demographic, and anthropometric parameters was conducted between the AH + and AH– groups (Table 1). The groups were fully comparable in terms of key oncological parameters: the distribution of breast cancer stages, molecular biological subtypes of the tumor, and the cumulative dose of doxorubicin. The frequency of obesity and smoking status also showed no statistical differences between the cohorts.

Table 1
Baseline clinical characteristics of patients in the AH + and AH– groups

Parameter	AH+ n = 33	AH- n = 67	p
Age, years, Me [Q1; Q3]	59 [54; 66]	49 [42,5; 56]	< 0,001
Smoking status, n (%)	3 (9,1%)	12 (17,9%)	0,373
Obesity (BMI ≥ 30 kg/m²), n (%)	16 (48,5%)	19 (28,4%)	0,074
Breast Cancer Stage, n (%)			
Stage I	13 (39,4%)	19 (28,4%)	0,362
Stage II	13 (39,4%)	39 (58,2%)	0,091
Stage III	7 (21,2%)	9 (13,4%)	0,387
Breast Cancer Subtype, n (%)			
Luminal A	16 (48,5%)	33 (49,2%)	1,000
Luminal B (HER2-negative)	9 (27,3%)	18 (26,9%)	1,000
Triple-negative	8 (24,2%)	16 (23,9%)	1,000
Doxorubicin Dose, n (%)			
240 mg/m² (4 cycles)	24 (72,7%)	58 (86,6%)	0,104
360 mg/m² (6 cycles)	9 (27,3%)	9 (13,4%)	0,104

Despite the age difference between the groups, the cumulative incidence of CTRCD after the completion of chemotherapy was comparable: 18.2% (6/33) in the AH+ group versus 19.4% (13/67) in the AH– group (p = 0.884). We hypothesize that within the framework of this study, age was not a determining factor in the manifestation of the damaging effects of chemotherapy; instead, the primary differences in the functional myocardial response are attributed to AH status and the genetic profile of the patients.

Comparative analysis of baseline echocardiographic parameters (before chemotherapy)

Before the initiation of doxorubicin therapy, left ventricular systolic function parameters (LVEF and GLS) did not differ statistically between the AH + and AH– groups (p = 0.589 and p = 0.507, respectively), confirming the comparability of the groups regarding the baseline myocardial contractile reserve (Fig. 3A, B). The full spectrum of baseline morphofunctional parameters is presented in the supplementary materials (Table S1).

However, signs of pre-existing hypertensive remodeling were recorded in the AH+ group. Left ventricular mass (LVM) and the left ventricular mass index (LVMI) were significantly higher in patients with

hypertension ($p < 0.001$; Fig. 3C), indicating the presence of an established structural substrate. Additionally, the AH+ group exhibited higher left ventricular volumes (EDVI $p = 0.005$; ESVI $p = 0.031$) and stroke volume (SV $p = 0.006$).

The diastolic profile in the AH+ group also showed pronounced differences: a statistically significant decrease in the E/A ratio ($p < 0.001$; Fig. 3D) and enlargement of the left atrium (LAVI $p = 0.006$) were observed. An increase in the E/e' ratio ($p = 0.007$) in the AH+ group indicates baseline higher LV filling pressures compared to patients without hypertension.

Comparative analysis of echocardiographic parameters after chemotherapy

Comparison of the median echocardiographic parameters in the AH + and AH– groups after the completion of doxorubicin chemotherapy revealed the persistence of trends recorded at baseline, as well as the emergence of new significant differences in the diastolic profile (Table S2). Systolic function (LVEF and GLS) showed no statistically significant intergroup differences at this stage ($p = 0.761$ and $p = 0.792$, respectively; Fig. 4A, 4B).

The most pronounced changes were recorded in the parameters of myocardial diastolic relaxation. In the AH+ group, a decrease in the median e' to 9.0 cm/s was observed, which is statistically significantly lower than the values in the AH– group (11.1 cm/s; $p < 0.001$; Fig. 4C) and falls below the lower limit of the physiological range. The E/e' ratio in the hypertensive group reached "gray zone" values (8.8 vs. 7.2; $p < 0.001$; Fig. 4D), indicating an increase in LV filling pressure. The combination of these changes (↓e', ↓E/A, ↑E/e') confirms the formation of a more severe phenotype of diastolic dysfunction in AH patients under the influence of anthracyclines.

Structural remodeling in the AH+ group was characterized by the persistence of higher values for left ventricular mass (LVM, $p = 0.023$) and its index (LVMI, $p = 0.018$), as well as a higher relative wall thickness (RWT, $p = 0.006$). At the same time, the differences in volumetric parameters (LAVI, EDVI, ESVI) observed before treatment were neutralized ($p > 0.05$), which may be due to the multidirectional dynamics of cardiac chamber volumes during the course of chemotherapy.

Dynamics of echocardiographic parameters in the AH+ group with the development of cardiotoxicity (CTRCD+)

The proportion of patients with verified cardiotoxicity (CTRCD+) in the AH+ group was 18.2% (6 out of 33). Analysis of the dynamics of parameters in this subgroup revealed a classical scenario of anthracycline-induced injury focused on the systolic component (Table S3).

After the completion of chemotherapy, a statistically significant decrease was recorded in global longitudinal strain (GLS) from 19.9% to 15.6% ($p = 0.027$; Fig. 5A) and ejection fraction (LVEF) from 72%

to 68% (p = 0.043; Fig. 5B). Notably, in these patients, baseline diastolic function parameters (e’ = 8.9 cm/s, E/e’ = 7.5) were already at the borderline of normal or showed signs of initial dysfunction; during chemotherapy, they remained stable and depressed without significant further negative dynamics (p > 0.05; Fig. 5C, 5D).

A slight decrease in the median LAVI was also noted (p = 0.043), while structural and geometric parameters (LVMI, RWT) and ventricular volumes did not undergo significant changes. Thus, the CTRCD+ scenario in hypertensive patients is characterized by the manifestation of systolic impairment against the background of pre-existing diastolic compromise.

For a more detailed assessment of myocardial contractility, an individual analysis of LVEF dynamics was conducted for patients in the AH+ CTRCD+ subgroup (Table 2). It was established that 5 out of 6 patients (83.3%) exhibited a decrease in LVEF after the completion of chemotherapy. In 2 out of 6 cases (33.3%), the decrease exceeded 10% from the baseline level, which formally meets the criteria for overt CTRCD; however, absolute LVEF values in all patients remained within the normal range (> 50%).

This dynamic indicates that in patients with AH, anthracycline-induced cardiomyocyte injury has already led to a reduction in contractile reserve. However, due to an initially high ejection fraction (hyperdynamic type) and compensatory mechanisms, global myocardial function remains preserved.

Table 2
Individual LVEF dynamics (%) before and after doxorubicin chemotherapy in the AH+ CTRCD+ subgroup (n = 6)

Patient	**Baseline (Before CTx)**	**Post-CTx**	**Decrease (%)**	**Dynamics relative to normal values, % Me 64% [Q1 54%; Q3 74%] Normal – 1, abnormal – 0**
№29	72	68	-5,9	0
№34	68	59	-15,3	1
№35	71	68	-4,4	0
№46	72	61	-18,0	1
№67	77	75	-2,7	0
№82	67	67	0,0	0

Dynamics of echocardiographic parameters in the AH+ subgroup without overt cardiotoxicity (CTRCD–)

The most significant results were obtained from the analysis of the subgroup of hypertensive patients who did not exhibit a decline in GLS or LVEF below the threshold values (CTRCD– subgroup, n = 27). This cohort revealed an isolated diastolic scenario of myocardial injury (detailed data in Table S4).

Despite complete stability in contractility parameters (GLS remained at 20.4%, LVEF at 64%; p > 0.5; Fig. 6A, 6B), a critical worsening of diastolic relaxation parameters was recorded. The early diastolic velocity e' decreased from 11.8 cm/s to 9.1 cm/s (p < 0.001; Fig. 6C), indicating that the value shifted beyond the physiological norm under the toxic influence of doxorubicin. Concurrently, an increase in the E/e' ratio from 7.9 to 8.9 was noted (p = 0.009; Fig. 6D), indicating an increase in left ventricular filling pressure.

A statistically significant decrease in EDVI was also identified (p = 0.032), which, combined with increased stiffness (↑E/e'), may reflect the formation of a restrictive remodeling pattern. Thus, in 81.8% of patients with AH, anthracycline cardiotoxicity manifests as diastolic dysfunction, which remains undiagnosed when using only standard GLS and LVEF criteria.

Dynamics of echocardiographic parameters in the AH– group with cardiotoxicity (CTRCD+)

The proportion of patients with verified cardiotoxicity (CTRCD+) in the AH– group was 19.4% (13 out of 67), which is comparable to the incidence in the AH+ group (p > 0.05). An isolated scenario of systolic myocardial injury was observed in this subgroup (Table S5).

The primary marker of damage was a statistically significant decrease in global longitudinal strain (GLS) from 20.5% to 15.9% (p = 0.001; Fig. 7A). Notably, unlike hypertensive patients, the development of CTRCD in patients without AH occurred with stable global contractility (LVEF 65% vs. 65%, p = 0.387; Fig. 7B) and an absence of significant changes in diastolic function (e', E/e', E/A; p > 0.05; Fig. 7C, 7D, 7E).

Left ventricular geometry (EDVI, ESVI) and structural myocardial parameters (LVMI, RWT) also remained stable. Thus, in patients without AH, anthracycline cardiotoxicity manifests primarily at a subclinical level through impairment of myocardial deformation properties, with complete preservation of diastolic reserve.

Dynamics of echocardiographic parameters in the AH– subgroup without overt cardiotoxicity (CTRCD–)

In patients without concomitant AH who did not meet the criteria for cardiotoxicity (CTRCD– subgroup, n = 54), no significant pathological changes in the morphofunctional state of the heart were identified (Table S6).

The median global longitudinal strain (GLS) remained stable throughout the observation period (20.3% vs. 20.3%, p = 0.095; Fig. 8A). Regarding LVEF, a statistically significant decrease in the median from 69% to 66% was recorded (p = 0.001; Fig. 8B), which, however, remained within normal physiological limits and showed no clinical manifestation.

Analysis of cardiac-specific biomarkers

Analysis of biomarker dynamics in the overall patient cohort following the completion of doxorubicin CTx revealed a statistically significant increase in high-sensitivity troponin levels: cTnI (from 1.7 to 2.1 pg/ml; $p = 0.006$) and cTnT (from 3.3 to 3.7 pg/ml; $p = 0.003$), as well as the natriuretic peptide NT-proBNP (from 5.7 to 8.8 pg/ml; $p = 0.040$) (Table S7).

Despite the systemic increase in markers across the entire sample, intergroup analysis revealed no statistically significant differences in their absolute concentrations between the CTRCD + and CTRCD– subgroups ($p > 0.05$). This suggests that a single measurement of troponin and NT-proBNP levels after the completion of CTx has lower predictive value for the development of systolic dysfunction compared to the assessment of their individual dynamics during treatment.

A detailed analysis of the biochemical response patterns based on the presence of AH revealed two fundamentally different patterns of myocardial injury (Tables S8, S9). The AH+ group (Direct cardiomyocyte injury): Patients with AH exhibited the most consistent increase in troponin levels: cTnI ($p = 0.019$) and cTnT ($p = 0.006$). A critical finding was the significant elevation of troponin concentrations in the subgroup of patients without overt cardiotoxicity (AH+ CTRCD–): $p = 0.023$ for cTnI and $p = 0.011$ for cTnT (Fig. 9A, B). This suggests that in hypertensive patients, cardiomyocyte injury occurs at a subclinical level and precedes a significant decline in myocardial deformation characteristics (GLS). The AH– group (Hemodynamic stress): In patients without AH, the dynamics of troponin levels did not reach statistical significance ($p > 0.05$). However, this group showed a significant increase in NT-proBNP levels ($p = 0.040$), which was most pronounced in patients with verified cardiotoxicity (AH– CTRCD+; $p = 0.028$; Fig. 9C). This indicates that in patients without AH, the development of systolic dysfunction is primarily accompanied by volumetric myocardial stress.

Association of candidate gene polymorphisms with the dynamics of echocardiographic parameters

Given the identified differences in clinical scenarios of CTRCD, an exploratory analysis of the associations between 15 single nucleotide polymorphisms (SNPs) and the dynamics of echocardiographic parameters (Δ, %) was conducted. The genes were grouped according to functional cascades: transport and metabolism, antioxidant defense and survival regulation, and extracellular matrix remodeling. Summary data for statistically significant associations ("genetic signals") are presented in Table 3.

Table 3
Summary of genetic predictors of morphofunctional cardiac changes (Exploratory Analysis)

Group	Functional Block	Gene (rs-number)	Genotype / Allele	Effect on ECHO	Δ, % [Me]	p-value
AH+	Metabolism	*CBR3* (rs1056892)	**GG**	GLS reduction (systolic function)	-11,6	0,012
	Transport	*ABCC2* (rs8187710)	**GG**	Increase in E/e' ratio (filling pressure)	+ 12,1	0,029
	Regulation	*CELF4* (rs1786814)	**GG**	Change in LAVI (left atrium)	-65,9*	0,002
	Defense	*SOD2* (rs4880)	**C**	LVEF reduction (systolic function)	-7,2	0,041
	ECM Remodeling	*HAS3* (rs2232228)	**A**	Increase in RWT (LV geometry)	+ 6,1	0,041
	ECM Remodeling	*MMP2* (rs243865)	**C**	Increase in RWT (LV geometry)	+ 2,2	0,028
AH-	Defense	*GSTP1* (rs1695)	**GG**	Risk of overt CTRCD	3 fold	0,028
	Defense	*GSTP1* (rs1695)	**A**	Decrease in E/A ratio (diastolic function)	-15,9	0,002

Anthracycline transport and metabolism genes. In the AH+ group, polymorphisms determining intracellular toxin concentration played a key role in the manifestation of systolic injury. Carriage of the unfavorable GG genotype of the CBR3 gene (rs1056892) was associated with the most pronounced reduction in global longitudinal strain (ΔGLS − 11.6% [–18.9; − 1.8], p = 0.012) (Fig. 10A) and a trend toward an increase in end-diastolic volume index (EDVI, p = 0.026). The ABCC2 (rs8187710) polymorphism demonstrated an association with both systolic and diastolic dysfunction in hypertensive patients: carriers of the GG genotype exhibited decreased contractility (ΔGLS − 5.7%, p = 0.037) and a significant increase in filling pressure (ΔE/e' +12.1% [2.3; 42.7], p = 0.029) (Fig. 10B).

Antioxidant defense and survival regulation genes. The impact of oxidative stress factors was more pronounced in AH+ patients. Carriage of the C allele of the SOD2 gene (rs4880) in the AH+ group was associated with a decrease in ejection fraction (ΔLVEF − 7.2%, p = 0.041). The GG genotype of the CELF4 gene (rs1786814) demonstrated a strong association with left atrial volume dynamics (ΔLAVI, p = 0.002). In the AH– group, the GSTP1 (rs1695) polymorphism became the leading genetic risk factor: the GG genotype was significantly more frequent in patients with verified CTRCD (p = 0.028), while carriage of the A allele was associated with worsening diastolic filling (ΔE/A − 15.9%, p = 0.002).

Structural remodeling and matrix genes. Genetic determination of myocardial geometry changes was predominantly characteristic of the AH+ group. Carriage of the A allele of the HAS3 gene (rs2232228)

and the C allele of the MMP2 gene (rs243865) was accompanied by an increase in relative wall thickness (ΔRWT + 6.1% and + 2.2%, respectively; $p < 0.05$) (Fig. 10C). Polymorphisms of the MMP3 and MMP9 systems in both groups showed an association with the dynamics of the left ventricular mass index (LVMI) and LV geometry, confirming the involvement of matrix remodeling processes in post-chemotherapy remodeling.

(A) Significant reduction in global longitudinal strain (GLS) in carriers of the CBR3 GG genotype (rs1056892); (B) Elevation of LV filling pressure (E/e' ratio) in carriers of the ABCC2 GG genotype (rs8187710); (C) Increase in relative wall thickness (RWT) associated with the HAS3 A allele (rs2232228) and MMP2 C allele (rs243865). Data are presented as medians and interquartile ranges.

DISCUSSION

In this study, a comparative analysis of ECHO parameters was conducted between AH + and AH– groups of breast cancer patients receiving doxorubicin chemotherapy. The study included patients categorized as low and moderate risk according to the HFA-ICOS criteria. Differences in systolic and diastolic cardiac function parameters between the AH + and AH– groups were identified at two checkpoints—baseline and after treatment completion—followed by an analysis of "before/after" dynamics. The core objective of this work was to evaluate the necessity of distinguishing patients with AH from the general risk group and to develop management strategies for them when they are categorized as low or moderate risk for cardiovascular events (HFA-ICOS).

Although the problem of cardio-oncology is receiving increasing attention in contemporary literature, there is still a lack of prospective data to develop effective methods for individual risk assessment in oncology patients. There is also a critical need to establish an evidence base to improve current cardioprotection strategies both during chemotherapy and years after its completion, when cardiovascular mortality often exceeds that of the primary oncological disease.

In a study by Belenkov et al. (2024) [20], experts emphasize the importance of baseline myocardial assessment using ECHO before the start of chemotherapy. Cardiac imaging plays a vital role in identifying cardio-oncology patients with subclinical signs of myocardial injury, especially before deciding on a chemotherapy regimen, and serves as a reliable method for detecting early CTRCD during treatment and in the long term. EDV, LVMI, GLS, LVEF, E/e', and LAVI are highlighted as some of the most critical ECHO parameters.

Furthermore, a study by Vasyuk et al. (2025) [21] reflects the values of several ECHO parameters in patients categorized as high and very high risk for CTRCD (HFA-ICOS). A history of AH before the initiation of CTx was noted in 84.5% of the patients in the primary group included in the study and receiving CPT. However, a division into CTRCD + and CTRCD– subgroups was not performed, nor was there a separation into AH + and AH– within the analyzed primary group. When comparing the data obtained in our study with the authors' findings – even taking into account the different CTRCD risk categories (HFA-ICOS) – similar trends should be noted in the group of patients with AH by the

completion of CTx. The authors also indicated that in the primary group of patients receiving specialized CPT, 5.9% of early CTRCD cases were identified based on GLS reduction. In contrast, in the comparison group of patients not receiving specialized CPT – analogous to the patients included in our study – early CTRCD was detected in 19.7% of cases, which is comparable to our data in the AH+ group (18.0%).

Kononchuk et al. (2025) [22] established that in BC patients without a history of AH, LVM and LVMI values are statistically significantly higher compared to a healthy control group without AH. The authors report an increase in these parameters associated with the presence of malignant disease. In our study, LVM and LVMI values in the AH+ group were statistically significantly higher compared to the AH– group.

In the work of Satalkina et al. (2025) [23], the researchers primarily examine the development of AH during doxorubicin chemotherapy; however, they identified a group of BC patients with AH prior to the start of treatment. A decrease in LVEF before/after chemotherapy was noted for all patient subgroups regardless of the presence of AH. This is consistent with the dynamics of this parameter observed in our study, which held true for both the AH + and AH– groups.

Berezikova et al. (2024) [24] demonstrated a link between the presence of AH before the start of anthracycline chemotherapy and the development of early CTRCD in BC patients. Similarly to the results obtained in our study, LVEF and GLS values in the AH+ group before the start of chemotherapy did not differ from those in the AH– group, while the LVMI was statistically significantly higher in the AH+ group ($p < 0.001$ in both cases). Berezikova et al. also suggest the necessity of developing specific approaches for prescribing CPT and managing hypertensive patients receiving chemotherapy.

Wernhart et al. (2025) [25] studied the development of AH as a manifestation of the toxic effect of chemotherapy. One of the inclusion criteria for their study was the absence of AH before the start of treatment. In BC patients without AH, an ECHO assessment of diastolic function parameters was performed. It was determined that before the start of chemotherapy, function was preserved, and all parameters were within the physiological range. In our study, e'lat and E/e' in patients of both AH + and AH– groups were also within normal limits; however, E/e' was statistically significantly lower in the AH– group ($p = 0.007$). The median LVMI according to Wernhart et al. was comparable to the median obtained in our study for the AH– group, while in the AH+ group, this parameter was statistically significantly higher.

Terui et al. (2025) [26] demonstrated that in breast cancer patients receiving only doxorubicin, early CTRCD after chemotherapy developed more frequently compared to patients receiving additional trastuzumab. The authors also noted an approximately equal distribution of patients with AH between the CTRCD + and CTRCD– subgroups, which, in their opinion, suggests that pre-existing AH is not a critical risk factor. This is consistent with our findings. Although Terui et al. did not perform a separation into AH + and AH–, they reported the dynamics of echocardiographic parameters before and after chemotherapy. A statistically significant decrease in LVEF and GLS was identified in the combined (initial) group, while e' and E/e' values remained stable.

Terluk et al. (2024) [27] found that the presence of AH before chemotherapy is a risk factor for myocardial injury after treatment, with GLS decreasing more frequently in patients with AH. In our study, no statistically significant difference was found in GLS dynamics before/after chemotherapy between the AH + and AH– groups.

Based on the research data presented above, as well as the results obtained in our study, two main pathways for the development of CTRCD in breast cancer patients with pre-existing AH can be hypothesized. The systolic scenario (AH+ CTRCD+): a decrease in GLS > 12% and a decrease in LVEF by more than 10%, reflecting subclinical systolic dysfunction caused by the direct toxic effect of doxorubicin against the background of an already reduced functional reserve. The diastolic scenario (AH+ CTRCD–): the absence of a significant decline in GLS and LVEF, accompanied by a pronounced worsening of diastolic parameters (e' and E/e' moving beyond normal limits), which corresponds to a restrictive phenotype with preserved systolic function but impaired relaxation.

The current strategy for CTRCD monitoring assigns a key role to the combination of imaging and laboratory diagnostics. However, despite the inclusion of high-sensitivity troponins and natriuretic peptides in the ESC and HFA-ICOS guidelines, the interpretation of their dynamics at low cumulative doses of anthracyclines (up to 250 mg/m²) remains a subject of debate. It is important to note that the isolation of patients with arterial hypertension before the start of treatment is extremely rare due to small sample sizes and/or different research focuses. In our study, we analyzed individual trajectories of biochemical marker changes rather than absolute threshold values (cut-offs), which allowed us to identify hidden patterns of myocardial injury, including those based on the presence of AH. A central observation of this stage of the work was the phenomenon of "biochemical lead" specifically in the AH+ group. We recorded a statistically significant increase in median troponin levels (cTnI by 29.4% and cTnT by 21.2%) in patients of the AH+ CTRCD– subgroup, whose GLS and LVEF parameters remained within the normal range.

In the work of Li et al. (2026) [28], an analysis of serial biomarker measurements in BC patients showed that an increase in hs-cTnI levels is observed in both the CTRCD + and CTRCD– groups, averaging 34.5% from baseline, with AH patients present in both groups. The dynamics of NT-proBNP were of a fundamentally different nature. In our study, no significant changes in the peptide were identified in the AH+ CTRCD– group ($p = 0.407$), while a 71.7% increase was recorded in the AH– CTRCD+ group. In the study by Li et al., a sevenfold increase in NT-proBNP levels from baseline was observed in the CTRCD+ group, whereas its level remained stable in the CTRCD– group.

In the work of A. F. Kaya and M. A. Özbek (2026) [29], a statistically significantly higher proportion of BC patients with a history of AH prior to treatment was described in the CTRCD+ group. The authors recorded an elevation in hs-TnI levels ($p < 0.001$) as early as one month after the start of therapy, while NT-proBNP failed to demonstrate independent predictive value. It is likely that for patients with AH, high-sensitivity troponin serves as the most reliable "early indicator" of toxicity.

Kozhukhov and Dovganych (2025) [30] observed an average increase in hs-cTnT levels of 94.2% in BC patients during chemotherapy, which, even while remaining within reference values (< 14 ng/L), was regarded by them as a manifestation of "biochemical cardiotoxicity." Their analysis was conducted on a mixed sample without separation into AH + and AH– groups. Our study, employing such a division, showed that the dynamics of troponin levels can be heterogeneous.

This suggests that the presence of AH, even in patients categorized as low and moderate risk according to the HFA-ICOS scale, may act as a modifier of the biochemical response, potentially lowering the threshold of cardiomyocyte resistance to anthracycline loading. While in the general population troponin may serve as an average predictor of LVEF decline, in the isolated AH+ group, it is likely an earlier indicator of subclinical injury. Thus, AH status may determine the "biochemical vulnerability" that requires more close monitoring, even if current protocols do not classify such patients as high-risk individuals and their global ejection fraction remains preserved.

The genetic associations identified in this study may indicate the presence of specific molecular profiles of myocardial injury in patients with different blood pressure statuses. Our data suggest that the presence of arterial hypertension (AH), even in patients categorized as low and moderate risk (HFA-ICOS), is associated with certain genetic polymorphism features whose role is less pronounced in the AH– group.

In the AH+ group, the identified "signals" are primarily concentrated in loci responsible for intracellular transport and structural matrix remodeling. The association of the CBR3 GG genotype (rs1056892) and the ABCC2 GG genotype (rs8187710) with a more pronounced decrease in GLS (–11.6%) and an increase in filling pressure (E/e’ +12.1%) finds certain support in the results of functional validation in human induced pluripotent stem cell-derived cardiomyocytes (Fonoudi H. et al., 2024) [31]. In that study, the "knockout" of the ABCC2 and CBR3 genes increased the susceptibility of cardiomyocytes to doxorubicin, which may be related to impaired efflux and excessive conversion of the drug into its toxic metabolite, doxorubicinol. In patients of the AH+ group, this process is likely complemented by features of genes associated with extracellular matrix balance (MMP2 rs243865, MMP3 rs35068180, MMP9 rs17576, HAS3 rs2232228). According to Tanase D.M. et al. (2025) [32], metalloproteinases can trigger the degradation of structural proteins and mitochondrial failure, which pathophysiologically aligns with the increase in RWT (Δ + 6.1%) and the "troponin drift" observed specifically in patients with AH.

In the AH– group, a different pattern of genetic associations was observed. The leading predictor for the development of overt CTRCD in this cohort was the GSTP1 (rs1695) polymorphism. Notably, in the experimental models by Fonoudi H. et al. (2024), the knockout of this gene was not accompanied by excessive production of reactive oxygen species. This suggests that in patients without concomitant AH, the key mechanism of injury may be a deficiency in direct anthracycline detoxification systems, whereas oxidative stress and matrix remodeling play a less significant role.

Such heterogeneity of genetic "signals" may indicate that AH status qualitatively modifies the landscape of cardiotoxicity. In patients without AH, the process is likely more limited by the state of antioxidant

defense systems (GSTP1 rs1695), while in patients with AH, mechanisms of active toxicity accumulation (CBR3 rs1056892, ABCC2 rs8187710), impaired calcium homeostasis (CELF4 rs1786814), and myocardial fibrosis (MMP, HAS3) may come to the fore. This points to the expediency of a differentiated approach to genetic profiling: for patients with AH, even at low clinical risk, priority should be given to monitoring loci responsible for metabolism and matrix structure.

Conclusion

In summary, the presence of arterial hypertension fundamentally modifies the morphofunctional, biochemical, and genetic landscape of CTRCD. The identified heterogeneity of myocardial injury pathways necessitates a differentiated approach to monitoring patients traditionally categorized as low or moderate risk. The summary characteristics of the identified phenotypes, along with proposed personalized surveillance algorithms based on blood pressure status, are presented in Table 4. We believe that accounting for these features will shorten the "diagnostic window" and ensure the timely initiation of cardioprotective therapy in the most vulnerable patient categories.

Table 4
Differentiated approach to monitoring low and moderate risk patients (HFA-ICOS) based on AH status

Parameter	**AH– Patients (Low/Moderate Risk)**	**AH+ Patients (Low/Moderate Risk)**
Key genetic indicators	GSTP1 (rs1695)	CELF4 (rs1786814); CBR3 (rs1056892); ABCC2 (rs8187710)
Biochemical marker (dynamics, % before/after CTx)	Stable cTnI/cTnT levels; NT-proBNP increase > 70% (in CTRCD+)	hs-cTnI/hs-cTnT increase > 20%
Imaging priority (ECHO)	Systolic function (GLS and LVEF)	Diastolic function and structure (e', E/e', LAVI, RWT)
Recommended ECHO frequency	Standard (at baseline and after CTx)	? Increased: intermediate control (after the 2nd cycle) to assess trends
Management strategy	Monitoring according to HFA-ICOS guidelines	In-depth screening for timely initiation of CPT when "signals" are detected

HIGHLIGHTS

In breast cancer patients with pre-existing AH categorized as low or moderate risk (HFA-ICOS), CTRCD can manifest through a diastolic scenario (increased filling pressure, elevated LAVI, and myocardial wall thickening), which often precedes a clinically significant decline in LVEF.

The AH+ group is characterized by the development of "biochemical cardiotoxicity" – an individual increase in troponin levels (cTnI/cTnT > 20–30%) within the normal reference range. This phenomenon can be regarded as an early marker of injury, necessitating shorter intervals between follow-up examinations.

Genetic predisposition to injury in the AH+ group is associated with the GG genotypes of the CELF4 (rs1786814), CBR3 (rs1056892), and ABCC2 (rs8187710) loci, whereas the GG genotype of the GSTP1 (rs1695) gene remains a significant predictor in the AH– group.

AH status qualitatively alters the cardiotoxicity profile, justifying the need for active monitoring of patients with AH (including low-to-moderate risk groups). Assessment of individual biomarker trends and diastolic function parameters is recommended for timely decision-making regarding the initiation of cardioprotective therapy.

STUDY LIMITATIONS

Sample Size: The relatively small number of participants (n = 100) limits the statistical power, particularly for the analysis of rare genotypes.

Study Design: The single-center nature of the study may limit the generalizability of the findings to broader populations.

Follow-up Period: The study focused exclusively on early CTRCD (immediately following chemotherapy completion); a longer follow-up period is required to assess long-term cardiac effects.

Exploratory Nature: The identified genetic associations, particularly concerning matrix metalloproteinases, are exploratory in nature and require further validation in larger cohorts.

Abbreviations

AH
Arterial hypertension
BC
Breast cancer
BMI
Body mass index
BNP
Brain natriuretic peptide
CPT
Cardioprotective therapy
CTRCD
Cancer therapy-related cardiac dysfunction

CTx
Chemotherapy
ECHO
Echocardiography
EDVI
End-diastolic volume index
ECM
Extracellular matrix
ESVI
End-systolic volume index
GLS
Global longitudinal strain
hs-cTnI
High-sensitivity cardiac troponin I
hs-cTnT
High-sensitivity cardiac troponin T
HWE
Hardy-Weinberg equilibrium
LAVI
Left atrial volume index
LVEF
Left ventricular ejection fraction
LVMI
Left ventricular mass index
NT-proBNP
N-terminal pro-brain natriuretic peptide
RWT
Relative wall thickness
SNP
Single nucleotide polymorphism

Declarations

Competing Interests:

The authors have no relevant financial or non-financial interests to disclose.References

Ethics Approval:

The study was approved by the local Ethics Committee (Protocol No. 26 dated October 9, 2020) and was conducted in accordance with the principles of the Declaration of Helsinki.

Consent to Participate:

Informed consent was obtained from all individual participants included in the study.

Victor A. Snezhitskiy

Supervision, Project administration, Resources, Funding acquisition, Writing – review & editing.

Mikhail N. Kurbat

Conceptualization, Methodology, Validation, Writing – review & editing.

Alexander Y. Rubinskij

Investigation (echocardiography and GLS measurements), Formal analysis.

Dmitry A. Zinovkin

Methodology, Validation, Writing – review & editing (critical revision of the manuscript).

Zahidul I. Pranjol

Methodology, Validation, Writing – review & editing (English language editing and formatting advice).

Andrei S. Babenka

Methodology, Software, Formal analysis (statistical processing), Data curation, Visualization (figure preparation), Investigation (genetic analysis), Writing – review & editing.

Funding:

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Author Contribution

Irina A. Karputs: Conceptualization, Methodology, Investigation (clinical data collection and patient management), Formal analysis, Writing – original draft.Victor A. Snezhitskiy: Supervision, Project administration, Resources, Funding acquisition, Writing – review & editing.Mikhail N. Kurbat:

Conceptualization, Methodology, Validation, Writing – review & editing.Volga A. Harustovich: Investigation (biochemical analysis: troponins and NT-proBNP), Data curation.Alexander Y. Rubinskij: Investigation (echocardiography and GLS measurements), Formal analysis.Dmitry A. Zinovkin: Methodology, Validation, Writing – review & editing (critical revision of the manuscript).Zahidul I. Pranjol: Methodology, Validation, Writing – review & editing (English language editing and formatting advice).Andrei S. Babenka: Methodology, Software, Formal analysis (statistical processing), Data curation, Visualization (figure preparation), Investigation (genetic analysis), Writing – review & editing.

Data Availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request

References

1. Khabarova NV, Kirichenko YY, Belenkov YN, Tarlovskaya EI, Shestakova KM, Vasyuk YA. Multiparametric Integrative Model for Predicting the Risk of Developing Cardiovascular Vasculotoxicity in Antitumor Therapy: Prospects for Personalized Stratification of Cancer Patients. Kardiologiia. 2025 Oct 23;65(9):19–25. Russian, English. doi: 10.18087/cardio.2025.9.n3017. PMID: 41129247.
2. Keramida K, Constantinidou A, Tsekoura D, Kampouroglou E, Aidarinis C, Saloustros E, et al. Cardiotoxicity in Elderly Breast Cancer Patients. Cancers (Basel). 2025;17(13):2198. doi: 10.3390/cancers17132198.
3. Bloom MW, Vo JB, Rodgers JE, Ferrari AM, Nohria A, Deswal A, et al. Cardio-Oncology and Heart Failure: a Scientific Statement From the Heart Failure Society of America. J Card Fail. 2025;31(2):415–455. doi: 10.1016/j.cardfail.2024.08.045.
4. Damachi U, Onukwugha E, Mysore MM, Camelo Castillo W. Antihypertensive Past Adherence Trajectories and Risk of Cardiotoxicity Among Adults Initiating Anthracycline Treatment. Pharmacoepidemiol Drug Saf. 2026;35(2):e70318. doi: 10.1002/pds.70318.
5. Philip LJ, Findlay SG, Gill JH. Baseline blood pressure and development of cardiotoxicity in patients treated with anthracyclines: A systematic review. Int J Cardiol Cardiovasc Risk Prev. 2022;15:200153. doi: 10.1016/j.ijcrp.2022.200153.
6. Lyon AR, Lopez-Fernandez T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). Eur Heart J. 2022;43(41):4229–4361. doi: 10.1093/eurheartj/ehac244.
7. Gomes C, Geels J, Debray TPA, Malekzadeh A, Asselbergs FW, Linschoten M, et al. Risk prediction models for cancer therapy related cardiac dysfunction in patients with cancer and cancer survivors:

systematic review and meta-analysis. BMJ. 2025;390:e084062. doi: 10.1136/bmj-2025-084062.

8. Nganou-Gnindjio CN, Okobalemba EA, Tasong LA, Zende AM, et al. Evaluation of the cardiotoxicity risk based on the HFA-ICOS score in a group of sub-Saharan African women before breast cancer treatment by chemotherapy and/or radiotherapy. Cardiooncology. 2025;11(1):89. doi: 10.1186/s40959-025-00390-x.
9. Elmekawy HA, Abdelkawy K, Magdy G, Sadaka E, El-Azab G, Ali A, et al. Genetic polymorphisms of ABCC2 and CBR3 can influence the efficacy and toxicity of doxorubicin therapy in Egyptian patients with non-Hodgkin lymphoma. Xenobiotica. 2025;55(5):349–359. doi: 10.1080/00498254.2025.2508814.
10. Aba N, Ducos C, Morel E, et al. Influence of genetic biomarkers on cardiac diseases in childhood cancer survivors: a systematic review. Pharmacogenomics J. 2025;25:15. doi: 10.1038/s41397-025-00369-y.
11. Marinko T, Stojanov Konda JT, Dolžan V, Goričar K. Genetic Variability of Antioxidative Mechanisms and Cardiotoxicity after Adjuvant Radiotherapy in HER2-Positive Breast Cancer Patients. Dis Markers. 2020;2020:6645588. doi: 10.1155/2020/6645588.
12. Karput IA, Snezhitsky VA, Kurbat MN, Gorustovich OA, Kopytsky AV, Babenko AS. Molecular genetic indicators of the probability of early myocardial systolic dysfunction signs in doxorubicin chemotherapy in patients with breast cancer of moderate and low HFA-ICOS risk groups. Russ J Cardiol. 2024;29(10):5993. Russian. doi: 10.15829/1560-4071-2024-5993.
13. Giau HTN, An TV, Cua TTH, Dung BT. Association Between rs243866 Polymorphism of the MMP-2 Gene and Target Organ Damage in Patients with Uncontrolled Hypertension. Acta Inform Med. 2025;33(1):47–49. doi: 10.5455/aim.2024.33.47-49.
14. Tuan Huynh A, Vu HA, Chuong HQ, Anh TH, Viet Tran A. The rs243865 Polymorphism in Matrix Metalloproteinase-2 and its Association With Target Organ Damage in Patients With Resistant Hypertension: Cross-Sectional Study. JMIR Cardio. 2025;9:e71016. doi: 10.2196/71016.
15. Buraczynska M, Wrzos S, Zaluska W. MMP9 Gene Polymorphism (rs3918242) Increases the Risk of Cardiovascular Disease in Type 2 Diabetes Patients. J Clin Med. 2023;12(22):6990. doi: 10.3390/jcm12226990.
16. Demir H, Altug Tuncer M, Sheikhvatan M, Abuqalben SM. rs17576 polymorphism of matrix metalloproteinase-9 in predicting coronary artery disease severity and its adverse outcome. ARYA Atheroscler. 2025;21(3):16–27. doi: 10.48305/arya.2025.43384.3019.
17. Nikulina S, Kuznecova O, Chernova A. Results of the association study of the type 3 matrix metalloproteinase gene – 1171 5A/6A (rs35068180) and dilated cardiomyopathy. Eur Heart J Acute Cardiovasc Care. 2021;10(Suppl 1):zuab020.010. doi: 10.1093/ehjacc/zuab020.010.
18. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42(36):3599–3726. doi: 10.1093/eurheartj/ehab368.

19. Curigliano G, Lenihan D, Fradley M, Ganatra S, Barac A, Blaes A, et al. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. Ann Oncol. 2020;31(2):171–190. doi: 10.1016/j.annonc.2019.10.023.
20. Belenkov YN, Ilgisonis IS, Khabarova NV, Kirichenko YY. Modern Instrumental Methods of Diagnostics and Risk Assessment of Developing Antitumor Therapy Cardiovasculotoxicity. Kardiologiia. 2024;64(8):3–12. Russian. doi: 10.18087/cardio.2024.8.n2753.
21. Vasyuk YA, Novosel EO, Shupenina EY, Vyzhigin DA, Khabarova NV, Belenkov YN. Results of a Single-Center Prospective Observational Study: How to Take Care of the Heart of a Cancer Patient. Kardiologiia. 2025;65(8):12–21. Russian. doi: 10.18087/cardio.2025.8.n2944.
22. Kononchuk NB, Grigorenko EA, Mitkovskaya NP. Cardiovascular risk factors in patients with breast cancer before initiating antitumor therapy. Cardiology in Belarus. 2025;17(4):526–537. Russian. doi: 10.34883/PI.2025.17.4.004.
23. Satalkina TS, Brodskaya TA, Geltser BI, Kotelnikov VN. Arterial stiffness and 24-hour blood pressure profile in women with breast cancer before and after chemotherapy with doxorubicin and cyclophosphamide. Russ J Cardiol. 2025;30(2):5920. Russian. doi: 10.15829/1560-4071-2025-5920.
24. Berezikova EN, Shilov SN, Popova AA, Neupokoeva MN, Teplyakov AT, Grakova EV, et al. Course of arterial hypertension during breast cancer chemotherapy with anthracyclines. Bull Sib Med. 2024;23(3):5–15. Russian. doi: 10.20538/1682-0363-2024-3-5-15.
25. Wernhart S, Fiorentini C, Glowka S, Madl B, Grill S, Kiechle M, et al. Evaluating cardiovascular risk factors in breast cancer survivors: The role of echocardiography and cardiopulmonary exercise testing in the Munich Cardio-Oncology-Exercise retrospective Registry. Int J Cardiol. 2025;436:133421. doi: 10.1016/j.ijcard.2025.133421.
26. Terui Y, Nochioka K, Ota H, Tada H, Sato H, Miyata S, et al. Risk Prediction Models of Cardiotoxicity in Patients With Breast Cancer: Multicenter Prospective CHECK HEART-BC Study. JACC Asia. 2026;6(2):229–241. doi: 10.1016/j.jacasi.2025.08.018.
27. Terluk A, Stefani L, Boyd A, Vo K, Byth K, Hui R, et al. Redefining anthracycline-related subclinical cardiotoxicity: 'Absolute' and 'relative' change in longitudinal strain. ESC Heart Fail. 2024;11(5):3210–3221. doi: 10.1002/ehf2.14884.
28. Li H, Li X, Tang S. Clinical Value of Cardiac Troponin I in Assessing Anthracycline-Induced Cardiotoxicity in Postoperative Breast Cancer Patients. Breast Cancer (Dove Med Press). 2026;18:580515. doi: 10.2147/BCTT.S580515.
29. Kaya AF, Özbek M. A multimodal approach to early detection of anthracycline-induced cardiotoxicity: complementary roles of left ventricular global longitudinal strain, left atrial reservoir strain, and high-sensitivity troponin I. J Cardiovasc Imaging. 2026;34(1):9. doi: 10.1186/s44348-026-00071-y.
30. Kozhukhov S, Dovganych N. The Prognostic Value of High-Sensitive Troponin T Rise Within the Upper Reference Limit in Breast Cancer: A Prospective Pilot Study. Cancers (Basel). 2025;17(14):2412. doi: 10.3390/cancers17142412.

31. Fonoudi H, Jouni M, Cejas RB, Magdy T, Blancard M, Ge N, et al. Functional Validation of Doxorubicin-Induced Cardiotoxicity-Related Genes. JACC CardioOncol. 2024;6(1):38–50. doi: 10.1016/j.jaccao.2023.11.008.
32. Tanase DM, Valasciuc E, Anton IB, Gosav EM, Dima N, Cucu AI, et al. Matrix Metalloproteinases: Pathophysiologic Implications and Potential Therapeutic Targets in Cardiovascular Disease. Biomolecules. 2025;15(4):598. doi: 10.3390/biom15040598.

Figures

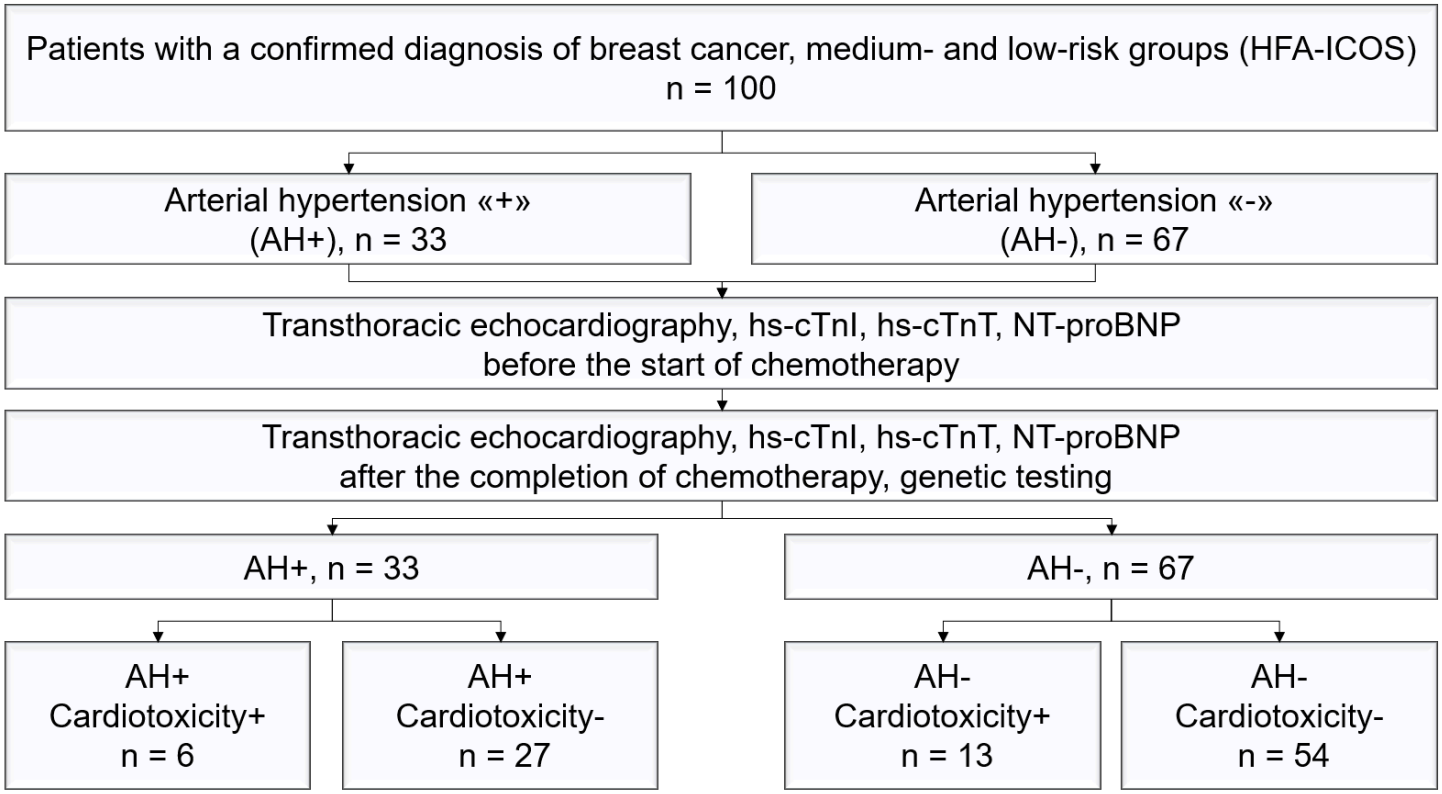


Figure 1

study design

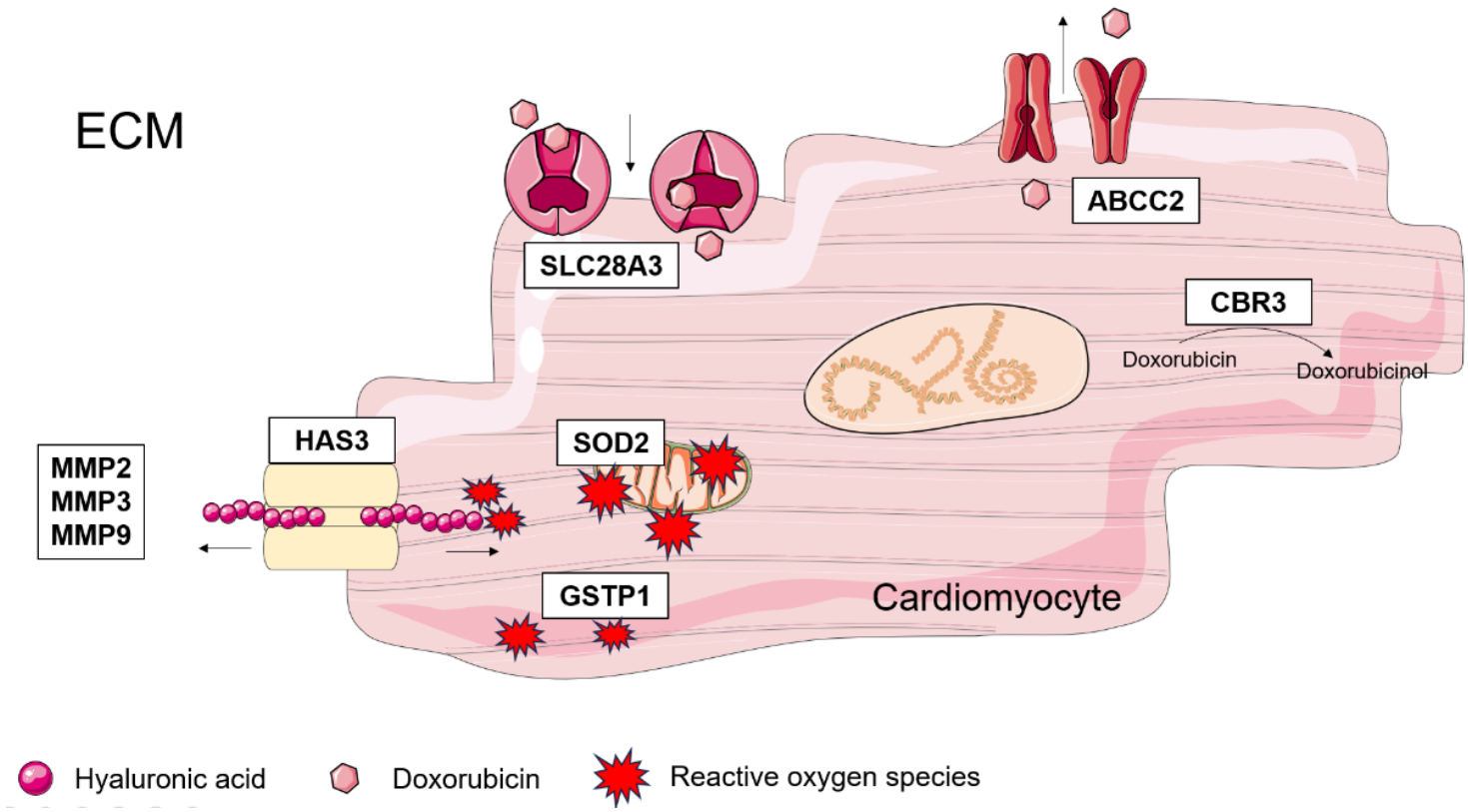


Figure 2

Pathophysiological rationale for the 15-gene polymorphism panel selection

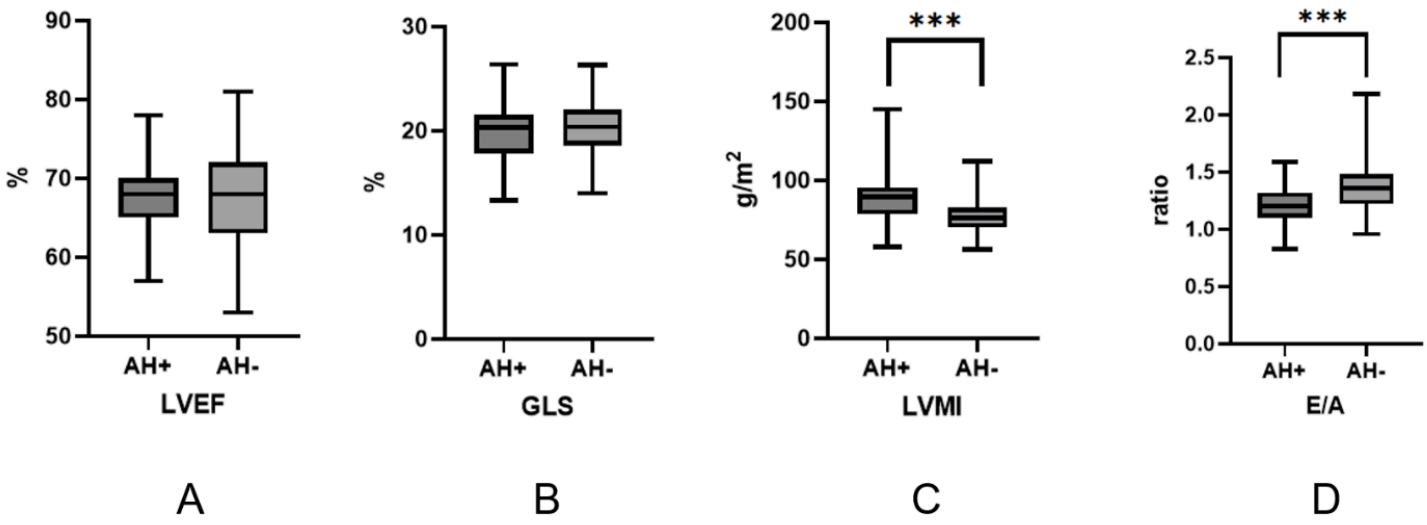


Figure 3

Comparison of baseline echocardiographic parameters between AH+ and AH– groups. (A) Left ventricular ejection fraction (LVEF); (B) Global longitudinal strain (GLS); (C) Left ventricular mass index

(LVMI); (D) E/A ratio. Data are presented as medians and interquartile ranges. Significant differences ($p < 0.05$) are indicated for structural and diastolic parameters, while systolic function remains comparable.

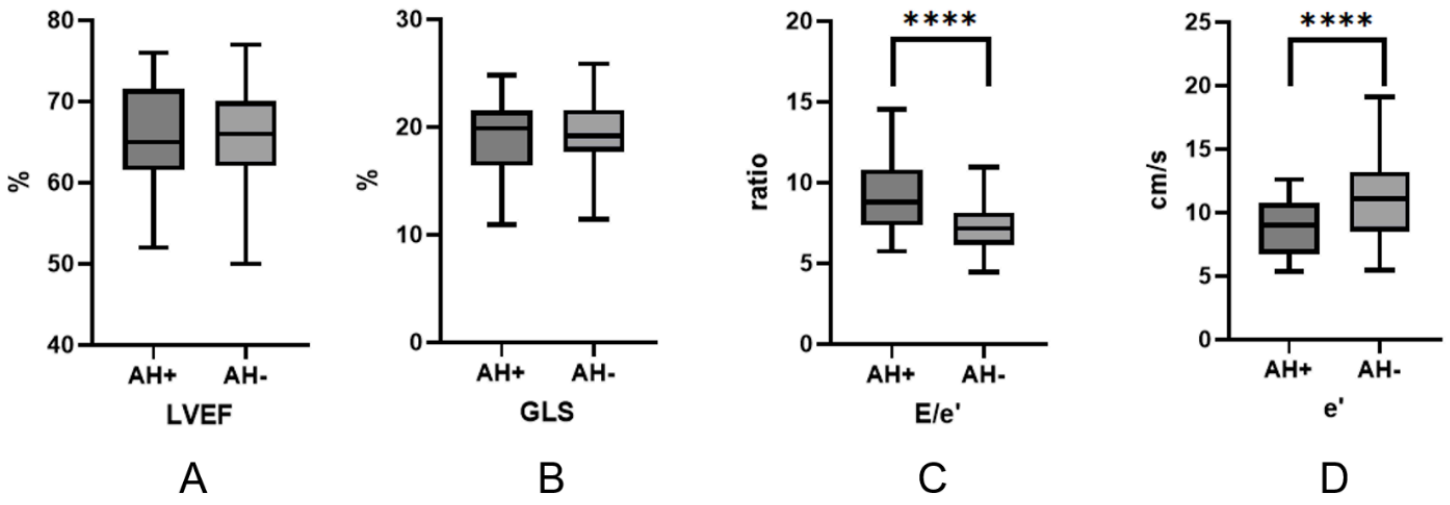


Figure 4

Post-chemotherapy systolic and diastolic myocardial function. (A) LVEF and (B) GLS remain comparable between groups. (C) Significant impairment of diastolic relaxation (e' velocity) and (D) increased LV filling pressure (E/e') in the AH+ group compared to the AH– group. Data are expressed as medians and interquartile ranges.

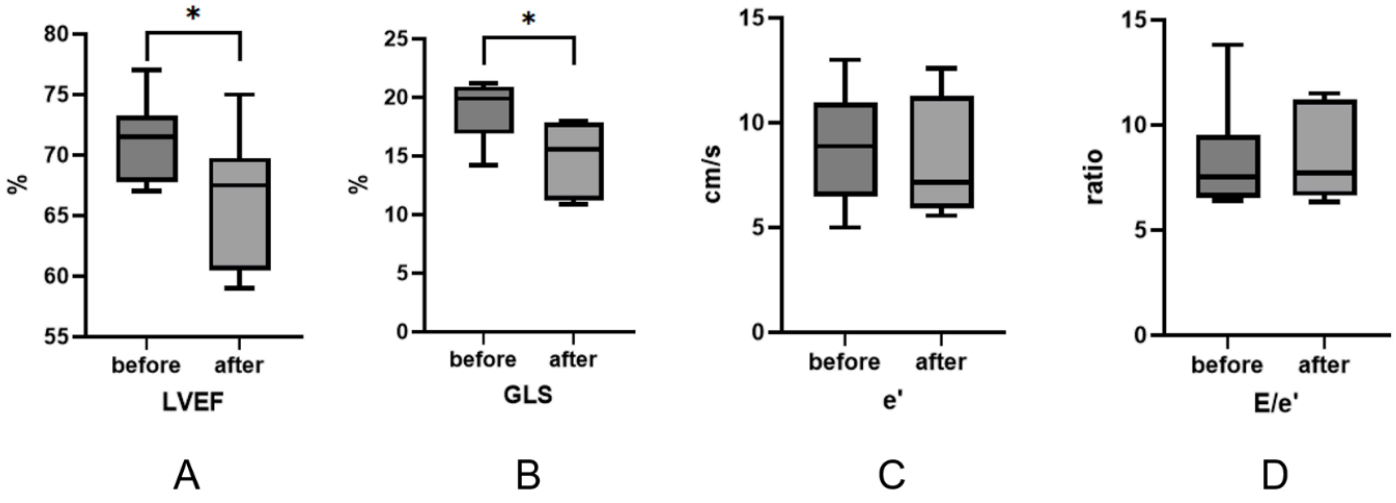


Figure 5

Longitudinal changes in myocardial function within the AH+ CTRCD+ subgroup. (A) Significant reduction in global longitudinal strain (GLS) and (B) left ventricular ejection fraction (LVEF) following chemotherapy. (C, D) Diastolic parameters (e’ velocity and E/e’ ratio) remain stably impaired, reflecting

pre-existing hypertensive heart disease without significant further decline. Data are presented as medians and interquartile ranges.

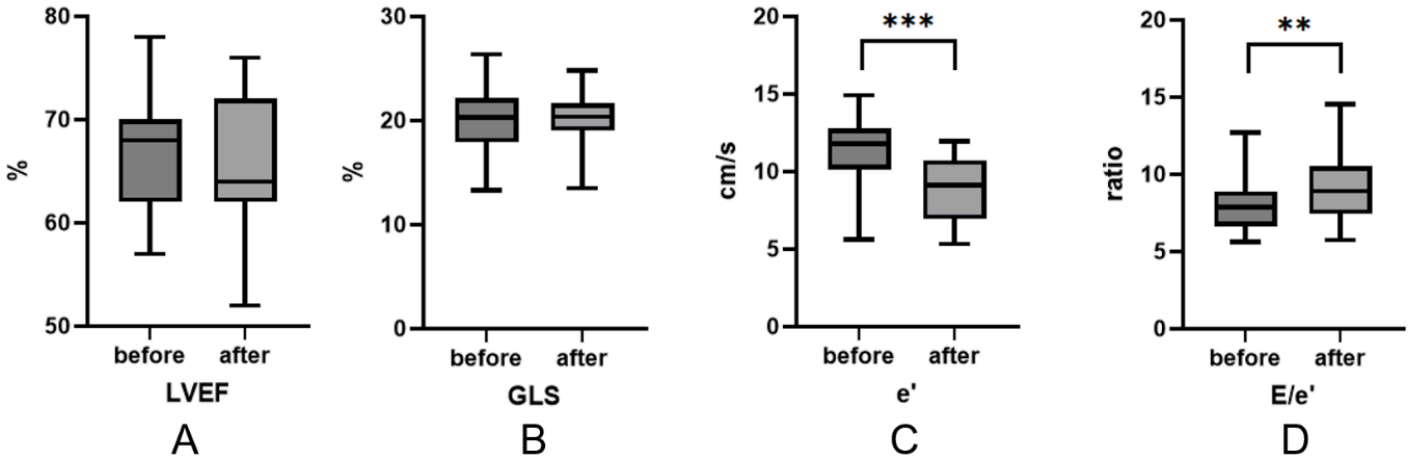


Figure 6

Dynamics of myocardial function in the AH+ CTRCD– subgroup (n = 27). Panels (A) and (B) demonstrate the stability of systolic markers (GLS and LVEF) throughout the treatment. Panels (C) and (D) illustrate a significant subclinical decline in diastolic performance, characterized by a reduction in e’ velocity ($p < 0.001$) and an elevation in E/e’ ratio ($p = 0.009$). This pattern represents a "hidden" diastolic phenotype of anthracycline-induced damage.

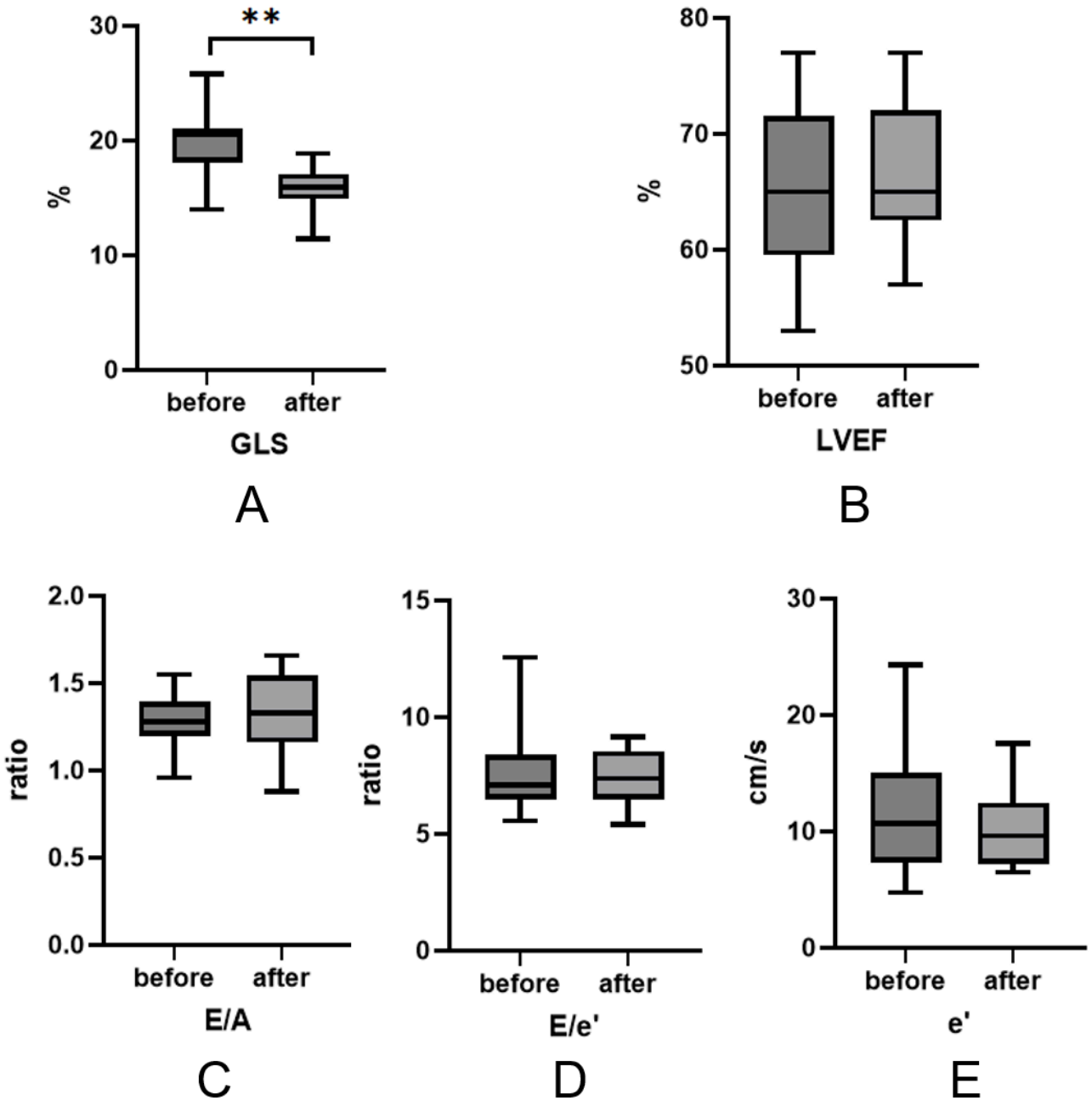


Figure 7

Dynamics of myocardial function in the AH– CTRCD+ subgroup. (A) Significant decline in global longitudinal strain (GLS) as the hallmark of subclinical systolic injury; (B) Stable left ventricular ejection fraction (LVEF); (C–E) Diastolic parameters, including (C) e’ velocity, (D) E/e’ ratio, and (E) E/A ratio, showing no significant changes. Data are presented as medians and interquartile ranges. p-values reflect the significance of intra-subgroup changes before and after CTx.

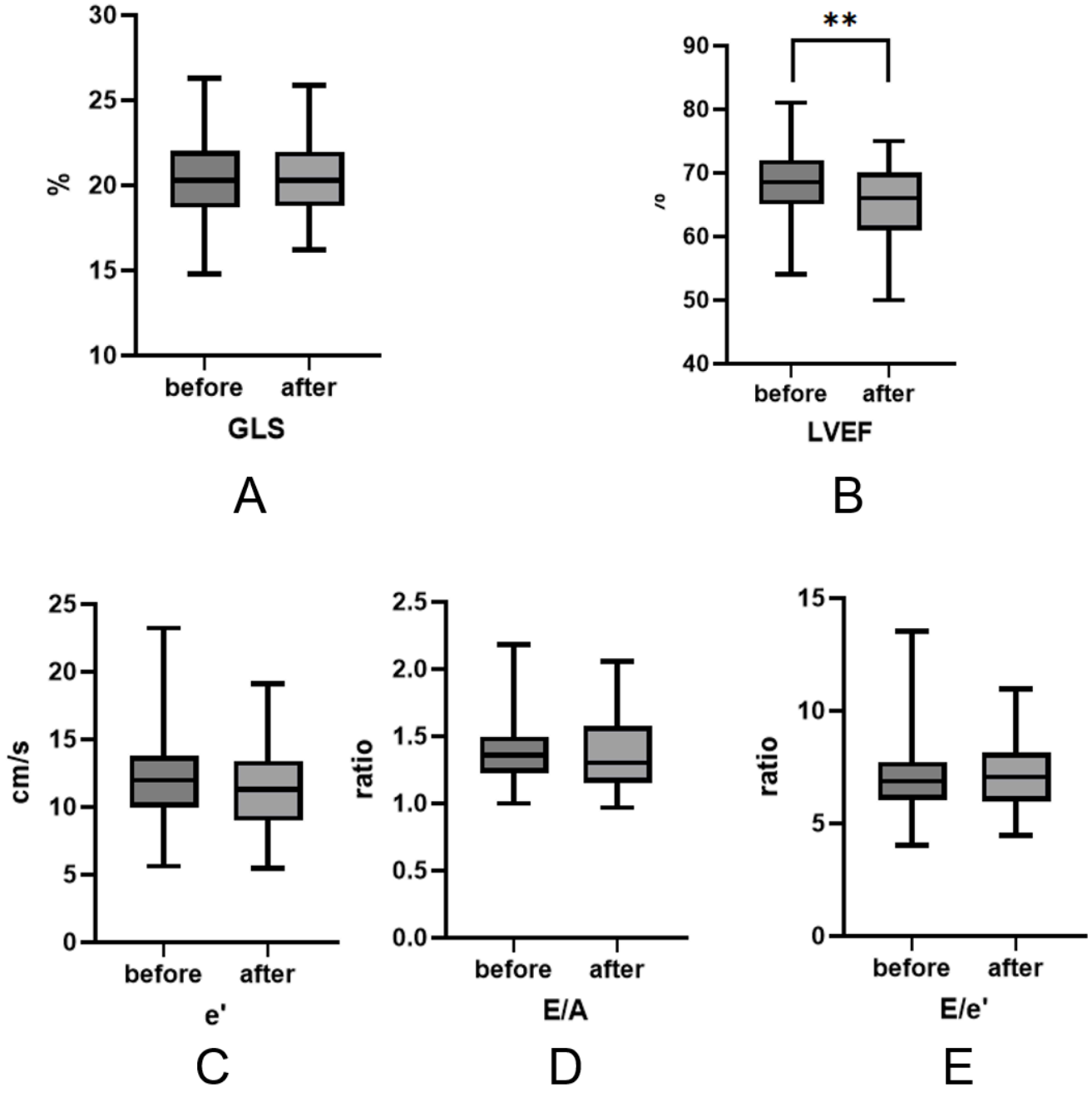


Figure 8

Stability of myocardial function in the AH– CTRCD– subgroup. (A) Stability of global longitudinal strain (GLS) during follow-up; (B) Statistically significant but minor reduction in left ventricular ejection fraction (LVEF) within the normal physiological range; (C–E) Preservation of diastolic parameters, including (C) e' velocity, (D) E/e' ratio, and (E) E/A ratio. Data are presented as medians and interquartile ranges. p-values represent the significance of intra-subgroup changes after chemotherapy.

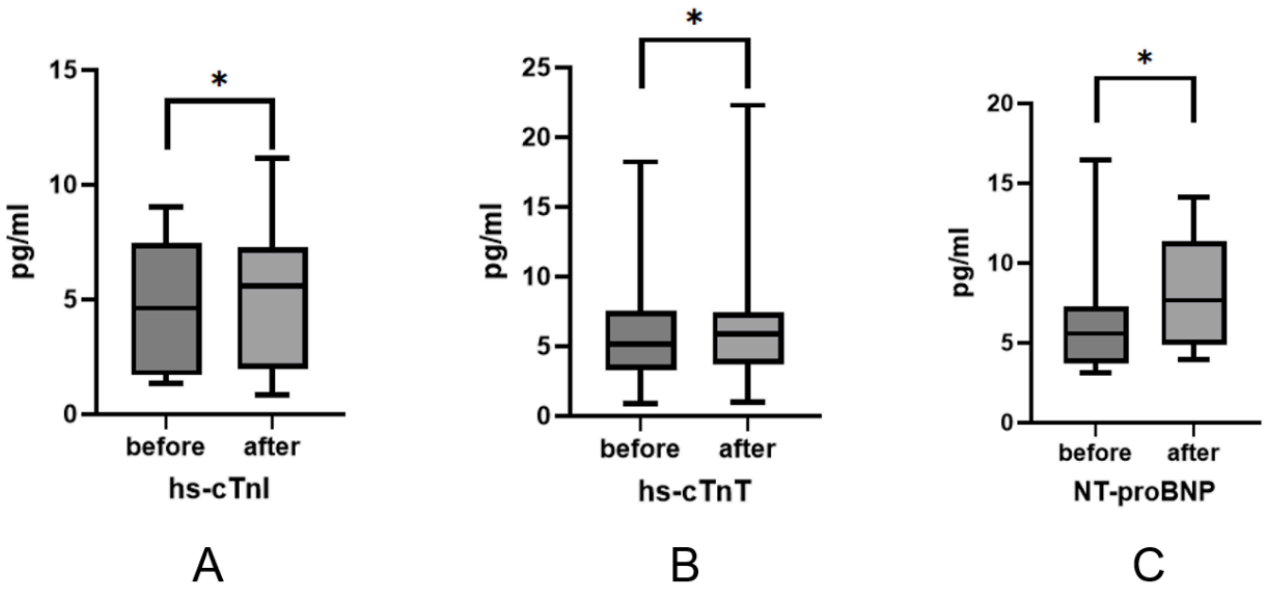


Figure 9

Distinct biochemical response patterns in AH+ and AH– groups following doxorubicin exposure. (A, B) Significant increase in high-sensitivity (A) cTnI and (B) cTnT levels within the AH+ CTRCD– subgroup, indicating subclinical cardiomyocyte injury; (C) Pronounced elevation of NT-proBNP levels in the AH– CTRCD+ subgroup, reflecting hemodynamic stress associated with systolic dysfunction. Data are presented as medians and interquartile ranges.

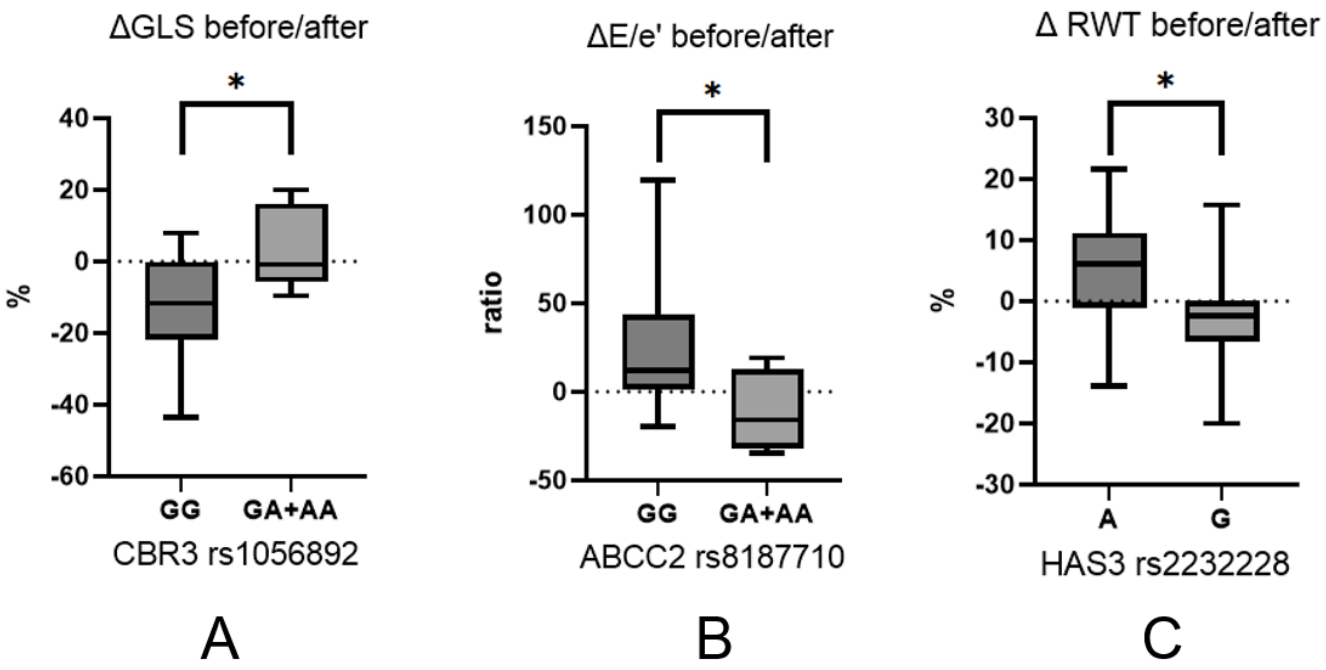


Figure 10

Key genetic associations with echocardiographic parameters in the AH+ group.

(A) Significant reduction in global longitudinal strain (GLS) in carriers of the CBR3 GG genotype (rs1056892); (B) Elevation of LV filling pressure (E/e’ ratio) in carriers of the ABCC2 GG genotype (rs8187710); (C) Increase in relative wall thickness (RWT) associated with the HAS3 A allele (rs2232228) and MMP2 C allele (rs243865). Data are presented as medians and interquartile ranges.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- KarputsIASupplementary.docx
- image2.png