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Assessment of Early Cardiac Dysfunction Related to Cancer Therapy in Patients Receiving Hematopoietic Stem Cell Transplantation: An Echocardiographic Analysis

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ABSTRACT

Hematopoietic stem cell transplantation (HSCT) is an effective treatment for various blood cancers, but it carries a risk of developing cardiac dysfunction related to cancer therapy. This study aimed to investigate the occurrence of subclinical cancer therapy-related cardiac dysfunction (CTRCD) one year after HSCT and to explore clinical factors that may contribute to its development. The study included 55 patients who underwent either autologous or allogeneic HSCT. Echocardiographic evaluations were performed prior to transplantation and repeated at a 12-month follow-up to detect cardiac changes.

At one year post-transplant, 15 patients (27.3%) showed evidence of asymptomatic CTRCD, including 9 with mild and 6 with moderate dysfunction. A history of anthracycline chemotherapy was more frequent among patients with CTRCD (60%) compared to those without (22.5%). Similarly, the use of the BEAM conditioning regimen was associated with higher CTRCD incidence (33.3% vs. 5%). Subclinical cardiac dysfunction affects over a quarter of patients one year after HSCT. Prior exposure to anthracyclines and receiving the BEAM conditioning regimen appear to increase the likelihood of developing CTRCD.

Keywords: Echocardiography, Cancer therapy-related cardiac dysfunction, Cardiovascular complications, Hematopoietic stem cell transplantation, Cardiotoxicity

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Introduction

Hematopoietic stem cell transplantation (HSCT) is an established curative intervention commonly employed for patients with hematologic malignancies, certain solid tumors, and non-malignant bone marrow disorders [1]. The procedure requires a preparative phase known as conditioning, which involves the ablation of bone marrow through high-dose chemotherapy, total-body irradiation, or a combination of both. Following conditioning, patients receive an infusion of hematopoietic stem cells, which may be either autologous, derived from the patient, or allogeneic, obtained from a donor [2, 3].

With the expanding indications for HSCT, complications associated with the procedure, such as graft-versus-host disease in allogeneic transplantation or cardiovascular complications, are also increasing. The Worldwide Network of Blood and Marrow Transplantation (WBMT) reports that the annual number of HSCT procedures has grown by over 7% per year in the past decade, averaging approximately 90,000 transplants annually [4]. Despite improvements in post-transplant survival and overall outcomes, survivors remain at significant risk of developing long-term complications, including cardiovascular events [1]. Although cardiovascular complications represent less than 10% of HSCT-related adverse events, they are linked to higher mortality and substantially impair long-term quality of life [5, 6].

Cardiac events after HSCT may be triggered by various aspects of the procedure, including conditioning regimens such as total-body irradiation combined with multi-agent chemotherapy [7]. Agents commonly used for mobilization or conditioning, such as cyclophosphamide, cytarabine, and carmustine, have notable cardiotoxic

potential. Additionally, dimethyl sulfoxide (DMSO), used in stem cell preservation, may contribute to cardiac adverse effects [8].

Recent studies emphasize the importance of identifying patients at high risk for cardiac complications to reduce post-HSCT morbidity. However, a standardized approach for pre-transplant cardiac risk assessment is lacking [1]. This study aimed to evaluate the prevalence of subclinical cancer therapy-related cardiac dysfunction (CTRCD) one year after HSCT and to examine the influence of clinical factors on its development. Cardiac function was assessed using two-dimensional echocardiography, following the CTRCD diagnostic criteria outlined in the 2022 European Society of Cardiology (ESC) guidelines in collaboration with EHA/ESTRO/IC-OS [9].

Materials and Methods

This prospective study was conducted at the Hospital of the Lithuanian University of Health Sciences, Kaunas Clinics, between October 2021 and February 2024. A total of 55 patients undergoing autologous or allogeneic HSCT at the Department of Oncology and Hematology were enrolled. Ethical approval was granted by the Kaunas Regional Bioethics Committee (No. BE-2-96), and the study adhered to the principles of the Helsinki Declaration. All participants provided written informed consent.

Inclusion criteria included:

- Age ≥18 years at the time of HSCT
- Written informed consent

Exclusion criteria included:

- Previous HSCT
- Withdrawal of consent at any point

Participants completed a questionnaire detailing cardiovascular risk factors (smoking, dyslipidemia, diabetes), personal or family history of cardiovascular disease (hypertension, early coronary heart disease), and use of cardiovascular medications. Hypertension was defined according to the 2018 ESC/ESH guidelines as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg [10]. Early coronary heart disease was defined as a cardiovascular event (e.g., stroke, myocardial infarction, interventional cardiac procedure) or death from a cardiovascular event in a first-degree relative (men <55 years, women <60 years).

Patients underwent HSCT for various underlying conditions. Autologous HSCT involved stem cell collection after chemotherapy and granulocyte colony-stimulating factor (G-CSF) administration (Filgrastim 10 µg/kg/d). Conditioning regimens were tailored to disease type: multiple myeloma patients received melphalan (200 mg/m²); lymphoma patients received the BEAM protocol (carmustine, etoposide, cytarabine, melphalan); and patients with primary CNS diffuse large B-cell lymphoma received thiotepa plus BCNU (carmustine). Allogeneic HSCT conditioning used reduced-intensity fludarabine and busulfan.

Autologous HSCT stem cells were collected via peripheral blood apheresis using the Fresenius Kabi COM.TEC system and cryopreserved in 10% DMSO with autologous plasma in a controlled-rate freezer.

Echocardiography was performed to monitor cardiac function: autologous HSCT patients underwent three assessments—before mobilization, pre-transplantation (conditioning), and at a 12 ± 1-month follow-up—while allogeneic HSCT patients were evaluated twice, pre-transplant and at 12 ± 1 months post-HSCT. For the purposes of this study, pre-transplant and 12-month post-HSCT echocardiographic data were analyzed to assess the cardiac impact of both autologous and allogeneic HSCT procedures. The echocardiography workflow is illustrated in **Figure 1**.

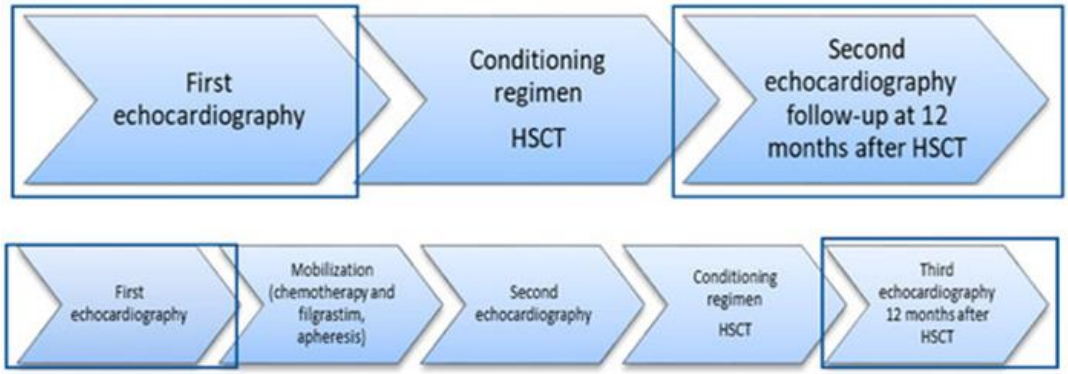


Figure 1. Echocardiography workflow for the study. The first diagram illustrates the allogeneic HSCT process, and the second diagram depicts the autologous HSCT process. HSCT—hematopoietic stem cell transplantation.

Echocardiographic assessments were conducted by a single experienced cardiologist using an EPIQ 7 ultrasound system (Phillips Ultrasound Inc., Bothell, WA, USA). Standard echocardiographic parameters, including cardiac chamber dimensions and function, as well as global longitudinal strain (GLS), were measured.

Cardiac chamber size and functional assessment followed the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging for Cardiac Chamber Quantification [11]. From the parasternal long-axis view, the left ventricular end-diastolic diameter (LVEDD, mm) and its body surface area–indexed value (LVEDDi, mm/m²) were recorded. Left ventricular mass (LVM) was calculated using the Cube formula: $0.8 \times (1.04 \times (IVS + LVID + PWT)^3 - LVID^3) + 0.6$ g, where IVS is the interventricular septum, LVID is the LV internal diameter, and PWT is the inferolateral wall thickness. Relative wall thickness (RWT) was calculated as $(2 \times PWT)/LVID$. LV hypertrophy was classified as concentric (RWT > 0.42) or eccentric (RWT ≤ 0.42), whereas normal LV mass with increased RWT (>0.42) was considered concentric remodeling. The left atrial (LA) diameter at end-systole was also measured.

In apical views, left ventricular ejection fraction (LVEF) was determined from LV end-diastolic and end-systolic volumes. LA volume was calculated using the disk summation method from four- and two-chamber views and indexed to BSA. Right ventricular (RV) systolic function was evaluated by measuring RV free wall peak systolic velocity (S′, cm/s) via tissue Doppler. Early LV diastolic filling velocities (e′) at the lateral wall and septum were also measured, and the E/e′ ratio was calculated as the average of these values.

Global longitudinal strain (GLS) of the LV was assessed with speckle-tracking echocardiography using high-quality apical four-, three-, and two-chamber views. GLS was calculated from a single cardiac cycle, averaging the longitudinal strain values across all LV myocardial segments.

Echocardiographic data were collected both prior to HSCT and at a 12 ± 1-month follow-up after transplantation for both autologous and allogeneic procedures. Statistical analyses were then performed to evaluate the results.

Based on the 2022 European Society of Cardiology (ESC) cardio-oncology guidelines, developed in collaboration with EHA/ESTRO/IC-OS [9], patients were classified into two groups: those with subclinical CTRCD and those without, using changes in LVEF and GLS as diagnostic criteria. The study aimed to determine the prevalence of CTRCD and identify clinical factors associated with its development. The CTRCD classification criteria are summarized in **Table 1**, and examples of baseline and follow-up echocardiographic images are shown in **Figures 2 and 3**.

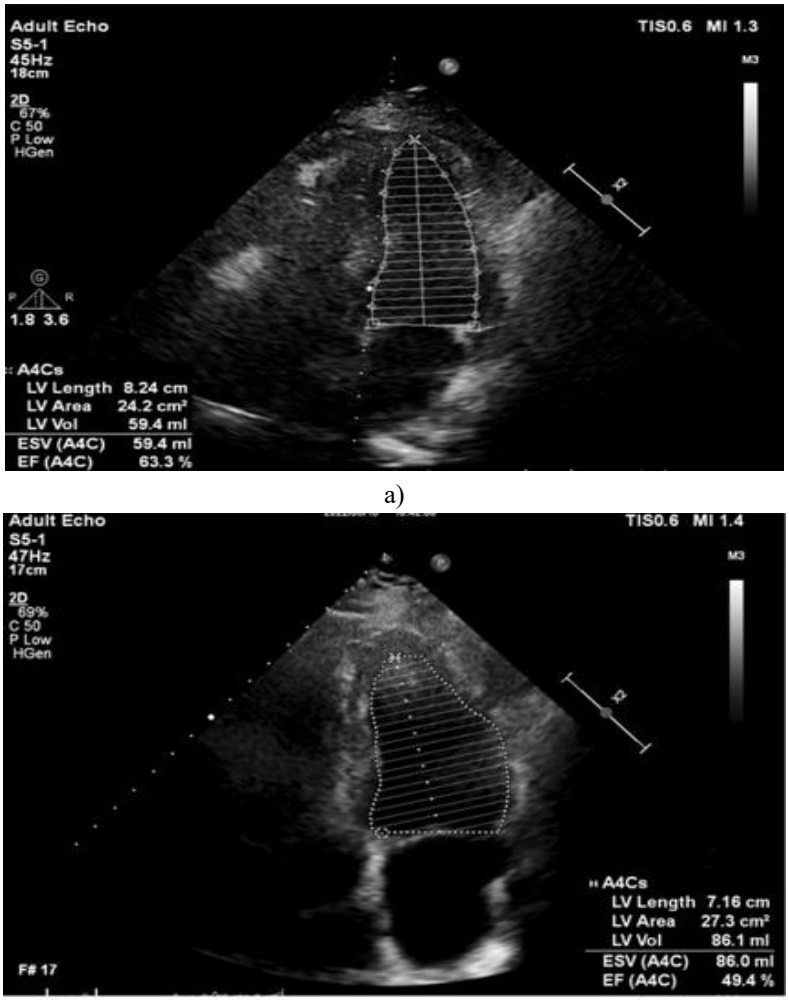
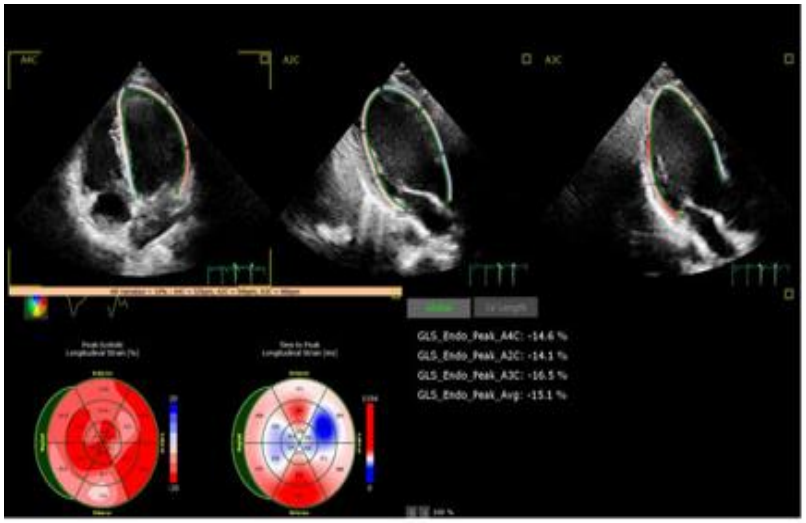
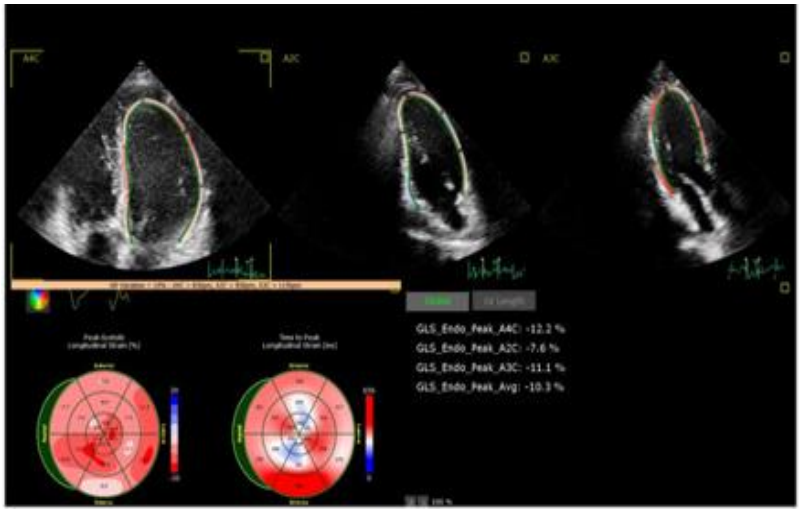


Figure 2. Decline in LVEF from 63.3% to 49.4%, measured using the modified biplane Simpson's method. (a) Echocardiogram at baseline; (b) Echocardiogram at 12-month follow-up after HSCT. LVEF—left ventricular ejection fraction; HSCT—hematopoietic stem cell transplantation.





b)

Figure 3. Reduction in GLS from −15.1% to −10.3%. (a) Echocardiogram at baseline; (b) Echocardiogram at 12-month follow-up after HSCT. GLS—global longitudinal strain; HSCT—hematopoietic stem cell transplantation.

Table 1. Definition criteria of CTRCD and distribution of patients.

Grade	Criteria	Number of Patients
Severe	New LVEF reduction to <40%	0
Moderate	New LVEF reduction by ≥10% to LVEF of 40–49%	3
Serine	New LVEF reduction by <10% to LVEF of 40–49% AND new relative decline in GLS by >15% from baseline	3
Mild	LVEF ≥50% AND new relative GLS reduction >15% from baseline	9

LVEF—left ventricular ejection fraction. GLS—global longitudinal strain.

Statistical analyses were conducted using IBM SPSS Statistics version 29.0 (IBM Corp., Armonk, NY, USA). Categorical variables were expressed as counts (n) and percentages (%), while continuous variables were presented as mean ± standard deviation if normally distributed, or as median with minimum and maximum values if the normality assumption was not met. Comparisons between two related groups were performed using either the paired t-test or the Wilcoxon signed-rank test, depending on data distribution. Associations between cardiotoxicity occurrence and patient clinical characteristics were evaluated using Pearson's chi-square test or Fisher's exact test, as appropriate. Binary logistic regression analyses, including both univariate and multivariate models, were applied to estimate odds ratios (OR) with 95% confidence intervals (CI). For the multivariate model, the bootstrap method with bias-corrected and accelerated (BCa) confidence intervals was employed, based on 1,000 resampled datasets. A p-value < 0.05 was considered statistically significant.

Results and Discussion

Clinical and demographic characteristics

The study included 55 patients, of whom 30 (54.5%) were male and 25 (45.5%) were female. The median age was 61 years, with a range of 18–74 years. Autologous HSCT was performed in 48 patients (87.3%), while 7 patients (12.7%) underwent allogeneic HSCT. Detailed patient demographics, clinical characteristics, and primary disease types are summarized in **Table 2**.

Table 2. Characteristics of the patients.

Sex	
Male, n (%)	30 (54.5)
Female, n (%)	25 (45.5)

Age, years (median (minimum–maximum))	61 (18–74)
Autologous transplantation, n (%)	48 (87.3)
Main disease	
Multiple myeloma, n (%)	33 (68.8)
Mantle cell lymphoma, n (%)	4 (8.3)
Hodgkin's lymphoma, n (%)	2 (4.2)
PCNS diffuse large B cell lymphoma, n (%)	5 (10.4)
Peripheral T cell lymphoma, n (%)	1 (2.1)
Ewing sarcoma, n (%)	2 (4.2)
NK-/T-cell lymphoma, n (%)	1 (2.1)
Allogeneic transplantation, n (%)	7 (12.7)
Main disease	
Acute myeloid leukemia, n (%)	5 (71.4)
Acute myelomonocytic leukemia, n (%)	1 (14.3)
MDS-EB, n (%)	1 (14.3)

PCNS—primary central nervous system, NK—natural killer, MDS-EB—myelodysplastic syndrome with excess blasts.

Analysis of CTRCD and associated risk factors

During the 12-month follow-up after HSCT, three patients (5.5%) developed clinically apparent cardiovascular events, all presenting as supraventricular arrhythmias: two cases of supraventricular tachycardia and one case of atrial fibrillation.

Using the 2022 ESC cardio-oncology guidelines and echocardiographic criteria, subclinical CTRCD was identified in 15 patients (27.3%) at one year post-transplant [9]. Among these, six patients were classified as having moderate CTRCD, defined as either a new reduction in LVEF of ≥10% resulting in an LVEF of 40–49%, or a decrease of <10% to an LVEF of 40–49% accompanied by a relative GLS decline of >15% from baseline. The remaining nine patients exhibited mild CTRCD, characterized by an LVEF ≥50% combined with a new relative GLS reduction exceeding 15% compared to baseline.

Overall patient characteristics and comparisons between the CTRCD and non-CTRCD groups are summarized in **Table 3**.

Table 3. Characteristics of the patients with and without CTRCD.

Characteristic	All Patients (n = 55)	Non-CTRCD (n = 40; 72.7%)	CTRCD (n = 15; 27.3%)	p
Age (years), median (Min–max)	61 (18–74)	61 (18–74)	61 (23–74)	0.502
Sex				
Male	30 (54.5)	21 (52.5)	9 (60.0)	0.764
Female	25 (45.5)	19 (47.5)	6 (40.0)	48 (87.3)
Disease				
Multiple myeloma	33 (60.0)	27 (67.5)	6 (40.0)	0.121
Lymphoma	12 (23.6)	7 (17.5)	6 (40.0)	0.151
Leukemia and MDS-EB	7 (12.7)	4 (10.0)	3 (20.0)	0.376
Other diseases (Ewing sarcoma)	2 (3.6)	2 (5.0)	0 (0.0)	1.000
Auto/allo				
Allogeneic HSCT	7 (12.7)	4 (10.0)	3 (20.0)	0.376
Autologous HSCT	48 (87.3)	36 (90.0)	12 (80.0)	1 (2.1)
CVD risk factors				

CAD	3 (5.5)	1 (2.5)	2 (13.3)	0.177
Arterial hypertension	21 (38.2)	15 (37.5)	6 (40.0)	1.000
Diabetes mellitus	4 (7.3)	4 (10.0)	0 (0.0)	0.565
Family history of CAD	8 (14.5)	6 (15.0)	2 (13.3)	1.000
Dyslipidemia	43 (78.2)	31 (77.5)	12 (80.0)	1.000
Previous smoking	5 (9.1)	4 (10.0)	1 (6.7)	1.000
Medications				
Beta-blockers	12 (21.8)	10 (25.0)	2 (13.3)	0.477
ACEis	10 (18.2)	7 (17.5)	3 (20.0)	1.000
ARBs	5 (9.1)	3 (7.5)	2 (13.3)	0.606
Statins	6 (10.9)	4 (10.0)	2 (13.3)	0.660
Previous use of anthracyclines	18 (32.7)	9 (22.5)	9 (60.0)	0.021
Conditioning regimen				
Melphalan	35 (63.6)	28 (70.0)	7 (46.7)	0.128
BEAM	7 (12.7)	2 (5.0)	5 (33.3)	0.013
Carmustine+TT	5 (9.1)	5 (12.5)	0 (0.0)	0.308
RIC	7 (12.7)	4 (10.0)	3 (20.0)	0.376
TnI, median (min–max)	0.02 (0.02–0.64)	0.02 (0.02–0.64)	0.02 (0.02–0.16)	0.958
BNP, median (min–max)	21.75 (4.00–118.70)	19.90 (4.00–118.70)	23.60 (9.30–56.20)	0.719

MDS-EB: myelodysplastic syndrome with excess blasts; HSCT: hematopoietic stem cell transplantation; CV: cardiovascular; CAD: coronary artery disease; ACEis: angiotensin converting enzyme inhibitors; ARBs: angiotensin receptor blockers; BEAM: carmustine, etoposide, cytarabine, melphalan; TT: thiotepa; RIC: reduced intensity conditioning.

No significant differences were observed between the CTRCD and non-CTRCD groups in terms of age, sex, underlying disease, type of HSCT, cardiovascular risk factors, or use of cardiovascular medications. However, prior exposure to anthracyclines was more frequently seen in patients who developed CTRCD, occurring in nine patients (60%) in the CTRCD group compared to nine patients (22.5%) in the non-CTRCD group, a difference that reached statistical significance (p = 0.021). Additionally, the conditioning regimen appeared to influence CTRCD occurrence: five patients (33.3%) in the CTRCD group had received the BEAM protocol, versus two patients (5%) in the non-CTRCD group (p = 0.013).

A univariate logistic regression analysis was performed to examine potential predictors of CTRCD, including sex, primary disease, type of HSCT, preexisting cardiovascular conditions, cardiovascular risk factors, prior anthracycline exposure, and the conditioning regimen used. This analysis identified two significant factors associated with the development of CTRCD: previous anthracycline therapy (OR 5.167, 95% CI 1.448–18.433, p = 0.011) and use of the BEAM conditioning protocol (OR 9.500, 95% CI 1.599–56.426, p = 0.013) **(Table 4)**.

Table 4. Univariate logistic regression analysis of factors possibly influencing the development of CTRCD.

Univariate Logistic Regression			
Covariate	**OR**	**95% CI**	**p**
Sex (male versus female)	1.357	0.407–4.529	0.619
Multiple myeloma (myeloma versus other disease)	0.321	0.094–1.095	0.069
Lymphoma (lymphoma versus other disease)	3.143	0.843–11.720	0.088
Allogeneic HSCT (allo versus auto)	2.250	0.439–11.522	0.330
Autologous HSCT (auto versus allo)	0.444	0.087–2.276	0.330
CAD (present versus absent)	6.000	0.502–71.731	0.157
Arterial hypertension (present versus absent)	1.111	0.330–3.746	0.865

Family history of CAD (yes versus no)	0.872	0.156–4.884	0.876
Dyslipidemia (present versus absent)	1.161	0.268–5.034	0.842
Previous smoking (yes versus no)	0.643	0.066–6.264	0.704
Beta-blockers (use versus non-use)	0.462	0.088–2.408	0.359
ACEis (use versus non-use)	1.179	0.262–5.310	0.831
ARBs (use versus non-use)	1.897	0.285–12.654	0.508
Statins (use versus non-use)	1.385	0.226–8.477	0.725
Previous use of anthracyclines (use versus non-use)	5.167	1.448–18.433	0.011
Melphalan used for conditioning (use versus non-use)	0.375	0.111–1.269	0.115
BEAM used for conditioning (use versus non-use)	9.500	1.599–56.426	0.013

HSCT: hematopoietic stem cell transplantation; CAD: coronary artery disease; ACEis: angiotensin converting enzyme inhibitors; ARBs: angiotensin receptor blockers; BEAM: carmustine, etoposide, cytarabine, melphalan.

To evaluate whether prior anthracycline exposure and the BEAM conditioning regimen independently contribute to the development of CTRCD, a multivariate logistic regression analysis was conducted, adjusting for various cardiovascular risk factors. In this analysis, the associations identified in the univariate model lost statistical significance, likely because the two variables—BEAM regimen and previous anthracycline use—are interrelated, as all patients receiving BEAM had a history of anthracycline-based chemotherapy. Nonetheless, when applying the bootstrap method with 1,000 resamples, the multivariate analysis suggested that the BEAM conditioning protocol may still represent a potentially independent risk factor for CTRCD (p = 0.039, **(Table 5)**). These findings indicate that further research with a larger cohort is required to confirm this potential independent effect.

Table 5. Multivariate logistic regression analysis of factors possibly influencing the development of CTRCD.

		Multivariate Model			**Bootstrap Method**	
Covariate		**OR**	**95% CI**	**p**	**95% Bca CI**	**p**
Risk factors	CAD	3.701	0.172–79.583	0.403	−20.156–38.064	0.085
	Arterial hypertension	0.568	0.120–2.692	0.476	−36.130–1.889	0.484
	Family history of CAD	0.355	0.035–3.642	0.384	−35.882–0.743	0.231
	Dyslipidaemia	3.893	0.476–31.860	0.205	−1.423–73.298	0.099
	Previous smoking	1.224	0.105–14.270	0.872	−20.161–2.551	0.545
Previous use of anthracyclines		3.913	0.712–21.501	0.117	−19.701–47.749	0.092
BEAM		6.654	0.660–67.061	0.108	−0.605–42.489	0.039

CAD: coronary artery disease; BEAM: carmustine, etoposide, cytarabine, melphalan; OR: odds ratio; CI: confidence interval; 95% BCa CI: Bias-corrected and accelerated confidence interval.

The influence of the BEAM conditioning regimen and prior anthracycline exposure on CTRCD development, independent of other cardiovascular risk factors, was assessed using separate multivariate logistic regression analyses. Patients receiving the BEAM regimen showed a markedly increased risk of CTRCD (OR 14.910, 95% CI 1.764–126.038, p = 0.013, **(Table 6)**), and this association was further supported by bootstrap analysis (p = 0.006). Similarly, prior anthracycline therapy was associated with a significantly higher likelihood of developing CTRCD (OR 6.996, 95% CI 1.530–31.997, p = 0.012, **(Table 7)**), with bootstrap validation confirming the robustness of this finding (p = 0.009).

Table 6. Multivariate logistic regression analysis. Cardiovascular risk factors and conditioning regimen possibly influencing the development of CTRCD.

		Multivariate Model			**Bootstrap Method**	
Covariate		**OR**	**95% CI**	**p**	**95% Bca CI**	**p**
Risk factors	CAD	4.868	0.261–90.681	0.289	−20.403–24.326	0.062

	Arterial hypertension	0.614	0.133–2.841	0.533	−35.672–2.044	0.552
	Family history of CAD	0.398	0.043–3.688	0.418	−37.910–1.255	0.297
	Dyslipidaemia	2.729	0.351–21.220	0.337	−1.589–55.820	0.257
	Previous smoking	0.858	0.080–9.225	0.900	−20.385–1.907	0.549
BEAM		14.910	1.764–126.038	0.013	−0.469–41.661	0.006

CAD: coronary artery disease; BEAM: carmustine, etoposide, cytarabine, melphalan; OR: odds ratio; CI: confidence interval; 95% BCa CI: Bias-corrected and accelerated confidence interval.

Table 7. Multivariate logistic regression analysis. Cardiovascular risk factors and previous use of anthracyclines possibly influencing the development of CTRCD.

		Multivariate Model			Bootstrap Method	
Covariate		**OR**	**95% CI**	**p**	**95% Bca CI**	**p**
Risk factors	CAD	4.131	0.216–79.078	0.346	−19.808–22.766	0.075
	Arterial hypertension	0.595	0.133–2.662	0.497	−3.286–1.312	0.522
	Family history of CAD	0.597	0.078–4.561	0.619	−20.325–1.024	0.437
	Dyslipidaemia	2.643	0.419–16.692	0.301	−1.072–21.330	0.235
	Previous smoking	1.295	0.112–14.945	0.836	−20.105–2.645	0.508
Previous use of anthracyclines		6.996	1.530–31.997	0.012	−0.100–37.590	0.009

CAD: coronary artery disease; OR: odds ratio; CI: confidence interval; 95% BCa CI: Bias-corrected and accelerated confidence interval.

This study aimed to evaluate the occurrence of CTRCD following HSCT and to identify factors that may predict or influence its development. At the 12-month follow-up, asymptomatic CTRCD was observed in 15 patients (27.3%), with six exhibiting moderate and nine mild dysfunction, based on the 2022 ESC cardio-oncology criteria. Previous studies have used varying definitions of CTRCD, which makes direct comparisons challenging. For instance, Moriyama *et al*. retrospectively evaluated 136 allogeneic HSCT patients, defining early LV systolic dysfunction as an LVEF decrease of ≥10% or an LVEF ≤53% within 100 days post-transplant, and found a 17% incidence, with higher mortality among affected patients [12]. Other research examining late-onset CTRCD in 274 autologous HSCT patients, defining LV systolic dysfunction as LVEF <50%, reported a 15.7% incidence, with 5.1% asymptomatic [13]. Overall, these findings suggest that LV systolic dysfunction tends to increase several years after HSCT, regardless of definition.

In terms of potential contributing factors, univariate logistic regression in our cohort suggested that the BEAM conditioning regimen and prior anthracycline exposure may influence CTRCD risk. Multivariate analysis initially failed to confirm these as independent predictors, likely due to the strong overlap between the two variables, as all patients receiving BEAM were lymphoma cases who had previously undergone anthracycline-based chemotherapy. However, bootstrap analysis indicated that the BEAM regimen might independently contribute to CTRCD, highlighting the need for larger studies to verify this effect.

The BEAM protocol includes carmustine, etoposide, cytarabine, and melphalan, with cytarabine and melphalan particularly linked to increased heart failure risk [14, 15]. Etoposide inhibits topoisomerase 2 and impairs mitochondrial biogenesis. CTRCD following BEAM therapy likely arises from multiple mechanisms, including direct myocardial injury, oxidative stress, vascular damage, inflammation, and fibrosis. These processes generate reactive oxygen species and disrupt antioxidant defenses, impairing mitochondrial energy production and promoting apoptosis. Chemotherapy-induced myocardial inflammation leads to cytokine release and immune cell infiltration, while fibrosis increases stiffness, contributing to diastolic dysfunction and eventual systolic impairment [16].

Anthracycline cardiotoxicity is well-documented and dose-dependent [17], with multiple studies corroborating its association with CTRCD prior to HSCT [18–20]. Even in patients without preexisting cardiovascular risk factors, anthracycline exposure can trigger CTRCD [21], particularly at high cumulative doses or in the presence of underlying cardiac conditions [22, 23]. Mechanisms include topoisomerase 2β inhibition, oxidative stress, mitochondrial dysfunction, inflammation, and possibly accelerated cardiac aging [24–28]. The involvement of

etoposide in BEAM therapy, which also affects topoisomerase 2, may partially explain the synergistic effect on CTRCD risk.

Early-onset CTRCD after HSCT is associated with reduced overall survival, underscoring the importance of early detection and intervention [29, 30]. Preventive strategies, such as cardioprotective agents during anthracycline therapy, may help mitigate risk, though efficacy varies, and ongoing research is essential to optimize cancer treatment while minimizing cardiac toxicity [31].

ESC cardio-oncology guidelines highlight that allogeneic HSCT, uncontrolled cardiovascular risk factors, preexisting heart disease, and direct cardiotoxic effects of therapy negatively influence CTRCD development [9]. While our study did not show a statistically significant difference based on HSCT type—likely due to the small number of allogeneic cases (n = 7)—three of these patients did develop CTRCD, suggesting a potential trend. Similarly, no significant effect of cardiovascular risk factors was observed, possibly due to the limited sample size. Other studies have shown that hypertension and other cardiovascular conditions can significantly affect CTRCD risk [32, 33]. Clinicians should continue to optimize modifiable risk factors and further research is warranted.

Limitations

The primary limitation of this study is the relatively small cohort. Although bootstrap analysis suggests that the BEAM regimen may independently increase CTRCD risk, larger studies are needed to confirm this. The small number of allogeneic HSCT patients also limits conclusions regarding this subgroup. Furthermore, the influence of cardiovascular risk factors may have been underestimated due to the limited sample size.

Conclusion

At 12 months post-HSCT, asymptomatic CTRCD was detected in 27.3% of patients. Prior anthracycline therapy followed by the BEAM conditioning protocol was identified as a factor associated with the development of CTRCD, highlighting the need for careful cardiac monitoring in these patients.

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