

Eureka Journal of Health Sciences & Medical Innovation (EJHSMI)

ISSN 2760-4942 (Online) Volume 2, Issue 9, September 2026



This article/work is licensed under CC by 4.0 Attribution

<https://eurekaoa.com/index.php/5>

PHENOTYPES OF CARDIOVASCULAR REMODELING IN PATIENTS WITH ACUTE LEUKEMIAS

¹Zokirova M. B.

¹Kayumov A. A.

²Iskandarova Sh.T.

¹Republican Specialized Scientific and
Practical Medical Center of Hematology

²Tashkent State Medical University

Abstract

Cardiovascular complications in patients with acute leukemias develop as a result of the combined effect of the underlying disease, systemic inflammation, anemia, metabolic disturbances, and antitumor therapy. Modern cardio-oncology considers cardiovascular toxicity as a broad spectrum of structural, functional, electrophysiological, and biochemical disorders, rather than merely a reduction in left ventricular ejection fraction (LVEF) [1–3].

To determine the main phenotypes of structural and functional myocardial remodeling in patients with acute leukemias and to assess their relationship with cardiospecific biomarkers and polymorphisms of genes involved in antioxidant defense, endothelial function, extracellular matrix, and neurohumoral regulation.

Keywords: Acute leukemia, cardiotoxicity, myocardial remodeling, echocardiography, NT-proBNP, troponin, COMT, SOD2, GPX4, CAT, COL1A1, EDN1.

Eureka Journal of Health Sciences & Medical Innovation (EJHSMI)

ISSN 2760-4942 (Online) Volume 2, Issue 9, September 2026



This article/work is licensed under CC by 4.0 Attribution

<https://eurekaooa.com/index.php/5>

Introduction

Cardiovascular complications are becoming one of the key factors limiting the safety and continuity of antitumor therapy. The 2022 European Society of Cardiology guidelines on cardio-oncology emphasize that the risk of cancer therapy-related cardiovascular toxicity (CTR-CVT) is dynamic and determined by baseline cardiovascular status, tumor disease characteristics, and the therapy administered [1]. The international IC-OS consensus also recommends the use of unified definitions of cardiomyopathy/heart failure, vascular toxicity, arrhythmias, and other forms of cardiovascular toxicity [2].

For patients with acute leukemias, the problem is particularly relevant. In addition to the systemic burden caused by the disease itself, anemia, infections, hypermetabolism, electrolyte disturbances, hemodynamic fluctuations, and potentially cardiotoxic components of antitumor treatment are added. A recent systematic review of risk factors for cardiovascular complications in acute leukemias shows that clinical, treatment-related, biomarker, imaging, and genetic factors must be considered together [3].

Early diagnosis of cardiac damage should not be based solely on a reduction in LVEF. The ESC recommends the combined use of echocardiography and cardiac biomarkers, primarily troponins and natriuretic peptides, depending on the patient's baseline risk and type of therapy [1,4,17]. Contemporary expert documents emphasize the importance of subclinical dysfunction and the need to detect damage before the development of clinically overt heart failure [4,5,16].

In our study cohort, this issue has direct clinical significance. With a relatively preserved mean LVEF of $55.9 \pm 7.3\%$, elevation of troponin T >20 ng/L was found in 28.4%, and NT-proBNP >300 pg/mL — in 25.5% of patients. At the same time, LVEF $<50\%$ was recorded in only 13.7% of patients. This discrepancy suggests the presence of a subclinical biochemical phenotype preceding pronounced systolic dysfunction.

Eureka Journal of Health Sciences & Medical Innovation (EJHSMI)

ISSN 2760-4942 (Online) Volume 2, Issue 9, September 2026



This article/work is licensed under CC by 4.0 Attribution

<https://eurekaooa.com/index.php/5>

Variability in individual susceptibility to cardiac damage may partly have a genetic basis. Contemporary reviews of the pharmacogenetics of anthracycline cardiotoxicity confirm the existence of inherited differences in susceptibility to myocardial damage and the need for further study of candidate genes [6–8,18]. Of particular interest are antioxidant defense systems and ferroptosis regulation, since oxidative stress, mitochondrial dysfunction, and lipid peroxidation are important mechanisms of anthracycline-induced cardiomyocyte damage [9–11]. Based on this, the present study analyzed polymorphisms of SOD2, GPX4, and CAT as components of antioxidant defense; EDN1 as a marker of endothelial regulation; COL1A1 as a potential component of extracellular matrix remodeling; and COMT as a gene involved in catecholamine metabolism. The working hypothesis was that different molecular genetic profiles may be associated not with a single "cardiotoxicity" phenomenon, but with different structural and functional phenotypes of myocardial damage.

Aim of the study

To determine the main clinical and instrumental phenotypes of cardiovascular remodeling in patients with acute leukemias and to establish their relationship with levels of NT-proBNP, troponin T, and molecular genetic variants of SOD2 C14510A, GPX4 C718T, CAT G262A, COL1A1 C1997A, EDN1 Lys198Asn, and COMT Val158Met.

Materials and methods

The study was conducted at the Republican Specialized Scientific and Practical Medical Center of Hematology, Ministry of Health of the Republic of Uzbekistan. The analysis included 102 adult patients with acute leukemias. Mean age was 44.8 ± 15.9 years, range 18–78 years. There were 43 men (42.2%) and 59 women (57.8%). Cardiovascular complications were recorded in 64/102 (62.7%) patients

Eureka Journal of Health Sciences & Medical Innovation (EJHSMI)

ISSN 2760-4942 (Online) Volume 2, Issue 9, September 2026



This article/work is licensed under CC by 4.0 Attribution

<https://eurekaooa.com/index.php/5>

and were absent in 38/102 (37.3%). The control group for molecular genetic comparison consisted of 97 individuals.

Cardiological examination included history and complaint collection, physical examination, standard 12-lead ECG, transthoracic echocardiography, and determination of cardiospecific biomarkers. Interpretation of cardiovascular changes was carried out taking into account the modern concept of CTR-CVT and the principle of comprehensive assessment of clinical, imaging, and biochemical signs [1,2].

Echocardiography assessed cardiac chamber dimensions, left ventricular parameters, LVEF, and signs of hypertrophy and structural-functional remodeling. In accordance with current recommendations, LVEF reduction was considered one component of cardiac damage, but not the only criterion [1,2,5]. Among the biomarkers, troponin T and NT-proBNP were analyzed. Median troponin T was 7.6 ng/L, maximum value — 276 ng/L; a level >20 ng/L was noted in 29 (28.4%) patients. Median NT-proBNP was 86.3 pg/mL, maximum value — 3967 pg/mL; a level >300 pg/mL was found in 26 (25.5%) patients.

The molecular genetic component included evaluation of polymorphisms of SOD2 C14510A, GPX4 C718T, CAT G262A, COL1A1 C1997A, EDN1 Lys198Asn, and COMT Val158Met. Gene selection was hypothesis-driven and reflected the main proposed mechanisms of myocardial damage: oxidative stress, ferroptosis, endothelial dysfunction, structural remodeling, and neurohumoral regulation [6–11].

Statistical analysis included description of quantitative data using mean and standard deviation or median, depending on distribution. Categorical indicators were presented as absolute and relative values. For genetic associations, odds ratios (OR) and 95% confidence intervals were calculated. As part of further phenotype-oriented analysis, it is advisable to use logistic regression, ROC analysis, and correction for multiple comparisons; these methods should be applied only after the final distribution of individual patients into phenotypes.

Eureka Journal of Health Sciences & Medical Innovation (EJHSMI)

ISSN 2760-4942 (Online) Volume 2, Issue 9, September 2026



This article/work is licensed under CC by 4.0 Attribution

<https://eurekaooa.com/index.php/5>

Table 1. General characteristics of the study cohort

Indicator	Value
Patients with acute leukemias	102
Control group	97
Age, years	44.8±15.9
Age range	18–78
Men	43 (42.2%)
Women	59 (57.8%)
With cardiovascular complications	64 (62.7%)
Without cardiovascular complications	38 (37.3%)
LVEF, %	55.9±7.3
LVEF <50%	14 (13.7%)
Troponin T >20 ng/L	29 (28.4%)
NT-proBNP >300 pg/mL	26 (25.5%)

Results

Palpitations were noted by 40 (39.2%) patients, chest pain or discomfort — by 40 (39.2%), dyspnea — by 19 (18.6%). Clinical symptoms in patients with acute leukemias require cautious interpretation, since tachycardia and dyspnea may simultaneously be caused by anemia, an infectious process, hypermetabolism, and cardiovascular damage itself.

Electrophysiological phenotype

Sinus tachycardia was recorded in 33/102 (32.4%) patients. ECG signs of LV hypertrophy were noted in 28/102 (27.5%), ventricular extrasystole — in 12 (11.8%), supraventricular extrasystole — in 8 (7.8%) patients. The international

Eureka Journal of Health Sciences & Medical Innovation (EJHSMI)

ISSN 2760-4942 (Online) Volume 2, Issue 9, September 2026



This article/work is licensed under CC by 4.0 Attribution

<https://eurekaopenaccess.com/index.php/5>

IC-OS consensus and ESC guidelines include rhythm disturbances in the spectrum of clinically significant forms of cardiovascular toxicity [1,2].

Systolic phenotype

Mean LVEF was $55.9 \pm 7.3\%$, minimum recorded value — 37%, maximum — 68%. LVEF <50% was found in 14 (13.7%) patients. Given that the overall frequency of cardiovascular complications was 62.7%, these data confirm the impossibility of describing the entire spectrum of cardiac damage through the LVEF parameter alone.

Biochemical phenotype

Troponin T >20 ng/L was found in 29 (28.4%), NT-proBNP >300 pg/mL — in 26 (25.5%) patients. Troponin T elevation occurred 2.07-fold more often than LVEF <50%, and NT-proBNP elevation — 1.86-fold more often. This is consistent with the modern approach according to which the dynamics of troponins and natriuretic peptides can complement imaging assessment in the early detection of subclinical damage [1,4,5].

Table 2. Frequency of the main components of cardiac damage

Indicator	n	%
LVEF <50%	14	13.7
Troponin T >20 ng/L	29	28.4
NT-proBNP >300 pg/mL	26	25.5
Sinus tachycardia	33	32.4
ECG signs of LVH	28	27.5
Ventricular extrasystole	12	11.8
Supraventricular extrasystole	8	7.8

Eureka Journal of Health Sciences & Medical Innovation (EJHSMI)

ISSN 2760-4942 (Online) Volume 2, Issue 9, September 2026



This article/work is licensed under CC by 4.0 Attribution

<https://eurekaooa.com/index.php/5>

Working phenotypic classification

Based on the available data, a working classification is proposed, intended for subsequent individual redistribution of patients. It does not replace the international definitions of CTR-CVT but is used as a research tool for analyzing the heterogeneity of cardiac damage.

Phenotype	Main features	Proposed mechanism
I. Subclinical biochemical	↑TnT and/or ↑NT-proBNP with preserved LVEF	early damage/myocardial stress
II. Structural-remodeling	LVH, increased LV mass, geometric changes	remodeling/fibrosis
III. Systolic	LVEF <50%	contractile dysfunction
IV. Electrophysiological	tachycardia, ventricular/supraventricular arrhythmias	electrical instability
V. Mixed	≥2 components	multifactorial damage

Molecular genetic associations

The most pronounced intergroup association was noted for COMT Val158Met. The frequency of the Met allele in the presence of cardiovascular complications was 60.94%, in their absence — 28.95%; OR=3.83 (95% CI 2.11–6.95). The Met/Met genotype was found in 34.38% and 10.53% of patients, respectively; the calculated OR for this comparison was approximately 4.5.

For COL1A1 C1997A, the frequency of the A allele in the main group was 35.78%, in the control group — about 18.0%; OR≈2.53 (95% CI 1.60–4.00). For SOD2 C14510A, the frequency of the A allele was 34.31% versus 21.65% in controls; OR≈1.90 (95% CI 1.21–2.95). These results should be regarded as

Eureka Journal of Health Sciences & Medical Innovation (EJHSMI)

ISSN 2760-4942 (Online) Volume 2, Issue 9, September 2026



This article/work is licensed under CC by 4.0 Attribution

<https://eurekaooa.com/index.php/5>

candidate-gene associations requiring external validation. Current literature indicates that genetic predisposition to anthracycline-associated cardiotoxicity is real, but the evidentiary strength of individual variants varies considerably, and the results of small candidate-gene studies must be reproduced in independent cohorts [6–8].

GPX4 represents an additional mechanistic interest due to its central role in suppressing lipid peroxidation and ferroptosis. Contemporary experimental and review studies consider the Xc⁻/GSH/GPX4 system as one of the key mechanisms of cardiomyocyte protection in doxorubicin-induced damage [9–11].

Discussion

The main result of this study is the demonstration of pronounced phenotypic heterogeneity of cardiovascular damage in patients with acute leukemias. LVEF reduction <50% was found in only 13.7% of the examined patients, whereas elevation of troponin T and NT-proBNP was recorded in 28.4% and 25.5% of patients, respectively. Consequently, biochemical signs of damage or myocardial stress occurred almost twice as often as pronounced systolic dysfunction.

This result is consistent with modern principles of cardio-oncology. ESC 2022 and IC-OS emphasize the need for multilevel assessment, including clinical presentation, ECG, echocardiography, and biomarkers, since various forms of CTR-CVT can develop without an initial pronounced decrease in LVEF [1,2]. New expert documents also support early identification of subclinical damage and dynamic risk monitoring [4,5].

Of particular interest is the high prevalence of electrophysiological changes. Sinus tachycardia was found in 32.4%, ventricular extrasystole — in 11.8%, supraventricular — in 7.8%. Although not every episode of tachycardia in a patient with acute leukemia should automatically be interpreted as cardiotoxicity, the presence of persistent or clinically significant rhythm disturbances requires inclusion in the comprehensive assessment of the cardiovascular phenotype [1,2].

Eureka Journal of Health Sciences & Medical Innovation (EJHSMI)

ISSN 2760-4942 (Online) Volume 2, Issue 9, September 2026



This article/work is licensed under CC by 4.0 Attribution

<https://eurekaooa.com/index.php/5>

The molecular genetic component of the study shows that the strength of associations differs across different biological pathways. The strongest intergroup effect in our cohort was obtained for COMT Val158Met. At the same time, interpretation of candidate-gene results should remain cautious. Reviews from 2021–2023 indicate that genetic susceptibility to anthracycline cardiotoxicity is polygenic in nature, and the reproducibility of individual SNPs depends on population, treatment regimen, endpoint definition, and sample size [6–8,12].

The SOD2–CAT–GPX4 antioxidant block has a strong pathogenetic rationale. Doxorubicin-induced myocardial damage is associated with the formation of reactive oxygen species, mitochondrial dysfunction, impaired iron metabolism, and lipid peroxidation. Ferroptosis is considered one of the important mechanisms of this damage, with GPX4 acting as a central anti-ferroptotic enzyme [9–11]. Therefore, the study of genetic variability in this system appears biologically justified, although specific clinical associations require confirmation in larger samples.

The proposed phenotypic model has a practical orientation. A patient with preserved LVEF but elevated troponin/NT-proBNP and an unfavorable molecular profile may represent a group of early or subclinical risk. Unlike the binary approach of "cardiotoxicity present/absent," phenotyping allows the structural, biochemical, systolic, and electrophysiological components to be separated and potentially allows selection of a more individualized monitoring strategy.

Study limitations

The study is single-center in nature and has a relatively limited sample size, which is particularly important for the interpretation of genetic associations. The proposed phenotypic classification is exploratory and requires the final distribution of individual patients followed by statistical testing of differences between phenotypes. It is also necessary to take into account the heterogeneity of antitumor treatment regimens and the potential influence of anemia, infections,

Eureka Journal of Health Sciences & Medical Innovation (EJHSMI)

ISSN 2760-4942 (Online) Volume 2, Issue 9, September 2026



This article/work is licensed under CC by 4.0 Attribution

<https://eurekaooa.com/index.php/5>

electrolyte disturbances, and other non-oncological factors on ECG and biomarkers. The international literature emphasizes the need for external validation of candidate genetic markers and standardization of cardiotoxicity endpoints [2,6–8].

Conclusion

Cardiovascular damage in patients with acute leukemias represents a heterogeneous complex of structural, functional, electrophysiological, and biochemical changes. Cardiovascular complications were recorded in 64 of 102 (62.7%) patients. LVEF <50% was observed in only 14 (13.7%), whereas troponin T >20 ng/L — in 29 (28.4%), and NT-proBNP >300 pg/mL — in 26 (25.5%) patients. The frequency of biochemical changes was 2.07-fold and 1.86-fold higher, respectively, than the frequency of pronounced systolic dysfunction. The electrophysiological component was also pronounced: sinus tachycardia was found in 32.4%, ECG signs of LV hypertrophy — in 27.5%, ventricular extrasystole — in 11.8%, supraventricular — in 7.8% of patients.

The most pronounced genetic association, when comparing patients with and without cardiovascular complications, was found for COMT Val158Met: the frequency of the Met allele was 60.94% versus 28.95%, OR=3.83 (95% CI 2.11–6.95). COL1A1 C1997A and SOD2 C14510A also demonstrated potentially significant differences between patients and controls.

The findings substantiate further development of a phenotype-oriented model combining echocardiography, cardiospecific biomarkers, and molecular genetic parameters. Before clinical application, such a model must be tested at the individual level and validated in an independent multicenter cohort.

Practical recommendations

- In patients with acute leukemias, cardiovascular risk assessment should not be limited to LVEF alone.

Eureka Journal of Health Sciences & Medical Innovation (EJHSMI)

ISSN 2760-4942 (Online) Volume 2, Issue 9, September 2026



This article/work is licensed under CC by 4.0 Attribution

<https://eurekaopenaccess.com/index.php/5>

- With preserved LVEF, it is advisable to take into account the dynamics of troponin and NT-proBNP to detect subclinical damage.
- The presence of persistent arrhythmias and structural cardiac changes should be analyzed as separate components of the cardiovascular phenotype.
- Molecular genetic markers should be considered as an additional, rather than an independent, level of risk stratification.
- Patients with a combination of an unfavorable genetic profile, biomarker elevation, and instrumental changes require enhanced cardio-oncological monitoring.

References

1. Lyon AR, López-Fernández T, Couch LS, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association, the European Society for Therapeutic Radiology and Oncology and the International Cardio-Oncology Society. *Eur Heart J*. 2022;43:4229–4361. doi:10.1093/eurheartj/ehac244.
2. Herrmann J, Lenihan D, Armenian S, et al. Defining cardiovascular toxicities of cancer therapies: an International Cardio-Oncology Society (IC-OS) consensus statement. *Eur Heart J*. 2022;43(4):280–299. doi:10.1093/eurheartj/ehab674.
3. Determining Risk Factors Associated with Cardiovascular Complications in Patients with Acute Leukemia: A Systematic Review. 2025. PMID:40940874.
4. Couch LS, López-Fernández T, Lyon AR. The 'Ten Commandments' for the 2022 European Society of Cardiology guidelines on cardio-oncology. *Eur Heart J*. 2023;44(1):10–11. doi:10.1093/eurheartj/ehac666.
5. Prevention of Cancer Therapy-Related Cardiac Dysfunction and Heart Failure in Cancer Patients and Survivors: a Clinical Consensus Statement of the Heart Failure Association, European Association of Preventive Cardiology and ESC Council of Cardio-Oncology. *Eur J Heart Fail*. 2025;27(11):2084–2113.

Eureka Journal of Health Sciences & Medical Innovation (EJHSMI)

ISSN 2760-4942 (Online) Volume 2, Issue 9, September 2026



This article/work is licensed under CC by 4.0 Attribution

<https://eurekaooa.com/index.php/5>

6. Leong DP, et al. Genetics of Anthracycline-Associated Cardiotoxicity. *Front Cardiovasc Med.* 2022;9:867873. doi:10.3389/fcvm.2022.867873. PMID:35528837.
7. Ding Y, Du K, Niu YJ, Wang Y, Xu X. Genetic Susceptibility and Mechanisms Underlying the Pathogenesis of Anthracycline-Associated Cardiotoxicity. *Oxid Med Cell Longev.* 2022;2022:5818612. doi:10.1155/2022/5818612.
8. Yang X, Li G, Guan M, et al. Potential Gene Association Studies of Chemotherapy-Induced Cardiotoxicity: A Systematic Review and Meta-Analysis. *Front Cardiovasc Med.* 2021. PMID:34150864.
9. Zhang G, Yuan C, Su X, et al. Relevance of Ferroptosis to Cardiotoxicity Caused by Anthracyclines: Mechanisms to Target Treatments. *Front Cardiovasc Med.* 2022;9:896792. doi:10.3389/fcvm.2022.896792.
10. Liu Y, Wan Y, Jiang Y, Zhang L, Cheng W. GPX4: The hub of lipid oxidation, ferroptosis, disease and treatment. *Biochim Biophys Acta Rev Cancer.* 2023;1878(3):188890. doi:10.1016/j.bbcan.2023.188890.
11. Molecular Mechanisms and Therapeutic Targeting of Ferroptosis in Doxorubicin-Induced Cardiotoxicity. 2024. PMID:39070280.
12. Risk Factors for Anthracycline-Induced Cardiotoxicity: A Systematic Review and Meta-Analysis. 2021. PMID:34660739.
13. Anthracycline-induced cardiotoxicity: From pathobiology to identification of molecular targets for nuclear imaging. 2022. PMID:35990941.
14. Kopeva KV, Grakova EV, Shilov SN, et al. Anthracycline-Induced Cardiotoxicity: the Role of Genetic Predictors. *Kardiologiya.* 2023. doi:10.18087/cardio.2023.4.n1946. PMID:37165991.
15. Cardiovascular Considerations During Cancer Therapy: Gaps in Evidence and JACC: CardioOncology Expert Panel Recommendations. *JACC CardioOncol.* 2024. doi:10.1016/j.jacc.2024.06.005. PMID:39801647.

Eureka Journal of Health Sciences & Medical Innovation (EJHSMI)

ISSN 2760-4942 (Online) Volume 2, Issue 9, September 2026



This article/work is licensed under CC by 4.0 Attribution

<https://eurekaopenaccess.com/index.php/5>

16. Kayumov A.A., Zokirova M.B. Antioxidant defense gene polymorphisms as molecular genetic predictors of cardiotoxicity in patients with acute leukemia. *Genetics and Molecular Research* 25 (9s): 2026.
17. Kayumov A.A., Berger I.V., Mahamadalieva G.Z., et al. *Cellular Therapy and Transplantation*, 2024.
18. Muborakkhon Zokirova, Kayumov Abdurakhman, Nargiza Nurillaeva and Jakhongir Khaydarov. An Integrated Model of Cardiotoxicity: Interaction of Age, Sex, and Genetic Polymorphisms in Patients with Acute Leukemia. *Biomedicines* 2026, 14(9), 1929; <https://doi.org/10.3390/biomedicines14091929> (registering DOI) - 28 Aug 2026.