

Cardiotoxicity Associated with Antineoplastic Therapy: A Multidisciplinary Approach to Personalized Monitoring Using Radionuclide Imaging and Molecular Biomarkers

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Rezumat

Cardiotoxicitatea asociată terapiei antineoplazice: abordare multidisciplinară pentru monitorizarea personalizată prin imagistică radionuclidică și biomarkeri moleculari

Introducere: Cardiotoxicitatea asociată terapiei antineoplazice poate compromite atât prognosticul cardiovascular, cât și continuitatea tratamentului oncologic. Am evaluat o strategie multimodală bazată pe imagistică radionuclidică și biomarkeri moleculari pentru detectarea precoce a disfuncției cardiace subclinice și pentru monitorizarea personalizată aplicabilă în îngrijirea oncologică multidisciplinară.

Material și Metodă: În acest studiu prospectiv, observațional, monocentric, 90 de adulți cu cancer mamar, limfoame sau cancer pulmonar, tratați cu regimuri potențial cardiotoxice, au fost evaluați la momentul inițial (T0), după 3-4 cicluri (T1), la finalizarea tratamentului (T2) și la 6 luni de urmărire (T3). Expunerea oncologică a fost clasificată în funcție de profilul cardiotoxic dominant, incluzând regimuri cu antraciclina, terapie anti-HER2, chimioterapie pe bază de platină/taxani, imuno-terapie sau terapii țintite, atunci când au fost utilizate. Monitorizarea a inclus evaluare clinică, ECG, MUGA/gated SPECT, ecocardiografie cu LVEF și GLS, precum și determinări seriate de hs-Tn, NT-proBNP și sST2.

Rezultate: Vârsta mediană a fost de 56 de ani, iar 62% dintre pacienți au fost femei. LVEF medie la momentul inițial a fost $60 \pm 5\%$, iar GLS mediu $-19,5 \pm 2,1\%$. În timpul tratamentului, hs-Tn, NT-proBNP și sST2 au crescut progresiv, în timp ce LVEF a scăzut la $57 \pm 6\%$, iar GLS la $-16,6 \pm 2,5\%$ la finalizarea tratamentului. Disfuncția cardiacă definită imagistic a apărut la 30% dintre pacienți, inclusiv cardiotoxicitate manifestă la 10%. Modificările hs-Tn au prezentat cea mai puternică corelație cu GLS ($r = -0,42$, $p = 0,002$). Modelul integrat a avut cea mai bună performanță predictivă (ASC 0,91).

Concluzii: Dincolo de valoarea diagnostică, acest model multimodal poate susține decizia multidisciplinară în oncologia chirurgicală, prin identificarea pacienților care necesită supraveghere intensificată, cardioprotecție precoce optimizare preoperatorie

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sau adaptarea secvenței terapeutice. Rezultatele trebuie interpretate ca ipoteză clinică promițătoare, care necesită validare multicentrică înainte de implementarea de rutină.

Cuvinte cheie: cardiotoxicitate, terapie antineoplazică, imagistică radionuclidică, strain longitudinal global, biomarkeri, îngrijire multidisciplinară

Abstract

Background: Cardiotoxicity associated with antineoplastic therapy may compromise both cardiovascular outcomes and continuity of cancer treatment. We evaluated a multimodal strategy based on radionuclide imaging and molecular biomarkers for early detection of subclinical cardiac dysfunction and for personalized monitoring applicable in multidisciplinary oncologic care.

Methodology: In this prospective, observational, single-center study, 90 adults with breast cancer, lymphoma, or lung cancer receiving potentially cardiotoxic regimens were evaluated at baseline (T0), after 3-4 cycles (T1), at treatment completion (T2), and at 6-month follow-up (T3). Antineoplastic exposure was classified according to dominant cardiotoxic profile, including anthracycline-containing regimens, anti-HER2 therapy, platinum/taxane-based chemotherapy, immunotherapy, and targeted agents when used. Monitoring included clinical assessment, ECG, MUGA/gated SPECT, echocardiography with LVEF and GLS, and serial hs-Tn, NT-proBNP, and sST2.

Results: Median age was 56 years, and 62% of patients were women. Mean baseline LVEF was $60 \pm 5\%$ and mean GLS $-19.5 \pm 2.1\%$. During treatment, hs-Tn, NT-proBNP, and sST2 increased progressively, while LVEF declined to $57 \pm 6\%$ and GLS to $-16.6 \pm 2.5\%$ at treatment completion. Imaging-defined cardiac dysfunction occurred in 30% of patients, including overt cardiotoxicity in 10%. Changes in hs-Tn correlated most strongly with GLS ($r = -0.42$, $p = 0.002$). The integrated model showed the best predictive performance (AUC 0.91).

Conclusions: Beyond diagnostic value, this multimodal model may support multidisciplinary decision-making in surgical oncology by identifying patients who require intensified surveillance, early cardioprotection, preoperative optimization, or adjustment of treatment sequencing. The findings should be interpreted as clinically promising and hypothesis-generating, requiring multicenter validation before routine implementation.

Keywords: cardiotoxicity, antineoplastic therapy, radionuclide imaging, global longitudinal strain, biomarkers, multidisciplinary care

Introduction

The increasing effectiveness of contemporary cancer therapy has improved survival across multiple malignancies. At the same time, cardiovascular complications related to cancer treatment have become more frequent and clinically relevant. Cardiotoxicity is particularly important because it may compromise both cardiovascular prognosis and continuity of oncologic treatment (1,2). Surveillance has traditionally relied on left ventricular ejection fraction (LVEF), but LVEF often declines only after myocardial injury is already established (3). Earlier abnormalities may be detected through myocardial deformation analysis and biomarker dynamics, which can reveal subclinical dysfunction before overt heart failure develops (3,4).

In the present study, early surveillance was based on the integration of radionuclide imaging, echocardiographic global longitudinal strain (GLS), and a bio-

marker panel including high-sensitivity troponin (hs-Tn), NT-proBNP, and soluble ST2 (sST2). This approach is consistent with contemporary cardio-oncology recommendations that support baseline cardiovascular risk stratification and serial surveillance using imaging and biomarkers in patients receiving potentially cardiotoxic therapy (2,5). Radionuclide imaging offers reproducible ventricular function assessment, whereas biomarkers provide complementary information on myocardial injury, hemodynamic stress, and remodeling (6,7). In multimodal cancer care, early recognition of cardiac dysfunction may also influence surgical timing, perioperative risk estimation, and the safe continuation of systemic therapy.

The aim of the present study was to evaluate a multimodal strategy for early detection of antineoplastic therapy-related cardiotoxicity by combining radio-nuclide imaging, echocardiographic strain analysis, and circulating biomarkers, and to translate these findings into a clinically applicable model of

personalized monitoring within multidisciplinary cancer care.

Materials and Methods

Study Design and Population

This was a prospective, observational, single-center cohort study conducted at the Prof. Dr. Alexandru Trestioreanu Institute of Oncology, Bucharest. Patients were enrolled consecutively between January 1, 2023 and August 31, 2025 after ethics approval and written informed consent. The study included 90 adult patients with histologically confirmed breast cancer, lymphoma, or lung cancer scheduled to receive potentially cardiotoxic systemic treatment. The target size was approximately 30 patients per oncologic subgroup, allowing longitudinal assessment across serial evaluations.

Inclusion and Exclusion Criteria

Inclusion criteria were age >18 years, confirmed malignancy, indication for cardiotoxic chemotherapy or targeted therapy, documented baseline cardiac function, absence of overt heart failure at baseline, and signed informed consent. Exclusion criteria included advanced pre-existing heart failure, severe uncontrolled arrhythmias, contraindications to radionuclide imaging, advanced renal disease, and major cardiovascular comorbidities that could confound evaluation of treatment-related cardiac dysfunction.

Antineoplastic Therapy Exposure

Antineoplastic exposure was recorded from oncology charts and classified according to the dominant cardiotoxic profile. Categories included anthracycline-containing chemotherapy, anti-HER2 therapy, platinum- or taxane-based cytotoxic regimens, immune checkpoint inhibitors, targeted agents, and thoracic or mediastinal radiotherapy exposure when present. For breast cancer, monitoring mainly addressed anthracycline and anti-HER2 sequences; for lymphoma, anthracycline-containing protocols and previous mediastinal radiotherapy; and for lung cancer, platinum-based chemotherapy, taxane or pemetrexed combinations, immune checkpoint inhibitors, and targeted agents when indicated. This classification was used for descriptive interpretation of subgroup differences; the study was not powered to compare individual regimens.

Monitoring Schedule

Patients were evaluated at four predefined time points: before initiation of therapy (T0), after 3-4 cycles or approximately 6-8 weeks after treatment initiation (T1), at completion of planned antineoplastic therapy (T2), and at approximately 6 months after treatment completion (T3). At each time point, patients underwent cardiovascular clinical examination, ECG, biomarker testing, and imaging assessment according to protocol.

Imaging Protocol

Cardiac imaging included radionuclide imaging by MUGA/gated SPECT and transthoracic echocardiography with 2D/3D LVEF assessment and GLS analysis. Radionuclide imaging was used for assessment of left ventricular ejection fraction and regional wall motion, particularly at baseline and in higher-risk cases or when biological warning signals were present. Echocardiography was performed with strain assessment, and a relative reduction in GLS of at least 15% from baseline was considered indicative of subclinical dysfunction. Cardiac magnetic resonance imaging was used selectively when further tissue characterization or clarification of inconclusive findings was required.

Biomarker Assessment

The biomarker panel included high-sensitivity troponin (hs-Tn), NT-proBNP, and soluble ST2 (sST2). These markers were selected because they reflect complementary mechanisms: hs-Tn for myocardial injury, NT-proBNP for ventricular wall stress and dysfunction, and sST2 for remodeling, inflammation, and fibrosis. Samples were collected at all four study time points under standardized conditions and processed using validated laboratory platforms.

Biomarker thresholds were predefined for longitudinal surveillance. A biological warning signal was considered present when hs-Tn rose above the assay-specific 99th percentile upper reference limit or increased more than twofold from baseline; when NT-proBNP increased more than twofold from baseline or exceeded the age- and renal function-adjusted laboratory reference range; or when sST2 was ≥ 35 ng/mL or increased by at least 25% from baseline. These thresholds were interpreted together with imaging findings and clinical context, rather than as standalone diagnostic criteria. For multivariable modeling, hs-Tn $>2\times$ baseline was retained as the biomarker variable with the strongest association with GLS deterioration.

Definitions

Overt cancer therapy-related cardiac dysfunction was defined as an LVEF decrease of at least 10 percentage points to below 50% (3). Subclinical dysfunction was defined as a relative reduction in GLS of at least 15% compared with baseline, even in the absence of an abnormal LVEF (8). Imaging-defined dysfunction in the present study included both overt cardiotoxicity and subclinical myocardial dysfunction.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 29.0. Descriptive statistics were used for demographic, oncologic, and cardiovascular characteristics. Longitudinal changes in LVEF, GLS, and biomarkers across T0-T3 were evaluated using repeated-measures methods. Correlations between imaging and biomarker variables were assessed using Pearson or Spearman coefficients depending on variable distribution. Multivariable logistic regression was used to identify independent predictors of cardiotoxicity. ROC analysis and decision-curve analysis were used to assess predictive performance and clinical utility of the integrated model.

Results

Baseline Characteristics

Baseline demographic and cardiovascular characteristics of the study population are summarized in

Table 1. The median age of the overall cohort was 56 years (48-64), and 62% of patients were women. The cohort included equal numbers of patients with breast cancer, lymphoma, and lung cancer. Baseline cardiovascular risk factors included hypertension, dyslipidemia, diabetes, smoking, and prior mediastinal radiotherapy, supporting the relevance of individualized baseline risk assessment in this population. At T0, no patient had overt clinical heart failure. Baseline ventricular function was preserved, with mean LVEF of $60 \pm 5\%$ and mean GLS of $-19.5 \pm 2.1\%$, without significant differences between oncologic subgroups. However, patients with cardiovascular risk factors already showed slightly less negative GLS values despite preserved LVEF, suggesting possible baseline vulnerability detectable by strain imaging rather than by conventional systolic function alone.

Biomarker Dynamics

Serial changes in imaging and biomarker parameters during follow-up are summarized in *Table 2*. LVEF showed a gradual decline during treatment with partial recovery at follow-up, whereas GLS deteriorated earlier and more markedly. Biomarkers displayed a sequential pattern, with early hs-Tn elevation, progressive NT-proBNP increase, and more persistent sST2 elevation. This pattern is compatible with progressive biological stages of cardiotoxicity, from early injury to hemodynamic stress and remodeling.

Post-hoc analyses showed significant early increases in hs-Tn from T0 to T1 and from T0 to T2, followed by partial reduction at T3. NT-proBNP and sST2

Table 1. Baseline characteristics of the study population

Variable	Breast cancer (n=30)	Lymphoma (n=30)	Lung cancer (n=30)	Total (n=90)
Age (years), median (IQR)	54 (46–62)	49 (38–60)	63 (56–69)	56 (48–64)
Women, n (%)	30 (100%)	16 (53%)	10 (33%)	56 (62%)
Men, n (%)	0 (0%)	14 (47%)	20 (67%)	34 (38%)
ECOG 0–1, n (%)	27 (90%)	26 (87%)	24 (80%)	77 (86%)
Active smoking, n (%)	5 (17%)	7 (23%)	14 (47%)	26 (29%)
Hypertension, n (%)	13 (43%)	10 (33%)	11 (37%)	34 (38%)
Dyslipidemia, n (%)	12 (40%)	9 (30%)	10 (33%)	31 (34%)
Diabetes mellitus, n (%)	5 (17%)	4 (13%)	5 (17%)	14 (16%)
Prior mediastinal radiotherapy	0 (0%)	9 (30%)	1 (3%)	10 (11%)
Advanced stage (III–IV), n (%)	9 (30%)	18 (60%)	22 (73%)	49 (54%)
Baseline LVEF (%), mean $\pm$ SD	61 $\pm$ 5	60 $\pm$ 5	59 $\pm$ 6	60 $\pm$ 5
Baseline GLS (%), mean $\pm$ SD	-19.8 $\pm$ 2.0	-19.6 $\pm$ 2.2	-19.0 $\pm$ 2.1	-19.5 $\pm$ 2.1
hs-Tn (ng/L), median (IQR)	4 (3–7)	5 (3–8)	6 (4–9)	5 (3–8)
NT-proBNP (pg/mL), median (IQR)	105 (70–180)	120 (80–190)	145 (90–210)	125 (80–190)
sST2 (ng/mL), median (IQR)	24 (19–31)	26 (20–34)	28 (22–37)	26 (20–34)

Abbreviations: ECOG, Eastern Cooperative Oncology Group performance status; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; hs-Tn, high-sensitivity troponin; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sST2, soluble suppression of tumorigenicity-2.

Table 2. Serial changes in imaging and biomarker parameters during follow-up (T0–T3)

Parameter	T0 (Baseline)	T1 (6–8 weeks)	T2 (End of treatment)	T3 (6-month follow-up)	p value (global)
LVEF (%), mean $\pm$ SD	60 $\pm$ 5	59 $\pm$ 5	57 $\pm$ 6	58 $\pm$ 6	<0.001
GLS (%), mean $\pm$ SD	-19.5 $\pm$ 2.1	-18.2 $\pm$ 2.3	-16.6 $\pm$ 2.5	-17.3 $\pm$ 2.4	<0.001
hs-Tn (ng/L), median (IQR)	5 (3–8)	11 (7–19)	15 (10–25)	8 (5–13)	<0.001
NT-proBNP (pg/mL), median (IQR)	120 (80–190)	175 (120–270)	210 (150–320)	160 (110–230)	<0.001
sST2 (ng/mL), median (IQR)	26 (20–34)	29 (23–37)	33 (26–42)	30 (24–39)	0.015

Abbreviations: LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; hs-Tn, high-sensitivity troponin; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sST2, soluble suppression of tumorigenicity-2. Imaging values are expressed as mean $\pm$ SD; biomarker values are expressed as median (IQR). Biomarker analysis was available for 84 patients at serial follow-up.

increased significantly from T0 to T2 and remained above baseline at T3, suggesting persistent hemodynamic stress and remodeling signals in a subset of patients.

Imaging Changes Over Time

The longitudinal evolution of the main imaging parameters is shown in *Fig. 1*. LVEF declined gradually during treatment, from 60 $\pm$ 5% at T0 to 59 $\pm$ 5% at T1 and 57 $\pm$ 6% at T2, with partial recovery at T3. In contrast, GLS deteriorated earlier and more markedly, from -19.5 $\pm$ 2.1% at T0 to -18.2 $\pm$ 2.3% at T1 and -16.6 $\pm$ 2.5% at T2, followed by only partial recovery at follow-up. Imaging-defined cardiac dysfunction was documented in 30% of patients overall, and overt cardiotoxicity occurred in 10%. These data support the role of GLS as a more sensitive parameter for early detection of subclinical myocardial dysfunction.

Subgroup Analysis

Subgroup analysis according to cancer type is summarized in *Table 3*. The breast cancer subgroup showed the highest burden of both overt cardiotoxicity and subclinical dysfunction, whereas the lung cancer subgroup had the lowest incidence of overt dysfunction. Differences between subgroups were significant for mean Δ GLS, but not for mean Δ LVEF. This distribution is compatible with different therapy exposures, including anthracycline and anti-HER2 therapy in breast cancer, anthracycline-containing protocols and mediastinal irradiation in lymphoma, and platinum-based chemotherapy, taxanes, pemetrexed, immune checkpoint inhibitors, or targeted therapy in lung cancer. Because of the modest sample size, these findings should be interpreted descriptively rather than as definitive comparisons between regimens.

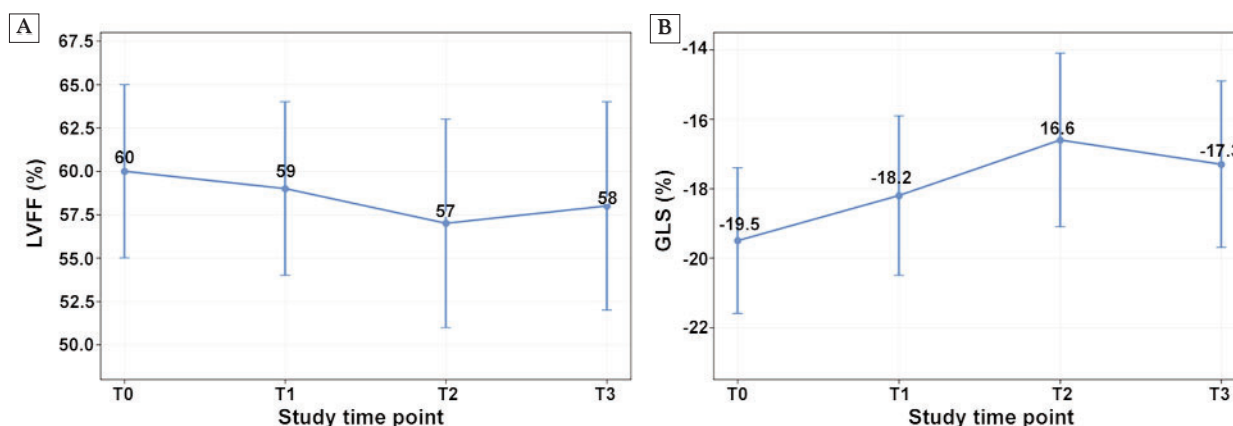


Figure 1. Longitudinal changes in LVEF and GLS across T0–T3 (A) Left ventricular ejection fraction (LVEF) showed a gradual decline from baseline to the end of treatment, followed by partial recovery at 6-month follow-up. (B) Global longitudinal strain (GLS) demonstrated an earlier and more pronounced deterioration during treatment, with incomplete recovery at follow-up. Data are presented as mean $\pm$ standard deviation. T0 = baseline; T1 = after 3–4 cycles (approximately 6–8 weeks); T2 = end of planned systemic therapy; T3 = 6-month follow-up.

Table 3. Subgroup analysis by cancer type

Parameter	Breast cancer (n=30)	Lymphoma (n=30)	Lung cancer (n=30)	p value
Overt cardiotoxicity, n (%)	6 (20%)	2 (7%)	1 (3%)	-
Subclinical dysfunction, n (%)	9 (30%)	6 (20%)	3 (10%)	-
Mean Δ GLS (%), mean $\pm$ SD	-17.2 $\pm$ 4.3	-13.8 $\pm$ 3.7	-9.4 $\pm$ 2.8	0.009
Mean Δ LVEF (%), mean $\pm$ SD	-4.5 $\pm$ 2.1	-3.1 $\pm$ 2.0	-2.0 $\pm$ 1.9	0.18

Abbreviations: GLS, global longitudinal strain; LVEF, left ventricular ejection fraction. Overt cardiotoxicity was defined as cancer therapy-related cardiac dysfunction with LVEF decrease ≥ 10 percentage points to $< 50\%$. Subclinical dysfunction was defined as relative GLS reduction $\geq 15\%$ without overt LVEF-defined dysfunction. Between-group comparisons were performed by ANOVA for continuous variables.

Correlations Between Biomarkers and Imaging Parameters

The strongest association was observed between changes in hs-Tn and GLS ($r = -0.42$; $p = 0.002$). Significant correlations were also found between NT-proBNP and GLS, and between sST2 and GLS, while correlations with LVEF were weaker. In multivariable analysis, a relative GLS reduction of at least 15% and hs-Tn increase above twofold baseline remained independent predictors of cardiotoxicity. These findings indicate that biological injury and strain abnormalities precede substantial reduction in global systolic function (Fig. 2).

Predictive Model Performance and Clinical Utility

In the adjusted multivariable model, Δ GLS $\geq 15\%$ and hs-Tn $> 2\times$ baseline remained independent predictors of cardiotoxicity (OR 4.7; 95% CI 1.6–13.8; $p = 0.005$) (Table 4).

The integrated model combining hs-Tn, NT-proBNP, sST2, and GLS achieved the highest predictive performance (AUC 0.91), with significant improvement over both the biomarker-only and GLS-only models (Table 5).

Decision-curve analysis confirmed the clinical advantage of the integrated model. Net benefit was 0.31 for GLS alone, 0.34 for biomarkers alone, and 0.46 for the integrated strategy, corresponding to an approximately 35% improvement over standard approaches. In practical terms, this could identify 3-4

Table 4. Independent predictors of cardiotoxicity and predictive model performance

Variable	Result
Relative GLS reduction $\geq 15\%$	Independent predictor
hs-Tn increase $> 2\times$ baseline	Independent predictor
Overall adjusted multivariable model	OR 4.7; 95% CI 1.6–13.8; $p = 0.005$

Additional pairwise model comparisons (DeLong test): integrated model vs. GLS-only, $p = 0.018$; integrated model vs. biomarkers-only, $p = 0.007$. Calibration of the logistic model was adequate (Hosmer–Lemeshow $p = 0.41$).

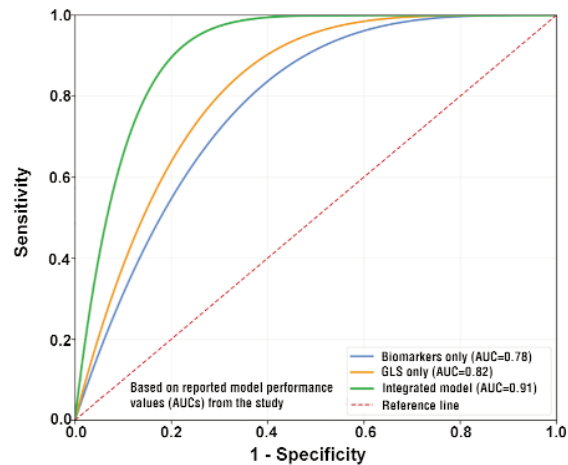


Figure 2. ROC curves for prediction of cardiotoxicity. Comparative ROC curves for the biomarker-only model, the imaging-only model based on GLS, and the integrated multimodal model. The integrated model showed the highest discriminatory performance (AUC 0.91), out-performing both the biomarker-only model (AUC 0.78) and the GLS-only model (AUC 0.82), supporting the additive value of combining circulating biomarkers with functional imaging parameters.

Table 5. Predictive model performance

Model	Parameters included	AUC (95% CI)	Sensitivity (%)	Specificity (%)	NRI	p vs. reference model
Model 1 – Biomarkers only	hs-Tn + NT-proBNP + sST2	0.78 (0.69–0.86)	72	70	-	-
Model 2 – Imaging only	GLS	0.82 (0.74–0.89)	77	75	+0.08	0.041
Model 3 – Integrated multimodal	hs-Tn + NT-proBNP + sST2 + GLS	0.91 (0.84–0.97)	87	82	+0.21	< 0.001

Abbreviations: GLS, global longitudinal strain; hs-Tn, high-sensitivity troponin; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sST2, soluble suppression of tumorigenicity-2; AUC, area under the curve; NRI, net reclassification improvement; CI, confidence interval.

additional high-risk patients per 100 monitored patients for intensified cardio-oncology review. This estimate should be regarded as a decision-support signal and requires prospective outcome validation.

Discussion

The present study supports the concept that cancer therapy-related cardiac dysfunction evolves as a continuum rather than as a late binary event defined only by LVEF decline (2,5,9). In this cohort, biomarker elevation and GLS deterioration appeared before more substantial LVEF changes. This pattern suggests that subclinical myocardial injury can be detected before overt systolic dysfunction becomes clinically apparent. The findings are concordant with cardio-oncology recommendations that emphasize baseline risk stratification and serial surveillance in patients exposed to potentially cardiotoxic therapy (10,11).

GLS showed earlier and more pronounced deterioration than LVEF. This supports the use of myocardial deformation analysis as a sensitive surveillance parameter, particularly when baseline LVEF is preserved (12). Previous studies and meta-analyses have similarly shown that longitudinal strain can predict subsequent cancer therapy-related cardiac dysfunction better than early LVEF changes (13-15). Our results are therefore aligned with the current direction of the literature, while also reinforcing the need to interpret GLS dynamically and in relation to the individual baseline value.

The biomarker results add biological context to the imaging findings. hs-Tn was the marker most strongly associated with GLS deterioration, consistent with its role as an early signal of cardiomyocyte injury (16,17). NT-proBNP was useful as a marker of ventricular wall stress, although it is less specific because it can be influenced by loading conditions, age, renal function, and volume status (16-18). sST2 increased more gradually and remained more persistently abnormal, suggesting a possible association with inflammation and remodeling. Because sST2 remains less validated in cardio-oncology, our findings support its use as an adjunct within a multimarker strategy rather than as an isolated decision-making tool (19-22).

The role of radionuclide imaging should also be interpreted pragmatically. Echocardiography remains the first-line modality for most serial surveillance protocols, particularly when GLS is available (23,24). However, MUGA and gated SPECT provide highly reproducible ventricular function measurements and remain useful when echocardiographic windows are suboptimal, when serial LVEF precision is important, or

when complementary nuclear information is clinically relevant (25,26). Thus, our data support a complementary multimodality framework, not replacement of echocardiography by radionuclide imaging.

The subgroup findings are clinically plausible but should not be overinterpreted. The higher burden of dysfunction in breast cancer is compatible with exposure to anthracyclines and anti-HER2 therapy. The lymphoma subgroup showed an intermediate profile, likely reflecting anthracycline-containing regimens and prior mediastinal radiotherapy in some patients. Lung cancer patients had fewer overt events but still showed measurable GLS and biomarker changes. This emphasizes that lower overt event rates do not exclude subclinical injury, especially when treatment includes platinum-based chemotherapy, taxanes, immune checkpoint inhibitors, or targeted agents (27).

The integrated model had the best predictive performance, with higher AUC and net benefit than either imaging-only or biomarker-only approaches. This suggests that structural-functional data and biological signals are additive rather than competitive (28,29). Nevertheless, the results should remain carefully framed. Randomized data on GLS-guided cardioprotection are nuanced, and the SUCCOUR trial did not demonstrate a consistent advantage for GLS-guided management in all endpoints (30). Therefore, the present model should be viewed as a tool for risk stratification and surveillance, not as proof that multimodal monitoring alone improves hard cardiovascular or oncologic outcomes.

Clinical Implications in Surgical Oncology

In surgical oncology, cardiovascular status may influence perioperative risk, timing of operation, and the feasibility of completing multimodal therapy. A patient with preserved LVEF but worsening GLS and rising biomarkers may appear clinically stable, yet may already be entering a phase of relevant myocardial injury. In such cases, the proposed model may help identify patients who need cardiology review, optimization of blood pressure or volume status, initiation of cardioprotective medication, or closer perioperative monitoring before surgery.

The model may also support treatment sequencing. After neoadjuvant systemic therapy, detection of subclinical cardiotoxicity can inform whether surgery should proceed as planned, whether a short period of cardiovascular optimization is reasonable, or whether systemic therapy intensity should be reconsidered by the tumor board. This does not imply that surgery should be delayed solely because of a biomarker change. Instead, biomarker and imaging signals

should be integrated with oncologic urgency, anesthetic risk, functional status, and expected benefit of resection (11,31-34).

Limitations

Several limitations should be acknowledged explicitly. This was a single-center study with a relatively small cohort, and the three cancer groups were heterogeneous in terms of systemic therapy, previous radiotherapy, and baseline cardiovascular risk. Treatment categories were analyzed descriptively, and the study was not powered to compare individual oncologic regimens. Cardiac magnetic resonance was not performed serially in all patients, which limited tissue characterization and independent validation of imaging abnormalities. Biomarker thresholds were operational and assay-dependent, and the integrated model was internally derived without external validation. For these reasons, the findings should be considered hypothesis-generating and clinically promising. Larger multicenter cohorts are required to confirm calibration, test generalizability, and determine whether this surveillance strategy reduces treatment interruption, perioperative events, long-term cardiac dysfunction, or oncologic compromise.

Conclusions

In this prospective single-center cohort, the combined use of radionuclide imaging, echocardiographic strain analysis, and circulating biomarkers enabled earlier identification of antineoplastic therapy-related cardiac dysfunction than surveillance based on LVEF or biomarkers alone. GLS was more sensitive than LVEF for identifying early myocardial dysfunction, while hs-Tn, NT-proBNP, and sST2 added complementary information on injury, stress, and remodeling. The integrated model demonstrated the highest predictive performance and the best clinical net benefit in this cohort. The proposed multimodal approach may function as a practical decision-support tool for multidisciplinary teams, including in surgical oncology, where it can help guide perioperative risk assessment, preoperative optimization, and treatment sequencing. However, its immediate applicability should be approached cautiously and within protocolized pathways. External validation in larger multicenter studies is required before routine implementation or use as a standalone basis for therapeutic decisions.

Author's Contributions

All authors contributed equally to this work and share

first authorship. All authors participated in the conception and design of the study, the acquisition, analysis, or interpretation of data, and the drafting or critical revision of the manuscript. All authors have reviewed and approved the final version of the manuscript and accept responsibility for its content and integrity.

Conflicts of Interest

The authors declare no conflict of interest.

Ethics Statement

The study was approved by the Ethics Committee of the Prof. Dr. Alexandru Trestioreanu Institute of Oncology, Bucharest (No. 25067/18.12.2025). All procedures were performed in accordance with institutional ethical standards and the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

References

1. Contaldi C, D'Aniello C, Panico D, Zito A, Calabrò P, Di Lorenzo E, et al. Cancer-therapy-related cardiac dysfunction: latest advances in prevention and treatment. *Life (Basel)*. 2025;15(3):471.
2. Bychowski J, Sobiczewski W. Current perspectives of cardio-oncology: epidemiology, adverse effects, pre-treatment screening and prevention strategies. *Cancer Med*. 2023; 12:14545-14555.
3. Soh CH, Marwick TH. Surveillance of left ventricular function among cancer survivors. *Heart*. 2025;111(24):1199-1206.
4. Tavernese A, Rizza V, Cammalleri V, Mollace R, Carresi C, Antonelli G, et al. Early echocardiographic markers in heart failure with preserved ejection fraction. *J Cardiovasc Dev Dis*. 2025;12(6):229.
5. Lyon AR, Dent S, Stanway S, Earl H, Brezden-Masley C, Cohen-Solal A, et al. Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies: a position statement and new risk assessment tools from the Cardio-Oncology Study Group of the Heart Failure Association of the European Society of Cardiology in collaboration with the International Cardio-Oncology Society. *Eur J Heart Fail*. 2020;22(11):1945-1960.
6. Donisan T, Sykora D, Balanescu DV, Chang IC, Lin G, Herrmann J, et al. Radionuclide imaging in cardio-oncology: a clinical decision-making tool. *Prog Cardiovasc Dis*. 2025;93:66-74.
7. Smiseth O, Rider O, Cvijic M, et al. Myocardial strain imaging: theory, current practice, and the future. *JACC Cardiovasc Imaging*. 2025;18(3):340-381.
8. Sławiński G, Hawryszko M, Liżewska-Springer A, Nabiałek-Trojanowska I, Lewicka E. Global longitudinal strain in cardio-oncology: a review. *Cancers (Basel)*. 2023; 15(3): 986.
9. Ghadirzadeh E, Padash Y, Ahvar S. Cancer therapy related cardiac dysfunction: mechanisms, surveillance, and management in contemporary cardio-oncology. *Cardio Trend J*. 2025;1(1):10-22.
10. Tse G, Shao Q, Liu J, Zhang Y. The potential impact of the 2022 ESC cardio-oncology guidelines on clinical practice in China. *JACC CardioOncol*. 2023;5(1):153-155.
11. Addison D, Neilan TG, Barac A, Scherrer-Crosbie M, Okwuosa TM, Plana JC, et al. Cardiovascular imaging in contemporary cardio-oncology: a scientific statement from the American Heart Association. *Circulation*. 2023;148(16):1271-1286.
12. Genç M, Yüksel UÇ. Subclinical myocardial dysfunction detected by speckle-tracking in asymptomatic individuals with exercise-induced premature ventricular complexes. *Cardiovasc Ultrasound*. 2025;23(1):22.
13. Oikonomou EK, Kokkinidis DG, Kampaktsis PN, Amir EA, Marwick TH, Gupta D, et al. Assessment of prognostic value of left ventricular global longitudinal strain for early prediction of chemotherapy-induced cardiotoxicity: a systematic review and meta-

- analysis. *JAMA Cardiol.* 2019;4(10):1007-1018.
14. Gripp EA, Oliveira GE, Feijó LA, Garcia MI, Xavier SS, Sousa AS. Global longitudinal strain accuracy for cardiotoxicity prediction in a cohort of breast cancer patients during anthracycline and/or trastuzumab treatment. *Arq Bras Cardiol.* 2018;110(2):140-150.
15. Borowiec A, Ozdowska P, Rosinska M, Zebrowska AM, Jasek S, Kotowicz B, et al. Predictive value of baseline left ventricular global longitudinal strain for cardiac dysfunction in patients with moderate to high risk of cancer therapy-related cardiovascular toxicity. *Pharmaceuticals (Basel).* 2025;18(10):1530.
16. Bracun V, de Boer RA. Troponins and natriuretic peptides to detect cardiotoxicity: useful biomarkers or paradise lost? *Eur J Heart Fail.* 2020;22(2):362-365.
17. Alexandraki A, Papageorgiou E, Zacharia M, Keramida K, Papakonstantinou A, Cipolla CM, et al. New insights in the era of clinical biomarkers as potential predictors of systemic therapy-induced cardiotoxicity in women with breast cancer: a systematic review. *Cancers (Basel).* 2023;15(13):3290.
18. Volpe M, Carnovali M, Mastromarino V. The natriuretic peptides system in the pathophysiology of heart failure: from molecular basis to treatment. *Clin Sci (Lond).* 2016;130(2):57-77.
19. Suci H, Călburean PA, Huțanu A, Opris DR, Scurtu AC, et al. Natriuretic peptides and soluble ST2 improve echocardiographic and invasive long-term survival prediction in patients evaluated for diastolic dysfunction. *Int J Mol Sci.* 2025;26(8): 3713.
20. Alzaabi MA, Abdelsalam A, Alhammadi M, Hani HB, Almheiri A, Al Matrooshi N, et al. Evaluating biomarkers as tools for early detection and prognosis of heart failure: a comprehensive review. *Card Fail Rev.* 2024;10:e06.
21. Huang S, Yu LJ, Sun GF, Zhang ZX. Short-term predictive value of sST2 in patients with STEMI following primary PCI: a prospective observational study. *BMC Cardiovasc Disord.* 2025;25(1):21.
22. Yan Y, Zhuang Y, Li H, Wang DW. Plasma soluble ST2 as a prognostic biomarker for cardiovascular events and mortality in COVID-19 patients. *J Cardiovasc Dev Dis.* 2025;12(7):273.
23. Seraphim A, Westwood M, Bhuvana AN, et al. Advanced imaging modalities to monitor for cardiotoxicity. *Curr Treat Options Oncol.* 2019;20:73.
24. Mateescu AD, Mincu RI, Jurcut RO. How to use multimodality imaging in cardiovascular oncology. *J Cardiovasc Dev Dis.* 2026;13(1):27.
25. Tian Y, Wang Y, Wang J, Shao X, Zhang F. Application of radionuclide myocardial imaging in the diagnosis and treatment of heart failure with preserved ejection fraction. *Rev Cardiovasc Med.* 2025;26(10):41231.
26. Parlati ALM, Nardi E, Marzano F, Madaudo C, Di Santo M, Cotticelli C, et al. Advancing cardiovascular diagnostics: the expanding role of CMR in heart failure and cardiomyopathies. *J Clin Med.* 2025;14(3):865.
27. Cronin M, Seher M, Arsang-Jang S, Lowery A, Kerin M, Wijns W, et al. Multimodal imaging of cancer therapy-related cardiac dysfunction in breast cancer: a state-of-the-art review. *J Clin Med.* 2023;12(19):6295.
28. Bayes-Genis A, de Antonio M, Galán A, Sanz H, Urrutia A, Cabanes R, et al. Combined use of high-sensitivity ST2 and NT-proBNP to improve the prediction of death in heart failure. *Eur J Heart Fail.* 2012;14(1):32-38.
29. Grande D, Leone M, Rizzo C, Terlizze P, Parisi G, Gioia MI, et al. A multiparametric approach based on NT-proBNP, ST2, and Galectin-3 for stratifying one-year prognosis of chronic heart failure outpatients. *J Cardiovasc Dev Dis.* 2017;4(3):9.
30. Negishi T, Thavendiranathan P, Penicka M, Lemieux J, Murbaech K, Miyazaki S, et al. Cardioprotection using strain-guided management of potentially cardiotoxic cancer therapy: 3-year results of the SUCCOUR trial. *JACC Cardiovasc Imaging.* 2023;16(3):269-278.
31. Ionescu CA, Cozaru GC, Aschie M, Leopa N, Cîmpineanu B, Voinea F, et al. Toward personalized surgery in advanced prostate cancer: stratification by PTEN, AR-V7, TP53, TMPRSS2-ERG, and ERBB2 genetic alterations. *Chirurgia (Bucur).* 2025;120(3): 265-274.
32. Kim IC, Yoo BS. Multidimensional approach of heart failure diagnosis and prognostication utilizing cardiac imaging with biomarkers. *Diagnostics (Basel).* 2022;12(6): 1366.
33. Pundiche M, Sarbu V, Unc OD, Grasa C, Martinescu A, Bădăraș V, et al. Role of procalcitonin in monitoring the antibiotic therapy in septic surgical patients. *Chirurgia (Bucur).* 2012;107(1):71-78.
34. Moore DC, Guinigundo AS. The role of biomarkers in guiding clinical decision-making in oncology. *J Adv Pract Oncol.* 2023;14(Suppl 1):15-37.