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EVALUATION OF CARDIAC DAMAGE USING DIFFERENT IMAGING MODALITIES IN PATIENTS UNDERGOING HAEMATOPOIETIC STEM CELL TRANSPLANTATION

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CONTENTS

ABBREVIATIONS

ACEi – angiotensin converting enzyme inhibitor
ARB – angiotensin receptor blocker
ASE – American Society of Echocardiography
BCNU – carmustine
BEAM – carmustine, etoposide, cytarabine, melphalan
BNP – B type natriuretic peptide
BSA – body surface area
CAD – coronary artery disease
CCTA – coronary computed tomography angiography
CHF – congestive heart failure
CHOEP – cyclophosphamide, doxorubicin, etoposide, vincristine, and prednisone
CMR – cardiovascular magnetic resonance
cTn – cardiac troponin
CTRCD – cancer therapy related cardiac dysfunction
CV – cardiovascular
CW – continuous doppler
DMSO – dimethyl sulfoxide
EBMT – European Society for Blood and Marrow Transplantation
ECG – electrocardiography
ECV – extracellular volume
EHA – European Hematology Association
ESC – European Society of Cardiology
ESMO – European Society for Medical Oncology
ESTRO – European Society for Therapeutic Radiology and Oncology
FAC – fractional area change
G-CSF – granulocyte colony stimulating factors
GLS – global longitudinal strain
GvHD – graft versus host disease
GVL – graft *versus* leukaemia
HLA – human leucocyte antigen
HSCT – hematopoietic stem cell transplantation
IC-OS – International Cardio-Oncology Society
IE – ifosfamide, etoposide
IHD – ischemic heart disease
IVS – interventricular septum
LGE – late gadolinium enhancement
LA – left atrium
LAi – left atrium volume index

LV – left ventricular
LVEDD – left ventricular end-diastolic diameter
LVEDDi – left ventricular end-diastolic diameter indexed to BSA
LVEDV – left ventricular end-diastolic volume
LVEDVi – left ventricular end-diastolic volume indexed to BSA
LVEF – left ventricular ejection fraction
LVESV – left ventricular end-systolic volume
LVESVi – left ventricular end-systolic volume, indexed to BSA
LVSD – left ventricular systolic dysfunction
MAC – myeloablative conditioning
MACE – major adverse cardiac event
MDS-EB – myelodysplastic syndrome with excess blasts
MM – myocardial mass
MMI – myocardial mass index
MOCO – motion correction
MOLLI – modified Look-Locker inversion
MUGA – multi-gated radionuclide angiography
NK – natural killer
NPs – natriuretic peptides
NT-proBNP – N-terminal pro-BNP
OR – odds ratio
PCNS – primary central nervous system
PW – posterior wall
RA – right atrium
RIC – reduced-intensity conditioning
ROC – receiver operating characteristic
RV – right ventricular
RVEDD – right ventricular end-diastolic diameter
RVEDV – right ventricular end-diastolic volume
RVEDVi – right ventricular end-diastolic volume index
RVESV – right ventricular end-systolic volume
RVESVi – right ventricular end-systolic volume index
RVEF – right ventricular ejection fraction
RWT – relative wall thickness
S' – tricuspid lateral annular systolic velocity wave
SD – standard deviation
STE – speckle tracking echocardiography
TAPSE – tricuspid annular plane systolic excursion
TBI – total body irradiation
TDI – tissue doppler
TR – tricuspid regurgitation
WBMT – Worldwide Network of Blood and Marrow Transplantation

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is known as a potentially curative procedure for different malignant hematologic disorders and some solid tumors, where high dose chemotherapy can be beneficial for treatment [1,2].

According to the Worldwide Network of Blood and Marrow Transplantation (WBMT) the number of haematopoietic stem cell transplants worldwide has been increasing steadily at a rate of about 7 % per year, to an average of about 90,000 per year. By 2019, a total of one and a half million patients have undergone HSCT worldwide since 1957 [3]. Post-HSCT patients who survive more than five years without relapse have a high probability of surviving another 15 years [4]. Although HSCT offers much higher survival rates compared to the past, it is still associated with some serious acute or chronic complications [5].

There is a growing awareness of the adverse effects of HSCT on the cardiovascular (CV) system, and HSCT recipients are at increased risk of cardiovascular disease later in life. Studies suggest that the risk of cardiovascular disease is at least four times higher than in the general population [5,6]. According to the literature, of all HSCT-related complications, cardiovascular complications account for approximately 10–16.84 % for both allogeneic and autologous HSCT. They reduce the quality of life of long-term survivors and can lead to a high mortality rate [7,8].

Cardiac adverse events can be associated with various components of HSCT, such as ablative therapy, including total body irradiation combined with a multidrug conditioning regimen. Most of the drugs used for mobilization or conditioning, including cyclophosphamide, cytarabine, carmustine and melphalan, are associated with significant toxicity. In addition, effects of dimethyl sulfoxide, which is used to preserve stem cells, are also thought to contribute to cardiac events. Monoclonal antibodies and other targeted therapies used before and after HSCT can have a negative impact on heart damage too. Cardiac complications can also occur as a result of other HSCT-related comorbidities such as graft versus host disease (GvHD), sepsis, thrombotic microangiopathy or hepatic veno-occlusive disease [9].

Not only clinically overt CV complications may occur, subclinical damage may be even more common, and the exact frequency is not known. Subclinical damage may be associated with clinical cardiovascular disease later in life; therefore, it is important to detect early changes in order to prevent clinically overt complications [10].

The aim of our study was to identify impact of HSCT on heart sizes, function and tissue characteristics, and clinical factors influencing the development of cancer therapy related cardiac dysfunction (CTRCD). Two different imaging modalities – echocardiography and cardiovascular magnetic resonance – were chosen to evaluate possible cardiotoxicity following HSCT.

The aim of the study

To identify impact of HSCT on cardiac morphology, function and tissue characteristics with different imaging modalities, and factors influencing and prognosing the development of subclinical CTRCD.

The objectives of the study

1. To evaluate changes in cardiac chamber sizes and ventricular function on echocardiography and to identify the frequency of subclinical CTRCD after mobilization process in patients undergoing autologous HSCT.
2. To evaluate changes in cardiac chamber sizes and ventricular function on echocardiography and cardiovascular magnetic resonance (CMR) at follow-up 12 months after HSCT.
3. To identify changes in myocardial tissue characteristics, including diffuse myocardial fibrosis and oedema with the help of CMR native T1 and T2 mapping techniques at follow-up 12 months after HSCT.
4. To identify the frequency of subclinical CTRCD and factors influencing and prognosing the development of CTRCD in patients undergoing HSCT.

Novelty and relevance of the study

Cardio-oncology is a new rapidly evolving field in cardiology. The impact on cardiac damage of some cancer therapies, e.g. anthracyclines, anti-HER2 therapies, immune checkpoint inhibitors are of great interest and already quite well analysed. There is increase in the number of HSCT procedures every year, patients have good survival rates and the impact of HSCT on cardiac damage, especially subclinical, has not been analysed widely.

To our knowledge this is one of the first prospective studies analysing impact of HSCT on subclinical cardiac damage including CMR evaluation. CMR has a unique ability to assess changes in myocardial tissue, and could, therefore, be important for assessing subclinical as well as clinical myocardial damage. In our study we have found that native T1 mapping value in patients increases at 12 months follow-up, thus showing possible progress of diffuse myocardial

fibrosis. Increase in E/e' ratio revealed on follow-up echocardiography could be a consequence of progressing diffuse myocardial fibrosis.

Moreover, identifying patients which are at the greatest risk for cardiotoxicity would allow us to provide closer follow-up and better care for patients to avoid clinically overt cardiac damage in the future. In our study we have identified that patients, undergoing BEAM (carmustine, etoposide, cytarabine, melphalan) conditioning regimen, statistically significantly more often are affected by subclinical CTRCD. We have also identified that patients, who are affected by subclinical CTRCD, tend to have bigger indexed left ventricular end diastolic diameter (LVEDDi) on the baseline echocardiography and those, affected by moderate subclinical CTRCD have bigger indexed left ventricular end diastolic volume (LVEDVi) and indexed left ventricular end systolic volume (LVESVi) on baseline CMR. Cut-off values for prognosing development of CTRCD have been established.

1. LITERATURE REVIEW

1.1. Hematopoietic stem cell transplantation

HSCT is a potentially curative procedure for various malignant hematologic and lymphoid diseases, some solid tumours, and some certain benign conditions [1,2]. Initially developed as a rescue therapy for patients with cancer after high doses of chemotherapy and radiation or the correction of severe deficiencies in the hematopoietic system, it has evolved into an adoptive immune therapy for malignancies and autoimmune disorders [11].

First HSCT was performed successfully by Donnall Thomas and the group at the Fred Hutchinson Cancer Centre during the 1960s [11]. According to the Worldwide Network of Blood and Marrow Transplantation (WBMT), the global count of HSCTs has been consistently rising by approximately 7 % annually, reaching an average of around 90,000 per year. By 2019, a total of 1.5 million patients had undergone HSCT worldwide since 1957 [3].

The procedure involves the administration of haematopoietic stem cells to replace the recipient's haematopoietic cells. It is a multi-step procedure that includes collection of haematopoietic stem cells, treatment of the patient's main disease with a conditioning regimen followed by the infusion of haematopoietic stem cells and subsequent evolvement of a new haematopoietic and immune system [12].

There are two fundamentally different types of HSCT characterized by the source of stem cells:

1. Autologous HSCT, where the stem cells are collected from the recipient him/herself and are later reinfused.
2. Allogeneic HSCT, where the cells originate from a different person who can be related or unrelated to the patient [12,13].

1.1.1. Autologous HSCT

The major benefit of autologous HSCT is achieved by the effects of the conditioning treatment. The infusion of haematopoietic stem cells allows to deliver toxic therapies for treatment of main disease, which would otherwise result in prolonged myelosuppression and a high risk of complications [14]. The process flow of autologous HSCT is presented in Figure 1.1.1.1.

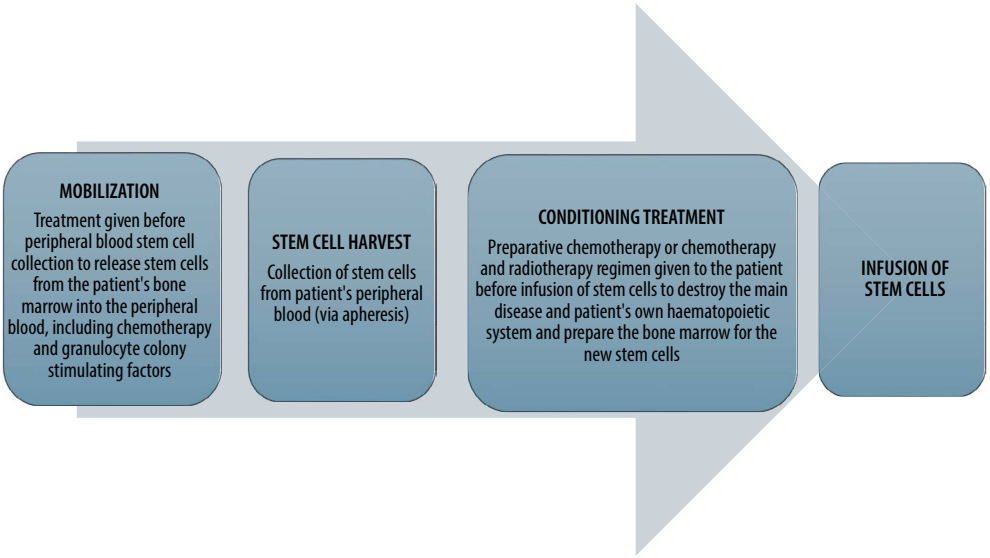


Fig. 1.1.1.1. *Process of autologous hematopoietic stem cell transplantation.*

According to the survey of European Society for Blood and Marrow Transplantation (EBMT), in the EBMT-reporting countries 42 171 transplants were performed in 37 626 patients in 2015 of which 59 % were autologous and 41 % allogeneic. Almost 99 % of autologous haematopoietic stem cell transplants were performed for malignancies, of which 90 % were for plasma cell diseases (multiple myeloma and others, 52 %) or lymphoma (38 %). Autoimmune diseases accounted for 1 % of indications for autologous haematopoietic stem cell transplant [15].

1.1.2. Allogeneic HSCT

The main feature of allogeneic transplantation is that hematopoietic stem cells are obtained from the donor. This is needed in the case when patient‘s bone marrow are critically ill and cannot produce normal immune and blood cells.

Acute and chronic leukaemia are the most common indications for allogeneic HSCT. There are two main mechanisms by which HSCT can cure leukaemia: high doses of chemotherapy and radiation the patients receive before infusion of the hematopoietic stem cell graft (conditioning or preparatory regimen); and the immune-mediated graft *versus* leukaemia (GVL) reaction. It is not clear which mechanism is more important, but as the GVL reaction is better understood, more patients are being prepared with less intense doses of chemotherapy and radiation, favouring engraftment but reducing toxicity and transplant-related mortality [11].

The main difference from autologous HSCT is that the bone marrow used for transplantation are collected not from the patient, but from a healthy person – a donor. The process of allogeneic HSCT is presented in Figure 1.1.2.1.

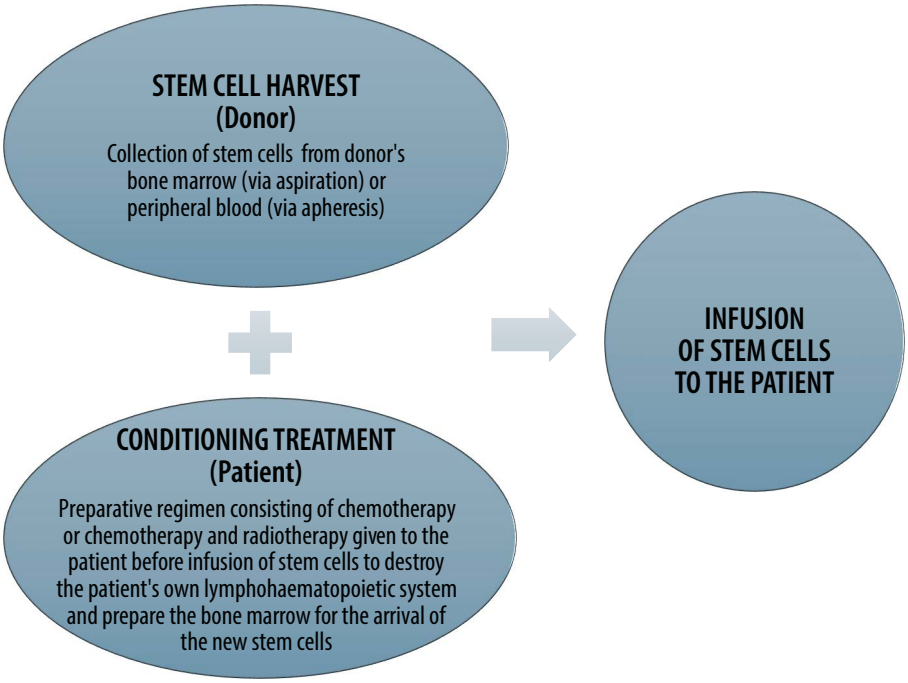


Fig. 1.1.2.1. *Process of allogeneic hematopoietic stem cell transplantation.*

Allogeneic HSCT is associated with numerous complications. Mortality related to allogeneic HSCT can exceed 30 % within the first-year post-transplant [16]. Survivors of allogeneic HSCT experience significantly higher rates of organ dysfunction (cardiac, endocrine, pulmonary, and musculoskeletal), infertility, and secondary cancers compared to the general population. The most significant complication limiting allogeneic HSCT is graft-versus-host disease (GvHD), an immune response in which donor lymphocytes attack host tissues, resulting in symptoms such as skin rash, diarrhea, and liver disease. GvHD can become chronic, leading to a condition resembling systemic sclerosis. The most important factor that determines the incidence and severity of GvHD is human leucocyte antigen (HLA) matching [12]. Patients require prolonged immunosuppression for prevention and treatment of GvHD and rejection. Consequently, the risk of infections is increased for many months until immune reconstitution develops [17].

1.2. Cardiovascular complications in HSCT patients

According to the literature among all HSCT-related complications, cardiovascular complications account for around 10–16.84 % for both allogeneic and autologous HSCT. They decrease the quality of life for long-term survivors and lead to a higher mortality rate [7,8]. In a retrospective, single-centre study which included 265 allogeneic HSCT survivors, the cumulative incidence of a coronary or peripheral arterial event was 22 % at 25 years post-transplantation [18].

1.2.1. Short-term cardiotoxicity

During HSCT and within the first 100 days after HSCT arrhythmias, acute heart failure, pericardial effusion, or cardiac arrest can occur. The incidence of these complications is quite low: arrhythmia 2–10 % of patients [9,19,20], with atrial fibrillation or flutter being the most frequent arrhythmia; new congestive heart failure (CHF) 0.4–2.2 % [21–23]; pericardial effusion rate was low, with higher in young children – up to 9,3 % [23,24]. In a retrospective analysis including 2821 HSCT (45 % allogeneic) patients, 26 of these patients (0.9 %, 19 adults and 7 children) were either diagnosed with severe CHF, severe cardiac tamponade, significant electrocardiographic abnormalities or died due to cardiovascular dysfunction within the first 100 days post-HSCT [23].

1.2.2. Long-term cardiotoxicity

More investigations on long-term HSCT-related cardiovascular complications have been conducted. Ischemic heart disease (IHD), cardiomyopathy, vascular disorders, stroke, CHF have been reported [23,25]. In an observational study of 1244 patients undergoing autologous HSCT cumulative incidence of CHF was 4.8 % at 5 years post-HSCT and increased to 9.1 % at 15 years post-transplantation. HSCT recipients had a 4.5-fold higher risk of CHF compared to the general population, while female HSCT survivors showed a higher risk of developing CHF compared to male recipients [26]. Compared to general population, HSCT patients showed higher risk of developing cardiovascular diseases such as cardiomyopathy, stroke, diabetes, and IHD [27,28].

1.3. Possible causes and mechanisms of cardiovascular complications in HSCT

Main factors thought to induce cardiotoxicity during and after HSCT:

- Previous treatment history (chemotherapy, e.g., anthracyclines, targeted therapy, e.g. tyrosine kinase inhibitors (TKI), and radiotherapy);
- Mobilization and conditioning regimens (Table 1.3.1);
- Effects of dimethyl sulfoxide (DMSO) used for stem cell preservation;
- HSCT complications (GvHD, sepsis, infections, thrombotic microangiography, hepatic veno-occlusive disease) [9,23].

Table 1.3.1. *Effect of therapeutics used in hematopoietic stem cell transplantation on cardiovascular system. Modified from Rotz et al, 2021[9]*

Therapeutics	**Effects on CV system**
Cyclophosphamide	Congestive heart failure, haemorrhagic myocarditis, pericarditis
Cytarabine	Dysrhythmia, congestive heart failure, pericarditis
Carmustine (BCNU)	Myocardial ischemia
Melphalan	Dysrhythmia, congestive heart failure
Dimethyl sulfoxide (DMSO)	Bradycardia, cardiac arrest
Calcineurin Inhibitors	Hypertension
Alemtuzumab	Congestive heart failure, dysrhythmia, tachycardia
Vinca Alkaloids	Dysautonomia
Total body irradiation	Pericarditis, congestive heart failure

Pathological changes of cardiotoxicity in the tissue level present in myocardial oedema, cytoplasmic vacuolization, apoptosis or necrosis, and fibrosis [29–31]. Effects of different therapeutics are presented in Table 1.3.1.

1.3.1. Antracyclines

Anthracyclines are often used for treatment of haematologic malignancies, such as acute leukaemia or lymphoma before HSCT. Anthracycline-induced CV complications are already well analysed and characterized, and their toxicities mostly directly correlate to their cumulative dose. There is a dose-dependent correlation between pre-transplantation exposure to anthracyclines and the incidence of CHF in HSCT patients. The risk of CHF increased substantially for patients receiving ≥ 250 mg/m^2 of cumulative anthracycline exposure (OR: 9.9, $p < 0.01$), the presence of hypertension among recipients of high-dose anthracycline (≥ 250 mg/m^2) resulted in a 35-fold higher risk (OR: 35.3, $p < 0.01$) of CHF; the risk was nearly 27-fold (OR: 26.8, $p < 0.01$) for high-dose anthracycline recipients with diabetes. This study shows that

hypertension and diabetes may be critical modifiers of anthracycline-related myocardial injury after HSCT [26].

1.3.2. Molecular-targeted therapy

Molecular targeted therapy is nowadays frequently used in cancer treatment either as a single treatment or as a part of traditional chemotherapy protocols. One of the targeted therapies – tyrosine kinase inhibitors (TKIs) – have been reported to be associated with cardiovascular complications, when TKIs were used as pre-treatment in HSCT survivors [23]. Sorafenib was reported to be associated with adverse cardiac effects, e.g., left ventricular systolic dysfunction [32].

Another type of targeted therapies – Bruton TKIs. The adverse effects are most widely analysed of the first Bruton TKI ibrutinib, used for treatment of chronic lymphocytic leukaemia and mantle cell lymphoma. Ibrutinib can cause arrhythmia (atrial fibrillation) or arterial hypertension, increase the risk of bleeding [32–34]. What is more, a wide range of cardiac adverse effects, i.e., dysrhythmias, myocarditis/pericarditis, pulmonary hypertension, myocardial ischemia, and cerebral and peripheral vascular events, have been reported to be associated with other targeted-therapy substances [32].

1.3.3. Radiotherapy

Chest radiotherapy can increase the risk of cardiac dysfunction in HSCT patients. Exposure dose ≥30 Gy is considered to be a risk factor for radiotherapy-induced cardiotoxicity. The risk for cardiotoxicity induced by anthracycline at a lower dose might be further increased by additional low-dose radiotherapy [23,35].

Another cardiovascular complication after radiotherapy is coronary artery disease (CAD). Armenian et al reported, that CAD risk in HSCT survivors increased by 9.5-fold in patients who received chest radiotherapy before transplantation [36]. Coronary computed tomography angiography (CCTA) was performed in a group of adult survivors of childhood Hodgkin lymphoma who received radiation therapy (≥ 30 Gy in 48 % of patients) pre-HSCT. CCTA indicated coronary artery disease in 12 of 31 (39 %) patients [37].

1.3.4. Mobilization and conditioning regimens

Pre-transplant conditioning is a critical aspect of HSCT, aimed at eradicating the recipient's bone marrow/cancer cells, inducing immunosuppression, and facilitating the engraftment of donor cells. These conditioning regimens are typically categorized into three types: myeloablative conditioning (MAC),

reduced-intensity conditioning (RIC), and non-myeloablative conditioning. The choice of conditioning protocol for HSCT recipients depends on factors such as the patient's age, underlying disease, and any accompanying health issues. These regimens may involve total body irradiation (TBI), chemotherapy, or a combination of both. Common chemotherapeutic agents used include busulfan, cytarabine, fludarabine, cyclophosphamide, idarubicin, thiotepa, and melphalan [25,38].

Cyclophosphamide poses a cardiotoxic risk, particularly when administered in high doses [9,39,40]. As an alkylating agent, it possesses both antineoplastic and immunosuppressive properties, making it integral to mobilization regimens and high-dose conditioning regimens for HSCT [41]. Additionally, the administration of high doses of cyclophosphamide post-transplant in haplo-identical transplants has demonstrated efficacy in in preventing GvHD [42]. It is frequently employed in MAC regimens due to its anti-leukemia and immunosuppressive effects, although doses exceeding 100 mg/kg are associated with cardiac damage. The spectrum and severity of cardiotoxicity reported include pericarditis, arrhythmias, hemorrhagic myocarditis, and CHF [9,39]. Cardiotoxic effects are typically observed only after the administration of high doses, highlighting the importance of dose limitation [43]. The pathophysiology of high-dose cyclophosphamide-induced cardiac toxicity, as analyzed in postmortem examinations, is believed to involve toxic endothelial damage leading to the extravasation of toxic metabolites, resulting in myocyte damage, interstitial hemorrhage, and oedema [40].

The use of RIC regimens is recommended for HSCT patients with compromised organ function or significant comorbidities [44]. RIC is recommended for patients with reduced LV EF $\leq$ 45 % [45]. However, even with RIC regimens, cardiac complications such as arrhythmias, myocardial infarction, and CHF have been reported [44]. Melphalan, commonly used before autologous HSCT, is the most arrhythmogenic agent increasing the risk of atrial fibrillation up to 11 % in patients receiving > 140 mg/m^2 [46]. Fludarabine may induce cardiac dysfunction and heart failure in 8 % of patients. Specific drug combinations, such as melphalan and fludarabine, have been associated with substantial cardiotoxicity of about 14 % cases [47]. The combination can cause atrial fibrillation and cardiac dysfunction [44,48]. Carmustine can cause hypotension and tachyarrhythmias, and cases of pericarditis has been described using cytarabine [49].

The administration of pre-HSCT TBI can further increase damage to the CV system. TBI may induce diabetes mellitus, dyslipidaemia, metabolic syndrome, or arterial hypertension and increases the risk of heart failure, CAD, conductions disorders, and pericardial effusion [50,51].

1.3.5. Graft-versus-host disease

GvHD is one of the most common life-threatening complications after allogeneic HSCT. Immune competent T cells of the donor (the graft) recognize the recipient (the host) as a foreign body. Because of this mechanism, the immune response activates donor T cells and attacks the recipient to eliminate the foreign antigen(s)-bearing cells. GvHD may contribute to the higher incidence of cardiac events in allogeneic HSCT patients compared to autologous HSCT patients [52]. GvHD is classified into two main clinical forms, acute and chronic GvHD [53]. There are several hypotheses regarding the effect of GvHD on allogeneic HSCT patients' cardiovascular function. A retrospective clinical study showed that patients who developed acute grade II–IV GvHD also developed risk factors for cardiovascular complications, such as diabetes mellitus, hypertension, and hypersensitivity lung disease. One explanation could be that patients with a higher grade of GvHD are treated with steroids and calcineurin inhibitors, which can cause cardiotoxicity [54]. Also, ibrutinib and ruxolitinib as new treatments of GvHD are also reported to be associated with the incidence of cardiac events, such as atrial fibrillation and hyperlipidaemia [55,56]. On the other hand, GvHD may induce inflammation and damage to endothelium of the arteries and in this way directly affect artery function [57].

1.4. Diagnosis of cancer therapy related cardiac dysfunction

CTRCD includes structural and functional changes in the myocardium, pericardium, coronary arteries, valves, and large vessels, and may lead to major adverse cardiac events (MACEs) [58].

The clinical diagnosis of cancer therapy-related cardiac dysfunction (CTRCD) primarily relies on the detection of an abnormal left ventricular ejection fraction (LVEF) and the presence of heart failure symptoms [59]. Various diagnostic cardiotoxicity criteria have been established by several academic organizations, such as the American Society of Echocardiography (ASE), the European Society of Cardiology (ESC), the European Society for Medical Oncology (ESMO), and the International Cardio-Oncology Society (IC-OS), and joint criteria from ESC and IC-OS [60] (Table 1.4.1).

Table 1.4.1. *Diagnostic criteria of CTRCD proposed by different societies*

Society and Year of Publication	Diagnostic Criteria of CTRCD
ASE/EACVI, 2014	Decrease in LVEF of > 10 %, to LVEF < 53 % Relative drop in GLS > 15 % from baseline suggests subclinical LV dysfunction
ESC, 2016	Decrease in LVEF of > 10 % from baseline, to LVEF < 50 % Decrease in GLS of > 15 % from baseline may suggest risk of cardiotoxicity
ESMO, 2020	LVEF drop by ≥10–15 %, or to < 50 %
IC-OS, 2021	Mild: LVEF ≥ 50 % and new relative decrease in GLS by > 15 % from baseline, and/or new rise in cardiac biomarkers (cardiac troponin I/T > 99th percentile, BNP > 35 pg/mL, NT-proBNP ≥ 125 pg/mL). New reduction in LVEF by ≥10 % or < 10 %, to absolute 40 % < LVEF < 50 %, and new relative decrease in GLS by > 15 % from baseline, and/or new rise in cardiac biomarkers. Severe: new LVEF reduction to < 40 %. For symptomatic patients: mild heart failure symptoms or more.
ESC/EHA/ESTRO/ IC-OS, 2022	Severe: New LVEF reduction to < 40 % Moderate: New LVEF reduction by ≥10 percentage points to an LVEF of 40–49 % OR New LVEF reduction by < 10 percentage points to an LVEF of 40–49 % AND either new relative decline in GLS by > 15 % from baseline OR new rise in cardiac biomarkers Mild: LVEF ≥ 50 % AND new relative decline in GLS by > 15 % from baseline AND/OR new rise in cardiac biomarkers

ASE – American Society of Echocardiography; EACVI – European Association of Cardiovascular Imaging; ESC – European Society of Cardiology; ESMO – European Society of Cardiology; IC-OS – International Cardio-Oncology Society; EHA – European Hematology Association, ESTRO – European Society for Therapeutic Radiology and Oncology; LVEF – left ventricular ejection fraction; GLS – global longitudinal strain; BNP – B-type natriuretic peptide; NT-proBNP – N-terminal pro-BNP. Modified from [60,61].

There is no unified consensus on the optimal modality and/or biomarkers, particularly for symptomatic patients. Various methods, including electrocardiograms, cardiac biomarkers, echocardiography, multi-gated radionuclide angiography (MUGA), and CMR, have been employed to detect cardiotoxicity [60]. There is a growing need to evaluate functional changes and myocardial injury due to cardiotoxicity using a safe, non-invasive, and accurate approach. The following principles are recommended when selecting diagnostic modalities: (1) consistently using the same modality and/or biomarker with high sensitivity and reproducibility throughout the treatment; (2) providing comprehensive clinical information, including assessments

of right ventricular (RV) function, valvular function, and the pericardium; (3) avoiding radiation exposure when possible; and (4) considering the use of left ventricular (LV) global longitudinal strain (GLS) [58,61,62].

1.5. Echocardiography

Echocardiography is the most widely used tool to monitor cardiac function because of its safety, availability, feasibility, and low cost. Echocardiography can evaluate not only LVEF, which is a cornerstone of diagnosing CTRCD but also diastolic dysfunction, pericardium, valves and right chambers, which can be damaged by cancer therapy as well [63].

There are three main timepoints of echocardiographic screening for patients with cancer: baseline (prior to the initiation of cardiotoxic chemotherapy); during the chemotherapy; and after completion of chemotherapy.

The baseline imaging provides a further risk stratification beyond the baseline characteristics (the patient is considered high risk when he/she has concomitant cardiac disease, cardiovascular risk factors, previous cardiotoxic treatment). According to the results of baseline echocardiography, cancer therapy can be planned or adjusted, including alternative chemo-regimens with less cardiotoxicity (less cardiotoxic agents, dose adjustment, continuous infusion), radiation planning (lower cumulative dose, avoid cardiac exposure), and/or prophylactic administration of cardioprotective therapy. During chemotherapy, the echocardiogram results can inform whether any adjustment is required for the planned cancer therapy, including initiation of cardioprotective therapy during subclinical myocardial damage, modifying the planned chemo- or radiotherapy. The main aim of echocardiography after the completion of cancer therapy is surveillance for late cardiac toxicity (e.g. in childhood cancer survivors, and/or after radiation therapy) and planning of further follow-up [64].

1.5.1. Left ventricular systolic function

LVEF is the most widely used parameter for routine monitoring of cardiotoxicity in cancer patients. Changes in LVEF should be evaluated in cancer patients when comparing baseline and follow-up studies [63]. Recently published guidelines in cardio-oncology recommend the schedule of echocardiographic evaluation timing depending on different chemotherapy treatment and risk for CTRCD development [61].

1.5.2. Strain imaging

GLS assessment has already a role in cardio-oncology[65]. Measurements of LVEF are highly dependant on hemodynamic conditions and is not sensitive enough to detect minor changes and to precede cardiotoxicity. LV and RV GLS assessment can help to identify patients ar risk for developing systolic dysfunction and heart failure [66]. Speckle tracking echocardiography (STE) utilizes 2D gray-scale images to evaluate global and regional functions of the LV. Myocardial strain resembles tissue deformation changes at each cardiac cycle and is referenced to the original length. Cardiomyocytes shorten during systole, therefore, GLS is negative number [67]. Metaanalysis data suggest that LV GLS values > 18 % should be considered normal and values 16 %–18 % should be considered borderline [68].

GLS has been widely studied to detect early changes in LV contractile dysfunction in patients undergoing oncological treatment. A relative decrease in GLS of > 15 % from baseline is considered an indicator of subclinical LV dysfunction [69].

1.5.3. Left ventricular diastolic function

Diastolic parameters did not predict CTRCD; however, a conventional evaluation of LV diastolic function, including the grading of diastolic function and non-invasive estimation of LV filling pressures, should be incorporated together with assesing LV systolic function [63].

1.5.4. Evaluation of right ventricle

Echocardiographic evaluation of the RV in patients receiving cardiotoxic treatment should include the following measurements: basal diameter and area, tricuspid annular plane systolic excursion (TAPSE), peak of tricuspid lateral annulus systolic velocity by tissue doppler (TDI) (S') and fractional area change (FAC) [70]. According to the literature, TDI is the most sensitive tool for the early detection of RV damage caused by chemotherapy [63].

1.6. Cardiovascular magnetic resonance

CMR imaging stands as the gold standard non-invasive imaging method for comprehensively evaluating both structural and functional alterations in the heart, employing a range of imaging sequences [60]. Dark-blood sequences, cine sequences, and phase-contrast flow sequences enable assessment of changes in LV and RV morphology and function, valvular function, pericardial integrity, and vascular structures. Specifically, cine sequences offer the ability to measure functional parameters like LVEF and

identify any abnormalities in wall motion. Furthermore, advanced techniques such as gadolinium enhancement sequences and mapping techniques provide insights into myocardial tissue characteristics, allowing to identify myocardial oedema, inflammation, and fibrosis [60].

1.6.1. Left ventricular morphology and function

1.6.1.1. Left ventricular mass

CMR offers precise and highly reproducible quantification of LV mass [60,71]. Reduction in LV mass may indicate myocardial atrophy. Numerous studies have shown myocardial atrophy due to cancer therapy. A study of anthracycline treatment has shown loss of cardiomyocytes [72]. In another study involving 91 patients, there was a negative correlation observed between the indexed LV mass and the dose of anthracycline. Moreover, multivariable regression analysis demonstrated that the indexed LV mass emerged as the most robust predictor of subsequent MACE, surpassing factors such as anthracycline dosage, glomerular filtration rate, and CMR-derived LVEF [73].

1.6.1.2. Left ventricular ejection fraction

CMR offers exceptional accuracy and reproducibility in monitoring changes in LVEF, owing to its high spatial and temporal resolution and reproducibility [60,74–76]. It is particularly recommended for baseline evaluation in patients with inadequate echocardiographic image quality. Early studies of cardiotoxicity assessed LVEF using echocardiography and MUGA. Although echocardiography serves as the primary imaging modality for LVEF evaluation in clinical settings, its reproducibility can be compromised due to high operator dependency, and accuracy may be hindered in patients with poor acoustic windows. Previous studies have reported variability in two-dimensional echocardiography LVEF ranging from 11.5 % to 26 % [76,77]. Additionally, research has shown that two-dimensional echocardiography overestimated mean LVEF by 5 % compared to CMR in adult survivors of childhood cancer. Furthermore, 11 % of patients were incorrectly classified as having an LVEF of 50 % or higher by echocardiography, leading to false-negative diagnoses [78].

CMR quantification of LVEF commonly involves analysing a series of short-axis slices from the cardiac apex to base in a steady-state free precession cine white-blood imaging technique. The LV endocardial border contours are delineated from end-diastolic and end-systolic frames within the cine sequence to obtain LV cavity areas for each slice. Multiplying the

area from the corresponding end-diastolic or end-systolic frame by the slice thickness yields the volume for each slice. By summing these volumes while accounting for interslice gaps, left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) can be calculated using the modified Simpson rule. Subsequently, LVEF is determined by subtracting LVESV from LVEDV and dividing this resulting value (LV stroke volume) by LVEDV [75].

A decrease in LVEF can be caused by a decrease in LVEDV or an increase in LVESV, or both. Some studies suggested that an increased LVESV was the main reason of reduced LVEF in patients treated with anthracycline and/or trastuzumab, which may be triggered by an increased LV afterload or by myocardial contractile dysfunction [79–81].

However, sometimes decline in LVEF can be due to an isolated decrease in LVEDV, which can be caused by volume depletion (diminished LV preload), when intravascular hypovolemia can be a result of poor oral intake, vomiting, or diarrhoea during cancer treatment. This may lead to a decrease in LVEDV and LVEF, and then incorrect implication of cardiotoxicity and erroneous termination of cancer treatment can occur [82].

1.6.1.3. Left ventricular strain

Recent evidence suggests that LV strain measured with feature-tracking CMR may also identify early LV dysfunction [83].

Myocardial strain refers to the myocardium's ability to deform, with LV strain representing the myocardial deformation of the LV throughout a cardiac cycle as a percentage of its initial length. By measuring the segmental and global strain of the myocardium in longitudinal, radial, and circumferential directions, one can gain insight into the internal contractile function of the myocardium [84]. Various studies have demonstrated a correlation between myocardial strain and LVEF in patients undergoing potentially cardiotoxic chemotherapy, often indicating changes in myocardial strain prior to significant alterations in LVEF [85,86]. This phenomenon may be explained by segmental changes in myocardial function preceding the overall decrease in LV function, as adjacent normal myocardium may contribute to maintaining a normal LVEF through compensatory mechanisms during early myocardial dysfunction [87], and LVEF being influenced not only by myocardial strain but also by factors such as end-diastolic wall thickness [88].

GLS reflects changes in myocardial length from base to apex in a cardiac cycle. It is highly sensitive to subclinical LV dysfunction; therefore, it is included in an expert consensus and recommendations for imaging evaluation

of cardiotoxicity. The consensus recommends that a decrease of > 15 % from the baseline in GLS is abnormal [61,89].

Circumferential strain shows the degree of circumferential shortening of the myocardial fibers of the LV. Circumferential strain was one of the strongest predictors of cardiotoxicity, and LV mean mid-wall circumferential strain is associated with a subclinical decline in LVEF [90,91].

However, evaluation of strain has some limitations: post-processing consumes additional time and costs; no universal reference range is established so far due to differences among different vendors [60,92].

1.6.1.4. Right ventricular function

RV function can also change due to cardiotoxicity and can be even more susceptible than LV. RV dysfunction was identified in 34 % of the patients (defined by a 10 % drop in CMR-RVEF) at 12 months, which correlated with early myocardial oedema [93]. A study of long-term cancer survivors also showed that RV function deteriorated more often than LV function: 18 % of patients demonstrated abnormal LVEF and 27 % demonstrated abnormal RV function quantified with CMR [94].

RV dysfunction can be a prognostic indicator for adverse outcomes across a range of cardiovascular conditions. Studies have revealed that individuals receiving trastuzumab treatment, exhibiting biventricular dysfunction, had less improvement in LVEF compared to those without RV dysfunction. Additional studies are necessary to assess the prognostic significance of RV dysfunction in cardiotoxicity [95].

1.6.2. Myocardial tissue characterization

CMR is the primary imaging modality for myocardial tissue characterization. Tissue characterization methods in CMR enable to identify microstructural alterations within the myocardium associated with various heart conditions. These techniques are extensively applied in diagnosing and monitoring cardiomyopathies, myocardial infiltration, and inflammatory disorders. CMR can non-invasively identify subtle changes in myocardial tissue and provide promising imaging biomarkers for the early detection and prognosis of cardiotoxicity associated with cancer therapies [96].

Standard sequences, such as T1-weighted, T2-weighted, and cine bright-blood steady-state free-precession sequences, offer fundamental morphological insights into the myocardium, adjacent structures like the pericardium and valves, and additional non-cardiac details such as pleural effusion and metastases. However, conventional T1- and T2-weighted imaging is insensitive to mild microstructural changes, and conventional T2-weighted

imaging sometimes may fail to recognize global myocardial oedema, therefore, parametric mapping can help in these situations [60].

Parametric mapping represents a cutting-edge imaging approach that achieves advanced tissue characterization by directly quantifying pixels without relying on normal tissue references. Techniques like T1 mapping, T2 mapping, and extracellular volume fraction (ECV) are part of parametric mapping and can surpass the limitations of traditional T1-weighted imaging, T2-weighted imaging, and late gadolinium enhancement (LGE) in evaluating diffuse myocardial inflammation or fibrosis [97,98]. T1 mapping and T2 mapping enhance objectivity and enable to detect microstructural myocardial changes before functional alterations occur, potentially establishing a new standard for comprehensive non-invasive myocardial tissue characterization in the future.

Quantified myocardial tissue parameters can be compared using native T1 and T2 mappings. Terminology of native parametric mappling is presented in Table 1.6.2.1. Quantitative myocardial parameters can be compared. Representative myocardial pathologies that result in changes in T1 values primarily include diffuse myocardial fibrosis; T1 prolongation can also occur due to edema, inflammation, and infiltrative diseases such as amyloidosis and Fabry disease. T2 relaxation time is utilized to differentiate between normal and abnormal myocardial tissues, too. An increase in the water content of myocardial tissues leads to longer T2 relaxation times, making myocardial edema the primary pathology responsible for variations in T2 mapping values. No contrast agent is used to obtain these sequences [99].

Table 1.6.2.1. *Terminology of native parametric mapping. Modified from [96]*

T1 (ms)	Time constant representing the recovery of longitudinal magnetization (spin–lattice relaxation)
Native T1	T1 in the absence of contrast agent
T2 (ms)	Time constant representing the decay of transverse magnetization (spin-spin relaxation)
Parametric mapping	A process where a secondary image is generated where each pixel represents a specific magnetic tissue property (T1, T2, or T2*) or a derivative such as ECV) derived from the spatially corresponding voxel of a set of co-registered magnetic resonance source images

ECV shows the volume of extracellular matrix as a percentage of the total volume of myocardial tissue, which can be calculated using pre- and post-contrast T1 mapping and haematocrit with good reproducibility. ECV is mainly affected by the interstitial space and myocellular volume or mass [100], and correlates with the histological collagen volume fraction and extracellular space [101].

The LGE technique is the main technique for tissue characterization and can identify regional myocardial fibrosis, providing prognostic information for a variety of cardiovascular diseases. Contrast agent is needed to acquire LGE sequences [102–104].

1.7. Biomarkers

Cardiac biomarkers have been investigated for identifying and monitoring drug-induced cardiotoxicity at an early stage. The most frequently used cardiac biomarkers are cardiac troponin (cTn) and natriuretic peptides (NPs) [105]. NPs and cTn measurements at baseline are particularly important for evaluating the cardiotoxicity risk prior to anti-cancer therapy [106]. When chemotherapy is initiated, troponin is released due to myocardial cell damage. Troponin can be detected within 2–4 h (high-sensitivity cardiac troponin already within 1 h) and reaches a peak concentration at 10–15 h and returns to the baseline level within 5–14 days depending on the degree of injury [107]. From all the NPs, B type natriuretic peptide (BNP) is the most often used biomarker which reflects intravascular and ventricular pressure and volume overload [105]. However, as there are fluid overload and shifts during HSCT, the accuracy of NPs for cardiac damage prediction might be questionable.

1.8. Management of cancer therapy related cardiac dysfunction

CV complications after HSCT is a major issue. Compared to the non-transplant population, the risk of late death due to CV complications is 4-fold higher after autologous HSCT in females and 2.3-fold higher after allogeneic HSCT to both females and males [51,108,109]. Therefore, aggressive management of CV risk factors according to clinical practice guidelines during HSCT process and after HSCT, close CV monitoring, including clinical, imaging and biomarker evaluation after HSCT is recommended [51,110,111].

Information regarding prevention of CV toxicity after HSCT are limited. Overall, according to literature, 58–89 % of patients with reduced LV EF because of cardiotoxicity do not recover fully [112–114]. Therefore, early detection of cardiotoxicity and findings like increase in natriuretic peptides (NPs), decrease in GLS > 15 % form baseline or a reduced LV EF, even asymptomatic, should prompt to considered initiation of cardioprotective treatment (angiotensin converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs) and beta-blockers) to prevent further remodelling of LV [58,61,110,115].

2. METHODS

2.1. Ethics

Kaunas regional Bioethics Committee permission was obtained for this prospective research (No. BE-2-96). The research was carried out in accordance with the Helsinki Declaration. All patients gave their informed consent to take part in the study.

2.2. Study population

The study was performed prospectively from October 2021 till February 2024 in the Hospital of the Lithuanian University of Health Sciences Kaunas Clinics. 60 patients undergoing autologous or allogeneic HSCT at the Department of Oncology and Haematology were included in the study.

Inclusion criteria:

- written consent to participate in the study;
- patients over the age of 18 years scheduled for HSCT for various reasons.

Exclusion criteria:

- contraindications to CMR, like non-MR conditional implants or claustrophobia;
- HSCT performed in the past;
- patient's refusal to participate at any time of the study.

2.3. Methodology and process of the study

Process of the study is presented in Figure 2.3.1. Methodology of the study is presented in Figure 2.3.2.

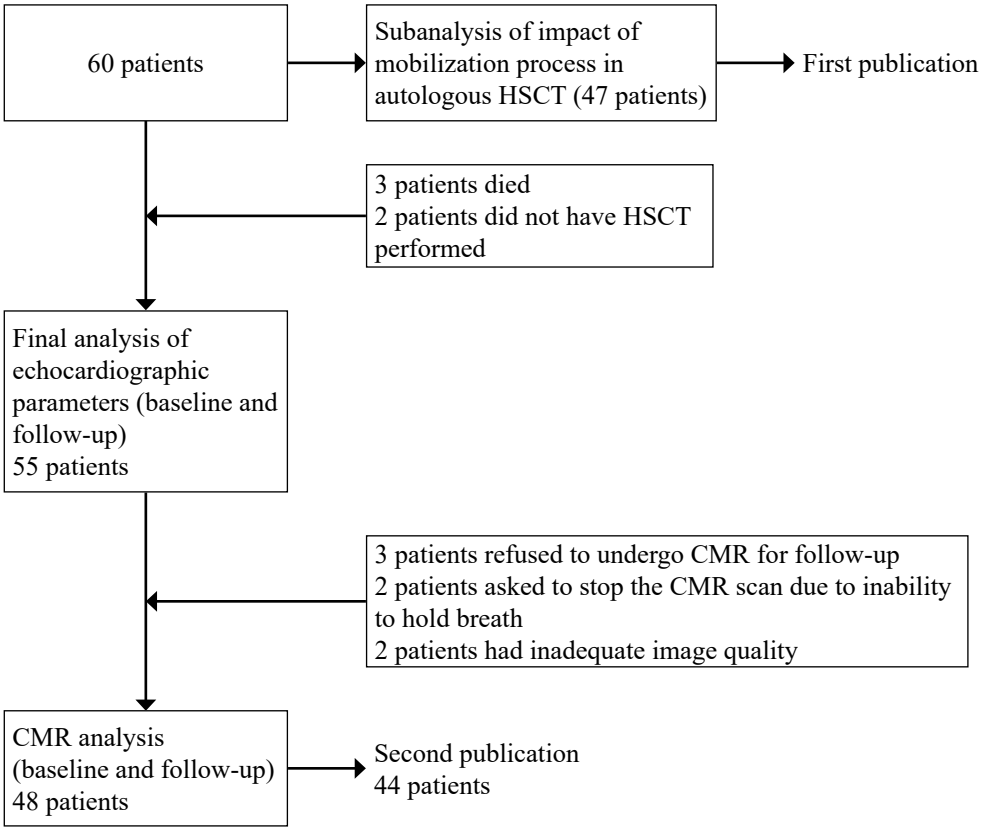


Fig. 2.3.1. *Process of the study.*

CMR – cardiovascular magnetic resonance; HSCT – hematopoietic stem cell transplantation..

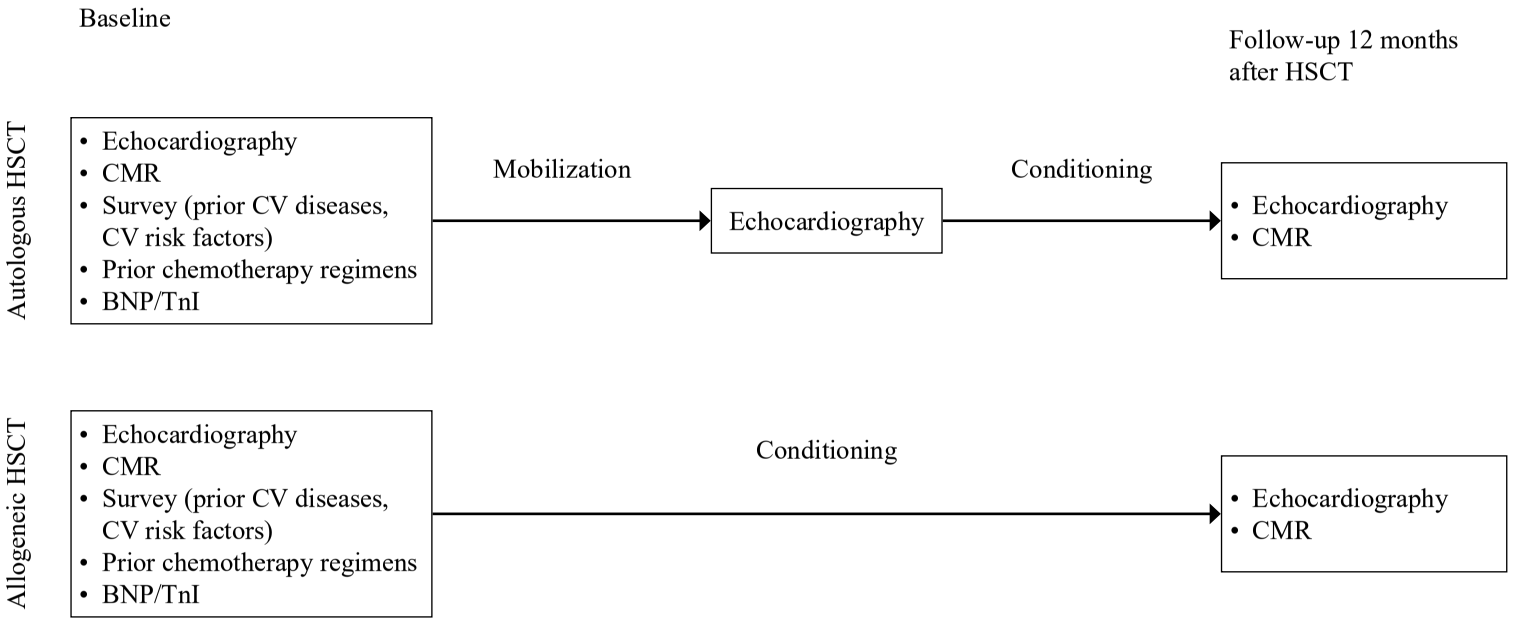


Fig. 2.3.2. *Methodology of the study.*

Process of the study included:

- Patient selection: after evaluating inclusion and exclusion criteria and signing the informed consent, the patient was included in the study. Then patients had interview and filled in a survey about CV risk factors and previous CV diseases, CV medication (Suppl. 1). The information was then double-checked from medical records.
- Baseline echocardiography and CMR were performed and blood for TnI and BNP was drawn before taking further steps (for autologous HSCT – before starting chemotherapy for mobilization and for allogeneic HSCT – before starting conditioning chemotherapy. Methodology of echocardiography and CMR is discussed separately.
- Autologous HSCT patients have undergone echocardiography after mobilization process before starting conditioning regimen. The first publication was prepared of this data analysis.
- Follow-up echocardiography and CMR was performed 12 ± 1 months after HSCT. Not all patients could have had follow-up CMR evaluated – 3 patients refused to undergo CMR again; 2 patients asked to stop the CMR scan due to inability to hold breath, 2 patients had inadequate image quality. Analysis of CMR data was performed and second publication was prepared.
- According to the objectives of the study 2 types of analysis were performed: 1) echocardiographic and CMR baseline and follow-up parameters of all patients were compared to evaluate impact of HSCT as a process on heart sizes, function and tissue characteristics; 2) subclinical heart damage was defined according to the diagnostic criteria of the cardiotoxicity of ESC guidelines on cardio-oncology, 2022 [61]. The patients were divided into two groups with and without subclinical heart damage. Analysis of factors influencing and prognosing CTRCD was performed.

2.4. Patients' demographics, risks factors, main diseases, and chemotherapy regimens

1. Anthropometrical data of the patients was collected: height (cm), weight (kg). Body surface area (BSA) was calculated using formula of DuBois and DuBois:
   $BSA = (W^{0.425} \times H^{0.725}) \times 0.007184$,
   where the weight (W) is in kilograms and the height (H) is in centimetres.
2. All patients filled in a survey about CV risk factors (arterial hypertension, smoking, early CAD family history, dyslipidaemia, diabetes mellitus), The survey is presented in Supplement No 1. Information

regarding CAD and cardiovascular medication was obtained during the interview and double-checked from medical records.

- Arterial hypertension was diagnosed, and grade was established according to the European Society of Cardiology and European Society of Hypertension guidelines published in 2018. Arterial hypertension was diagnosed if systolic ABP was ≥140 mmHg and/or diastolic was ≥ 90 mmHg.
- Early CAD family history was defined as cardiovascular event (stroke, myocardial infarction, revascularization procedures) or cardiovascular death in the first-degree relatives (men < 55 year old, women < 60 year old).

3. Patients underwent HSCT for various reasons. Distribution of diseases and type of transplantation are described in detail in Table 3.1. Hematologic malignancies were treated according to local institution treatment protocols based by international guidelines. Data about previous treatment of main disease was collected from medical records.
4. Hematopoietic stem cell harvesting for autologous HSCT was performed with chemotherapy and granulocyte colony stimulating factors (G-CSF) (chemo-mobilization). Multiple myeloma patients had cyclophosphamide 3000 mg/m^2; mantle cell lymphoma patients had rituximab 375 mg/m^2 and cytarabine 4 g/m^2; Hodgkin's lymphoma patients had cisplatin 30 mg/m^2 and cytarabine 3.5 g/m^2; primary central nervous system (PCNS) diffuse large B cell lymphoma patients had cytarabine and thiotepa at different doses and rituximab 375 mg/m^2; NK/T-cell lymphoma patient had CHOEP (cyclophosphamide, doxorubicin, etoposide, vincristine and prednisone) scheme; and Ewing sarcoma patient followed an IE scheme (ifosfamide with etoposide). All patients scheduled for autologous HSCT underwent apheresis procedures. Stem cells form peripheral blood were collected using Fresenius Kabi COM.TEC apheresis system. The cells were cryopreserved in a solution of 10 % DMSO and autologous plasma. Cryopreservation was performed in a controlled-rate freezer with liquid nitrogen (Consarctic equipment).
5. Conditioning was performed as follows: multiple myeloma using melphalan 200 mg/m^2, lymphomas with BEAM (carmustine, etoposide, cytarabine and melphalan) protocol, Primary central nervous system (PCNS) diffuse large B cell lymphoma – Thiotepa and BCNU (carmustine), all patients undergoing allogeneic HSCT received RIC conditioning with fludarabine and busulfan.

2.5. Methods of echocardiography

During the study period, echocardiography was performed at three time points for patients undergoing autologous HSCT: first, on evaluation and decision to enrol the patient in the transplantation process (before the mobilization procedure); second, before the transplantation (the conditioning regimen) procedure; and third, at follow-up 12 months after HSCT. For patients undergoing allogeneic HSCT echocardiography was performed 2 times: first, on evaluation and decision to enrol the patient in the HSCT process; second, at follow-up 12 months after HSCT. Echocardiographic workflow is presented in Figure 2.5.1.

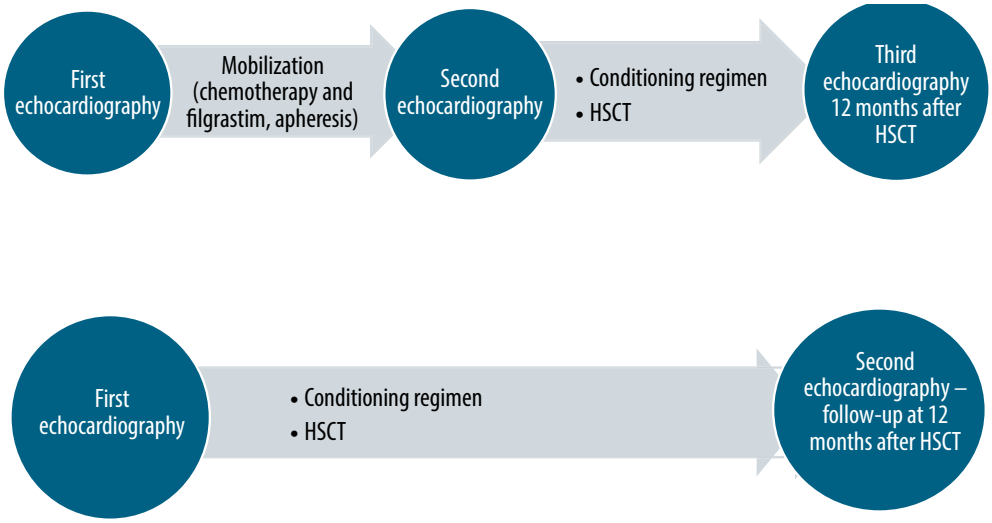


Fig. 2.5.1. *Echocardiography workflow of the study.*

HSCT – hematopoietic stem cell transplantation.

Echocardiography was performed and evaluated by one experienced cardiologist using a EPIQ 7 *(Phillips Ultrasound Inc., Washington, USA)* ultrasound machine. Routine echocardiographic parameters (quantification of cardiac chamber size and function) and global longitudinal strain were measured.

The quantification of cardiac chamber size and function were measured according to American Society of Echocardiography and the European Association of Cardiovascular Imaging recommendations for Cardiac Chamber Quantification [116].

Measurements from parasternal long-axis view were obtained perpendicular to the LV long axis and measured at the level of the mitral valve leaflet tips:

- Left ventricular end diastolic diameter (LVEDD), mm.
- LVEDD index was calculated according to body surface area (BSA) (LVEDDi), mm/m^2 at end-diastole;
- Thickness of interventricular septum (IVS) and inferolateral wall (PW) at end-diastole;
- LV mass was calculated using Cube formula:
- LV mass = $0.8 \times 1.04 \times (IVS + LVID + PWT)^3 - LVID^3 + 0.6$ g
  (IVS – interventricular septum; LVID – left ventricle internal diameter; PWT inferolateral wall thickness).
- Relative wall thickness (RWT) with the formula $(2 \times PWT)/LVID$ was calculated. Increase in LV mass was categorized as either concentric ($RWT > 0.42$) or eccentric ($RWT \leq 0.42$) hypertrophy. Normal LV mass increased $RWT > 0.42$ was categorized as concentric remodelling.
- Left atrium (LA) diameter, mm, at end-systole.

Measurements from apical views:

- LVEF was calculated from LV volumes, using the modified biplane Simpson method. Volumetric measurements LVEDV, mL, and LVESV, mL, were derived from tracings of the border between the myocardium and LV cavity in the end-systole and end-diastole in the apical two- and four- chamber views. Global LVEF was assessed by calculating the difference between the end-diastolic and end-systolic value, divided by the end-diastolic value.
  LVEF = (LVEDV – LVESV)/LVEDV
- LA volume, mL, was calculated from four- and two-chamber views, using disk summation algorithm. LA was traced at the blood-tissue interface at end-systole. At the mitral valve level, the contour was closed by connecting the two opposite sections of the mitral annulus with a straight line. Endocardial tracing excluded atrial appendage and pulmonary veins.
- LA volume was indexed to body surface area, LAi, mL/m^2;
- RV end diastolic diameter (RVEDD) was measured at the base in the apical four-chamber view at end-diastole;
- RV systolic longitudinal function which was evaluated using tricuspid lateral annular systolic velocity wave (S') was evaluated from the apical four-chamber view using TDI. Figure 2.5.2.

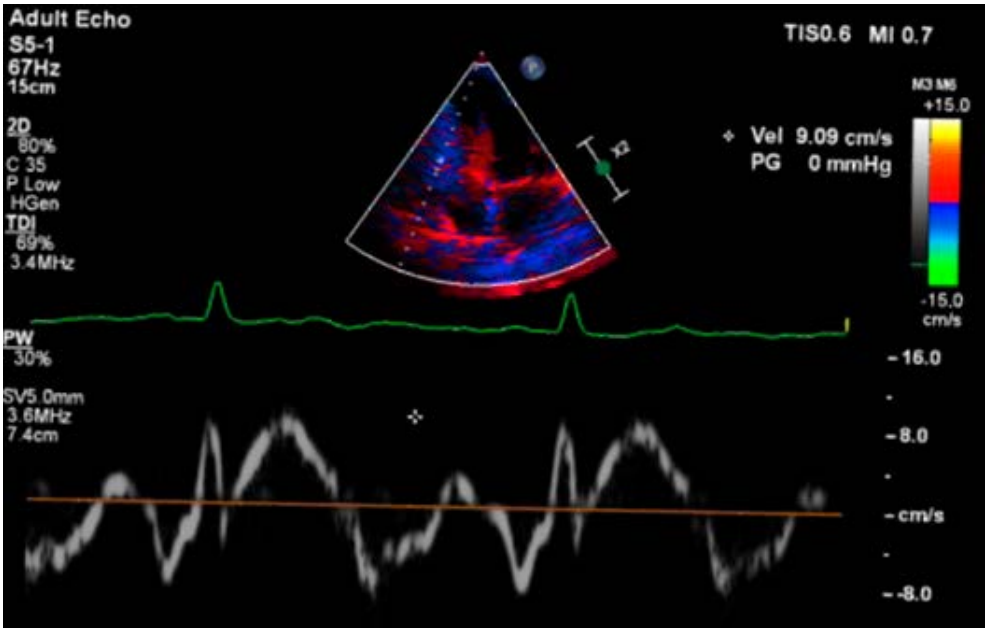


Fig. 2.5.2. *Tricuspid lateral annular systolic velocity wave (S') evaluation from the apical four-chamber view using tissue doppler.*

- Diastolic LV function was determined after calculating mitral E and A velocity, cm/s, mitral E/A ratio, pulsed wave TDI-derived mitral annular early diastolic velocity e', cm/s, early mitral inflow velocity/mitral annular early diastolic velocity (E/e') in the apical four-chamber view, tricuspid regurgitation (TR) velocity, m/s, and LAi, mL/m^2. Mitral E and A velocity were measured placing the pulse wave (PW) doppler between mitral leaflet tips (Figure 2.5.3). E/A ratio was calculated by dividing E velocity by A velocity. e' velocity, was measured using TDI placing PW doppler sample volume at lateral (Figure 2.5.4) and septal (Figure 2.5.5) basal regions, and average e' was computed. E/e' ratio was calculated by dividing E by e'. TR velocity was measured in apical for chamber and parasternal view to obtain highest doppler velocity aligned with continuous doppler (CW) [117].

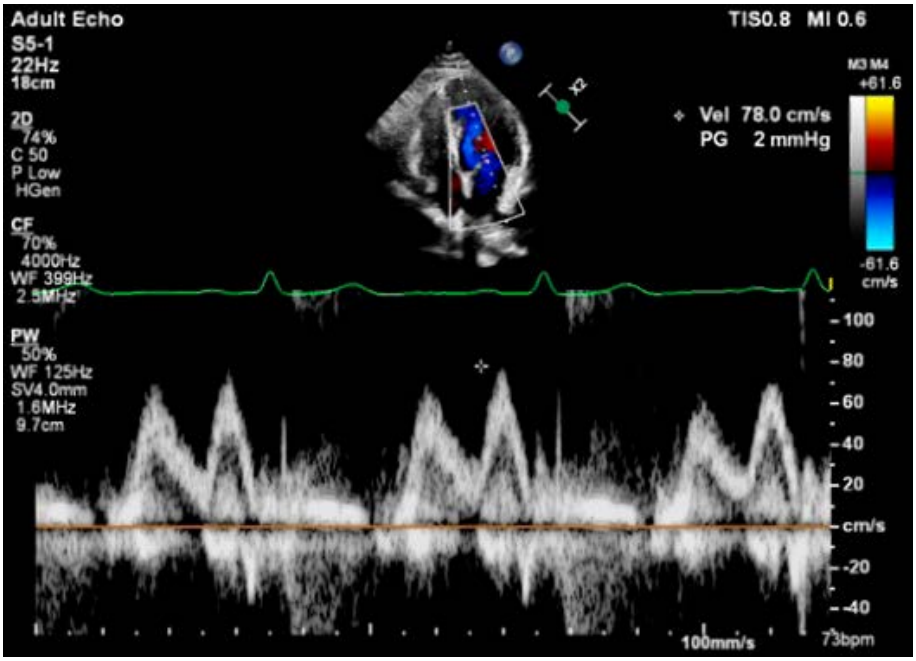


Fig. 2.5.3. *Measurement of mitral E and A velocity.*

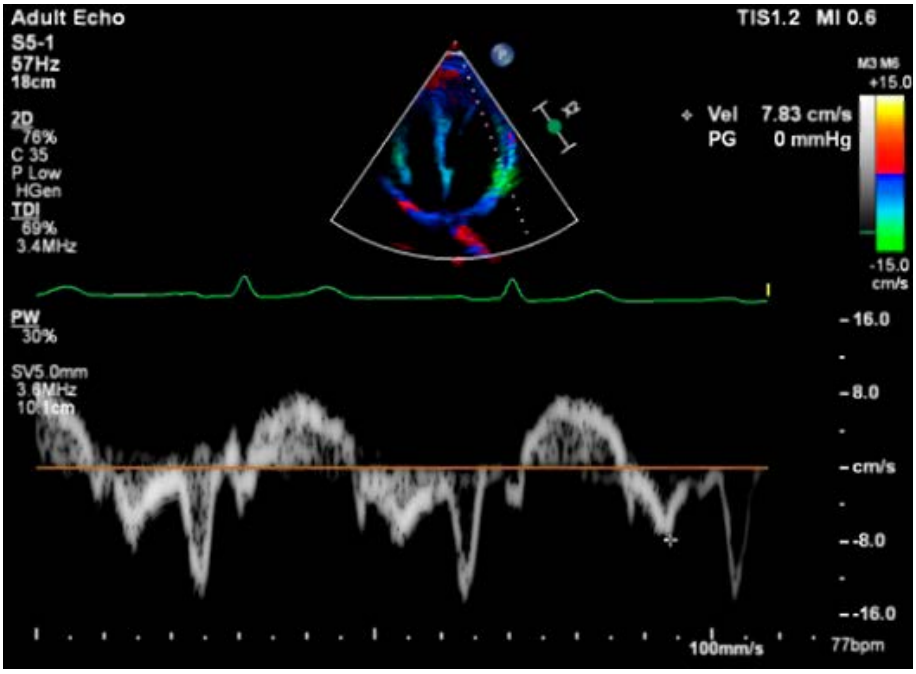


Fig. 2.5.4. *Measurement of lateral e' velocity using TDI.*

TDI – tissue doppler.

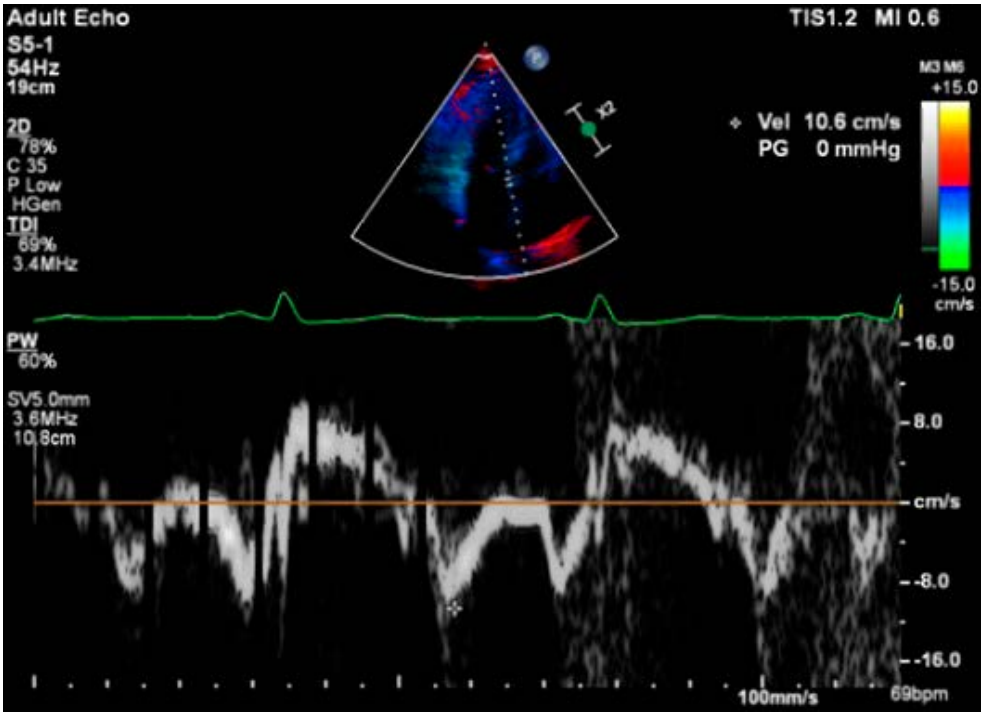


Fig. 2.5.5. *Measurement of septal e' velocity using TDI.*

TDI – tissue doppler.

- LV GLS was assessed by STE. Peak GLS describes the relative length change of the LV myocardium between end-diastole and end-systole: GLS(%) = (MLs – MLd)/MLd; where ML is myocardial length at end-systole (MLs) and end-diastole (MLd). Because MLs is smaller than MLd, peak GLS is a negative number.
  GLS was calculated automatically using a postprocessing system. The endocardial borders were traced in the end-systolic frame of the 2D images from the 3 apical views (two-, three-, and four-chamber). Speckles were tracked frame by frame throughout the LV wall during the cardiac cycle. Segments that failed to track were manually adjusted by the operator. Figure 2.5.6.

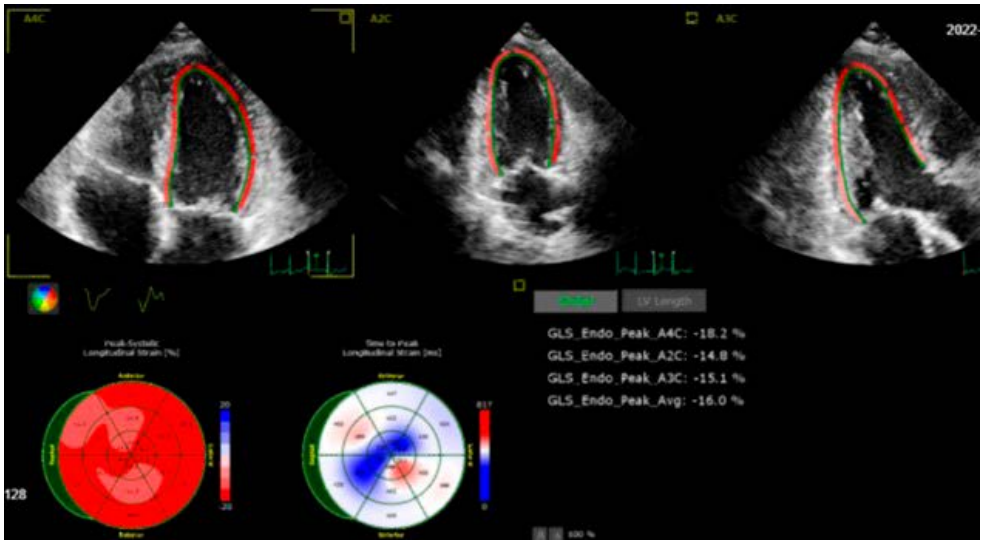


Fig. 2.5.6. *Assessment of left ventricular global longitudinal strain with speckle-tracking technique.*

GLS – global longitudinal strain; LV – left ventricle; A4C – four-chamber view; A2C – two-chamber view; A3C – three-chamber view; Avg – average.

2.6. Methods of cardiovascular magnetic resonance

The study participants underwent 3T CMR with an 18-channel cardiac coil (MAGNETOM Skyra, Siemens Healthcare, Erlangen, Germany). Black blood spin echo and bright blood spin echo sequences, standard electrocardiographic (ECG) triggered two-, three-, four-chamber and short-axis cine balanced steady-state free precession sequences, T1 and T2 mapping sequences were performed.

The quantitative analysis of LVEDV, RVEDV, LVESV, RVESV, LV mass and values indexed to body surface area (BSA), also LVEF and RVEF were analysed and calculated using Medis Suite 3.2 (Leiden, the Netherlands). The LV endo- and epi-contours were outlined manually in cine short axis views in the end-diastolic and end-systolic phase, with exclusion of the LV papillary muscles. RV endo contours were also outlined manually in cine short axis views. Global LV and RV systolic function was assessed by calculating the difference between the end-diastolic and end-systolic volumes, divided by the end-diastolic volume. An example of analysis is presented in Figure 2.6.1.

LVEF = (LVEDV – LVESV)/LVEDV

RVEF = (RVEDV – RVESV)/RVEDV

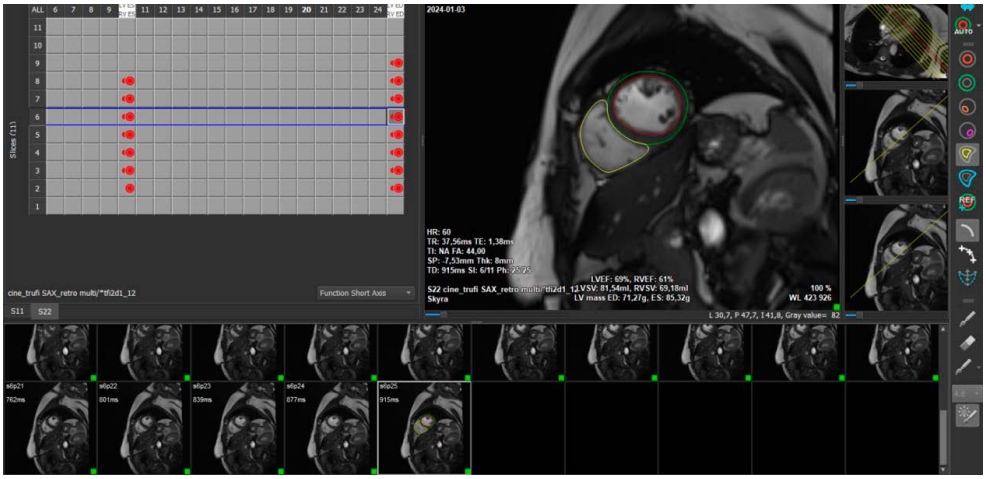


Fig. 2.6.1. *Calculation of LV and RV volumes, LV mass and LV and RV EF.*

LV – left ventricle; RV– right ventricle; EF – ejection fraction.

T1 and T2 mapping were obtained in end-diastole in short-axis orientation in three slices (basal, midventricular, and apical). For myocardial T1 mapping MOLLI (modified Look-Locker inversion) recovery acquisition scheme with motion correction (MOCO) was applied. T2 mapping was performed using T2-prepared balanced steady-state free precession sequence. T1 and T2 relaxation times were analysed using Syngo.via. Interventricular septum was outlined in three slices (basal, midventricular, apical) and average of all three measurements was obtained. Baseline mapping values were compared to values 12 months after HSCT. Methods of measurements are shown in Figures 2.6.2 and 2.6.3.

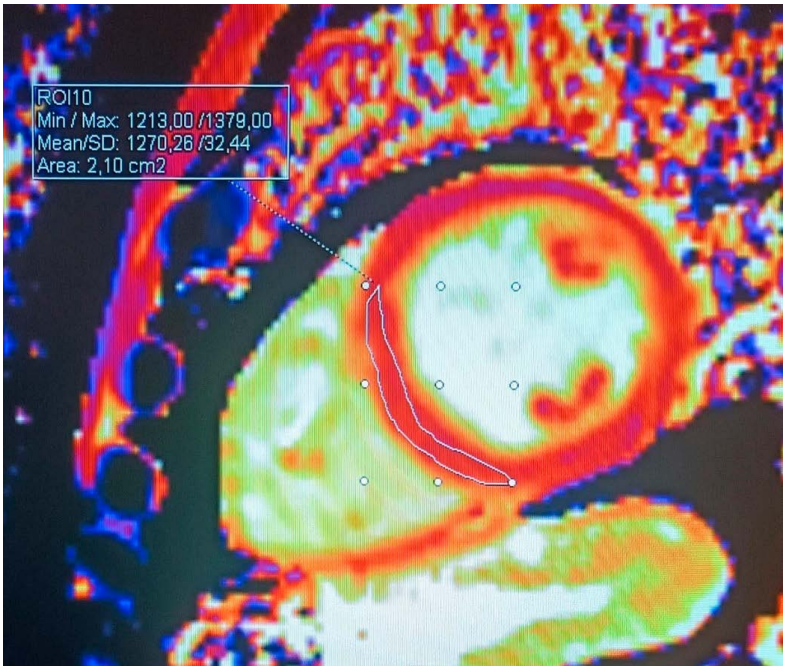


Fig. 2.6.2. *Measurement of T1 mapping value in midventricular slice.*

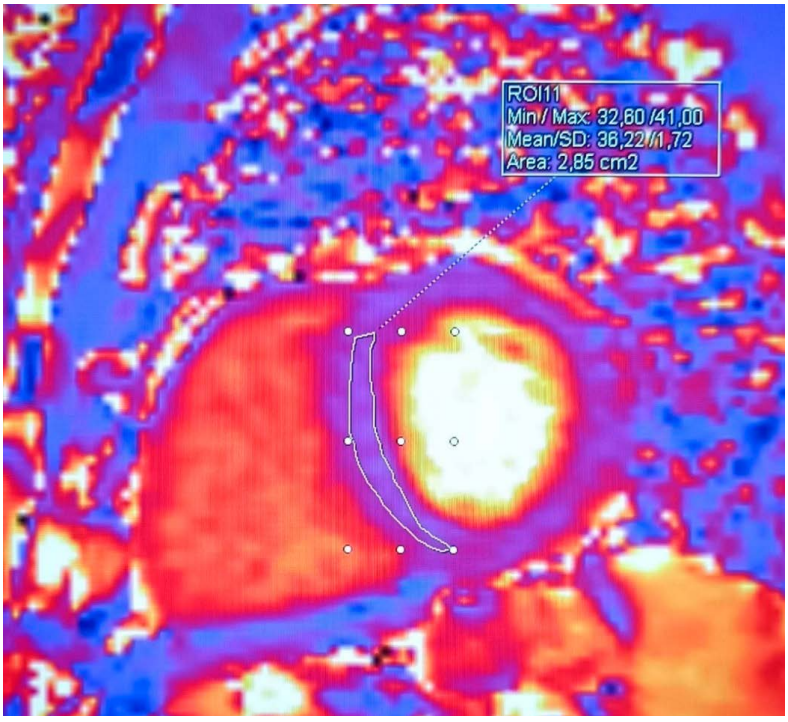


Fig. 2.6.3. *Measurement of T2 mapping value in midventricular slice.*

2.7. Definition of cancer therapy related cardiovascular dysfunction

In order to define the frequency of asymptomatic CTRCD and to analyse the influence of different factors on cardiotoxicity, the patients were divided into two groups with and without subclinical CTRCD according to the change in echocardiographic parameters (LVEF and GLS). This was performed according to the definition in the ESC guidelines on cardio-oncology developed in collaboration with EHA/ESTRO/IC-OS, 2022 [61]. The criteria of CTRCD and distribution of the patients are presented in Table 2.7.1.

Table 2.7.1. *Definition criteria of CTRCD and distribution of patients*

Grade	Definition criteria	No of patients
Severe	New LVEF reduction to < 40 %	0
Moderate	New LVEF reduction by ≥10 percentage points to an LVEF of 40–49 %	3
	New LVEF reduction by < 10 percentage points to an LVEF of 40–49 % AND new relative decline in GLS by > 15 % from baseline	3
Mild	LVEF ≥ 50 % AND new relative decline in GLS by > 15 % from baseline	9

GLS – global longitudinal strain; LVEF – left ventricular ejection fraction.

2.8. Statistical analysis

All statistical tests were performed in the IBM SPSS Statistics 29.0 software package (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to determine the data normality. The continuous variables are represented as mean (standard deviation (SD)) or median (minimum-maximum (min-max)) according to data distribution. The relationship between the values was evaluated by Pearson's or Spearman's correlation coefficient. Paired t-test, Wilcoxon test or Mann Whitney test was used to compare the data between two sets of measurements. The categorical variables are described as absolute numbers and percentages. The association between the development of cardiotoxicity and patients' clinical features was assessed with Pearson's Chi-square or Fisher's Exact tests. The binary logistic regression analysis was performed with univariate and multivariate models to estimate the odds ratio (OR) with a 95 % confidence interval (CI). The significance level in all statistical tests was defined as $p < 0.05$.

The sample size was calculated using Paniotto's formula as shown in equation:

$n = 1/(\Delta^2 + 1/N)$,

where n – sample size, Δ – sample error size (0.05), N – general size.

During the inclusion into the study period HSCT was performed in 65 patients at the Hospital of Lithuanian University Health Sciences Kaunas Clinics (Approx. 50 patients per year). According to Pannioto's formula sample size is 55 patients. We included 60 patients into the study, but 5 patients did not complete the study – 3 patients died and for 2 patients HSCT was not performed due to changed medical situation.

The power of analysis regarding diffuse fibrosis was calculated. The power using Spearman correlation coefficient was 0.9518 (> 0.8).

3. RESULTS AND DISCUSSION

3.1. Clinical and demographic characteristics

Data of 55 patients was analysed. There were 30 men (54.5 %) and 25 women (45.5 %). Median age was 61 years, ranging from 18 to 74. 48 patients (87.3 %) underwent autologous and 7 patients (12.7 %) – allogeneic HSCT. Patients underwent autologous HSCT for various reasons with the most common multiple myeloma – 33 patients (68.8 %). 5 patients (10.4 %) had PCNS diffuse large B cell lymphoma, 4 patients (8.3 %) had mantle cell lymphoma, 2 patients (4.2 %) Hodgkin's lymphoma, 2 patients (4.2 %) had Ewing sarcoma, 1 patient had peripheral T cell lymphoma, and 1 patient had NK-/T-cell lymphoma. Allogeneic HSCT was performed because of acute myeloid leukaemia (5 patients, 71.4 %), acute myelomonocytic leukaemia (1 patient, 14.3 %) and myelodysplastic syndrome with excess blasts (MDS-EB) (1 patient, 14.3 %)

Main characteristics of the patients and main diseases are listed in Table 3.1.1. Distribution of patients according to age is presented in Figure 3.1.1.

Table 3.1.1. *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.

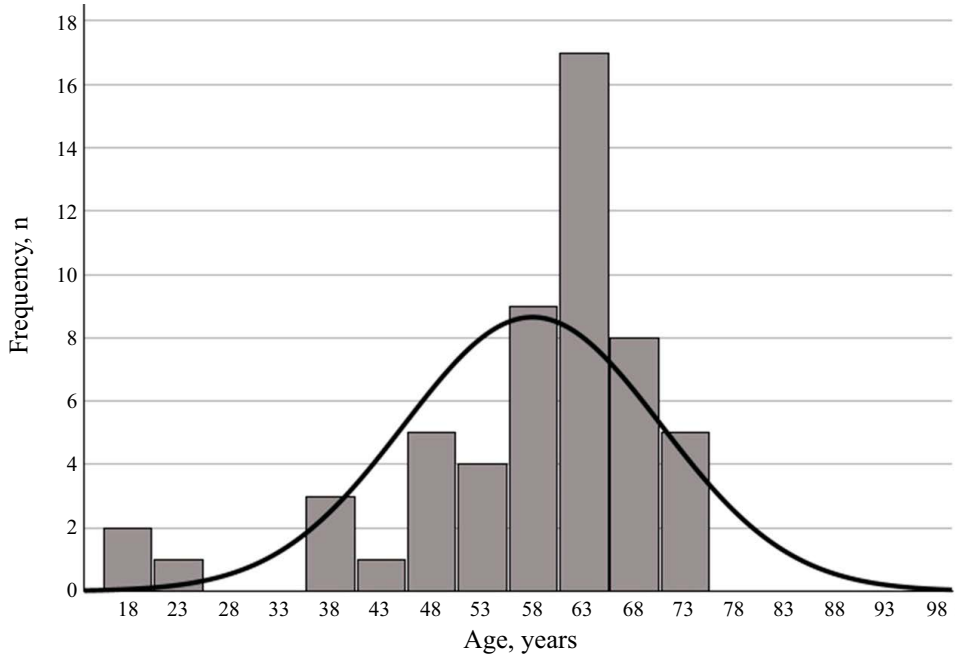


Figure 3.1.1. *Distribution of patients according to age.*

Discussion on clinical and demographic characteristics

The sample was not homogenous – patients with different main diseases and different types of HSCT (autologous and allogeneic) were included in the study because the main aim of the study was to evaluate impact on the heart as of the whole HSCT process. Secondary, we wanted to evaluate the impact of different risk factors, type of HSCT and different treatment regimens on cardiotoxicity.

3.2. Previous cardiovascular diseases and cardiovascular risk factors

Distribution of previous CV diseases and CV risk factors among the patients is presented in Table 3.2.1. 3 patients (5.5 %) had CAD diagnosed – one had previous myocardial infarction, one had elective stenting, and another one stable angina; 3 patients (5.5 %) had paroxysmal atrial fibrillation; 21 patient (38.2 %) had arterial hypertension; 4 (7.3 %) patients had diabetes mellitus; 8 (18.2 %) patients had positive family history of CAD; 43 (78.2 %) patients had dyslipidaemia; 0 (0 %) patients were current smokers; and 5 patients (9.1 %) were previous smokers.

Table 3.2.1. *Distribution of previous cardiovascular diseases and cardiovascular risk factors*

Previous cardiovascular diseases and cardiovascular risk factors	n (%)
Coronary artery disease (CAD)	3 (5.5)
Paroxysmal atrial fibrillation	3 (5.5)
Arterial hypertension (AH)	21 (38.2)
Diabetes mellitus (DM)	4 (7.3)
Family history of CAD	8 (14.5)
Dyslipidaemia	43 (78.2)
Previous smoking	5 (9.1)

For CV treatment and correction of CV risk factors some patients used medication that tend to have cardioprotective properties: 10 patients (22.7 %) used beta-blockers, 6 patients (13.6 %) ACEis, 3 patients (6.8 %) used ARBs, and 4 patients (9.1 %) used statins. Prevalence of medication use is presented in Table 3.2.2.

Table 3.2.2. *Prevalence of medication use among all patients*

Drugs	n (%)
Beta-blockers	10 (22.7)
ACEis	6 (13.6)
ARBs	3 (6.8)
Statins	4 (9.1)

ACEis – angiotensin converting enzyme inhibitors; ARBs – Angiotensin receptor blockers.

Disccusion on cardiovascular risk factors

This information is very important for finding the factors which could influence the developement of cardiotoxicity. According to the guidelines, it is important to know whether the patient had previous cardiotoxic treatment, previous CV diseases and any CV risk factors for stratifying patients' risk of cardiotoxicity development [61]. Most of the patients in our study had dislipidaemia (78.2 %), and the second most frequent risk factor was arterial hypertension (38.2 %).

3.3. Analysis of mobilization impact on echocardiographic parameters in patients undergoing autologous HSCT

In order to evaluate impact of mobilization process on cardiac size and function, subanalysis of echocardiographic parameters before and after mobilization was performed in patients undergoing autologous HSCT.

Out of 47 patients, there were 27 males (57.4 %) and 20 females (42.6 %). Median age was 61 (ranging from 18 to 74). A total of 35 (74.5 %) patients had multiple myeloma, 4 (8.5 %) had mantle cell lymphoma, 3 (6.4 %) had Hodgkin's lymphoma, 2 (4.3 %) had PCNS diffuse large B cell lymphoma, 1 (2.1 %) had anaplastic large cell lymphoma, 1 (2.1 %) had peripheral T cell lymphoma, and 1 (2.1 %) had Ewing sarcoma.

Timeframe between the two echocardiography scans was a median (min–max) of 49 (20–168) days. First echocardiography was performed before enrolling to the transplantation process and second before starting the conditioning regimen.

No patients had clinically relevant signs or symptoms of cardiotoxicity – heart failure, arrhythmias, pericardial effusion, new onset or worsening of arterial hypertension, or acute ischemic syndromes.

Statistically significant difference was observed in the change of RV function (S') – it slightly decreased. Mean RV S' before mobilization was 13.93 ± 2.85 cm/s and after mobilization 12.19 ± 2.64 cm/s (p = 0.003). No statistically significant change in LV size and systolic and diastolic function and RV size was observed. The values are presented in Table 3.3.1.

Table 3.3.1. *The change of echocardiographic parameters before and after the mobilization procedure*

Echocardiographic values	Before mobilization	After mobilization	p
LVEDD, mm	46.48 ± 4.05	46.02 ± 5.25	0.633
LVEDDi, mm/m^2	24.85 ± 2.78	24.75 ± 2.93	0.863
LVEF, %	60.49 ± 7.66	59.74 ± 7.08	0.622
GLS, %	−17.45 ± 3.62	−17.59 ± 3.65	0.309
E/e'	6.58 ± 3.28	6.91 ± 2.65	0.973
RVEDD, mm	36.02 ± 3.83	34.96 ± 4.44	0.217
S', cm/s	13.93 ± 2.85	12.19 ± 2.64	**0.003**

LVEDD – left ventricular end diastolic diameter; LVEDDi – LVEDD index according to body surface area (BSA); LVEF – left ventricular ejection fraction; GLS – left ventricular global longitudinal strain; E/e' – early mitral inflow velocity/mitral annular early diastolic velocity; RVEDD – right ventricle end-diastolic diameter; S' – tricuspid annular systolic velocity.

Six patients experienced a decrease in S' to less than 10 cm/s, indicating a clinically significant loss of RV function (12.8 %). Three of these patients were from the multiple myeloma group and had at least three CV risk factors. The remaining three patients had other diseases: one with mantle cell lymphoma, one with Hodgkin's lymphoma, and one with diffuse large B cell lymphoma. These patients received treatment regimens including either rituximab and

cytarabine or cisplatin and cytarabine. Only one patient had no CV risk factors, while the others had two (arterial hypertension and dyslipidemia) or three (arterial hypertension, diabetes mellitus, and dyslipidemia). A significant reduction in RV systolic function was observed in 8.6 % of patients in the multiple myeloma group and 25 % in the group with other diseases.

An analysis was conducted to examine the correlation between CV risk factors and the clinically relevant reduction of S' to less than 10 cm/s following mobilization. Due to the small sample size of only six patients with clinically significant reduction in S', no statistically significant impact of CV risk factors was observed. The distribution of risk factors among patients with and without clinically significant reductions in S' is presented in Table 3.3.2. The results of the univariate logistic regression analysis are provided in Table 3.3.3. Although no statistically significant impact of cardiovascular risk factors was identified, the odds ratios suggest a tendency for increased risk associated with CAD, arterial hypertension, and a family history of CAD.

Table 3.3.2. *Cardiovascular risk factors and cardiovascular diseases among all the patients and risk factors' distribution among the patients with and without clinically significant S' reduction after the mobilization procedure*

Cardiovascular risk ractors and cardiovascular diseases	**N among all patients (%)**	**Patients with S' after mobilization ≥ 10cm/s (n (%))**	**Patients with S' after mobilization < 10cm/s (n (%))**	**p**
Coronary artery disease (CAD)[1]	4 (8.5)	3 (75.0)	1 (25.0)	0.432
Arterial hypertension	23 (48.9)	19 (82.6)	4 (17.4)	0.416
Diabetes mellitus	6 (12.8)	5 (83.3)	1 (16.7)	1.000
Family history of CAD	10 (21.3)	8 (80.0)	2 (20.0)	0.594
Dyslipidaemia	41 (87.2)	36 (87.8)	5 (12.2)	1.000
Smoking	0 (0)	0 (0)	0 (0)	
Previous smoking	7 (14.9)	6 (85.7)	1 (14.3)	1.000

[1] Previous myocardial infarction or elective stenting.

Table 3.3.3. *Univariate logistic regression analysis showing measure of the strength of association between cardiovascular risk factors and final RV S' decrease (< 10 cm/s)*

Cardiovascular risk factors and cardiovascular diseases	Odds ratio	95 % Confidence interval	p
Coronary artery disease (CAD)	2.533	0.219–29.290	0.457
Arterial hypertension	2.316	0.381–14.079	0.362
Diabetes mellitus	1.440	0.138–14.978	0.760
Family history of CAD	2.062	0.320–13.313	0.447
Dyslipidaemia	0.694	0.067–7.223	0.760
Previous smoking	1.167	0.115–11.814	0.896

Discussion on mobilization impact on echocardiographic parameters

This subanalysis examines the impact of the mobilization procedure in patients undergoing autologous HSCT on early cardiovascular toxicity. No clinically relevant signs or symptoms of cardiotoxicity, such as arrhythmias, pericardial effusion, heart failure, or acute ischemic syndromes, were observed. To our knowledge, there are no published data evaluating echocardiographic LV and RV changes during mobilization procedures. The objective of this part of the study was to determine whether the mobilization procedure has any significant subclinical impact on the LV and RV, regardless of differences in the underlying disease, mobilization chemotherapy regimen, prior cardiotoxic chemotherapy, or CV risk factors. The results indicate a statistically significant difference in RV function, with a slight decrease in S' after mobilization. 12.8 % of patients experienced a clinically significant reduction in RV systolic function, with S' decreasing to less than 10 cm/s. No statistically significant changes were observed in RV size, LV size, or systolic and diastolic function of LV.

Data increasingly show that not only LV, but also RV function contribute to clinical heart failure. When there is evidence of RV dysfunction, quality of life, functional capacity and overall clinical outcomes are worsened among patients with heart failure [118]. RV function is also one of determinants of survival, irrespective of the underlying etiology of heart failure [119]. S' is an echocardiographic parameter used for the evaluation of longitudinal RV function. Validation studies have shown good correlations to MUGA- and CMR-derived RV EF [120]. RV systolic function is affected in shorter period of time than the LV [121]. Therefore, patients for whom clinically significant decrease of RV function was observed should undergo closer follow-up during the further treatment course and start cardioprotective treatment when there are indications.

Tekiner et al also noticed similar results [122]. They evaluated changes in RV function during the whole HSCT process and included patients who had undergone allogeneic HSCT. The study examined 137 patients undergoing autologous and allogeneic HSCT. Echocardiography was performed on the day before and 30 days after HSCT. Changes in S' velocity and TAPSE (tricuspid annular plane systolic excursion) has shown a statistically significant decrease too, whereas RV and LV sizes and LV EF have remained unchanged. We also got the same results in the further analysis of the patients – S' was statistically significantly decreased in the follow up – 12 months after HSCT process, too. The results of this subanalysis show that RV longitudinal function is affected very early in the process – already after the mobilization. All these results show that RV function may be affected earlier than LV function and can be used to assess early cardiotoxicity in HSCT recipients. Another study supporting this theory showed that systolic and diastolic functions of RV were affected in a rather short period of time and earlier than the LV [121].

From six patients that had a reduction of S' to less than 10 cm/s, half of the patients' (three) main disease was multiple myeloma and they all had at least three CV risk factors. The other three patients had other diseases: one had mantle cell lymphoma, another – Hodgkin's lymphoma, and the other– diffuse large B cell lymphoma. These patients received either rituximab and cytarabine or cisplatin and cytarabine. Only one of them had no risk factors; the others had two (arterial hypertension and dyslipidaemia) and three (arterial hypertension, diabetes mellitus, and dyslipidaemia). The difference of significant reduction in these groups was 8.6 % in the myeloma group and 25 % in the other diseases group. Although, neither univariate logistic regression nor multivariate regression showed a statistically significant impact of CV risk factors on RV function, odds ratio showed a tendency towards risk increase with CAD, arterial hypertension, and family history of CAD. These results lead us to believe that multiple risk factors might have an impact on the clinically significant reduction of RV function, and that other chemotherapy regimens used for mobilization and previous treatment might have more impact on RV function than cyclophosphamide used for mobilization and induction treatment of multiple myeloma, but further investigation of more cases is needed.

Literature shows that cyclophosphamide carries a cardiotoxic risk, especially when used in high doses [9,39,40]. The mechanism and possible complications were described in the literature review. The doses of cyclophosphamide used for mobilization were not very high, probably because of this we did not notice decrease of LV function.

Filgrastim, also known as G-CSF, was employed alongside chemotherapy for mobilization purposes. The existing literature lacks data concerning

G-CSF's potential cardiotoxic effects. Conversely, several experimental studies suggest that G-CSFs may possess regenerative properties for cardiomyocytes. Tomita et al. conducted research on mice with doxorubicin-induced cardiomyopathy, revealing that bone marrow could serve as a source of regenerated cardiomyocytes. Early administration of G-CSF was found to facilitate the migration of bone marrow stem cells into the heart and mitigate doxorubicin-induced cardiotoxicity [123]. Additionally, there are reports indicating that G-CSF might mitigate carbon monoxide (CO)-induced cardiac ischemia in patients suffering from acute CO poisoning [124]. Another study involving rats with diabetic cardiomyopathy demonstrated that G-CSF could alleviate cardiac diastolic dysfunction and morphological damage, thereby reducing myocardial fibrosis [125]. Furthermore, Haybar et al. suggested that G-CSF could potentially provide protective chemokines during chemotherapy treatment [126]. While these studies hint at G-CSF's cardioprotective potential, most of them are experimental or preliminary, necessitating further investigation.

3.4. Analysis of HSCT impact on the heart morphology and function at 12 months follow-up

3.4.1. Results of echocardiographic follow-up 12 months after HSCT

To evaluate the impact of HSCT on heart sizes and function, evaluation and comparisson of echocardiographic parameters before and 12 months after HSCT was performed. Statistically significant reduction of the longitudinal RV function (S') and increase of E/e' was observed. No statistically significant difference in LV size (LVEDD, LVEDDi), LV mass (MM, MMI), LV systolic function (LVEF), deformation parameters (GLS), LA size (LA diameter, LA volume and LAi volume), RV size (RVEDD) and RA size (RA) was observed. The values before and 12 months after HSCT are presented in Table 3.4.1.1.

Table 3.4.1.1. *Changes in echocardiographical parameters in patients before and 12 months after HSCT*

Echocardiographic parameters	Echocardiograpy before HSCT	Echocardiographic follow-up 12 months after HSCT	p
LVEDD (median (min–max))	46.50 (38.00–62.00)	45.00 (36.00–55.00)	0.603
LVEDDi (mean (SD))	24.52 (2.67)	24.58 (2.73)	0.851
LV MM (mean (SD))	167.13 (49.28)	163.37 (44.91)	0.454
LV MMI (mean (SD))	86.65 (20.20)	85.69 (18.74)	0.722
LVEF (mean (SD))	58.50 (7.36)	57.68 (6.99)	0.472

Table 3.4.1.1 cont.

Echocardiographic parameters	Echocardiograpy before HSCT	Echocardiographic follow-up 12 months after HSCT	p
GLS (mean (SD))	17.31 (3.49)	16.69 (3.54)	0.179
LA diameter (median (min–max))	37.00 (27.00–52.00)	37.00 (20.00–50.00)	0.222
LA volume (median (min–max))	57.00 (20.00–138.00)	58.00 (25.00–123.00)	0.822
LAi volume (mean (SD))	37.78 (5.41)	36.65 (5.77)	0.092
RVEDD (median (min–max))	35.00 (26.00–44.00)	34.00 (28.00–50.00)	0.517
S' (mean (SD))	13.82 (3.20)	12.41 (2.53)	**0.001**
RA (mean (SD))	39.16 (4.06)	38.52 (4.74)	0.243
E/e' (mean (SD))	6.16 (1.87)	7.45 (2.07)	**< 0.001**

LVEDD – left ventricular end diastolic diameter; LVEDDi – LVEDD indexed according to body surface area (BSA); LV MM – left ventricular myocardial mass; LV MMI – left ventricular myocardial mass index; LV EF – left ventricular ejection fraction; GLS – left ventricular global longitudinal strain; LA diameter – diameter of left atrium from parasternal long axis view; LA volume – volume of left atrium; LAi volume – volume of left atrium indexed according to BSA; RVEDD – right ventricle end-diastolic diameter; S' – tricuspid annular systolic velocity; RA – diameter of right atrium from 4 chamber view; E/e' – early mitral inflow velocity/mitral annular early diastolic velocity.

Discussion on echocardiographic follow-up 12 months after HSCT

When comparing the main echocardiographic parameters of all the patients before HSCT and 12 months after HSCT, statistically significant slight decrease of logitudinal RV function (S') and increase in E/e' ratio was observed. The other parameters of LV sizes, mass and function, LA, RV and RA sizes did not change statistically significantly in 12 months after HSCT period. The slight decrease of longitudinal RV fuction was already noticed in patients undergoing autologous HSCT after mobilization procedure. The results show that the longitudinal RV function is affected very early and the change does not return to baseline values even 12 months after HSCT.

To our knowledge there are not many studies analysing changes after HSCT prospectively. Tekiner with colleagues have also performed a prospective study evaluating echocardiographic parameters. They analysed changes in 137 patients undergoing autologous and allogeneic HSCT in the early period – 30 days after HSCT. No statistically significant changes in LVEDD, LV EF, RV and RA sizes were observed. They also noticed a statistically significant decrease in RV longitudinal function (S' decreased from 0.19 ± 0.06 m/s to 0.09 ± 0.04m/s and TAPSE decreased from 2.30 ± 0.39 cm to 1.63 ± 0.30 cm)

[122]. Rotz and colleagues have also analyzed changes in echocardiography parameters. 95 children and young adults had echocardiography performed before HSCT and 1–6 years after HSCT. No significant change in LV EF and GLS was noticed [127].

The other studies evaluated patients only after HSCT and mostly compared the data to healthy controls. Armenian et al evaluated 20 HSCT suvivors (median time from HSCT was 9,8 years ranging from 3 to 20 years) and also did not notice LV EF deterioration – median LV EF was 62 % ranging from 54 to 68 % [128].

The importance of increase in E/e' is not very clear. What concerns diastolic dysfunction on the whole it is recommended to assess diastolic parameters in cancer treatment patients' population, but its prognostic value so far is poorly understood [69,129–131]. There are numerous studies analysing diastolic dysfunction in patients who received doxorubicin and/or trastuzumab. While some studies state that diastolic dysfunction may predict systolic dysfunction in these patients [132–136], other studies have shown conflicting results [137,138]. Several investigators have demonstrated an early reduction in the e' velocity of the mitral annulus using Tissue Doppler Imaging (TDI), which remained reduced during chemotherapy and for several years after treatment [139,140]. Anyway, the use of the E/e' ratio remains questionable in the oncological setting because E and e' velocity fluctuations in these patients may be the consequence of changes in loading conditions associated with chemotherapy (e.g. nausea, vomiting, and diarrhoea) more than the result of a real change in LV diastolic performance. In contrast, the heterogeneous reduction in e' velocity in patients who developed cardiac dysfunction may suggest differences in regional wall stress, apoptosis, or fibrosis [141].

Several studies have analysed diastolic dysfunction in HSCT survivors. A study of pediatric HSCT survivors which conducted median follow-up of 7,4 years, have revealed that there is a progressive decline in diastolic function indices, which occur more rapidly than systolic function decline [142]. Another study analyzed 46 pediatric patients who have undergone HSCT due to severe aplastic anaemia. Subclinical progress of diastolic dysfunction was observed, authors think that iron overload might be the cause [143]. In our study, although the change was statistically significant, it was not significant clinically. This could promt that in 12 months period following HSCT clinically significant diastolic dysfunction does not occur, increase in E/e' ratio could show a slow progress of diffuse fibrosis.

3.4.2. Results of CMR follow-up 12 months after HSCT

Evaluation and comparison of CMR parameters before and 12 months after HSCT was performed. Statistically significant difference was observed in T1 mapping value. T1 mapping value increased from 1226.95 ± 36.31 ms to 1250.13 ± 39.65 ms ($p < 0.001$). LVEDV, LVEDVi, LVESV, LVESVi, LVEF, LV mass, LV mass index, RVEDV, RVEDVi, RVESV, RVESVi, RVEF and T2 mapping value did not differ statistically significantly. Values are presented in Table 3.4.2.1.

Table 3.4.2.1. *Change of CMR parameters 12 months after HSCT*

CMR values, n = 48	Before HSCT	After HSCT	p
LVEDV, mL (mean (SD))	146.30 (38.55)	149.64 (39.03)	0.448
LVEDVi, mL/m^2 (mean (SD))	76.63 (18.07)	78.24 (17.96)	0.447
LVESV, mL (mean (SD))	62.18 (19.72)	61.46 (18.98)	0.756
LVESVi, mL/m^2 (mean (SD))	31.99 (9.70)	32.39 (10.10)	0.718
LVEF, % (mean (SD))	58.21 (7.67)	58.96 (6.75)	0.493
LV mass, g (median (min–max))	105.81 (54.67–175.31)	102.55 (56.00–167.93)	0.182
LV mass index, g/m^2 (mean (SD))	57.47 (11.36)	55.78 (12.21)	0.332
RVEDV (mean (SD))	132.44 (40.96)	141.07 (36.64)	0.063
RVEDVi (mean (SD))	70.13 (16.99)	73.78 (16.72)	0.072
RVESV (mean (SD))	61.20 (18.41)	66.23 (19.26)	0.074
RVESVi (mean (SD))	32.13 (8.63)	34.08 (9.70)	0.176
RVEF (mean (SD))	54.10 (6.09)	53.50 (6.15)	0.594
T1 mapping value, ms (mean (SD))	1226.95 (36.31)	1250.13 (39.65)	**< 0.001**
T2 mapping value, ms (mean (SD))	39.04 (2.16)	38.70 (2.18)	0.329

LV – left ventricle; LVEDV – left ventricular end-diastolic volume; LVEDVi – LVEDV indexed according to body surface area (BSA); LVESV – left ventricular end-systolic volume; LVESVi – LVESV indexed according to BSA; LVEF – left ventricular ejection fraction; RVEDV – right ventricular end-diastolic volume; RVEDVi – RVEDV indexed according to body surface area (BSA); RVESV – right ventricular end-systolic volume; RVESVi – RVESV indexed according to BSA; RVEF – right ventricular ejection fraction.

Discussion on CMR follow-up

In this part of the study we evaluated subclinical changes in LV and RV function, volumes, and mass, and the myocardial tissue with the help of CMR in 12 months after HSCT, irrespectively of the type of HSCT.

Our results showed no significant change in LV volumes, mass, systolic function, also RV volumes and systolic function and T2 mapping, a marker

of myocardial edema. T1 mapping had significantly higher values in one year after HSCT. This could lead to an idea that HSCT procedure is related to increase in diffuse myocardial fibrosis.

T1 and T2 mapping values in CMR have been validated histologically in the context of cardiotoxicity. Park et al analyzed myocardial injury of rats, which had doxorubicin injections. T1, T2 and ECV values were calculated, myocardial biopsy was performed. The study showed that T1 and T2 measures correlate to histopathologic changes, and represent myocardial injury, in particular interstitial fibrosis, inflammation, and edema of myocardial biopsy with anthracycline-induced cardiotoxicity. T1 mapping and ECV showed highest correlation with histopathologic changes [144]. Another study states that native T1 and T2 mapping can be valuable in detecting and monitoring of cardiac involvement with cancer-related treatment, providing distinct biosignatures of early inflammatory involvement (raised native T1 and T2) and interstitial fibrosis and remodelling (raised native T1 but not T2) [145].

In our study LVEDV, LVEDVi, LVESV, LVESVi and LVEF did not change statistically significantly in 12 months after HSCT. The results are consistent with findings from other studies. Echocardiography of 95 children and young adults was performed before and 1–6 years after HSCT. Results show that LV EF after HSCT remained unchanged from the baseline [127].

We did not find a statistically significant change in RV volumes and function. Data regarding the impact of HSCT on RV is limited [146,147]. Most of those studies have evaluated RV function with the help of echocardiography and not CMR. Christiansen and colleagues have analyzed RV function in 246 childhood cancer survivors, mean 21,7 years after diagnosis and 211 matched controls. They evaluated FAC, TAPSE, S' and free wall strain. All these measurements were lower in childhood cancer survivors' group. The reduction of RV function was found in 30 % of survivors, but not in those who were not exposed to anthracyclines or mediastinal radiotherapy [148]. Another study also found reduction of echocardiographic RV function parameters compared to healthy controls (13 ± 6 years after diagnosis), but clinically significant RV dysfunction was of less extent than LV dysfunction (6.2 % vs. 30.8 %) [146]. Our study has also found reduction in echocardiographic RV systolic longitudinal function parameters (S'), but not in the CMR derived RVEF.

Although LVEDV, LVESV and EF did not change significantly, our results show that T1 mapping values resembling the progress of diffuse fibrosis increased. Changes in native T1 values in patients after HSCT compared to healthy individuals were also noticed in other studies. Paiman et al analyzed late effects of pediatric HSCT on LV function, aortic stiffness, and myocardial tissue characteristics. The study design was different – it was not a prospective study, they analyzed 16 HSCT childhood survivals

(14,8 ± 5 years after HSCT) and compared to 16 healthy controls. A trend towards a lower LVEF in HSCT survivors compared to healthy controls was noticed, but not statistically significant (54 ± 6 vs. 58 ± 5 %, p = 0.055). Native T1 (1211 ± 36 vs. 1227 ± 28 ms, p = 0.158) also tended to be higher in HSCT survivors but did not differ significantly. The comparison was different – they compared the values to healthy controls and not to the baseline values. Also, the sample was very small [149].

There are more studies analyzing cardiotoxicity with the help of T1 mapping. Most of the studies analyze anthracycline induced cardiotoxicity. A study conducted by Jordan et al concluded that elevation in myocardial T1 and ECV was noticed three years after anthracycline-based chemotherapy independently of underlying main disease or cardiovascular comorbidities. The comparison was performed in three groups – cancer patients three years post anthracycline based chemotherapy, cancer patients who have not started treatment yet, and healthy controls [150].

The other study analyzed childhood cancer survivors who received anthracycline based chemotherapy and had normal systolic function. CMR evaluation was performed 2.5 to 26.9 years after anthracycline exposure. Pre-contrast T1 values were higher in cancer survivors than in healthy controls, although the difference did not reach statistical significance [151].

In another study, T1 and ECV were found to be early tissue markers of ventricular remodeling representing diffuse fibrosis in children with normal EF post anthracycline therapy [152].

We did not get a significant change in T2 mapping values. Increase in T2 mapping parameters resemble features of edema. Our follow up was conducted 12 months after HSCT process, so the active inflammation and edema in the myocardium were not expected.

The strength of our study lies in its prospective design, allowing for the comparison of baseline and follow-up values. In contrast, most other studies compare post-treatment patients to healthy controls. We observed no significant impact of cardiovascular risk factors, underlying disease, or treatment regimens on T1 mapping values, which increased in all patients.

3.4.3. Analysis of CTRCD and factors influencing and prognosing CTRCD

Three patients (5.5 %) experienced clinically significant cardiovascular symptoms during the 12 months period after HSCT, all of them were supraventricular arrhythmia: two had supraventricular tachycardia and one had atrial fibrillation.

According to the ESC guidelines on cardio-oncology, 2022, definition and echocardiographic parameters, 15 patients (27.3 %) had asymptomatic CTRCD at 12 months follow-up. Six patients had moderate (either new LVEF reduction by ≥10 percentage points to an LVEF of 40–49 %, or new LVEF reduction by < 10 percentage points to an LVEF of 40–49 % and new relative decline in GLS by > 15 % from baseline) and 9 patients had mild CTRCD (LVEF ≥ 50 % and new relative decline in GLS by > 15 % from baseline).

Characteristics of the patients and differences among CTRCD and non-CTRCD groups are presented in Table 3.4.3.1.

Table 3.4.3.1. *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)	
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
Leukaemia 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)	
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
Dyslipidaemia	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

Table 3.4.3.1 cont.

Characteristic	All patients (n = 55)	Non-CTRCD (n = 40; 72.7 %)	CTRCD (n = 15; 27.3 %)	p
Previous use of anhtracyclines				
No	37 (67.3)	31 (77.5)	6 (40.0)	**0.021**
Yes	18 (32.7)	9 (22.5)	9 (60.0)	
Conditioning regimen				
Melfalan	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

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

Patients age, sex, main disease, type of HSCT, CV risk factors, CV medication did not differ statistically significantly among the two groups. Patients with previous use on antracyclines tended to have CTRCD more often: 9 patients (60 %) in the CTRCD group and 9 patients (22.5 %) in non-CTRCD group. The difference was statistically significant (p = 0.021). There was also a difference in conditioning regimens. Patients who received BEAM regimen for conditioning had CTRCD more often: 5 patients (33.3 %) in CTRCD group vs. 2 patients (5 %) in non-CTRCD group. The difference was statistically significant (p = 0.013).

Factors, possibly influencing the development of CTRCD, including sex, main disease, type of HSCT, previous CV diseases, CV risk factors, previous use of anthracyclines, different conditioning regimens were taken into account in univariate logistic regression analysis. We found that previous use of anthracyclines (OR 5.167, 95 % CI 1.448–18.433, p = 0,011), and BEAM used for conditioning regimen (OR 9.500, 95 % CI 1.599–56.426, p = 0,013) were significant factors in the development of CTRCD (Table 3.4.3.2)

Table 3.4.3.2. *Univariate logistic regression analysis of factors possibly infuencing the developement of CTRCD*

UNIVARIATE LOGISTIC REGRESSION			
Covariate	**OR**	**95 % CI**	**p**
Sex *(male versus female)*	1.357	0.407–4.529	0.619
Multiple myeloma *(mieloma 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
Dyslipidaemia *(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, citarabine, melphalan.

Similar results concerning the conditioning regimen were found in multivariate analysis. We determined that use of BEAM for conditioning had significantly higher risk for CTRCD (OR 19.599, 95 % CI 2.051–187.313, p = 0.010, Table 3.4.3.3.)

Table 3.4.3.3. *Multivariate logistic regression analysis on cardiovascular risk factors and conditioning regimen possibly influencing the development of CTRCD*

MULTIVARIATE LOGISTIC REGRESSION				
Covariate		**OR**	**95 % CI**	**p**
Risk factors	CAD	5.948	0.298–118.858	0.243
	Arterial hypertension	0.464	0.088–2.448	0.365
	Family history of CAD	0.364	0.038–3.527	0.383
	Dyslipidaemia	4.151	0.439–39.232	0.214
	Previous smoking	0.658	0.057–7.652	0.738
BEAM		19.599	2.051–187.313	**0.010**

CAD – coronary artery disease; BEAM – carmustine, etoposide, citarabine, melphalan.

Different baseline echocardiographic (LVEDD, LVEDDi, MM, MMI, LVEF, LV GLS, LA volume, LAi, LA diameter, S', E/A, E/e') and CMR (LVEDV, LVEDVi, LVESV, LVESVi, LVEF, LV MM, LV MMI, RVEDV, RVEDVi, RVESV, RVESVi, RVEF) parameters were analysed in the means of prognosing possible development of CTRCD and separately on moderate CTRCD.

Analysis revealed that LVEDDi was a statistically significant prognostic factor for the development of CTRCD. In Figure 3.4.3.1 we can see that patients for whom CTRCD developed at 12 months follow-up had a statistically significantly bigger LVEDDi on baseline echocardiography than patients who did not have CTRCD at 12 months follow-up, respectively, 24.1 (22.6–25.7) mm/m^2 and 26.7 (22.8–28.9) mm/m$^{2.}$ (p = 0.024) (Fig 3.4.3.1).

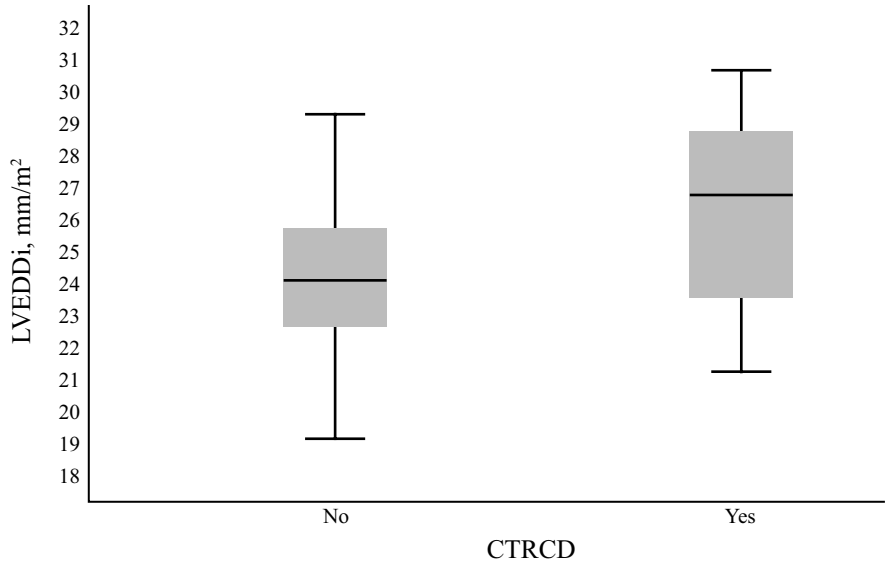


Fig. 3.4.3.1. *Box-plot diagram of left ventricular end-diastolic diameter index on baseline echocardiography according to the development of cancer therapy related cardiac dysfunction. Mann-Whitney test, p = 0.024.*

LVEDDi – left ventricular end diastolic diameter index; CTRCD – cancer therapy related cardiac dysfunction.

ROC (receiver operating characteristic) test revealed that patients, who's baseline LVEDDi was > 26.54 mm/m^2, tend to have 10.286 bigger OR (Odds ratio) for CTRCD development with sensitivity of 53.3 % and specificity of 90.0 %, p = 0.001 (Fig. 3.4.3.2).

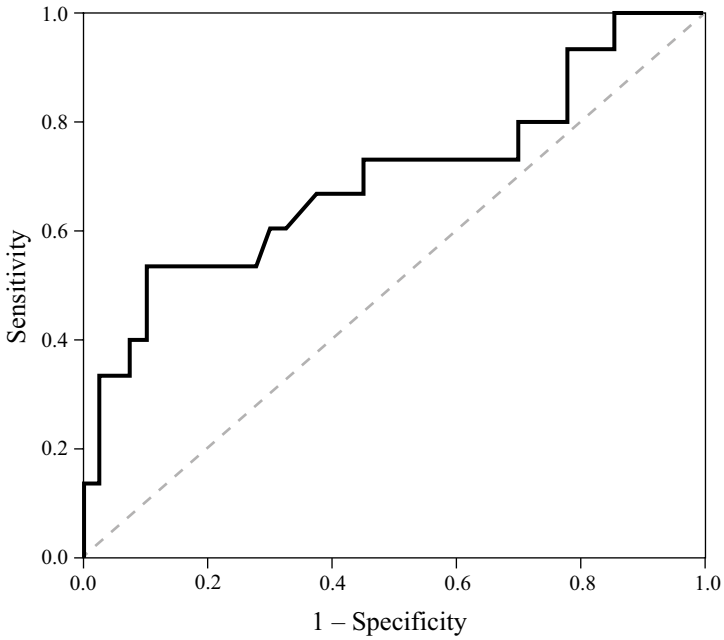


Fig. 3.4.3.2. *ROC curve for cut-off value of LVEDDi for the development of CTRCD. AUC 69.7 %.*

LVEDDi – left ventricular end-diastolic diameter index; CTRCD – cancer therapy related cardiac dysfunction; AUC – area under the curve.

Patients with moderate CTRCD also had bigger LVEDDi on baseline echocardiography and bigger LVEDVi and LVESVi on baseline CMR than patients without CTRCD or patients with mild CTRCD.

When LVEDDi on baseline echocardiography was > 26.54 mm/m^2, there was a 30-fold higher OR for moderate CTRCD development (95 % PI 3.034–296.629) with sensitivity of 83.3 % and specificity 85.7 % (p = 0.001). (Fig. 3.4.3.3 and 3.4.3.4).

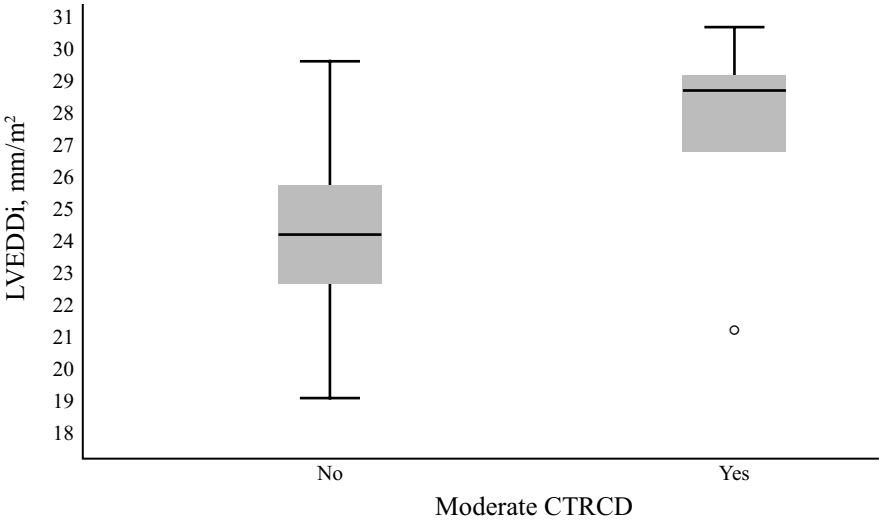


Fig. 3.4.3.3. *Box-plot diagram of left ventricular end-diastolic diameter index on baseline echocardiography according to the development of moderate cancer therapy related cardiac dysfunction. Mann-Whitney test, p = 0.012*

LVEDDi – left ventricular end diastolic diameter index.

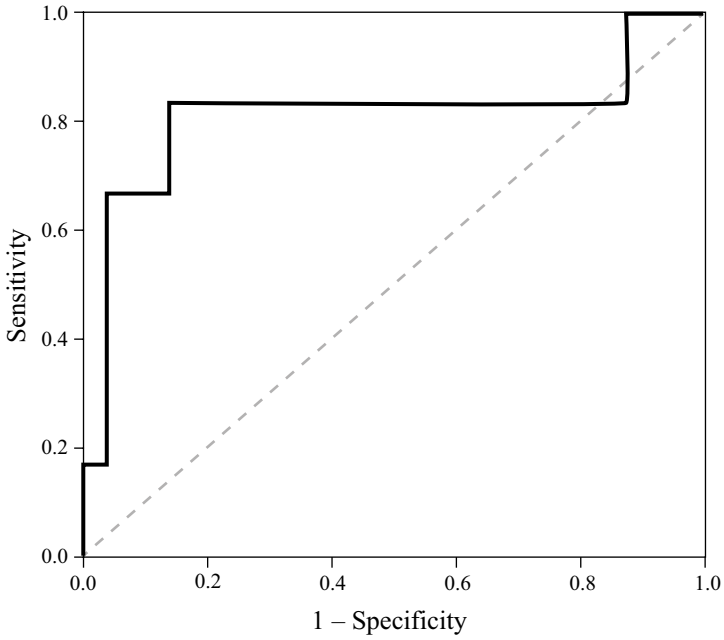


Fig. 3.4.3.4. *ROC curve for cut-off value of LVEDDi for the development of moderate CTRCD. AUC 81.0 %.*

ROC – receiver operating characteristic; LVEDDi – left ventricular end-diastolic diameter index; CTRCD – cancer therapy related cardiac dysfunction; AUC – area under the curve.

When LVEDVi was > 88.64 mL/m^2, there was a 48.75-fold higher OR for development of moderate CTRCD (95 % PI 4.508–527.205) with sensitivity of 83.3 % and specificity 90.7 % ($p < 0.001$). (Fig. 3.4.3.5 and 3.4.3.7). When LVESVi was > 32.43 mL/m^2 there was also higher risk for development of moderate CTRCD: sensitivity 100 %, specificity 60.5 % ($p = 0.007$) (Fig 3.4.3.6 and 3.4.3.7)

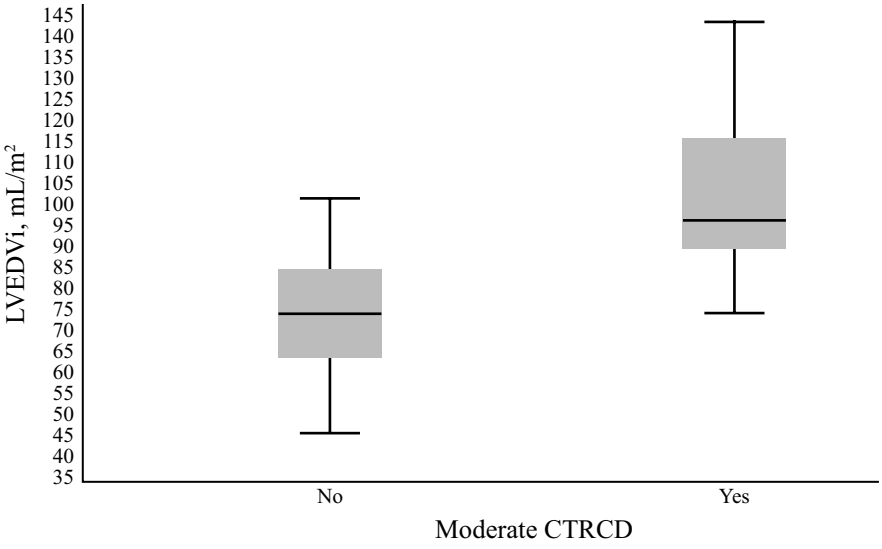


Fig. 3.4.3.5. *Box-plot diagram of left ventricular end-diastolic volume index on baseline CMR according to the development of moderate CTRCD. Mann-Whitney test, p = 0.012.*

LVEDVi – left ventricular end-diastolic volume index; CMR – cardiovascular magnetic resonance; CTRCD – cancer therapy related cardiac dysfunction.

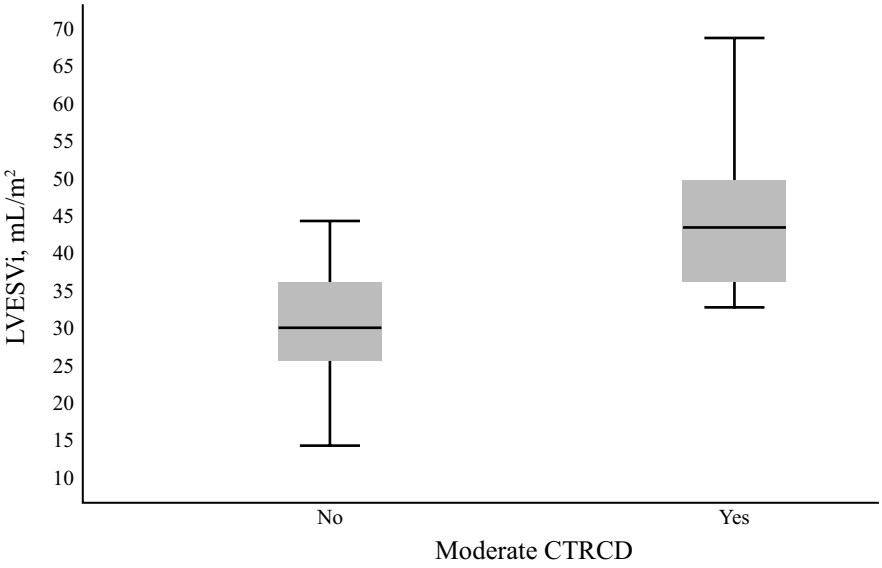


Fig. 3.4.3.6. *Box-plot diagram of left ventricular end-systolic volume index on baseline CMR according to the development of moderate CTRCD. Mann-Whitney test, p = 0.002.*

LVESVi – left ventricular end-systolic volume index; CMR – cardiovascular magnetic resonance; CTRCD – cancer therapy related cardiac dysfunction.

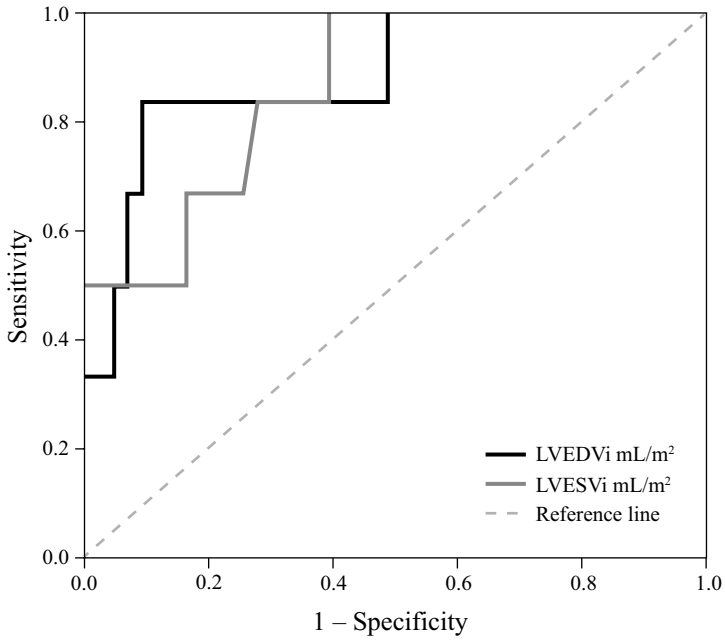


Fig. 3.4.3.7. *ROC curve for cut-off values of LVEDVi (AUC 88.4 %) and LVESVi (AUC 86.2 %) on baseline CMR for the development of moderate CTRCD.*

ROC – receiver operating characteristic; LVEDVi – left ventricular end diastolic volume index; LVESVi – left ventricular end systolic volume index; CTRCD – cancer therapy related cardiac dysfunction; AUC – area under the curve.

Discussion on analysis of CTRCD and factors influencing and prognosing the development of CTRCD

Our results show that asymptomatic CTRCD was observed in 27.3 % patients – with 6 patients having moderate CTRCD (10.9 %) and 9 patients having mild CTRCD (16.4 %) 12 months after HSCT. To our knowledge the data about asymptomatic CTRCD after HSCT is scarce. The methodology and definition of CTRCD in other studies was different. Moriyama and colleagues have analyzed early CTRCD after allogeneic HSCT. They retrospectively reviewed records of 136 patients and defined CTRCD as a decrease in LVEF of ≥ 10 % and an LVEF of ≤ 53 % within 100 days after HSCT. The incidence of CTRCD was 17 %, but the definition criteria were different. The issue even of asymptomatic cardiotoxicity is important, they observed that patients with early-onset CTRCD had insufficient overall survival with a higher primary disease mortality than those without early-onset CTRCD [153]. There are a few studies analyzing late CTRCD after HSCT. One study

analyzed 274 lymphoma survivors treated with autologous HSCT with mean follow-up time after lymphoma diagnosis being 13 ± 6 years. LV systolic dysfunction was defined as LVEF less than 50 % by echocardiography. Results were compared to age and sex matched control group. They found CTRCD in 15.7 % of lymphoma survivors with 5.1 % being asymptomatic. Compared to controls, lymphoma survivors had a substantially increased CTRCD risk (odds ratio, 6.6; 95 % CI, 2.5 to 17.6; $p < 0.001$) [154]. Another study included 104 patients after allogeneic HSCT with 17 ± 6 years of follow-up. This was a cross sectional study and definition of CTRCD was also different: LV systolic dysfunction (LVSD) was defined as reduced LVEF of < 52 % in men and < 54 % in women, and/or a reduced GLS of ≥ −17 %. LVSD was found in 44.2 % of patients, of whom 28.3 % were symptomatic [155]. Even though methodology of those studies was different, the results show that incidence of LVSD tend to increase with years after HSCT.

Our results show that previous use of anthracyclines and BEAM used for conditioning regimen were the factors influencing development of asymptomatic CTRCD. Other studies found the same results with anthracycline use [45,153–156]. Conditioning with BEAM (carmustine, etoposide, cytarabine and melphalan) protocol also increased the risk for occurrence of CTRCD. Cytarabine and melphalan are known to increase the incidence of heart failure [61,157].

The ESC guidelines of cardio-oncology define that the HSCT type (higher risk after allogeneic HSCT), multiple uncontrolled CV risk factors, pre-existing CV conditions, direct cardiotoxic effects of anticancer therapies received prior to and during HSCT (anthracycline-combined induction regimen, mediastinal RT, total body irradiation, or cyclophosphamide-based conditioning regimen) increase the risk of CTRCD. We did not get statistically significant results regarding the type of HSCT, probably because there were only 7 patients undergoing allogeneic HSCT. Anyway, the tendency towards cardiotoxicity was noticed – 3 patients out of 7 had CTRCD. There are also numerous studies analyzing effects of GvHD on cardiotoxicity [153,155,158]. We also could not check this hypothesis due to a low number of allogeneic HSCT patients. What concerns pre-existing CV conditions – we also noticed a tendency that CAD increases the risk of CTRCD, even though the finding was not statistically significant due to low number of patients with CAD.

In our study we found that LVEDDi measured on baseline echocardiography can be used as a prognostic factor for development of CTRCD. We have not found similar data in the literature. The finding seems very promising, because this measurement is performed for every patient before HSCT, does not require additional resources or time, and can stratify patient's risk for CTRCD development.

CONCLUSIONS

1. Mobilization procedure in patients undergoing autologous HSCT is associated with reduced longitudinal right ventricular systolic function – S' reduced from 13.93 ± 2.85 cm/s to 12.19 ± 2.64 cm/s ($p = 0.003$). No significant change in cardiac chamber size, left ventricular systolic function was observed.
2. Following 12 months after HSCT longitudinal right ventricular systolic function on echocardiography is reduced from 13.82 ± 3.2 cm/s to 12.41 ± 2.53 cm/s ($p = 0.001$), whereas right ventricular ejection fraction derived by cardiovascular magnetic resonance remains unchanged, together with slight increase in E/e' ratio from 6.16 ± 1.87 to 7.45 ± 2.07 ($p < 0.001$).
3. Native T1 mapping values following HSCT at 12 months follow-up increase compared to baseline values from 1226.95 ms ± 36.31 ms to 1250.13 ± 39.65 ms ($p < 0.001$), which could resemble progress of diffuse myocardial fibrosis and reflect subclinical injury before clinical cardiovascular complications manifest.
4. Asymptomatic CTRCD was observed in 27.3 % of patients. BEAM protocol for conditioning regimen was found to influence the development of CTRCD 19.599-fold ($p = 0.01$). The risk of developing CTRCD was 10.286-fold higher in patients with a left ventricular end-diastolic diameter index > 26.54 mm/m^2 on baseline echocardiography (sensitivity 53.3 %, specificity 90.0 %, $p = 0.001$).

LIMITATIONS OF THE STUDY

A weak point of our study is a relatively small number of patients. However, despite that, statistically significant results prove the impact of HSCT on subclinical heart changes, like increase in T1 relaxation times, possibly showing progress of diffuse fibrosis.

Due to small amount of patients undergoing allogeneic HSCT in our study impact of this procedure on CTRCD could have been underscored – we did not get statistically significant results.

And lastly, the follow-up period was 12 months after HSCT, therefore, further follow-up of patients is needed to evaluate long term consequencies on cardiac damage.

PRACTICAL RECOMMENDATIONS

According to our data, the risk of CTRCD in patients receiving BEAM protocol is increased 19.599-fold, therefore, a more intensive follow-up should be performed in order to ensure timely diagnosis of CTRCD and prevent its progression.

More intensive monitoring of cardiotoxicity should be performed in patients with a baseline LVEDDi > 26.54 mm/m^2 on echocardiography.

SANTRAUKA

ĮVADAS

Dėl kraujodaros kamieninių ląstelių transplantacijos (KKLT) pacientai, sergantys įvairiomis piktybinėmis hematologinėmis ligomis ir kai kuriais solidiniais navikais, kai reikalinga didelių dozių chemoterapija, gali visiškai pasveikti [1, 2].

Pasaulinio kraujo ir kaulų čiulpų transplantacijos tinklo (WBMT) duomenimis, KKLT skaičius pasaulyje nuolat didėja maždaug 7 proc. per metus ir vidutiniškai siekia apie 90 000 per metus. 1957–2019 m. visame pasaulyje KKLT atlikta apie pusantro milijono pacientų [3]. Pacientai, po KKLT išgyvenę ilgiau nei penkerius metus be atkryčio, turi didelę tikimybę išgyventi dar 15 metų [4]. Šiuolaikinė KKLT užtikrina daug didesnį išgyvenamumą, tačiau yra susijusi su kai kuriomis sunkiomis ūminėmis ar lėtinėmis komplikacijomis [5].

Vis dažniau kalbama apie neigiamą KKLT poveikį širdies ir kraujagyslių sistemai, o KKLT recipientams vėliau gyvenime didėja širdies ir kraujagyslių ligų išsivystymo rizika. Tyrimai rodo, kad širdies ir kraujagyslių ligų rizika po KKLT yra bent keturis kartus didesnė nei bendrosios populiacijos [5, 6]. Literatūros duomenimis, iš visų su KKLT susijusių komplikacijų širdies ir kraujagyslių komplikacijos sudaro apie 10–16,84 proc. tiek alogeninės, tiek autologinės KKLT atveju. Jos blogina gyvenimo kokybę ir gali lemti didelį mirštamumą [7, 8].

Širdies ir kraujagyslių ligų nepageidaujami reiškiniai gali būti nulemtì įvairių KKLT sudedamųjų procedūrų, pavyzdžiui, abliacinės terapijos, įskaitant viso kūno apšvitą kartu su kelių vaistų kondicionavimo režimu. Dauguma mobilizacijai ar kondicionavimui vartojamų vaistų, įskaitant ciklofosfamidą, citarabiną, karmustiną ir melfalaną, yra susiję su dideliu toksiškumu. Be to, manoma, kad dimetilsulfoksido (DMSO), kuris vartojamas kamieninėms ląstelėms išsaugoti, poveikis taip pat galbūt prisideda prie širdies veiklos sutrikimų. Monokloniniai antikūnai ir kitos taikinių terapijos, skiriamos prieš KKLT ir po jos, taip pat gali turėti neigiamos įtakos širdies pažeidimui. Širdies komplikacijos taip pat gali atsirasti dėl kitų su KKLT susijusių komplikacijų, pavyzdžiui, transplantato prieš šeimininką ligos, sepsio, trombozinės mikroangiopatijos ar kepenų venų okliuzinės ligos [9].

Galima ir besimptomė širdies pažaida, o tikslus jos dažnumas nėra žinomas. Besimptomė pažaida gali būti susijusi su klinikinėmis širdies ir kraujagyslių ligomis sulaukus vėlesnio amžiaus, todėl svarbu anksti nustatyti pokyčius, kad būtų išvengta vėlesnių komplikacijų [10].

Mūsų tyrimo tikslas buvo nustatyti KKLT įtaką širdies ertmių dydžiams, funkcijai ir audinių savybėms bei klinikinius veiksnius, turinčius įtakos onkologinių ligų gydymo sukeltai širdies pažaidai (OLGSŠP) išsivystyti. Galimam kardiotoksiškumui po KKLT įvertinti buvo pasirinkti du skirtingi vaizdinimo būdai – echokardiografija ir širdies magnetinio rezonanso tyrimas (ŠMRT).

Darbo tikslas

Nustatyti kraujodaros kamieninių ląstelių transplantacijos (KKLT) įtaką širdies ertmių dydžiams, skilvelių funkcijai ir miokardo audinio pažaidą skirtingais vaizdiniais tyrimais bei veiksnius, lemiančius ir prognozuojančius onkologinių ligų gydymo sukeltos širdies pažaidos (OLGSŠP) vystymąsi.

Tyrimo uždaviniai

1. Įvertinti echokardiografinius širdies ertmių, skilvelių funkcijos pokyčius po kamieninių kraujodaros ląstelių mobilizacijos pacientams, kuriems atliekama autologinė KKLT.
2. Įvertinti echokardiografija ir ŠMRT metodais išmatuotus širdies ertmių ir skilvelių funkcijos pokyčius praėjus 12 mėnesių po KKLT.
3. Įvertinti miokardo audinio pokyčius (difuzinę miokardo fibrozę ir miokardo edemą) pasitelkiant ŠMRT bekontrasčius T1 ir T2 relaksacijos laikų žemėlapius.
4. Nustatyti besimptomės OLGSŠP dažnį po KKLT ir veiksnius, įtakojančius bei prognozuojančius OLGSŠP išsivystymą.

Tyrimo naujumas ir aktualumas

Kardioonkologija yra nauja greitai besivystanti kardiologijos sritis. Kai kurių vėžio gydymo metodų, pavyzdžiui, antraciklinų, anti-HER2 terapijos, imuninės patikros taškų inhibitorių, poveikis širdies pažeidimams kelia didelį susidomėjimą ir jau yra gana gerai išanalizuotas. Kasmet daugėja KKLT procedūrų, pacientų išgyvenamumo rodikliai gerėja, o KKLT poveikis širdies pažaidai, ypač besimptomei, nėra plačiai analizuotas.

Mūsų duomenimis, tai vienas pirmųjų perspektyviųjų tyrimų, kuriame analizuojamas KKLT poveikis ikiklinikiniams širdies pažeidimams, naudojant ŠMRT. ŠMRT turi unikalią galimybę įvertinti miokardo audinio pokyčius, todėl gali būti svarbus vertinant tiek besimptomę, tiek klinikinę miokardo pažaidą. Savo tyrime nustatėme, kad natyvinio T1 žemėlapio vertė pacientams didėja praėjus 12 mėnesių po KKLT, taip atskleidžiant galimą difuzinės miokardo fibrozės progresavimą. E/e' santykio padidėjimas, nustatytas atliekant stebėsenos echokardiografiją, taip pat galėtų būti progresuojančios difuzinės miokardo fibrozės pasekmė.

Nustačius pacientus, kuriems gresia didžiausia kardiotoksiškumo rizika, būtų galima atidžiau stebėti pacientų širdies ir kraujagyslių būklę ir užtikrinti geresnę jų priežiūrą, kad ateityje būtų išvengta kliniškai ryškios širdies pažaidos. Savo tyrime nustatėme, kad pacientai, kuriems taikomas BEAM (karmustinas, etopozidas, citarabinas, melfalanas) kondicionavimo režimas, statistiškai reikšmingai dažniau patiria subklinikinę OLGSŠP. Taip pat nustatėme, kad pacientų, kuriems pasireiškia besimptomė OLGSŠP, pradinės echokardiografijos metu nustatytas didesnis indeksuotas kairiojo skilvelio galinis diastolinis dydis (KSGDDi), o pacientų, kuriems pasireiškia vidutinio sunkumo subklinikinė OLGSŠP, taip pat ir pradinio ŠMRT metu nustatytas didesnis indeksuotas kairiojo skilvelio galinis diastolinis tūris (KSGDTi) ir indeksuotas kairiojo skilvelio galinis sistolinis tūris (KSGSTi). Nustatytos šių parametrų prognozinės slenkstinės vertės, didinačios OLGSŠP vystymosi riziką.

DARBO METODIKA

Tyrimui buvo gautas Kauno regioninio bioetikos komiteto leidimas (Nr. BE-2-96). Tyrimas atliktas vadovaujantis Helsinkio deklaracija. Visi pacientai sutiko ir pasirašė informuoto paciento sutikimo dalyvauti tyrime formą.

Tiriamoji populiacija

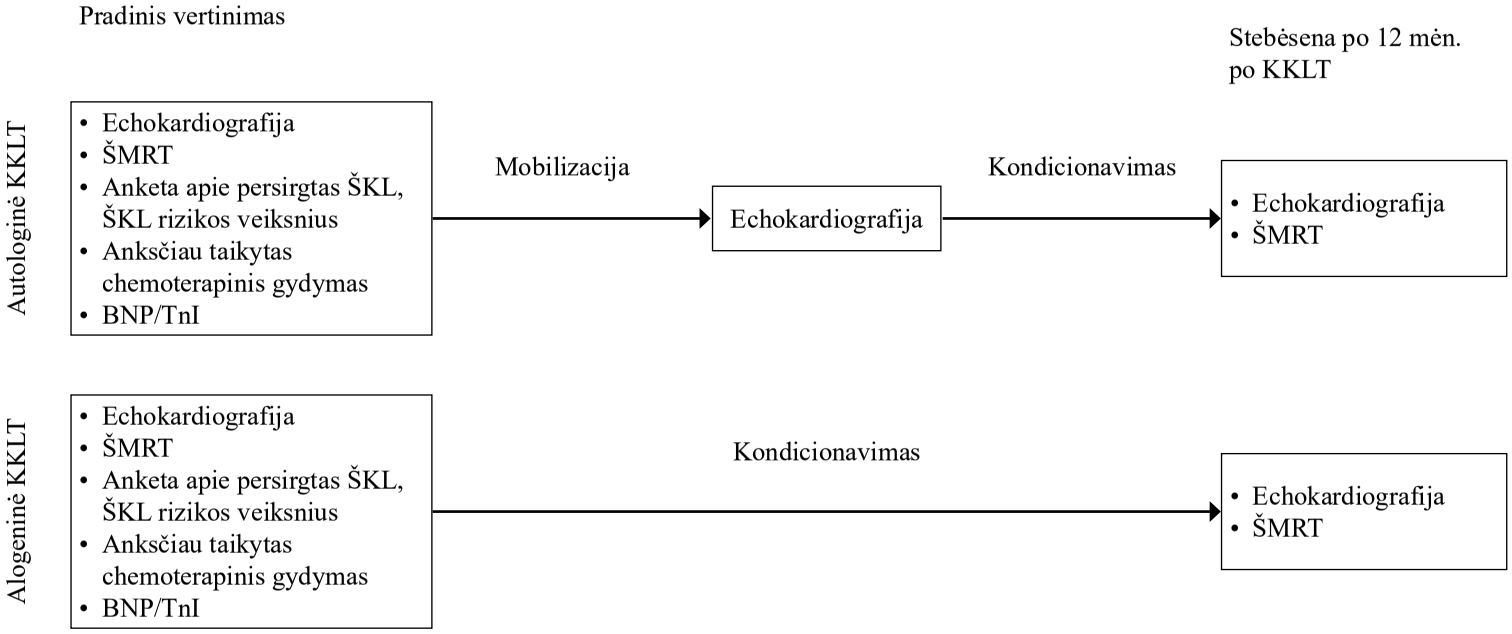
Tyrimas atliktas perspektyviai 2021 m. spalio–2024 m. vasario mėn. Lietuvos sveikatos mokslų universiteto ligoninės Kauno klinikose. Į tyrimą įtraukta 60 pacientų, kuriems Onkologijos ir hematologijos klinikoje atlikta autologinė arba alogeninė KKLT.

Įtraukimo kriterijai:
- Rašytinis sutikimas dalyvauti tyrime.
- Vyresni nei 18 metų pacientai, kuriems dėl įvairių priežasčių planuojama atlikti KKLT.

Neįtraukimo kriterijai:
- Kontraindikacijos atlikti ŠMRT, pavyzdžiui, implantuoti feromagnetiniai prietaisai, implantai ar klaustrofobija.
- Anamnezėje atlikta KKLT.
- Paciento atsisakymas dalyvauti tyrime bet kuriuo metu.

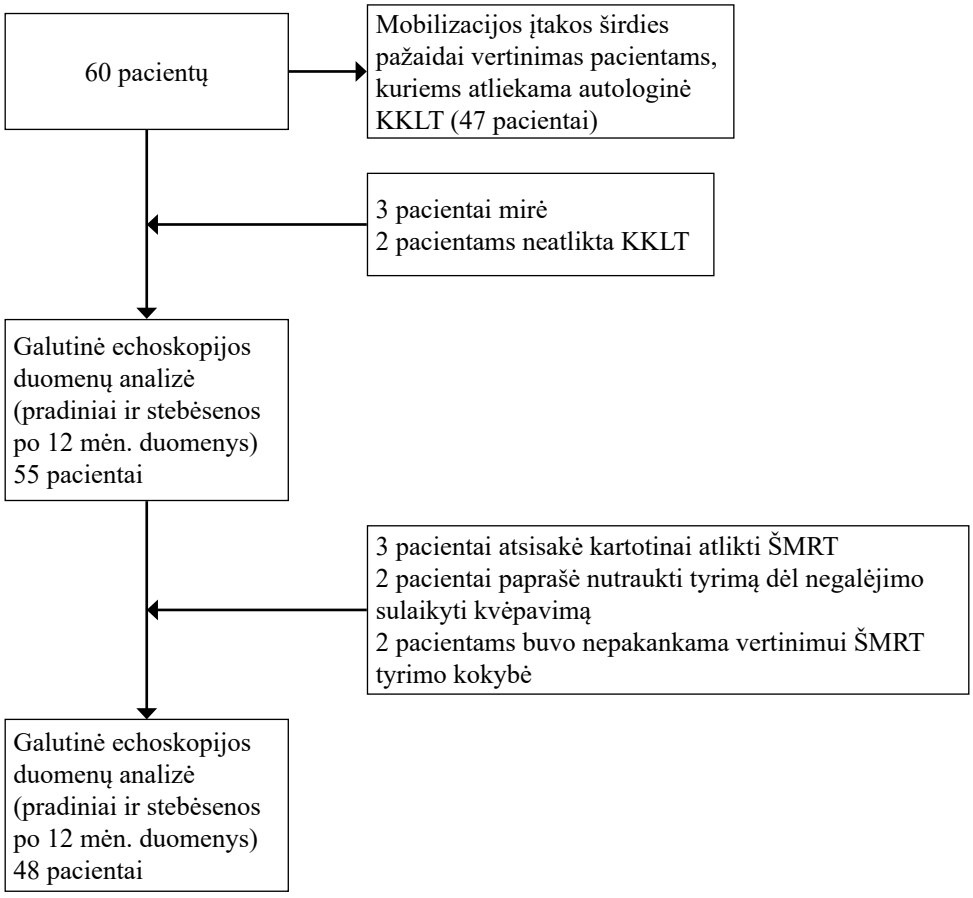
Tyrimo procesas

Tyrimo metodika pavaizduota 1 paveiksle, tyrimo procesas – 2 paveiksle.



1 pav. *Tyrimo metodika*

KKLT – kraujodaros kamieninių ląstelių transplantacija; ŠKL – širdies ir kraujagyslių ligos; ŠMRT – širdies magnetinio rezonanso tyrimas.



2 pav. *Tyrimo procesas*

KKLT – kraujodaros kamieninių ląstelių transplantacija; ŠMRT – širdies magnetinio rezonanso tyrimas.

Pacientų atranka:

- Įvertinus įtraukimo ir neįtraukimo kriterijus ir pasirašius informuoto asmens sutikimą, pacientas buvo įtrauktas į tyrimą. Tuomet pacientas buvo apklaustas ir užpildė anketą apie širdies ir kraujagyslių ligų (ŠKL) rizikos veiksnius, buvusias ar esamas ŠKL ligas, vartojamus vaistus. Informacija apie ŠKL ligas, vartojamus vaistus dar kartą patikrinta paciento medicininiuose dokumentuose.
- Prieš pradedant KKLT procesą atlikta pradinė echokardiografija ir ŠMRT, paimtas kraujas troponino I ir BNP (smegenų natriuretinio peptido) tyrimams (atliekant autologinę KKLT – prieš pradedant mobilizacijos chemoterapiją, o atliekant alogeninę KKLT – prieš pradedant

kondicionavimo chemoterapiją). Echokardiografijos ir ŠMRT metodika aptariama toliau atskirame paragrafe.

- Autologinės KKLT pacientams echokardiografija buvo atliekama po mobilizacijos proceso prieš pradedant taikyti kondicionavimo chemoterapiją. Parengta pirmoji publikacija iš šių duomenų analizės.
- Stebėsenos echokardiografija ir ŠMRT atlikti praėjus 12 ± 1 mėnesiams po KKLT. Stebėsenos ŠMRT buvo atliktas ne visiems pacientams – 3 pacientai atsisakė tyrimo; 2 pacientai paprašė nutraukti ŠMRT, nes negalėjo tinkamai sulaikyti kvėpavimo, 2 pacientų ŠMRT nevertinti dėl nepakankamos vaizdų kokybės. Atlikta ŠMRT duomenų analizė ir parengta antroji publikacija.
- Atsižvelgiant į tyrimo tikslą, atliktos 2 tipų analizės: siekiant įvertinti KKLT procedūros poveikį širdies ertmių dydžiams, skilvelių funkcijai ir miokardo audiniui, buvo lyginami visų pacientų echokardiografiniai ir ŠMRT pradiniai ir stebėsenos parametrai; 2) ikiklinikinė širdies pažaida buvo apibrėžta pagal Europos kardiologų draugijos (EKD) kardioonkologijos rekomendacijų OLGSŠP diagnostikos kriterijus, 2022 m. [64]. Pacientai buvo suskirstyti į dvi grupes: turintys ikiklinikinę OLGSŠP ir neturintys OLGSŠP, bei buvo atlikta veiksnių, lemiančių ir prognozuojančių OLGSŠP, analizė.

Pacientų demografiniai duomenys, rizikos veiksniai, pagrindinės ligos ir chemoterapijos schemos

Tyrimo metu surinkti antropometriniai pacientų duomenys: ūgis (cm), svoris (kg). Kūno paviršiaus plotas (KPP) apskaičiuotas pagal DuBois ir DuBois formulę. Visi pacientai užpildė anketą apie ŠKL rizikos veiksnius (arterinė hipertenzija, rūkymas, ankstyvos išeminės širdies ligos (IŠL) šeiminė anamnezė, dislipidemija, cukrinis diabetas), anketa pateikta 1 priede. Informacija apie ŠKL ir medikamentinį jų gydymą buvo surinkta pokalbio su pacientu metu ir dar kartą patikrinta medicininiuose dokumentuose.

Arterinė hipertenzija vertinta pagal 2018 m. Europos kardiologų draugijos ir Europos hipertenzijos draugijos gaires. Arterinė hipertenzija buvo laikoma, jei sistolinis arterinis kraujospūdis buvo ≥ 140 mm Hg ir (arba) diastolinis ≥ 90 mm Hg. Ankstyvos IŠL šeiminė anamnezė buvo apibrėžiama kaip širdies ir kraujagyslių įvykis (insultas, miokardo infarktas, intervencinė ar chirurginė revaskuliarizacija) arba mirtis nuo širdies ir kraujagyslių ligų pirmosios eilės giminaičiams (vyrams < 55 m., moterims < 60 m.).

Pacientams KKLT buvo atlikta dėl įvairių priežasčių. Ligos, dėl kurių buvo atlikta KKLT, ir transplantacijos tipai smulkiau aprašyti rezultatų skiltyje. Onkologinės ligos buvo gydomos pagal įstaigos gydymo protokolus, pagrįs-

tus tarptautinėmis rekomendacijomis. Duomenys apie ankstesnį pagrindinės ligos gydymą surinkti iš medicininių dokumentų.

Kraujodaros kamieninių ląstelių surinkimas autologinei KKLT buvo atliekamas skiriant chemoterapiją ir granulocitų kolonijas stimuliuojančius faktorius (chemomobilizacija). Daugine mieloma sergantiems pacientams buvo skiriama 3000 mg/m^2 ciklofosfamido; mantijos ląstelių limfoma sergantiems pacientams – 375 mg/m^2 rituksimabo ir 4 g/m^2 citarabino; Hodžkino limfoma sergantiems pacientams – 30 mg/m^2 cisplatinos ir 3,5 g/m^2 citarabino; pirminės centrinės nervų sistemos (PCNS) difuzine stambiųjų B ląstelių limfoma sergantiems pacientams buvo skiriamos skirtingos citarabino ir tiotepos dozės bei rituksimabo 375 mg/m^2; NK/T ląstelių limfoma sergančiam pacientui buvo taikoma CHOEP (ciklofosfamidas, doksorubicinas, etopozidas, vinkristinas, prednizolonas) schema, o Ewingo sarkoma sergantiems pacientams – IE schema (ifosfamidas, etopozidas). Visiems pacientams, kuriems buvo numatyta autologinė KKLT, atliktos aferezės procedūros. Kamieninės ląstelės iš periferinio kraujo buvo surinktos naudojant aferezės sistemą „Fresenius Kabi COM.TEC“. Ląstelės sušaldytos 10 proc. DMSO ir autologinės plazmos tirpale. Šaldymas atliktas kontroliuojamo greičio šaldiklyje su skystuoju azotu (*Consarctic* įranga).

Kondicionavimo chemoterapija buvo skiriama atsižvelgiant į ligą: daugi-nei mielomai naudotas melfalanas 200 mg/m^2, limfomoms – BEAM (karmustinas, etopozidas, citarabinas ir melfalanas) protokolas, pirminei centrinės nervų sistemos (PCNS) difuzinei stambiųjų B ląstelių limfomai – tiotepa ir BCNU (karmustinas), visiems pacientams, kuriems atlikta alogeninė KKLT, taikytas mažesnio intensyvumo kondicionavimas skiriant fludarabiną ir busulfaną.

Echokardiografinio tyrimo metodika

Tyrimo laikotarpiu echokardiografija pacientams, kuriems atliekama autologinė KKLT, buvo atlikta tris kartus: pirmoji – įvertinant širdies būklę prieš priimant sprendimą įtraukti pacientą į transplantacijos procesą (prieš mobilizacijos procedūrą); antroji – prieš transplantacijos (kondicionavimo) procedūrą; ir trečioji – stebėsenos, praėjus 12 mėnesių po KKLT. Pacientams, kuriems atlikta alogeninė KKLT, echokardiografija buvo atlikta 2 kartus: pirmoji – įvertinant širdies būklę prieš priimant sprendimą įtraukti pacientą į transplantacijos procesą; antroji – stebėsenos, 12 mėnesių po KKLT.

Echokardiografija atlikta vieno tyrėjo EPIQ 7 (*Phillips Ultrasound Inc*., *Washington*, JAV) ultragarso aparatu. Įvertinti įprastiniai echokardiografiniai parametrai (širdies kamerų dydžiai, masė, skilvelių funkcija) ir bendroji išilginė įtampa (BIĮ) taškelių žymėjimo metodika. Širdies kamerų dydžių, masės,

skilvelių funkcijos kiekybinis vertinimas atliktas pagal Amerikos echokardiografijos draugijos ir Europos širdies ir kraujagyslių vaizdinimo asociacijos rekomendacijas [110].

Parasternaliniame ilgosios ašies vaizde diastolės pabaigoje buvo įvertinti kairiojo skilvelio galinis diastolinis dydis (KSGDD), mm, jo indeksas pagal kūno paviršiaus plotą (KPP) (KSGDDi), mm/m^2, tarpskilvelinės pertvaros (TSP) ir užpakalinės sienelės (KSUS) storis, mm, kairiojo skilvelio (KS) masė apskaičiuota pagal Kubo formulę, apskaičiuotas santykinis sienelės storis (SSS). KS masės padidėjimas buvo klasifikuojamas kaip koncentrinė (SSS > 0,42) arba ekscentrinė (SSS ≤ 0,42) hipertrofija. Normali KS masė, esant SSS > 0,42, buvo priskiriama KS geometrijos persitvarkymui. Sistolės pabaigoje matuotas kairiojo prieširdžio (KPr) skersmuo, mm.

Viršūniniuose vaizduose KS išstūmio frakcija (KSIF) apskaičiuota taikant modifikuotą dviplanį Simpsono metodą. Tūriniai matavimai – KS galinis diastolinis tūris (KSGDT), ml, ir KS galinis sistolinis tūris (KSGST), ml, buvo gauti apibrėžus miokardo ir KS ertmės ribas sistolės ir diastolės pabaigoje viršūniniuose dviejų ir keturių kamerų vaizduose. Bendroji KSIF buvo vertinama apskaičiuojant skirtumą tarp KS galinio diastolinio ir sistolinio tūrių, padalijant iš KS galinio diastolinio tūrio. KPr tūris, ml, buvo apskaičiuotas iš keturių ir dviejų kamerų vaizdų, taikant diskų sumavimo algoritmą, KPr tūrio indeksas apskaičiuotas pagal KPP, ml/m^2. Dešiniojo skilvelio (DS) galinis diastolinis diametras (DSGDD), mm, pamatuotas pamatinėje dalyje iš viršūninio keturių kamerų vaizdo diastolės pabaigoje. DS išilginė sistolinė funkcija vertinta pamatavus audinių dopleriu DS laisvosios šoninės sienelės sistolinį judesio greitį (S', cm/s). Iš viršūninių keturių ertmių vaizdo impulsinio doplerio metodu buvo užrašomi kraujotakos greičiai per dviburį vožtuvą – ankstyvasis diastolinis KS prisipildymo greitis (E) ir greitis prieširdžių susitraukimo metu (A), apskaičiuojamas jų santykis – E/A. Audinių impulsiniu dopleriu įvertinti ir ankstyvojo KS diastolinio prisipildymo greičiai (e') ties šonine KS sienele ir TSP (cm/s) bei apskaičiuotas E/e' (e' − ties KS šonine sienele ir TSP vidurkis) santykis.

KS BIĮ įvertinta taškelių žymėjimo metodu. KS BIĮ apskaičiuota analizuojant viršūninės projekcijos keturių, trijų ir dviejų ertmių vaizdus. BIĮ apskaičiuota iš kokybiško vieno širdies ciklo vaizdo. Rankiniu būdu buvo apibrėžtas KS endokardo (vidinės ertmės) kontūras, toliau analizės programa automatiškai pažymėjo miokardo kontūrą iki epikardo. Esant netiksliam automatiniam sužymėjimui, rankiniu būdu koreguotas apibrėžtojo miokardo plotis. Patvirtinus atliktą taškelių žymėjimą, programa automatiškai suskaičiavo atskirų miokardo segmentų įtampą. Rezultatas pateikiamas skaitinėmis vertėmis ir kreivėmis. Keturių ertmių vaizde nustatyta apatinės TSP ir šoninės sienelės, trijų ertmių vaizde – priekinės TSP ir užpakalinės sienelės, o dviejų

ertmių vaizde – apatinės ir priekinės sienelių išilginė įtampa. Apskaičiavus visų KS sienelių išilgines įtampas, BIĮ apskaičiuota kaip aritmetinis visų miokardo segmentų vidurkis.

ŠMRT metodika

Tyrime dalyvaujantiems pacientams buvo atliktas 3T ŠMRT naudojant 18 kanalų širdies ritę (MAGNETOM Skyra, *Siemens Healthcare*, Erlangenas, Vokietija), sinchronizuojant su elektrokardiografija (EKG). Buvo atliktos tamsaus kraujo sukinio aido, šviesaus kraujo gradiento aidų apžvalginės sekos, dviejų, trijų, keturių kamerų ir trumposios ašies judesio vaizdų sekos, T1 ir T2 žemėlapių sekos.

Kiekybinė KSGDT, dešiniojo skilvelio galinis sistolinis tūris (DSGST), KSGST, dešiniojo skilvelio galinis diastolinis tūris (DSGDT), KS masės ir verčių, indeksuotų pagal KPP, analizė, taip pat KSIF ir dešiniojo skilvelio išstūmio frakcija (DSIF) buvo analizuojami ir apskaičiuojami naudojant programą „Medis Suite 3.2“ (Leidenas, Nyderlandai). KS endo- ir epikontūrai buvo apibrėžti rankiniu būdu trumposios ašies judesio vaizduose diastolėje ir sistolėje, neįtraukiant KS speninių raumenų. Analogiškai buvo apibrėžti DS endokontūrai. Bendroji KS ir DS sistolinė funkcija įvertinta apskaičiuojant skirtumą tarp GDT ir GST ir padalijus iš GDT.

T1 ir T2 žemėlapių sekos buvo atliktos diastolės pabaigoje trumposios ašies vaizdų trijuose pjūviuose (pamatiniame, viduriniame ir viršūniniame). T1 ir T2 relaksacijos laikai analizuoti naudojant Syngo.via analizės programą. Visuose trijuose pjūviuose (pamatiniame, viduriniame ir viršūniniame) buvo apibrėžta tarpskilvelinė pertvara ir išvestas visų trijų matavimų vidurkis. Pamatinės relaksacijos laikų vertės buvo palygintos su vertėmis praėjus 12 mėnesių po KKLT.

Onkologinių ligų gydymo sukeltos širdies pažaidos (OLGSŠP) apibrėžtis

Siekiant nustatyti besimptomės OLGSŠP dažnumą ir išanalizuoti įvairių veiksnių įtaką kardiotoksiškumui, pacientai pagal echokardiografinių parametrų (KSIF ir BIĮ) pokytį buvo suskirstyti į dvi grupes, turinčias ir neturinčias besimptomės OLGSŠP požymių, remiantis EKD kardioonkologijos gairėse, 2022 m., pateikta apibrėžtimi [64]. OLGSŠP kriterijai ir pacientų skirstinys pateikti 1 lentelėje.

1 lentelė. *OLGSŠP apibrėžimo kriterijai ir pacientų skirstinys*

Laipsnis	Kriterijai	Pacientų skaičius
Sunki	Naujas KSIF sumažėjimas < 40 proc.	0
Vidutinė	Naujas KSIF sumažėjimas ≥ 10 procentinių punktų iki KSIF 40–49 proc.	3
	Naujas KSIF sumažėjimas < 10 procentinių punktų iki KSIF 40–49 proc. IR naujas santykinis BIĮ sumažėjimas > 15 proc. nuo pradinio lygio	3
Lengva	KSIF ≥ 50 proc. IR naujas santykinis BIĮ sumažėjimas > 15 proc. nuo pradinio lygio	9

KSIF – kairiojo skilvelio išstūmio frakcija; BIĮ – bendroji išilginė įtampa.

Statistinė analizė

Statistinė analizė atlikta vartojant IBM SPSS *Statistics* 29.0 programinės įrangos paketą (IBM Corp., Armonk, NY, JAV). Hipotezėms apie kintamųjų normalųjį skirstinį tikrinti taikytas Kolmogorovo ir Smirnovo testas. Normaliojo skirstinio duomenimis buvo laikomi duomenys, atitinkantys normos testų sąlygas, kai $p > 0,05$. Kokybiniai požymiai aprašyti absoliučiaisiais skaičiais (n), nurodyta procentinė išraiška (proc.), kiekybiniai kintamieji, atitinkantys normalumo sąlygas, pateikti vidurkiais su standartiniais nuokrypiais, o netenkinantys normalumo sąlygų – medianomis ir minimaliomis bei maksimaliomis vertėmis. Duomenims tarp dviejų stebėtų matavimų grupių palyginti naudotas porinis t testas, Vilkoksono arba Man-Vitnio testas. Ryšys tarp kardiotoksiškumo išsivystymo ir pacientų klinikinių požymių įvertintas taikant Pearsono chi kvadrato arba Fišerio tiksliuosius testus. Binarinė logistinė regresinė analizė atlikta taikant vienaveiksnį ir daugiaveiksnį modelius, siekiant įvertinti šansų santykį (ŠS) su 95 proc. pasikliautinuoju intervalu (PI). Visuose statistiniuose testuose reikšmingumo lygmuo buvo apibrėžiamas kaip $p < 0,05$.

Imties tūrio apskaičiavimas

Kadangi imtis baigtinė, t.y. tiriamųjų įtraukimo laikotarpiu KKLT Lietuvos sveikatos universiteto ligoninės Kauno klinikų onkologijos ir hematologijos klinikoje buvo atlikta 65 pacientams (vidutiniškai KKLT atliekama 50 pacientų per metus), imties skaičiavimas atliktas remiantis Panijoto (Paniotto) formule:

$n = 1/(\Delta^2 + 1/N)$,

n – imties dydis, Δ – paklaidos dydis (0,05), N – generalinės visumos dydis

n = 55 pacientai.

Į tyrimą įtraukėme 60 pacientų, tačiau 5 pacientams nebuvo atlikta stebėsena – 3 pacientai mirė ir 2 pacientams KKLT nebuvo atlikta pasikeitus sveikatos būklei.

Tyrimo galia buvo įvertinta difuzinės fibrozės vertinimui T1 žemėlapio seka. Remiantis Spearman koreliacijos koeficientu, tyrimo galia 0,9518 (> 0,8).

REZULTATAI

Klinikiniai ir demografiniai veiksniai

Išanalizuoti 55 pacientų duomenys. Tarp jų buvo 30 vyrų (54,5 proc.) ir 25 moterys (45,5 proc.). Vidutinis amžius buvo 61 metai, svyravo tarp 18–74 metų. 48 pacientams (87,3 proc.) buvo atlikta autologinė, o 7 pacientams (12,7 proc.) – alogeninė HSCT. Pacientams autologinė KKLT dažniausiai atlikta dėl dauginės mielomos – 33 pacientams (68,8 proc.). 5 pacientai (10,4 proc.) sirgo pirmine centrinės nervų sistemos (PCNS) difuzine stambiųjų B ląstelių limfoma, 4 pacientai (8,3 proc.) – mantijos ląstelių limfoma, 2 pacientai (4,2 proc.) – Hodžkino limfoma, 2 pacientai (4,2 proc.) – Ewingo sarkoma, 1 pacientas – periferine T ląstelių limfoma ir 1 pacientas – NK/T ląstelių limfoma. Alogeninė KKLT atlikta dėl ūminės mieloidinės leukemijos (5 pacientai, 71,4 proc.), ūminės mielomonocitinės leukemijos (1 pacientas, 14,3 proc.) ir mielodisplazinio sindromo su blastų pertekliumi (MDS-EB) (1 pacientas, 14,3 proc.).

Pagrindinės pacientų charakteristikos ir pagrindinės ligos pateiktos 2 lentelėje.

2 lentelė. *Pacientų charakteristika*

Lytis	
Vyrai, n (proc.)	30 (54,5)
Moterys, n (proc.)	25 (45,5)
Amžius, metai (mediana (min–max)	61 (18–74)
Autologinė KKLT, n ((proc.))	48 (87,3)
Pagrindinė liga	
Dauginė mieloma, n (proc.)	33 (68,8)
Mantijos ląstelių limfoma, n (proc.)	4 (8,3)
Hodžkino limfoma, n (proc.)	2 (4,2)
PCNS difuzinė B ląstelių limfoma, n (proc.)	5 (10,4)
Periferinė T ląstelių limfoma, n (proc.)	1 (2,1)
Ewingo sarkoma, n (proc.)	2 (4,2)
NK/T ląstelių limfoma, n (proc.)	1 (2,1)

2 lentelės tęsinys

Alogeninė KKLT, n (proc.)	7 (12,7)
Pagrindinė liga	
Ūminė mieloidinė leukemija, n (proc.)	5 (71,4)
Ūminė mielomonocitinė leukemija, n (proc.)	1 (14,3)
MDS-EB, n (proc.)	1 (14,3)

PCNS – pirminė centrinės nervų sistemos; NK – natūralusis žudikas; MDS-EB – mielodisplazinis sindromas su blastų pertekliumi.

Širdies ir kraujagyslių ligos bei širdies ir kraujagyslių ligų rizikos veiksniai

Širdies ir kraujagyslių ligos bei ŠKL rizikos veiksnių skirstinys tarp pacientų pateikiamas 3 lentelėje.

3 lentelė. *Širdies ir kraujagyslių ligų ir rizikos veiksnių skirstinys*

ŠKL ir jų rizikos veiksniai	**n (proc.)**
Išeminė širdies liga (IŠL)	3 (5,5)
Paroksizminis prieširdžių virpėjimas	3 (5,5)
Arterinė hipertenzija (AH)	21 (38,2)
Cukrinis diabetas	4 (7,3)
Šeiminė ankstyvosios IŠL anamnezė	8 (14,5)
Dislipidemija	43 (78,2)
Rūkymas praeityje	5 (9,1)
Rūkymas šiuo metu	0 (0)

Širdies ir kraujagyslių ligoms gydyti ir ŠKL rizikos veiksniams koreguoti kai kurie pacientai vartojo kardioprotekcinių savybių turinčius vaistus: 10 pacientų (22,7 proc.) vartojo beta adrenoblokatorius, 6 pacientai (13,6 proc.) – angiotenziną konvertuojančiojo fermento inhibitorius (AKFi), 3 pacientai (6,8 proc.) – angiotenzino receptorių blokatorius (ARB) ir 4 pacientai (9,1 proc.) – statinus.

Pacientų, kuriems atlikta autologinė KKLT, mobilizacijos poveikio echokardiografiniams parametrams analizė

Siekiant įvertinti mobilizacijos proceso poveikį širdies ertmių dydžiui ir skilvelių funkcijai, atlikta echokardiografinių parametrų prieš ir po mobilizacijos subanalizė pacientams, kuriems atlikta autologinė KKLT.

Iš 47 pacientų buvo 27 vyrai (57,4 proc.) ir 20 moterų (42,6 proc.). Vidutinis amžius buvo 61 metai (18–74 m.). Iš viso 35 (74,5 proc.) pacientai sirgo

daugine mieloma, 4 (8,5 proc.) – mantijos ląstelių limfoma, 3 (6,4 proc.) – Hodžkino limfoma, 2 (4,3 proc.) – PCNS difuzine stambiųjų B ląstelių limfoma, 1 (2,1 proc.) – anaplazine stambiųjų ląstelių limfoma, 1 (2,1 proc.) – periferine T ląstelių limfoma ir 1 (2,1 proc.) – Ewingo sarkoma.

Laikotarpis tarp dviejų echokardiografijos tyrimų buvo 49 (20–168) dienos. Pirmoji echokardiografija buvo atlikta prieš įtraukiant į transplantacijos procesą, o antroji – prieš pradedant kondicionavimo režimą.

Nė vienam pacientui nestebėta klinikinių kardiotoksiškumo simptomų – širdies nepakankamumo, aritmijų, skysčio perikardo ertmėje, naujai atsiradusios arterinės hipertenzijos ar ūminių išeminių sindromų.

Stebėtas statistiškai reikšmingas išilginės sistolinės DS funkcijos kitimas – ji šiek tiek sumažėjo. Vidutinis S' prieš mobilizaciją buvo 13,93 ± 2,85 cm/s, o po mobilizacijos – 12,19 ± 2,64 cm/s (p = 0,003). Statistiškai reikšmingų KS dydžio, sistolinės ir diastolinės funkcijos bei DS dydžio pokyčių nepastebėta. Pokyčiai pateikti 4 lentelėje.

4 lentelė. *Echokardiografiniai parametrai prieš ir po mobilizacijos*

Echokardiografiniai parametrai	Prieš mobilizaciją	Po mobilizacijos	p
KSGDD, mm	46,48 ± 4,05	46,02 ± 5,25	0,633
KSGDDi, mm/m^2	24,85 ± 2,78	24,75 ± 2,93	0,863
KSIF, proc.	60,49 ± 7,66	59,74 ± 7,08	0,622
BIĮ, proc.	−17,45 ± 3,62	−17,59 ± 3,65	0,309
E/e'	6,58 ± 3,28	6,91 ± 2,65	0,973
DS, mm	36,02 ± 3,83	34,96 ± 4,44	0,217
S', cm/s	13,93 ± 2,85	12,19 ± 2,64	0,003

KSGDD – kairiojo skilvelio galinis diastolinis dydis; KSGDDi – KSGDD indeksuotas kūno paviršiaus plotui; KSIF – kairiojo skilvelio išstūmio frakcija; BIĮ – bendroji išilginė įtampa; E/e' – ankstyvasis diastolinis KS prisipildymo greitis/ankstyvasis dviburio žiedo diastolinis greitis; DS – dešiniojo skilvelio galinis diastolinis dydis bazėje keturių kamerų vaizde; S' – DS laisvosios šoninės sienelės sistolinis judesio greitis.

Šešiems pacientams S' sumažėjo iki mažiau nei 10 cm/s – jiems stebėtas kliniškai reikšmingas DS išilginės sistolinės funkcijos sumažėjimas (12,8 proc.). Trys pacientai priklausė dauginės mielomos grupei ir turėjo bent tris širdies ir kraujagyslių ligų rizikos veiksnius. Kiti trys pacientai sirgo kitomis ligomis: vienas sirgo mantijos ląstelių limfoma, kitas – Hodžkino limfoma, o trečias – difuzine stambiųjų B ląstelių limfoma. Šiems pacientams buvo skiriamas rituksimabas ir citarabinas arba cisplatina ir citarabinas. Tik vienas iš jų neturėjo jokių rizikos veiksnių; kiti turėjo du (arterinę hipertenziją ir dislipidemiją) ir tris (arterinę hipertenziją, cukrinį diabetą ir dislipidemiją) rizikos veiksnius. Reikšmingas DS sistolinės funkcijos sumažėjimas nustaty-

tas 8,6 proc. dauginės mielomos grupės pacientų ir 25 proc. – kitų ligų grupės pacientams.

Atlikta ŠKL rizikos veiksnių ir kliniškai reikšmingo S' sumažėjimo iki mažiau nei 10 cm/s po mobilizacijos koreliacijos analizė. Kliniškai reikšmingas S' sumažėjimas stebėtas tik šešiems pacientams, todėl statistiškai reikšmingos ŠKL veiksnių įtakos nenustatyta. Rizikos veiksnių skirstinys pateiktas 5 lentelėje. Vienaveiksnės logistinės regresijos analizės rezultatai pateikti 6 lentelėje. Statistiškai reikšmingos ŠKL rizikos veiksnių įtakos nebuvo stebėta, tačiau šansų santykis rodo rizikos didėjimo tendenciją, kai sergama IŠL, arterine hipertenzija ir esant ankstyvos IŠL šeiminei anamnezei.

***5 lentelė**. Širdies ir kraujagyslių rizikos veiksnių skirstinys visoje imtyje ir tarp pacientų, kuriems po mobilizacijos procedūros kliniškai reikšmingai sumažėjo ar nesumažėjo S'*

ŠKL ir ŠKL rizikos veiksniai	Atvejų skaičius visiems pacientams (proc.)	Atvejų skaičius pacientams, kurių S ≥ 10 cm/s (n (proc.))	Atvejų skaičius pacientams, kurių < 10 cm/s (n (proc.))	p
IŠL[1]	4 (8,5)	3 (75,0)	1 (25,0)	0,432
Arterinė hipertenzija	23 (48,9)	19 (82,6)	4 (17,4)	0,416
Cukrinis diabetas	6 (12,8)	5 (83,3)	1 (16,7)	1,000
Šeiminė ankstyvos IŠL anamnezė	10 (21,3)	8 (80,0)	2 (20,0)	0,594
Dislipidemija	41 (87,2)	36 (87,8)	5 (12,2)	1,000
Rūkymas	0 (0)	0 (0)	0 (0)	
Rūkymas praeityje	7 (14,9)	6 (85,7)	1 (14,3)	1,000

IŠL – išeminė širdies liga. [1] Persirgtas miokardo infarktas arba praeityje atlikta perkutaninė transluminalinė vainikinių arterijų angioplastika.

***6 lentelė.** Vienaveiksnė logistinės regresijos analizė, rodanti širdies ir kraujagyslių rizikos veiksnių ir dešinio skilvelio išilginės sistolinės funkcijos – S' sumažėjimo (< 10 cm/s) ryšio stiprumą*

ŠKL rizikos veiksniai	Šansų santykis	95 proc. pasikliautinasis intervalas	p
IŠL [1]	2,533	0,219–29,290	0,457
Arterinė hipertenzija	2,316	0,381–14,079	0,362
Cukrinis diabetas	1,440	0,138–14,978	0,760
Šeiminė ankstyvosios IŠL anamnezė	2,062	0,320–13,313	0,447
Dislipidemija	0,694	0,067–7,223	0,760
Rūkymas praeityje	1,167	0,115–11,814	0,896

IŠL – išeminė širdies liga; [1] Persirgtas miokardo infarktas arba perkutaninė transluminalinė vainikinių arterijų angioplastika.

Echokardiografijos stebėsenos rezultatai praėjus 12 mėnesių po KKLT

Siekiant įvertinti KKLT poveikį širdies ertmių dydžiams ir skilvelių funkcijai, buvo įvertinti ir palyginti echokardiografiniai parametrai prieš KKLT ir praėjus 12 mėnesių po jos. Stebėtas statistiškai reikšmingas išilginės DS funkcijos (S') sumažėjimas ir E/e' padidėjimas. Statistiškai reikšmingo KS dydžio (KSGDD, KSGDDi), KS masės (MM, MMI), KS sistolinės funkcijos (KSIF), deformacijos parametrų (BIĮ), KPr dydžio (KPr skersmens, KPr tūrio ir KPr tūrio indekso), DS dydžio (DS) ir DPr dydžio (DPr) skirtumo nestebėta. Vertės prieš ir 12 mėnesių po KKLT pateiktos 7 lentelėje.

7 lentelė. *Echokardiografinių parametrų pokyčiai prieš KKLT ir praėjus 12 mėnesių po jos*

Echokardiografiniai parametrai	Echokardiografija prieš HSCT	Echokardiografijos stebėsena praėjus 12 mėnesių po KKLT	p
KSGDD (mediana (min–max))	46,50 (38,00–62,00)	45,00 (36,00–55,00)	0,603
KSGDDi (vidurkis (SN))	24,52 (2,67)	24,58 (2,73)	0,851
KS MM (vidurkis (SN))	167,13 (49,28)	163,37 (44,91)	0,454
KS MMI (vidurkis (SN))	86,65 (20,20)	85,69 (18,74)	0,722
KSIF (vidurkis (SN))	58,50 (7,36)	57,68 (6,99)	0,472
BIĮ (vidurkis (SN))	17,31 (3,49)	16,69 (3,54)	0,179
KPr skersmuo (mediana (min–max))	37,00 (27,00–52,00)	37,00 (20,00–50,00)	0,222
KPr tūris (mediana (min–max))	57,00 (20,00–138,00)	58,00 (25,00–123,00)	0,822
KPr tūrio indeksas (vidurkis (SN))	37,78 (5,41)	36,65 (5,77)	0,092
DS (mediana (min–max))	35,00 (26,00–44,00)	34,00 (28,00–50,00)	0,517
S' (vidurkis (SN))	13,82 (3,20)	12,41 (2,53)	**0,001**
DPr (vidurkis (SN))	39,16 (4,06)	38,52 (4,74)	0,243
E/e' (vidurkis (SN))	6,16 (1,87)	7,45 (2,07)	**< 0,001**

KSGDD – kairiojo skilvelio galinis diastolinis dydis; KSGDDi – KSGDD, indeksuotas kūno paviršiaus plotui (KPP); KS MM – kairiojo skilvelio miokardo masė, KS MMI – kairiojo skilvelio miokardo masės indeksas; KSIF – kairiojo skilvelio išstūmio frakcija; BIĮ – bendroji išilginė įtampa; KPr skersmuo – kairiojo prieširdžio skersmuo iš parasternalinio ilgosios ašies vaizdo; KPr tūris – kairiojo prieširdžio tūris; KPr tūrio indeksas – kairiojo prieširdžio tūris, indeksuotas pagal KPP; DS – dešiniojo skilvelio galinis diastolinis skersmuo; S' – DS laisvosios šoninės sienelės sistolinis judesio greitis; E/e' – ankstyvasis mitralinio įtekėjimo greitis/ankstyvasis dviburio žiedo diastolinis greitis; SN – standartinis nuokrypis.

ŠMRT stebėsenos rezultatai praėjus 12 mėnesių po KKLT

ŠMRT parametrai vertinti prieš KKLT ir 12 mėnesių po jos. Stebėtas statistiškai reikšmingas T1 žemėlapio verčių kitimas. T1 žemėlapio vertės padidėjo nuo 1226,95 ± 36,31 ms iki 1250,13 ± 39,65 ms ($p < 0,001$). KSGDT, KSGDTi, KSGST, KSGSTi, KSIF, KS masė, KS masės indeksas, DSGDT, DSGDTi, DSGST, DSGSTi, DSIF ir T2 žemėlapio vertės statistiškai reikšmingai nesiskyrė. Vertės pateiktos 8 lentelėje.

8 lentelė. *ŠMRT parametrų pokyčiai praėjus 12 mėnesių po KKLT*

ŠMRT vertės	Prieš KKLT	Po KKLT	p
KSGDT, ml (vidurkis (SN))	146,30 (38,55)	149,64 (39,03)	0,448
KSGDTi, ml/m^2 (vidurkis (SN))	76,63 (18,07)	78,24 (17,96)	0,447
KSGST, ml (vidurkis (SN))	62,18 (19,72)	61,46 (18,98)	0,756
KSGSTi, ml/m^2 (vidurkis (SN))	31,99 (9,70)	32,39 (10,10)	0,718
KSIF, proc. (vidurkis (SN))	58,21 (7,67)	58,96 (6,75)	0,493
KS masė, g (mediana (min–max))	105,81 (54,67–175,31)	102,55 (56,00–167,93)	0,182
KS masės indeksas, g/m^2 (vidurkis (SN))	57,47 (11,36)	55,78 (12,21)	0,332
DSGDT (vidurkis (SN))	132,44 (40,96)	141,07 (36,64)	0,063
DSGDTi (vidurkis (SN))	70,13 (16,99)	73,78 (16,72)	0,072
DSGST (vidurkis (SN))	61,20 (18,41)	66,23 (19,26)	0,074
DSGSTi (vidurkis (SN))	32,13 (8,63)	34,08 (9,70)	0,176
DSIF (vidurkis (SN))	54,10 (6,09)	53,50 (6,15)	0,594
T1 žemėlapio vertė, ms (vidurkis (SN))	1226,95 (36,31)	1250,13 (39,65)	**< 0,001**
T2 žemėlapio vertė, ms (vidurkis (SN))	39,04 (2,16)	38,70 (2,18)	0,329

KS – kairysis skilvelis; KSGDT –kairiojo skilvelio galinis diastolinis tūris; KSGDTi – KSGDT, indeksuotas pagal kūno paviršiaus plotą (KPP); KSGST – kairiojo skilvelio galinis sistolinis tūris; KSGSTi – kairiojo skilvelio galinis sistolinis tūris, indeksuotas pagal KPP; KSIF – kairiojo skilvelio išstūmio frakcija; DSGDT – dešiniojo skilvelio galinis diastolinis tūris; DSGDTi – DSGDT, indeksuotas pagal KPP; DSGST – dešiniojo skilvelio galinis sistolinis tūris; DSGSTi – DSGST, indeksuotas pagal KPP; DSIF – dešiniojo skilvelio išstūmio frakcija; SN – standartinis nuokrypis.

OLGSŠP analizė ir veiksniai, lemiantys ir prognozuojantys OLGSŠP vystymąsi

Trims pacientams (5,5 proc.) per 12 mėnesių laikotarpį po KKLT pasireiškė supraventrikuliniai ritmo sutrikimai: dviems – supraventrikulinė tachikardija, vienam – prieširdžių virpėjimas.

Pagal EKD kardioonkologijos gairių, 2022 m., OLGSŠP apibrėžtį ir echokardiografinius parametrus 12 mėnesių stebėsenos laikotarpiu 15 pacientų (27,3 proc.) diagnozuota besimptomė OLGSŠP. Šešiems pacientams pasireiškė vidutinio sunkumo (naujai atsiradęs KSIF sumažėjimas ≥ 10 procentinių punktų iki 40–49 proc. KSIF arba naujai atsiradęs KSIF sumažėjimas < 10 procentinių punktų iki 40–49 proc. KSIF ir santykinis BIĮ sumažėjimas > 15 proc. nuo pradinio lygio) ir 9 pacientų stebėta lengva OLGSŠP (KSIF ≥ 50 proc. ir naujas santykinis BIĮ sumažėjimas > 15 proc. nuo pradinio lygio).

Pacientų charakteristika ir skirtumai tarp grupių pateikti 9 lentelėje.

9 lentelė. *Veiksnių, galbūt lemiančių OLGSŠP, skirstinys tarp pacientų, turinčių ir neturinčių OLGSŠP*

Veiksniai	Visi pacientai (n = 55)	Pacientai, neturintys OLGSŠP (n = 40; 72,7 proc.)	OLGSŠP (n = 15; 27,3 proc.)	p
Amžius (metai), mediana (min–max)	61 (18–74)	61 (18–74)	61 (23–74)	0,502
Lytis				
Vyrai	30 (54,5)	21 (52,5)	9 (60,0)	0,764
Moterys	25 (45,5)	19 (47,5)	6 (40,0)	
Pagrindinė liga				
Dauginė mieloma	33 (60,0)	27 (67,5)	6 (40,0)	0,121
Limfoma	12 (23,6)	7 (17,5)	6 (40,0)	0,151
Leukemija ir MDS-EB	7 (12,7)	4 (10,0)	3 (20,0)	0,376
Ewingo sarkoma	2 (3,6)	2 (5,0)	0 (0,0)	1,000
KKLT tipas				
Alogeninė KKLT	7 (12,7)	4 (10,0)	3 (20,0)	0,376
Autologinė KKLT	48 (87,3)	36 (90,0)	12 (80,0)	
ŠKL rizikos veiksniai				
IŠL	3 (5,5)	1 (2,5)	2 (13,3)	0,177
Arterinė hipertenzija	21 (38,2)	15 (37,5)	6 (40,0)	1,000
Cukrinis diabetas	4 (7,3)	4 (10,0)	0 (0,0)	0,565
Šeiminė ankstyvosios IŠL anamnezė	8 (14,5)	6 (15,0)	2 (13,3)	1,000

9 lentelės tęsinys

Veiksniai	Visi pacientai (n = 55)	Pacientai, neturintys OLGSŠP (n = 40; 72,7 proc.)	OLGSŠP (n = 15; 27,3 proc.)	p
Dislipidemija	43 (78,2)	31 (77,5)	12 (80,0)	1,000
Rūkymas praeityje	5 (9,1)	4 (10,0)	1 (6,7)	1,000
Vaistų grupės				
Beta blokatoriai	12 (21,8)	10 (25,0)	2 (13,3)	0,477
AKFi	10 (18,2)	7 (17,5)	3 (20,0)	1,000
ARB	5 (9,1)	3 (7,5)	2 (13,3)	0,606
Statinai	6 (10,9)	4 (10,0)	2 (13,3)	0,660
Ankstesnis gydymas antraciklinų grupės preparatais	18 (32,7)	9 (22,5)	9 (60,0)	**0,021**
Kondicionavimo režimas				
Melfalanas	35 (63,6)	28 (70,0)	7 (46,7)	0128
BEAM	7 (12,7)	2 (5,0)	5 (33,3)	**0,013**
Karmustinas + 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, mediana (min–max)	0,02 (0,02–0,64)	0,02 (0,02–0,64)	0,02 (0,02–0,16)	0,958
BNP, mediana (min–max)	21,75 (4,00–118,70)	19,90 (4,00–118,70)	23,60 (9,30–56,20)	0,719

MDS-EB – mielodisplazinis sindromas su blastų pertekliumi; KKLT – kraujodaros kamieninių ląstelių transplantacija; ŠKL – širdies ir kraujagyslių ligos; IŠL – išeminė širdies liga; AKFi – angiotenziną konvertuojančiojo fermento inhibitoriai; ARB – angiotenzino receptorių blokatoriai; BEAM – karmustinas, etopozidas, citarabinas, melfalanas; TT – tiotepa; RIC –mažesnio intensyvumo kondicionavimas, BNP – smegenų natriuretinis peptidas; TnI – troponinas I.

Pacientų amžius, lytis, pagrindinė liga, KKLT tipas, ŠKL rizikos veiksniai, ŠLK koreguoti vartojami vaistai tarp abiejų grupių statistiškai reikšmingai nesiskyrė. Pacientams, kuriems anksčiau taikytas gydymas antraciklinų grupės preparatais, dažniau stebėta OLGSŠP: 9 pacientai (60 proc.) OLGSŠP grupėje ir 9 pacientai (22,5 proc.) grupėje be OLGSŠP. Skirtumas statistiškai reikšmingas (p = 0,021). Taip pat skyrėsi kondicionavimo režimai. Pacientams, kuriems taikytas BEAM kondicionavimo protokolas, OLGSŠP pasireiškė dažniau: 5 pacientams (33,3 proc.) OLGSŠP grupėje, 2 pacientams (5 proc.) ne OLGSŠP grupėje. Skirtumas buvo statistiškai reikšmingas (p = 0,013).

Atliekant vienaveiksmę logistinės regresijos analizę buvo tiriama veiksnių, galinčių turėti įtakos OLGŠSP išsivystyti, įtaka. Nustatyta, kad ankstesnis antraciklinų vartojimas (ŠS 5,167, 95 proc. PI 1,448–18,433, p = 0,011) ir kon-

dicionavimo režimui naudotas BEAM (ŠS 9,500, 95 proc. PI 1,599–56,426, p = 0,013) buvo reikšmingi OLGSŠP išsivystymo veiksniai (10 lentelė). Siekant išsiaiškinti kondicionavimo protokolo įtaką OLGSŠP vystymuisi, atlikta daugiaveiksmė logistinės regresijos analizė, kuri atskleidė, kad BEAM protokolas didiną riziką OLGSŠP išsivystyti 19,599 karto (p = 0,01). Rezultatai pateikti 11 lentelėje.

10 lentelė. *Veiksnių, galinčių turėti įtakos OLGSŠP išsivystymui, vienaveiksmė logistinės regresijos analizė*

Vienaveiksmė logistinės regresijos analizė			
Kintamasis	**Šansų santykis**	**95 proc. pasikliautinasis intervalas**	**p**
Lytis *(vyrai plg. moterys)*	1,357	0,407–4,529	0,619
Dauginė mieloma	0,321	0,094–1,095	0,069
Limfoma	3,143	0,843–11,720	0,088
Alogeninė KKLT	2,250	0,439–11,522	0,330
Autologinė KKLT	0,444	0,087–2,276	0,330
IŠL	6,000	0,502–71,731	0,157
Arterinė hipertenzija	1,111	0,330–3,746	0,865
Šeiminė ankstyvos IŠL anamnezė	0,872	0,156–4,884	0,876
Dislipidemija	1,161	0,268–5,034	0,842
Rūkymas praeityje	0,643	0,066–6,264	0,704
Beta adrenoblokatorių vartojimas	0,462	0,088–2,408	0,359
AKFi vartojimas	1,179	0,262–5,310	0,831
ARB vartojimas	1,897	0,285–12,654	0,508
Statinų vartojimas	1,385	0,226–8,477	0,725
Anksčiau skirtas gydymas antraciklinais	5,167	1,448–18,433	**0,011**
Kondicionavimas melfalanu	0,375	0,111–1,269	0,115
Kondicionavimas BEAM	9,500	1,599–56,426	**0,013**

KKLT – kraujodaros kamieninių ląstelių transplantacija; IŠL – išeminė širdies liga; AKFi – angiotenziną konvertuojančiojo fermento inhibitoriai; ARB – angiotenzino receptorių blokatoriai; BEAM – karmustinas, etopozidas, citarabinas, melfalanas.

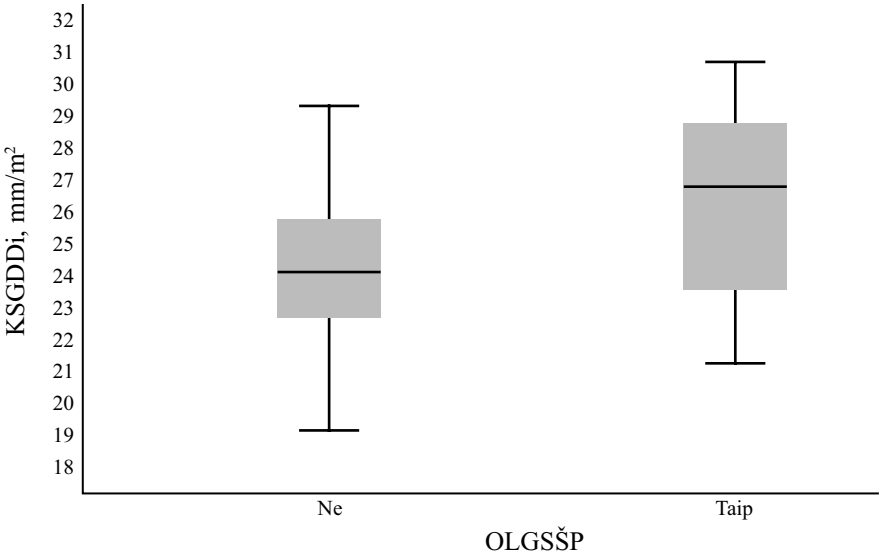
11 lentelė. *Daugiaveiksmė logistinės regresijos širdies ir kraujagyslių rizikos veiksnių ir kondicionavimo režimo įtakos analizė*

Daugiaveiksmė logistinės regresijos analizė				
Kintamasis		**OR**	**95 proc. PI**	**p**
Rizikos veiksniai	IŠL	5,948	0,298–118,858	0,243
	Arterinė hipertenzija	0,464	0,088–2,448	0,365
	Šeiminė ankstyvosios IŠL anamnezė	0,364	0,038–3,527	0,383
	Dislipidemija	4,151	0,439–39,232	0,214
	Rūkymas praeityje	0,658	0,057–7,652	0,738
BEAM		19,599	2,051–187,313	**0,010**

PI – pasikliautinasis intervalas; IŠL – išeminė širdies liga; BEAM – karmustinas, etopozidas, citarabinas, melfalanas.

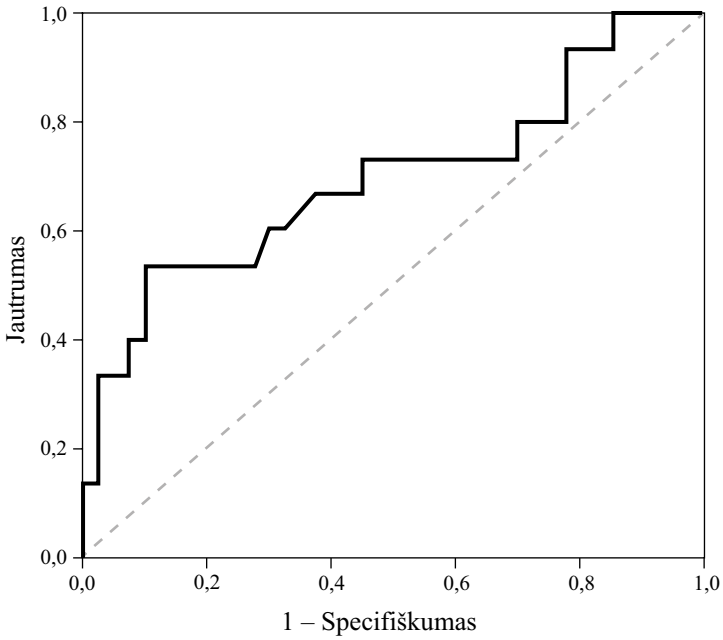
Siekiant prognozuoti galimą OLGSŠP vystymąsi, analizuoti pradinės echokardiografijos (KSGDD, KSGDDi, MM, MMI, KSIF, BIĮ, KPr tūris, KPr tūrio indeksas, KPr skersmuo, S', E/A, E/e') ir ŠMRT (KSGDT, KSGDTi, KSGST, KSGSTi, KSIF, MM, MMi, DSEDV, DSEDVi, DSESV DSESVi, DSIF) parametrai.

Pastebėta, KSGDDi prieš pradedant gydymą patikimai prognozuoja OLGSŠP vystymąsi, kuomet KSGDDi > 26,54 mm/m^2, šansų santykis vystytis OLGSŠP didėja 10,286 karto (95 proc. PI 2,418–43,751) (Specifiškumas 90,0 proc., jautrumas 53,3 proc.), p = 0,001. (3 ir 4 pav.)



3 pav. *Pacientų kairiojo skilvelio galinio diastolinio diametro indekso stačiakampė diagrama, atsižvelgiant į OLGSŠP*

OLGSŠP – onkologinių ligų gydymo sukelta širdies pažaida.

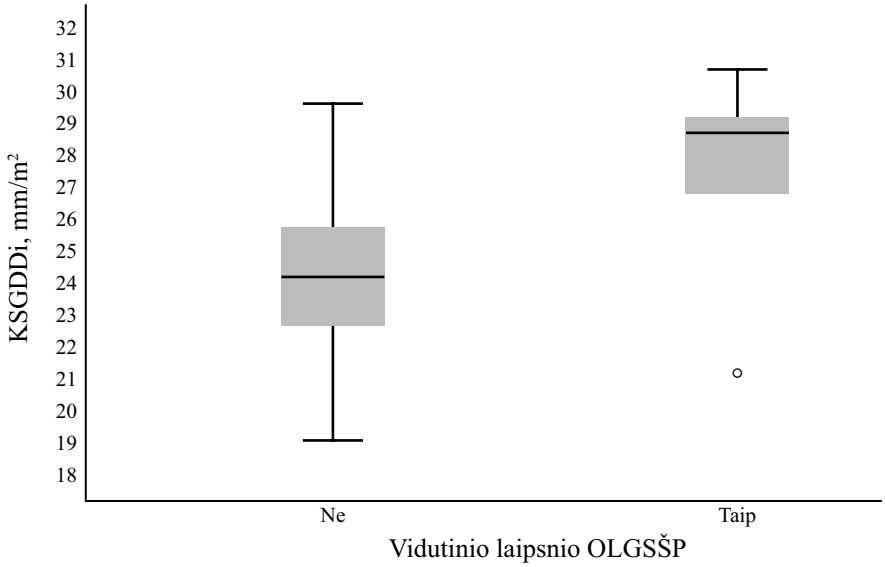


4 pav. *Pacientų ROC kreivė slenkstinei KSGDDi reikšmei nustatyti, atsižvelgiant į OLGSŠP vystymąsi. Plotas po kreive 69,7 proc.*

KSGDDi – kairiojo skilvelio galinio diastolinio dydžio indeksas; OLGSŠP – onkologinių ligų gydymo sukelta širdies pažaida.

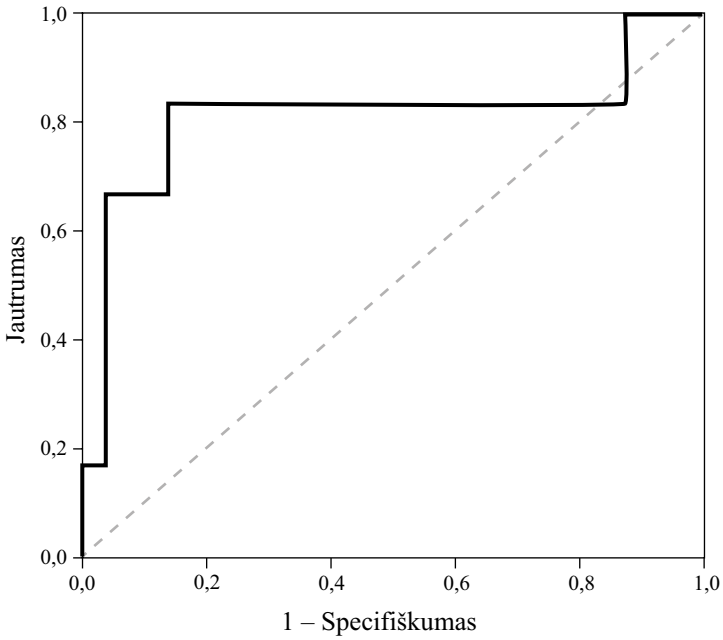
Pacientams, kuriems nustatyta vidutinio laipsnio OLGSŠP, pradinės echokardiografijos metu taip pat stebėtas didesnis KSGDDi ir didesnis KSGDTi ir KSGSTi pradinio ŠMRT metu nei pacientams be ar esant lengvo laipsnio OLGSŠP.

Kai KSGDDi buvo > 26,54 mm/m^2, vidutinio laipsnio OLGSŠP išsivystymo šansų santykis buvo 30 kartų didesnis (95 proc. PI 3,034–296,629) nei esant mažesniam KSGDDi, jautrumas 83,3 proc., o specifiškumas 85,7 proc. (p = 0,001) (5 ir 6 pav.).



5 pav. *Pacientų kairiojo skilvelio galinio diastolinio diametro indekso stačiakampė diagrama, atsižvelgiant į vidutinio laipsnio OLGSŠP.*

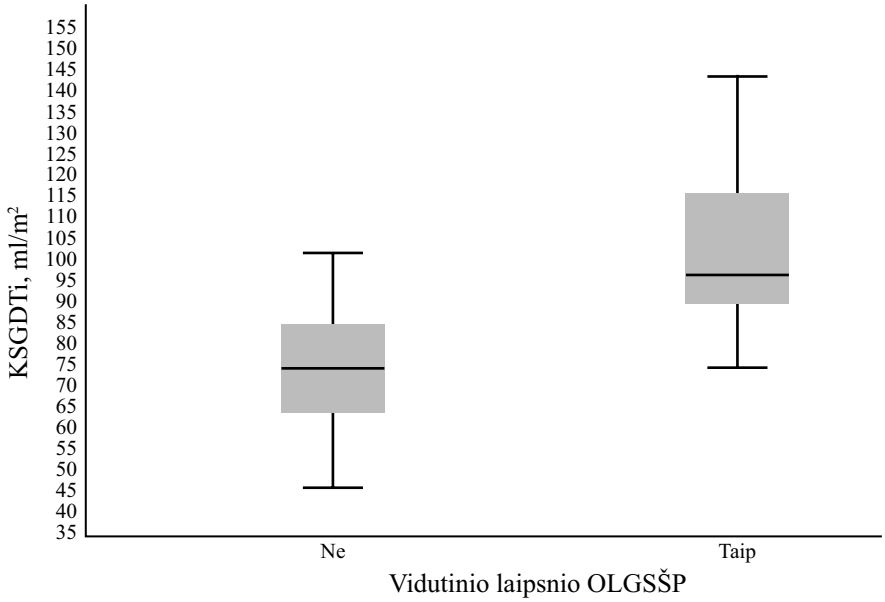
KSGDDi – kairiojo skilvelio galinio diastolinio diametro indesas; OLGSŠP – onkologinių ligų gydymo sukelta širdies pažaida.



6 pav. *Pacientų ROC kreivė slenkstinei KSGDDi reikšmei nustatyti, atsižvelgiant į vidutinio laipsnio OLGSŠP vystymąsi. Plotas po kreive 81 proc.*

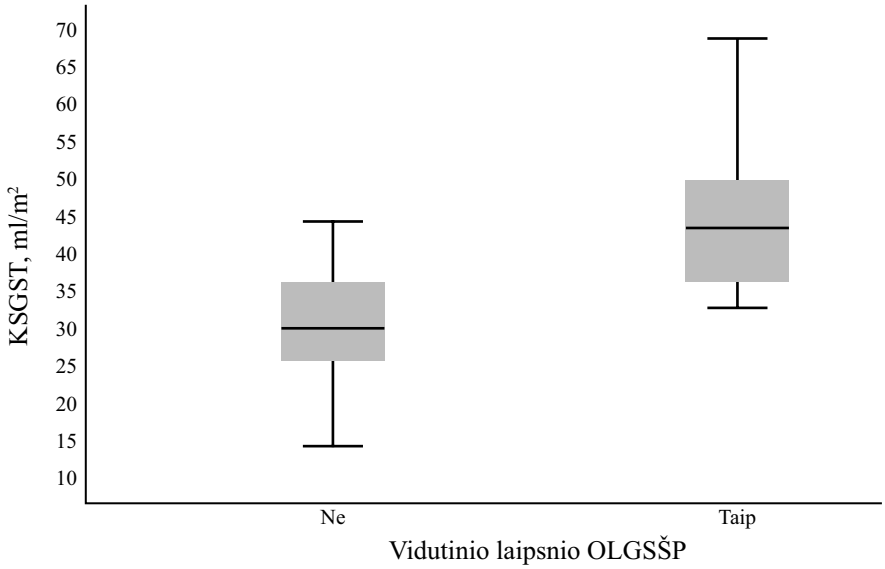
KSGDDi – kairiojo skilvelio galinio diastolinio dydžio indeksas; OLGSŠP – onkologinių ligų gydymo sukelta širdies pažaida.

KSGDTi ir KSGSTi, išmatuoti ŠMRT prieš pradedant gydymą, patikimai prognozuoja vidutinio laipsnio OLGSŠP vystymąsi, kuomet KSGDTi > 88,64 ml/m^2, šansų santykis vystytis OLGSŠP didėja 48,75 karto (95 proc. PI 4,508–527,205) (Specifiškumas 83,3 proc., jautrumas 90,7 proc.), $p < 0,001$; rizika didėja ir esant KSGST > 32,43ml/m^2 (specifiškumas 60,5 proc., jautrumas 100 proc., $p = 0,007$) Pav. Nr 7, 8, 9.



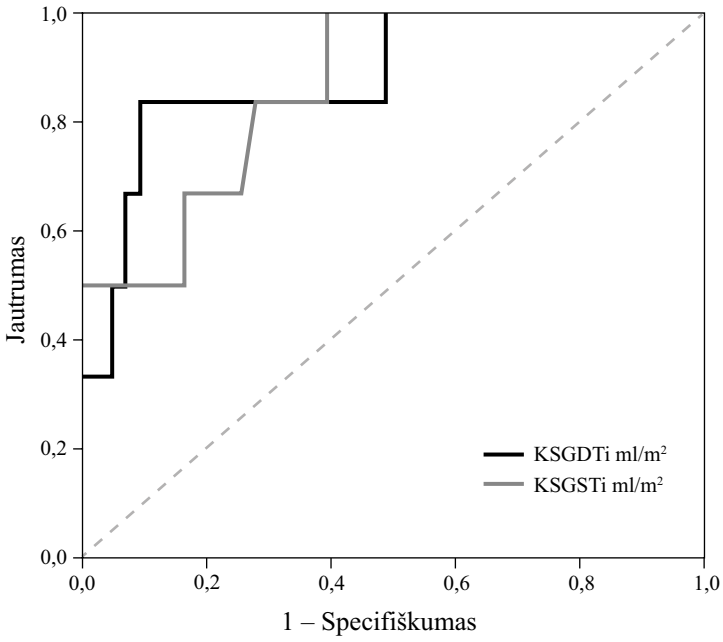
7 pav. *Kairiojo skilvelio galinio diastolinio tūrio indekso stačiakampė diagrama, atsižvelgiant į vidutinio laipsnio OLGSŠP*

KSGDTi – kairiojo skilvelio diastolinio tūrio indeksas; OLGSŠP – onkologinių ligų gydymo sukelta širdies pažaida.



8 pav. *Kairiojo skilvelio galinio sistolinio tūrio indekso stačiakampė diagrama, atsižvelgiant į vidutinio laipsnio OLGSŠP*

KSGSTi – kairiojo skilvelio sistolinio tūrio indeksas; OLGSŠP – onkologinių ligų gydymo sukelta širdies pažaida.



9 pav. *ROC kreivė slenkstinėms KSGDTi (plotas po kreive 88,4 proc.) ir KSGSTi (plotas po kreive 86,2 proc.) reikšmėms nustatyti, atsižvelgiant į vidutinės OLGSŠP vystymąsi*

KSGDTi –kairiojo skilvelio diastolinio tūrio indeksas; KSGSTi –kairiojo skilvelio sistolinio tūrio indeksas; OLGSŠP – onkologinių ligų gydymo sukelta širdies pažaida.

IŠVADOS

1. Pacientams, kuriems atlikta autologinė KKLT, po mobilizacijos procedūros stebėtas išilginės sistolinės dešiniojo skilvelio funkcijos – S' mažėjimas nuo 13,93 ± 2,85 cm/s iki 12,19 ± 2,64 cm/s (p = 0,003). Širdies ertmių, kairiojo skilvelio sistolinės funkcijos pokyčių nestebėta.
2. Praėjus 12 mėnesių po KKLT, echokardiografiškai stebimas išilginės dešiniojo skilvelio sistolinės funkcijos – S' mažėjimas nuo 13,82 ± 3,2 cm/s iki 12,41 ± 2,53 cm/s (p = 0,001), esant nepakitusiai dešiniojo skilvelio išstūmio frakcijai, apskaičiuotai ŠMRT metodu, ir E/e' santykio didėjimas nuo 6,16 ± 1,87 iki 7,45 ± 2,07 (p < 0,001).
3. Nekontrastinio T1 žemėlapio vertės, po KKLT praėjus 12 mėnesių, padidėjo nuo 1226,95 ± 36,31 ms iki 1250,13 ± 39,65ms (p < 0,001), tikėtinai atspindėdamos difuzinės miokardo fibrozės progresavimą ir besimptomę pažaidą prieš pasireiškiant klinikiniams širdies ir kraujagyslių ligų požymiams.
4. Besimptomė OLGSŠP stebėta 27,3 proc. pacientų. Nustatyta, kad BEAM (karmustinas, etopozidas, citarabinas ir melfalanas) kondicionavimo chemoterapijos protokolas turėjo įtakos OLGSŠP atsirasti – riziką didino 19,599 karto (p = 0,01). OLGSŠP vystymosi rizika 10,286 karto didesnė pacientams, kuriems prieš atliekant KKLT kairiojo skilvelio galinio diastolinio dydžio indeksas, pamatuotas echokardiografinio tyrimo metu, yra > 26,54 mm/m^2 (jautrumas 53,3 proc., specifiškumas 90,0 proc., p = 0,001).

TYRIMO SILPNOSIOS SAVYBĖS

Silpnoji mūsų tyrimo pusė – gana mažas pacientų skaičius. Tačiau statistiškai reikšmingi rezultatai įrodo KKLT įtaką ikiklinikiniams širdies pokyčiams, pavyzdžiui, T1 relaksacijos laiko pailgėjimui, tikėtinai rodančiam difuzinės fibrozės progresavimą.

Dėl mažo pacientų, kuriems buvo atlikta alogeninė KKLT, skaičiaus mūsų tyrime šio tipo KKLT poveikis OLGSŠP galėjo būti per mažai įvertintas – statistiškai reikšmingų rezultatų nenustatėme. Pacientų grupė buvo nehomogeniška, atsižvelgiant į pagrindinę ligą ir anksčiau skirtą gydymą, tačiau tyrimas buvo planuotas siekiant vertinti KKLT proceso įtaką širdies pažaidai neišskiriant pagrindinės ligos.

Galiausiai stebėsena buvo vykdyta 12 mėnesių po KKLT, todėl, norint įvertinti ilgalaikius padarinius širdies pažaidai, reikia tęsti šių pacientų stebėseną.

PRAKTINĖS REKOMENDACIJOS

Pacientams, kuriems KKLT metu taikomas kondicionavimo režimas pagal BEAM protokolą, tikslinga intensyvesnė stebėsena siekiant laiku diagnozuoti OLGSŠP ir išvengti pažaidos progresavimo.

Intensyvesnė stebėsena tikslinga ir pacientams, kuriems echokardiografiškai prieš pradedant KKLT kairiojo skilvelio galinio diastolinio dydžio indeksas yra > 26,54 mm/m^2.

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Early Impact of Mobilization Process on Cardiac Function and Size in Patients Undergoing Autologous Hematopoietic Stem Cell Transplantation

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Abstract: Background: The hematopoietic stem cell transplantation (HSCT) process is known to cause cardiac toxicity of different grades. In this paper, we aimed to evaluate the impact of mobilization procedure of hematopoietic stem cells for autologous HSCT process for left and right ventricle sizes and functions. **Material and Methods:** The data of 47 patients undergoing autologous HSCT were analyzed. All patients underwent hematopoietic stem cell mobilization with chemotherapy and filgrastim at 10 μg/kg/d. Echocardiography was performed two times: before enrolling in the transplantation process and after mobilization before the conditioning regimen for transplantation. Changes in left and right ventricle (RV) diameter and systolic and diastolic function of the left ventricle and systolic function of the RV were measured. **Results**: A statistically significant difference was observed in the change of right ventricular function (S′)—it slightly decreased. Mean S′ before mobilization was 13.93 ± 2.85 cm/s, and after mobilization it was 12.19 ± 2.64 cm/s ($p = 0.003$). No statistically significant change in left ventricular diameter and systolic and diastolic function and RV diameter was observed. **Conclusions**: The mobilization procedure in patients undergoing autologous HSCT is associated with reduced RV systolic function. S′ could be used as a reliable tool to evaluate early cardiotoxicity in HSCT patients and guide further follow-up.

Keywords: autologous hematopoietic stem cell transplantation; cardiotoxicity; mobilization

1. Introduction

Hematopoietic stem cell transplantation (HSCT) is a potentially curative procedure for various malignant hematologic and lymphoid diseases and some solid tumors [1,2]. Two fundamentally different types of HSCT are categorized by the source of the stem cells. Autologous HSCT represents infusion of the patient's own hematopoietic stem cells (HSCs), and allogeneic HSCT refers to the infusion of HSCs obtained from a donor via bone marrow harvest or apheresis [3].

Autologous HSCT provides hematopoietic support after high-dose chemotherapy and is used for treatment of patients with multiple myeloma (MM) or some types of

chemosensitive relapsed lymphomas and a few solid tumors [4]. Hematopoietic cells (HCs) and progenitor cells are released from the bone marrow into the peripheral blood through a process called mobilization. HSCs are then collected from the blood—the procedure is called apheresis—and cryopreserved for administration after treating the main disease with the high-dose preparative regimen (conditioning) [1].

According to the Worldwide Network of Blood and Marrow Transplantation (WBMT), the global count of HSCTs has been consistently rising by approximately 7% annually, reaching an average of around 90,000 per year. By 2019, a total of one-and-a-half million patients had undergone HSCT worldwide since 1957 [5]. There is a high likelihood that post-HSCT patients that have surpassed five years without relapse have a high probability of surviving for an additional 15 years [6]. Even though HSCT has reached much higher survival rates and is significantly improved compared to the past, this procedure is still related with some severe acute or chronic complications. Apart from the main complications, which are graft-versus-host disease or various infections, the HSCT process is also known to cause cardiac toxicity of different grades, which present either short-term or long-term complications [7].

In the course of HSCT, as well as within the initial 100 days following the HSCT, various cardiovascular events might occur, including acute heart failure, life-threatening arrhythmias, pericardial tamponade, and even cardiac arrest. Also, various long-term cardiovascular complications can arise, such as valvular dysfunction, cardiomyopathy, and ischemic heart disease [8]. There are numerous predisposing conditions that may worsen cardiac outcomes, for instance, diabetes mellitus, hypertension, age and, most importantly, previous treatment with chemotherapy [9]. Recently published guidelines of cardio-oncology developed by the European Society of Cardiology (ESC) classified cardiotoxicity risk according to the type of HSCT (allogeneic versus autologous), cardiovascular risk factors, preexisting cardiovascular morbidities, and previous cardiotoxic anticancer treatment effects [10].

In order to reduce the occurrence and intensity of cardiac complications, the guidelines mentioned above advise to conduct assessment of cardiac function before undergoing HSCT. One of the most used and currently available imaging methods is echocardiography, which is recommended for evaluation of left ventricular ejection fraction (LV EF). Two-dimensional echocardiography is the first-choice method for detecting cardiotoxic effects, as it is easily accessible, non-invasive, and does not cause adverse effects. When LV EF is >50%, it is considered to be safe to perform HSCT [10]. Further, it is advisable that patients, depending on the risk after HSCT procedures, should undergo a comprehensive clinical and echocardiographic evaluation [8]. In instances where the left ventricular ejection fraction is registered below 40%, it is recommended to start cardioprotective modalities and treatment of heart failure and aim for a therapeutic regimen that minimizes cardiotoxicity. More importantly, when LVEF is >50%, but it is reduced by more than 10% after the therapy starts, alteration of treatment of the main disease or cardioprotective medication should be contemplated [11]. Systolic longitudinal function of the right ventricle (RV) can also be evaluated with the help of echocardiography. The parameter is named S' and evaluated by tissue Doppler to measure the longitudinal velocity of the tricuspid annulus. S' has good correlations to radionuclide angiography- and cardiovascular magnetic resonance-determined RV ejection fraction [12].

To our knowledge there is not much published data on the cardiovascular impact of different parts of the HSCT process, in particular, mobilization. In this paper, we aimed to evaluate the impact of the mobilization procedure of autologous HSCT on left and right ventricle sizes and function.

2. Materials and Methods

The study was performed prospectively from October 2021 till September 2023 in the Hospital of the Lithuanian University of Health Sciences Kaunas Clinics. The data of 47 patients undergoing autologous HSCT at the Department of Oncology and Hematology

were analyzed. Bioethics approvement for the prospective study was obtained (No. BE-2-96). All patients gave their informed consent to take part in the study.

Inclusion criteria were

- Written consent to participate in the study;
- Patients over the age of 18 years scheduled for autologous HSCT for various reasons.

The only exclusion criterion was a patient's refusal to participate at any time of the study.

Patients underwent autologous transplantation for various reasons. The most common disease was multiple myeloma, following with mantle cell lymphoma, Hodgkin's lymphoma, diffuse large B cell lymphoma, anaplastic large cell lymphoma, peripheral T cell lymphoma, and Ewing sarcoma. All patients underwent HSC mobilization with chemotherapy and filgrastim 10 μg/kg/d. Multiple myeloma patients had cyclophosphamide 3000 mg/m^2; mantle cell lymphoma patients had rituximab 375 mg/m^2 and cytarabine 4 g/m^2; Hodgkin's lymphoma patients had cisplatin 30 mg/m^2 and cytarabine 3.5 g/m^2; primary central nervous system (PCNS) diffuse large B cell lymphoma patients had cytarabine and thiotepa at different doses and rituximab 375 mg/m^2; anaplastic large cell lymphoma and peripheral T cell lymphoma patients had a cisplatin-based salvage regimen; and Ewing sarcoma patients followed an IE scheme (ifosfamide with etoposide). All patients underwent apheresis procedures. Peripheral blood stem cells were collected from peripheral blood via an apheresis procedure with a Fresenius Kabi COM.TEC apheresis system. The cells were cryopreserved in a solution of 10% DMSO and autologous plasma. The cryopreservation was performed in a controlled-rate freezer with liquid nitrogen (Consarctic equipment).

During the study period, echocardiography was performed at three time points: first, on evaluation and decision to enroll the patient in the transplantation process (before the mobilization procedure); second, before the transplantation (the conditioning regimen) procedure; and third, at follow-up—12 months after HSCT. In this part of the study, we aimed to evaluate only the impact of mobilization procedure on the heart, so only the measurements of the first two echocardiography examinations were taken into account. The echocardiographic workflow is presented in Figure 1. The data of 47 patients were analyzed. Echocardiography was performed and evaluated by one experienced cardiologist using a Phillips Epiq 7 ultrasound machine. The typical timeframe between the two echocardiography scans was a median (min–max) of 49 (20–168) days. The left ventricular end diastolic diameter (LVEDD) from the parasternal long axis view was measured, and the LVEDD index according to body surface area (BSA) (LVEDDi) was calculated. Left ventricular ejection fraction (LV EF) was calculated from the apical two- and four-chamber views based on left ventricular (LV) volumes, using the modified biplane Simpson method. Volumetric measurements were derived from tracings of the border between the myocardium and LV cavity in the end-systole and end-diastole in the apical two- and four- chamber views. Global LV systolic function was assessed by calculating the difference between the end-diastolic and end-systolic value, divided by the end-diastolic value. Left ventricular global longitudinal strain (GLS) was calculated automatically using a postprocessing system. The endocardial borders were traced in the end-systolic frame of the 2D images from the 3 apical views (two-, three-, and four-chamber). Speckles were tracked frame by frame throughout the LV wall during the cardiac cycle. Segments that failed to track were manually adjusted by the operator. Diastolic LV dysfunction was evaluated using early mitral inflow velocity/mitral annular early diastolic velocity (E/E') in the apical four-chamber view using pulse and tissue doppler. Right ventricle (RV) end diastolic diameter (RVEDD) was measured at the base from the apical four-chamber view, and tricuspid annular systolic velocity (S') was also evaluated from the apical four-chamber view using tissue doppler. The measurements were collected before and after the mobilization process (before the conditioning regimen) and compared.

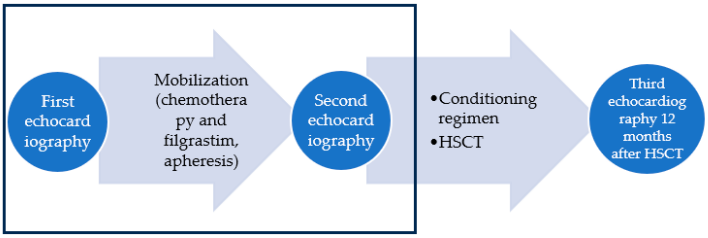

Figure 1. Echocardiography workflow of the study. Rectangular area shows the part of the data analyzed in the article.

Sub-analysis of the data of multiple myeloma patients was performed. The group was homogenous in the means of chemotherapy treatment—all patients received cyclophosphamide 3000 mg/m^2 for mobilization.

Patients filled out a survey regarding cardiovascular risk factors (arterial hypertension, smoking, cardiovascular family history, dyslipidaemia, diabetes mellitus). Information about coronary artery disease (CAD) and cardiovascular medication was obtained during the interview and double-checked from medical records. Arterial hypertension was evaluated and graded according to the European Society of Cardiology and European Society of Hypertension guidelines published in 2018. Arterial hypertension was diagnosed if systolic ABP was $\geq$140 mmHg and/or diastolic was $\geq$90 mmHg [13]. Cardiovascular family history was defined as cardiovascular event (stroke, myocardial infarction, revascularization procedures) or cardiovascular death in the first-degree relatives (men $\leq$ 55 year old, women $\leq$ 65 year old).

SPSS statistics 20 was used for statistical analysis. Qualitative data are presented as absolute values (N) and percentages (%), and quantitative parameters are given as average $\pm$ standard deviation or median. We used Student's *t*-test, ANOVA, the Mann–Whitney U test, or the Kruskal–Wallis H test to compare quantitative parameters. Chi-square or Fisher's exact test, as appropriate, was utilized to evaluate categorical variables between groups. The odds ratio (OR) and 95% confidence interval (CI) were used as a measure of the strength of association between cardiovascular risk factors and final RV S' decrease (<10 cm/s). Association analyses were conducted using univariate logistic regression, followed by multivariate regression. Statistically significant difference was considered when $p < 0.05$.

3. Results

Out of 47 patients, there were 27 males (57.4%) and 20 females (42.6%). Median age was 61 (ranging from 18 to 74). A total of 35 (74.5%) patients had multiple myeloma, 4 (8.5%) had mantle cell lymphoma, 3 (6.4%) had Hodgkin's lymphoma, 2 (4.3%) had PCNS diffuse large B cell lymphoma, 1 (2.1%) had anaplastic large cell lymphoma, 1 (2.1%) had peripheral T cell lymphoma, and 1 (2.1%) had Ewing sarcoma. The values are presented in Table 1.

No patients had clinically relevant signs or symptoms of cardiotoxicity—heart failure, arrhythmias, pericardial effusion, new onset or worsening of arterial hypertension, or acute ischemic syndromes.

Statistically significant difference was observed in the change of RV function (S')—it slightly decreased. Mean RV S' before mobilization was 13.93 $\pm$ 2.85 cm/s and after mobilization 12.19 $\pm$ 2.64 cm/s (p = 0.003). Six patients had a decrease of S' to less than 10 cm/s—a clinically significant loss of RV function (12.8%). Three patients were from the multiple myeloma group and had at least three cardiovascular risk factors. The other three patients had other diseases: one had mantle cell lymphoma, another had Hodgkin's lymphoma, and the other had diffuse large B cell lymphoma. These patients received

either rituximab and cytarabine or cisplatin and cytarabine. Only one of them had no risk factors; the others had two (arterial hypertension and dyslipidaemia) and three (arterial hypertension, diabetes mellitus, and dyslipidaemia). A significant reduction of RV systolic function was observed in 8.6% of patients in the multiple myeloma group and 25% in the other diseases group.

No statistically significant change in LV volumes and systolic and diastolic function and RV size was observed. The values are presented in Table 2.

Table 1. Characteristics of the patients.

Sex	
Male, n (%)	27 (57.4)
Female, n (%)	20 (42.6)
Age, years (median (min–max))	61 (18–74)
Main disease	
Multiple Myeloma, n (%)	35 (74.5)
Mantle cell lymphoma, n (%)	4 (8.5)
Hodgkin's lymphoma, n (%)	3 (6.4)
PCNS diffuse large B cell lymphoma, n (%)	2 (4.3)
Anaplastic large cell lymphoma, n (%)	1 (2.1)
Peripheral T cell lymphoma, n (%)	1 (2.1)
Ewing sarcoma, n (%)	1 (2.1)

PCNS: primary central nervous system.

Table 2. The change of echocardiographic parameters before and after the mobilization procedure.

Echocardiographic Values	Before Mobilization	After Mobilization	*p*
LVEDD, mm	46.48 ± 4.05	46.02 ± 5.25	0.633
LVEDDi, mm/m^2	24.85 ± 2.78	24.75 ± 2.93	0.863
LV EF, %	60.49 ± 7.66	59.74 ± 7.08	0.622
GLS, %	−17.45 ± 3.62	−17.59 ± 3.65	0.309
E/E'	6.58 ± 3.28	6.91 ± 2.65	0.973
RVEDD, mm	36.02 ± 3.83	34.96 ± 4.44	0.217
S', cm/s	13.93 ± 2.85	12.19 ± 2.64	0.003

LVEDD: Left ventricular end diastolic diameter; LVEDDi: LVEDD index according to body surface area (BSA); LV EF: left ventricular ejection fraction; GLS: left ventricular global longitudinal strain; E/E': early mitral inflow velocity/mitral annular early diastolic velocity; RVEDD: right ventricle end-diastolic diameter; S': tricuspid annular systolic velocity.

Analysis of correlation of cardiovascular risk factors and clinically relevant reduction of S' to less than 10 cm/s after mobilization was performed. No statistically significant impact of cardiovascular risk factors was noticed, probably because there were only six patients with clinically significant reduction of S'. The distribution of risk factors among the patients with and without clinically significant S' reduction is presented in Table 3. The results of the univariate logistic regression analysis are presented in Table 4. We could not find a statistically significant impact of cardiovascular risk factors, but the odds ratio shows a tendency for risk increase with CAD, arterial hypertension, and family history of CAD.

The patients with different cardiovascular risk factors used medication that is considered to be cardioprotective. A total of 17 patients (36.2%) used beta-blockers, 7 patients (14.9%) used angiotensin converting enzyme inhibitors (ACEis), 6 patients (12.8%) used angiotensin receptor blockers (ARBs), and 3 patients (6.4%) used statins.

In the clinically significant S' reduction group, three patients were using beta-blockers (50% of all patients with significant S' reduction), two patients were using ACEis (33.3%), one was using ARBs (16.7%), and one patient was using statins (16.7%). No statistically significant difference showing cardioprotective properties was observed.

Table 3. Cardiovascular risk factors among all the patients and risk factors' distribution among the patients with and without clinically significant S' reduction after the mobilization procedure.

Cardiovascular Risk Factors	N of Risk Factors among All Patients (%)	Patients with S' after Mobilization ≥ 10 (n (%))	Patients with S' after Mobilization < 10 (n (%))	*p*
Coronary artery disease (CAD) [1]	4 (8.5)	3 (75.0)	1 (25.0)	0.432
Arterial hypertension	23 (48.9)	19 (82.6)	4 (17.4)	0.416
Diabetes mellitus	6 (12.8)	5 (83.3)	1 (16.7)	1.000
Family history of CAD	10 (21.3)	8 (80.0)	2 (20.0)	0.594
Dyslipidaemia	41 (87.2)	36 (87.8)	5 (12.2)	1.000
Smoking	0 (0)	0 (0)	0 (0)	
Previous smoking	7 (14.9)	6 (85.7)	1 (14.3)	1.000

[1] Previous myocardial infarction or elective stenting.

Table 4. Univariate logistic regression analysis showing measure of the strength of association between cardiovascular risk factors and final RV S' decrease (<10 cm/s).

Cardiovascular Risk Factors	Odds Ratio	95% Confidence Interval	*p*
Coronary artery disease (CAD)	2.533	0.219–29.290	0.457
Arterial hypertension	2.316	0.381–14.079	0.362
Diabetes mellitus	1.440	0.138–14.978	0.760
Family history of CAD	2.062	0.320–13.313	0.447
Dyslipidaemia	0.694	0.067–7.223	0.760
Previous smoking	1.167	0.115–11.814	0.896

Sub-Analysis of Patients with Cyclophosphamide-Based Chemotherapy

The data of 35 patients in the multiple myeloma group receiving cyclophosphamide for mobilization were analyzed separately. All values are presented in Table 5. The results were similar. A statistically significant difference was observed in the change of RV systolic longitudinal function (S') as well. Mean RV S' before mobilization was 13.89 ± 3.12 cm/s, and after mobilization it was 12.20 ± 2.68 cm/s ($p = 0.018$).

Table 5. The change of echocardiographic parameters before and after the mobilization procedure in multiple myeloma subgroup patients treated with cyclophosphamide.

Echocardiographic Values	Before Mobilization	After Mobilization	*p*
LVEDD, mm	45.87 ± 3.91	45.08 ± 5.14	0.469
LVEDDi, mm/m^2	24.49 ± 2.76	24.29 ± 2.90	0.768
LV EF, %	61.67 ± 6.82	60.40 ± 7.09	0.449
GLS, %	−17.87 ± 3.89	−18.00 ± 3.59	0.886
E/E'	7.39 ± 3.29	7.05 ± 2.77	0.634
RVEDD, mm	36.26 ± 3.97	35.14 ± 4.74	0.290
S', cm/s	13.89 ± 3.12	12.20 ± 2.68	0.018

LVEDD: Left ventricular end diastolic diameter; LVEDDi: LVEDD index according to body surface area (BSA); LV EF: left ventricular ejection fraction; GLS: left ventricular global longitudinal strain; E/E': early mitral inflow velocity/mitral annular early diastolic velocity; RVEDD: right ventricle end diastolic diameter; S': tricuspid annular systolic velocity.

In addition, in this subgroup, no statistically significant change in LV volumes, systolic and diastolic function, and RV size was observed.

Three patients had a clinically significant reduction of S' to less than 10 cm/s after mobilization. Due to the very small number of patients, only univariate logistic regression analysis was performed, which did not reveal a statistically significant impact of cardiovascular risk factors.

4. Discussion

In this study, we aimed to describe the impact of mobilization procedures in autologous HSCT patients on early cardiovascular toxicity. No clinically relevant signs or symptoms of cardiotoxicity—heart failure, arrhythmias, pericardial effusion, new onset or worsening of arterial hypertension, or acute ischemic syndromes—were observed in all 47 patients. To our knowledge, there are no published data evaluating echocardiographic LV and RV changes during mobilization procedures. We aimed to determine whether there is any significant subclinical impact of the mobilization procedure on the right and left ventricles, not taking into account the difference in the main disease, mobilization chemotherapy regimen, previous cardiotoxic chemotherapy, or cardiovascular risk factors. There is a lot of evidence in the literature that subclinical cardiotoxicity should be evaluated; this helps to find cardiotoxicity in the early phase and avoid further damage, improve outcomes, and reduce the progression of heart failure and other cardiac complications [14–21]. Our results show that there was a statistically significant difference in right ventricular function—there was a slight decrease of S' after the mobilization. We found that 12.8% had a significant reduction in RV systolic function—S' decreased to less than 10 cm/s. No statistically significant change in RV size, LV size, and systolic and diastolic function was observed.

S' is an echocardiographic parameter used for the evaluation of longitudinal RV function. It is evaluated by tissue Doppler to measure the longitudinal velocity of the tricuspid annulus. A number of validation studies have shown good correlations to radionuclide angiography- and cardiovascular magnetic resonance-determined RV ejection fraction [12]. Recent data increasingly indicate that both LV and RV function contribute to clinical heart failure. Functional capacity, quality of life, and overall clinical outcomes are worsened among patients with heart failure when there is evidence of RV dysfunction [22]. Also, RV function is one of the determinants for survival in heart failure, irrespective of the underlying etiology; therefore, it is an important parameter [23]. RV systolic function is affected in shorter periods of time than the left ventricle [24]. Therefore, patients with a clinically significant decrease of RV function should undergo closer follow-up in the further treatment course and start cardioprotective treatment when needed.

Bearing in mind that different chemotherapy regimens might have a different impact on subclinical changes in ventricle size and function, we performed a sub-analysis of the multiple myeloma patient group. All 35 patients had the same chemotherapy regimen—cyclophosphamide 3000 mg/m^2. RV function in the multiple myeloma subgroup also changed statistically significantly—S' slightly decreased. We obtained the same results in the change of RV size, LV size, and systolic and diastolic function—no statistically significant change was observed.

Similar results were noticed by Tekiner et al. [25]. The difference from our study was that they evaluated the whole HSCT process, not only mobilization. They also included patients who had undergone allogeneic HSCT. The study examined 137 patients undergoing autologous and allogeneic HSCT. Echocardiography was performed on the day before and 30 days after HSCT. Changes in S' velocity and TAPSE (tricuspid annular plane systolic excursion) also showed a statistically significant decrease, whereas RV and LV sizes and LV EF remained unchanged. This prompts that RV function seems to be affected earlier than LV and can be used to assess early cardiotoxicity in HSCT recipients. Another study supporting this theory and evaluating the effects of cancer chemotherapy showed that RV systolic and diastolic functions were affected in a rather short period of time and earlier than the left ventricle [24].

From all six patients that had a reduction of S' to less than 10 cm/s, half of the patients (three) were from multiple myeloma group and had at least three cardiovascular risk factors. The other three patients had other diseases: one had mantle cell lymphoma, another—Hodgkin's lymphoma, and the other—diffuse large B cell lymphoma. These patients received either rituximab and cytarabine or cisplatin and cytarabine. Only one of them had no risk factors; the others had two (arterial hypertension and dyslipidaemia) and three (arterial hypertension, diabetes mellitus, and dyslipidaemia). The difference of

significant reduction in these groups was 8.6% in the myeloma group and 25% in the other diseases group. Although, neither univariate logistic regression nor multivariate regression showed a statistically significant impact of cardiovascular risk factors on RV function, odds ratio showed a tendency toward risk increase with CAD, arterial hypertension, and family history of CAD. These results lead us to believe that multiple risk factors might have an impact on the clinically significant reduction of RV function, but a bigger sample is needed to prove this hypothesis. Also, other chemotherapy regimens used for mobilization and previous treatment might have more impact on right ventricular function than cyclophosphamide and multiple myeloma induction treatment, but further investigation of more cases is needed.

The patients with different cardiovascular risk factors have used medication groups having cardioprotective properties for cardiovascular risk factor correction purposes. These include beta-blockers, ACEis, ARBs, and statins. Our study did not show positive effects on clinically significant reduction of RV systolic function. This should be further investigated with a bigger sample.

According to the literature, cyclophosphamide carries a cardiotoxic risk, especially when used in high doses [26–28]. It is an alkylating agent that has both immunosuppressive properties and antineoplastic activity. Therefore, it is used in mobilization regimens, and high-dose cyclophosphamide also has an important role in many conditioning regimens for HSCT [29]. Also, administration of post-transplant high doses of cyclophosphamide in haplo-identical transplant has shown results in preventing graft-versus-host disease [30]. Different types of manifestation and severity of cardiotoxicity have been reported, ranging from pericarditis and arrhythmias to hemorrhagic myocarditis and congestive heart failure [26,28]. Cardiotoxicity is usually observed only after administration of high doses; therefore, dose limitation is very important [31]. The pathophysiology of high-dose cyclophosphamide-associated cardiac toxicity was analyzed in postmortem examinations and is thought to depend on toxic endothelial damage followed by extravasation of toxic metabolites, which results in myocyte damage and interstitial hemorrhage and edema [27].

A study conducted by Poreba et al. [32] showed that administration of cyclophosphamide represented independent risk factors for worsening of left ventricular systolic function. In our study, a significant direct impact was noticed on subclinical RV function decrease, but not on LV function. Echocardiography was performed very early, after the mobilization procedure and before starting the conditioning, and this could also support the hypothesis that RV function is an earlier marker of cardiotoxicity than LV function.

The other agent used for mobilization together with chemotherapy was filgrastim—granulocyte colony stimulating factor (GCSF). There are no available data in the literature about GCSF's cardiotoxicity. On the contrary, there are a few experimental studies prompting that GCSFs can have regenerative properties for cardiomyocytes. Tomita et al. investigated mice with doxorubicin-induced cardiomyopathy. Their study showed that bone marrow could be one of the sources of regenerated cardiomyocytes in the doxorubicin-induced cardiomyopathic heart. Early administration of GCSF enhanced the migration of bone marrow stem cells into the heart and attenuated doxorubicin-induced cardiotoxicity [33]. Another study tested rats with diabetic cardiomyopathy and found out that GCSF can ameliorate cardiac diastolic dysfunction and morphological damage, leading to fibrosis of the myocardium [34]. There are data that GCSF could reduce carbon monoxide (CO)-induced cardiac ischemia in patients with acute CO poisoning [35]. Moreover, Haybar et al. stated that GCSF can play a role, offering protective chemokines during chemotherapy treatment [36]. These studies show that GCSF might have some cardioprotective properties, but most of them are experimental or very minor and need further investigation.

Limitations

The main limitation of the study is a relatively small sample. Therefore, the factors influencing clinically significant reduction of RV function could not be defined. Further

investigation with a bigger number of patients is needed. The nonhomogeneous group of patients regarding main disease and previous treatment could also be a limitation.

5. Conclusions

Mobilization procedure in patients undergoing autologous HSCT are associated with reduced RV systolic function. S' could be used as a reliable tool to detect early cardiotoxicity in HSCT patients and guide further follow-up.

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T1 Mapping in Cardiovascular Magnetic Resonance—A Marker of Diffuse Myocardial Fibrosis in Patients Undergoing Hematopoietic Stem Cell Transplantation

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Abstract: Introduction: Hematopoietic stem cell transplantation (HSCT) recipients are at increased risk of cardiovascular diseases. In our study, we aimed to find subclinical changes in myocardial tissue after HSCT with the help of cardiovascular magnetic resonance (CMR) tissue imaging techniques. **Methods:** The data of 44 patients undergoing autologous and allogeneic HSCT in the Hospital of Lithuanian University of Health Sciences Kaunas Clinics from October 2021 to February 2023 were analyzed. Bioethics approval for the prospective study was obtained (No BE-2-96). CMR was performed two times: before enrolling for the HSCT procedure (before starting mobilization chemotherapy for autologous HSCT and before starting the conditioning regimen for allogeneic HSCT) and 12 ± 1 months after HSCT. LV end-diastolic volume, LV end-systolic volume, LV mass and values indexed to body surface area (BSA), and LV ejection fraction were calculated. T1 and T2 mapping values were measured. **Results:** There was a statistically significant change in T1 mapping values. Before HSCT, mean T1 mapping was 1226.13 ± 39.74 ms, and after HSCT, it was 1248.70 ± 41.07 ms (p = 0.01). The other parameters did not differ significantly. **Conclusions:** Increases in T1 mapping values following HSCT can show the progress of diffuse myocardial fibrosis and may reflect subclinical injury. T2 mapping values remain the same and do not show edema and active inflammation processes at 12 months after HSCT.

Keywords: hematopoietic stem cell transplantation; cardiotoxicity; cardiovascular magnetic resonance; T1 mapping; cardio-oncology

1. Introduction

Hematopoietic stem cell transplantation (HSCT) can be a potentially curative procedure for various malignant hematologic diseases and some solid tumors, where high dose chemotherapy is used for treatment [1,2]. HSCT survival has significantly improved

over the last few decades [3]. Although HSCT is quite often followed by short- or long-term complications, improvements in transplantation techniques and supportive strategies have markedly decreased treatment-related mortality, and therefore, the number of HSCT survivors is expected to exceed half a million by 2030 [4].

The main characteristics of hematopoietic stem cells (HSC) are their capacity to self-renew and multipotency—the ability to generate all mature hematopoietic cell types by inducing a proliferation and differentiation program driven by the expression of sets of transcription factors. Because of these properties, multilineage hematopoiesis can be maintained throughout the whole life of an individual. HSC with properties of long-term hematopoietic reconstitution can be identified from bone marrow or chemotherapy and/or granulocyte colony-stimulating factors (G-CSF) mobilized peripheral blood or umbilical cord blood [5–7]. HSCs can be used for therapeutic purposes: the transplantation of autologous or allogeneic HSCs for the reconstitution of hematopoiesis in patients after intensive chemo- or radiotherapy when treating malignant disease; allogeneic HSCs in patients with the failure of bone marrow; or gene therapy via inserting normal gene copies into genetically defective stem cells, which could then be transplanted [8–10].

HSCT is a multi-step procedure that includes the collection of hematopoietic stem cells, the treatment of the patient's main disease with a conditioning regimen followed by the infusion of HSCs, and the subsequent evolvement of a new hematopoietic and immune system [11]. Two fundamentally different types of HSCT are characterized by the source of stem cells: autologous hematopoietic stem cell transplantation, where the stem cells are collected from the recipient him/herself during mobilization procedure and are later reinfused, and allogeneic hematopoietic stem cell transplantation, where the cells are taken from a different person (donor), who can be related or unrelated to the patient [11,12]. The major benefit of autologous HSCT is achieved by the effects of the conditioning treatment. The infusion of hematopoietic stem cells allows the delivery of toxic therapies for the treatment of main disease, which would otherwise result in prolonged myelosuppression and a high risk of complications, including fatal outcomes [13]. Allogeneic HSCT can cure certain hematologic malignancies through several mechanisms: high doses of chemotherapy and radiation that a patient receives before the infusion of the HSC graft (conditioning or preparatory regimen) and the immunity-mediated graft versus disease (GVD) reaction [14].

However, HSCT is associated with some serious complications, starting with different grade infections and sepsis. A specific and most limiting complication for allogeneic HSCT is graft versus host disease (GvHD), an immune rejection to host tissues mediated by donor lymphocytes which results in a skin rash, diarrhea, and liver disease. This condition can become chronic and produce a systemic sclerosis-like illness [12]. Allogeneic hematopoietic stem cell transplant-related mortality can be as high as over 30% at 1 year post-transplant [15]. Organ dysfunctions (cardiac, pulmonary, endocrine, and musculoskeletal), infertility, and secondary cancers are significantly more prevalent among allogeneic hematopoietic stem cell transplantation survivors than the general population [12]. Moreover, there is a growing awareness of the negative effects of HSCT-related therapies on the cardiovascular system, and HSCT recipients are at increased risk of cardiovascular disease later in life. Studies state that cardiovascular disease risk is at least fourfold higher than in general population [16,17]. According to the literature, among all complications related to HSCT, cardiovascular complications account for around 10–16.84% for both allogeneic and autologous transplantation, but they decrease the quality of life for long-term survivors and lead to a high mortality rate [18,19]. The most common complications are arrhythmias (mainly atrial fibrillation, atrial flutter, and supraventricular tachycardia), congestive heart failure, pericardial effusion including cardiac tamponade, ischemic heart disease, and rarely ventricular arrhythmias. Long-term complications can be crucial for patient survival [17,20,21].

According to the recently published guidelines of cardio-oncology developed by the European Society of Cardiology (ESC), together the European Hematology Association

(EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO), and the International Cardio-Oncology Society (IC-OS), cardiotoxicity risk can be classified according to cardiovascular risk factors, pre-existing cardiovascular morbidities, previous cardiotoxic anticancer treatment effects, and the type of HSCT: allogeneic versus autologous [11,22].

Cardiac adverse events can be related to different components of HSCT such as ablative therapy, including total body radiation combined with a multi-drug conditioning regimen. Most drugs used for mobilization or conditioning, including cyclophosphamide, cytarabine, carmustine, and melphalan, are associated with significant toxicity. Additionally, effects attributed to dimethylsulfoxide used to preserve stem cells are also thought to contribute to cardiac events. Moreover, monoclonal antibodies and other targeted therapies used before and after HSCT are also associated with many cardiac side effects. Cardiac complications may also arise as consequences of other HSCT-related comorbidities such as graft versus host disease, sepsis, thrombotic microangiopathy, or hepatic veno-occlusive disease [23].

What is more, not only can clinically obvious cardiovascular complications occur but subclinical damage may also be noticed even more often, and the exact frequency is not known. Subclinical damage can be related to clinical cardiovascular diseases later in life, so it is important to detect early changes in order to prevent subsequent complications. Pre-transplant or HSCT-related cardiotoxic treatment and the HSCT-related comorbidities mentioned above can cause myocyte cell death with reactive interstitial fibrosis [24,25]. Myocardial diffuse fibrosis is considered to reflect subclinical disease before cardiac dysfunction manifests in different types of cardiomyopathies [26].

There are numerous studies trying to identify different imaging markers which could indicate subclinical changes in the myocardium [27,28]. This would support the detection of high-risk groups of patients for closer monitoring or preventive treatment [16]. Cardiovascular magnetic resonance (CMR) is a non-invasive comprehensive imaging modality that provides not only precise anatomical information but also tissue characteristics and cardiometabolic assessment, which leads to its increased use in the early identification of cardiotoxicity [29]. CMR has the ability to depict changes at the tissue level, which could be a reflection of physiology and pathophysiology, in addition to data regarding left ventricular (LV) function (ejection fraction (EF), strain), volume, and mass [30]. Myocardial tissue characterization techniques, including gadolinium enhancement sequences and mapping techniques, enable the detection of myocardial edema, inflammation, and fibrosis [29]. There are numerous studies where CMR was analyzed for the comprehensive evaluation of the subclinical changes in the cardiovascular system after HSCT [16,29].

T1 and T2 mapping are parametric quantitative sequences which provide tissue-specific T1 and T2 values. No contrast agent is needed to obtain these sequences. The comparison of quantified myocardial tissue parameters can be performed. Representative myocardial pathologies leading to T1 changes involves mainly diffuse myocardial fibrosis, and T1 prolongation can also be observed in the presence of edema; inflammation; infiltrative diseases, such as amyloidosis; and Fabry disease. T2 relaxation time is also used to distinguish between normal and abnormal myocardial tissues. The increase in the water content of myocardial tissues causes longer T2 relaxation times. Therefore, myocardial edema is the main pathology responsible for variation in T2 values [31].

In this study, we aimed to evaluate changes in LV volumes and function and to find subclinical changes in myocardial tissue after HSCT with the help of CMR tissue imaging techniques.

2. Materials and Methods

The study was performed prospectively. The data of 44 patients undergoing autologous and allogeneic HSCT at the Department of Oncology and Hematology in the Hospital of Lithuanian University of Health Sciences Kaunas Clinics were analyzed. The study period lasted from October 2021 to February 2023. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, and approval of bioethics for the

prospective study was obtained (No BE-2-96). All the patients have read and signed the informed consent form.

The inclusion criteria were as follows: (1) written consent to participate in the study and (2) patients over the age of 18 years who were scheduled for autologous or allogeneic HSCT for various reasons. Exclusion criteria were: (1) contraindications to CMR, for example non-MR conditional implants or claustrophobia, and (2) patient's refusal to participate at any time in the study.

CMR for each patient was performed and evaluated twice: before enrolling for HSCT procedure (for patients undergoing autologous HSCT—before starting mobilization chemotherapy; and for patients undergoing allogeneic HSCT—before starting the conditioning regimen) and 12 ± 1 months after HSCT. The aim was to evaluate the changes in LV volumes, mass, and function and the parametric T1 and T2 mapping.

Patients underwent autologous or allogeneic HSCT for various reasons. The distribution of diseases and the type of transplantation are described in detail in Table 1. Hematologic malignancies were treated according to the local institution treatment protocols based on international guidelines. Hematopoietic stem cell harvesting for autologous HSCT was performed with chemotherapy and granulocyte colony stimulating factors (G-CSF)—chemo-mobilization. Multiple myeloma patients were given cyclophosphamide at 3000 mg/m^2; mantle cell lymphoma patients were given rituximab at 375 mg/m^2 and cytarabine at 4 g/m^2; Hodgkin's lymphoma patients were given cisplatin at 30 mg/m^2 and cytarabine at 3.5 g/m^2; primary central nervous system (PCNS) diffuse large B cell lymphoma patients were given cytarabine and thiotepa at different doses and rituximab at 375 mg/m^2; a NK/T-cell lymphoma patient underwent the CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone) scheme; and an Ewing sarcoma patient underwent an IE scheme (ifosfamide with etoposide). All patients scheduled for autologous HSCT underwent apheresis procedures. Hematopoietic stem cells from peripheral blood were collected using Fresenius Kabi COM.TEC apheresis system. The cells were then cryopreserved in a solution of 10% DMSO and autologous plasma. Cryopreservation was performed in a controlled-rate freezer with liquid nitrogen (Consarctic equipment). Conditioning was performed as follows: multiple myeloma patients with melphalan 200 mg/m^2, lymphomas with BEAM (carmustine, etoposide, cytarabine, melphalan) protocol, primary central nervous system (PCNS) diffuse large B cell lymphoma—thiotepa and BCNU. Hematopoietic stem cells for patients undergoing allogeneic transplantation were isolated from donors via apheresis procedures. All donors were unrelated, with an HLA match of 10/10. CMV, ABO blood groups, and sex were the best available options chosen by local protocols for donor selection criteria. Peripheral stem cells were harvested by G-CSF stimulation and apheresis procedure for all patients. Grafts were used for a maximum 48 h after the apheresis, and no grafts were frozen. All patients undergoing allogeneic HSCT received reduced intensity conditioning (RIC) with fludarabine and busulfan.

All patients filled in a survey regarding cardiovascular risk factors (arterial hypertension, smoking, cardiovascular family history, dyslipidemia, and diabetes mellitus). Information regarding coronary artery disease (CAD) and cardiovascular medication was obtained during the interview and double-checked against medical records. Arterial hypertension was diagnosed, and the grade of arterial hypertension was established according to the European Society of Cardiology and European Society of Hypertension guidelines, published in 2018. Arterial hypertension was diagnosed if systolic arterial blood pressure was $\geq$140 mmHg and/or diastolic arterial blood pressure was $\geq$90 mmHg [32]. A family history of early coronary artery disease was defined as a cardiovascular event (stroke, myocardial infarction, revascularization procedures) or cardiovascular death in first-degree relatives (men $\leq$ 55 years old; women $\leq$ 65 years old).

Table 1. Characteristics of patients. HSCT: hematopoietic stem cell transplantation; PCNS: primary central nervous system; NK: natural killer.

Sex	
Male, *n* (%)	24 (54.5)
Female, *n* (%)	20 (45.5)
Age, years (median (minimum–maximum))	61 (18–74)
Autologous HSCT, n (%)	39 (88.6)
Main disease	
Multiple Myeloma, *n* (%)	27 (69.2)
PCNS diffuse large B cell lymphoma, *n* (%)	4 (10.3)
Mantle cell lymphoma, *n* (%)	4 (10.3)
Hodgkin's lymphoma, *n* (%)	2 (5.1)
NK/T-cell lymphoma, *n* (%)	1 (2.6)
Ewing sarcoma, *n* (%)	1 (2.6)
Allogeneic HSCT, *n* (%)	5 (11.4)
Main disease	
Acute myeloid leukemia, *n* (%)	4 (80.0)
Acute myelomonocytic leukemia, *n* (%)	1 (20.0)

2.1. CMR Acquisition and Analysis

All study participants underwent 3T CMR with an 18-channel cardiac coil (MAGNETOM Skyra, Siemens Healthcare, Erlangen, Germany). Standard electrocardiographic (ECG) triggered two-, three-, and four-chamber sequences, and short-axis cine-balanced steady-state free precession sequences were performed. The quantitative analysis of LV end-diastolic volume (LV EDV), LV end-systolic volume (LV ESV), LV mass, and all these values indexed to body surface area (BSA); also, LV EFs were analyzed and calculated using Medis Suite 3.2 (Leiden, The Netherlands). The LV endo- and epi-contours were outlined manually in cine short axis views in the end-diastolic and end-systolic phases, with the exclusion of the LV papillary muscles. Global LV systolic function was assessed by calculating the difference between the LV end-diastolic and end-systolic volumes, divided by the end-diastolic volume.

$$\text{LV EF} = (\text{LVEDV} - \text{LVESV})/\text{LVEDV}$$

T1 and T2 mapping sequences were obtained in end-diastole in short-axis orientation in three slices (basal, midventricular, and apical). For myocardial T1 mapping, MOLLI (modified Look-Locker inversion) recovery acquisition scheme with motion correction (MOCO) was applied. T2 mapping was performed using T2-prepared balanced steady-state free precession sequence. T1 and T2 relaxation times were analyzed using a dedicated Syngo.via postprocessing system. The interventricular septum was outlined in all three slices (basal, midventricular, and apical) and the averages of all three measurements were obtained. Baseline mapping values before the beginning of HSCT were compared to values acquired 12 months after HSCT. The methods of measurements are shown in Figures 1 and 2.

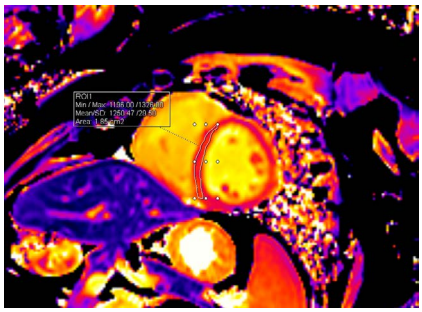

Figure 1. Measurement of T1 value in the midventricular slice.

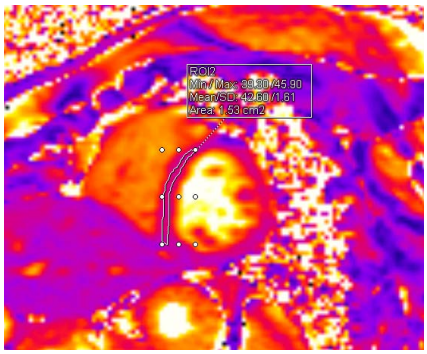

Figure 2. Measurement of T2 value in the midventricular slice.

2.2. Statistical Analysis

Statistical analysis was performed with the help of IBM SPSS Statistics 20.0. Qualitative data are presented as absolute values (N) and percentages (%). The normality of data distribution was evaluated with the Kolmogorov–Smirnov test, and quantitative parameters are given as average ± standard deviation or median (minimum–maximum). Variables were compared using Student's *t*-test. A statistically significant difference was considered when $p < 0.05$.

3. Results

The 44 patients comprised 24 men (54.5%) and 20 women (45.5%). The median age was 61 years, ranging from 18 to 74 years. Thirty-nine patients (88.6%) underwent autologous HSCT and five patients (11.4%) underwent allogeneic HSCT. HSCT was performed for various reasons. The main demographic characteristics of the patients and the main diseases for which HSCT was applied are listed in Table 1.

The distribution of different cardiovascular risk factors among patients is presented in Table 2. Four (9.1%) patients had coronary artery disease, fifteen (34.1%) patients had arterial hypertension, three (6.8%) patients had diabetes mellitus, eight (18.2%) patients had positive family history of early CAD, thirty-one (70.5%) patients had dyslipidemia, and zero (0%) patients were current smokers.

Table 2. Distribution of cardiovascular risk factors among the HSCT patients. CAD—coronary artery disease.

Cardiovascular Risk Factors	*n* (%)
CAD	4 (9.1)
Arterial hypertension	15 (34.1)
Diabetes mellitus	3 (6.8)
Family history of CAD	8 (18.2)
Dyslipidemia	31 (70.5)
Currently smoking	0 (0)

Patients with CAD and arterial hypertension tended to have a larger LV mass and LV mass index at the beginning of the study than patients without CAD and arterial hypertension. In CAD patients, LV mass before HSCT was 144.07 ± 29.45 g vs. 105.74 ± 26.31 g in patients with no CAD (p = 0.009). LV mass index was 67.54 ± 13.51 g/m^2 vs. 55.29 ± 10.46 g/m^2, respectively (p = 0.035). In patients with arterial hypertension LV mass before HSCT was 122.51 ± 32.05 g vs. 102.35 ± 24.30 g in patients with no arterial hypertension (p = 0.044). LV mass index was 60.64 ± 13.38 g/m^2 vs. 54.21 ±9.35 g/m^2, respectively (p = 0.041).

Two patients (4.5%) had clinical cardiovascular symptoms—the onset of supraventricular tachycardia during the 12-month observation period. No other clinically relevant signs or symptoms of cardiotoxicity—heart failure, pericardial effusion, new onset or worsening of arterial hypertension, or acute ischemic syndromes—were noticed.

There was a statistically significant change in T1 mapping value. Before HSCT, mean T1 mapping was 1223.13 ± 39.74 ms, and 12 months after HSCT, it was 1248.70 ± 41.07 ms (p = 0.010). No statistically significant change in T2 mapping values was noticed—T2 mapping mean value before HSCT was 38.91 ± 2.07 ms, and 12 months after HSCT, it was 38.53 ± 2.11 ms (p = 0.430). The change in T1 mapping was significant in all patients, independent of cardiovascular risk factors. The changes are listed in Table 3.

Table 3. Mean values of T1 mapping before and after HSCT in patients with cardiovascular risk factors. CAD—coronary artery disease.

Cardiovascular Risk Factor	Mean T1 Values before HSCT	Mean T1 Values after HSCT	No. of Patients
CAD	1212.54 ± 17.62	1235.27 ± 17.82	4
Arterial hypertension	1235.52 ± 42.24	1257.07 ± 50.14	15
Diabetes mellitus	1231.79 ± 11.35	1277.14 ± 47.68	3
Family history of CAD	1224.16 ± 34.53	1250.08 ± 43.54	8
Dyslipidemia	1227.49 ± 35.75	1245.69 ± 43.67	31

No statistically significant change in LV volumes, systolic function, or mass was observed. The mean LV EDV before HSCT was 142.45 ± 35.62 mL, and after HSCT, it was 145.29 ± 36.36 mL (p = 0.713). The mean indexed LV EDV before HSCT was 74.33 ± 15.23 mL/m^2 and after HSCT, it was 75.64 ± 15.10 mL/m^2 (p = 0.686). The mean LV ESV before HSCT was 60.82 ± 18.36 mL, and after HSCT, it was 60.15 ± 17.17 mL (p = 0.860), and the LV ESVi was 31.07 ± 8.36 mL/m^2 vs. 31.55 ± 8.61 mL/m^2, respectively (p = 0.791). The mean LV EF before HSCT was 58.10 ± 7.77%, and after HSCT, it was 58.58 ± 7.08% (p = 0.761). Th mean LV mass before HSCT was 109,22 ± 28,51 g, and after HSCT, it was 107.81 ± 29.44 g (p = 0.819), and the mean LV mass index was 56.40 ± 11.17 g/m^2 vs. 56.37 ± 12.92 g/m^2, respectively (p = 0.991). The changes are summarized in Table 4.

Table 4. The change in CMR parameters before and after HSCT. LV EDV—left ventricular end-diastolic diameter; LV EDVi—indexed left ventricular end-diastolic diameter; LV ESV—left ventricular end-systolic diameter; LV ESVi—indexed left ventricular end-systolic diameter; LV EF—left ventricular ejection fraction; LV—left ventricle.

CMR Values	Before HSCT (Mean ± SD)	After HSCT (Mean ± SD)	*p*
LV EDV, mL	142.45 ± 35.62	145.29 ± 36.36	0.713
LV EDVi, mL/m^2	74.33 ± 15.23	75.64 ± 15.10	0.686
LV ESV, mL	60.82 ± 18.36	60.15 ± 17.17	0.860
LV ESVi, mL/m^2	31.07 ± 8.36	31.55 ± 8.61	0.791
LV EF, %	58.10 ± 7.77	58.58 ± 7.08	0.761
LV mass, g	109.22 ± 28.51	107.81 ± 29.44	0.819
LV mass index, g/m^2	56.40 ± 11.17	56.37 ± 12.92	0.991
T1 mapping value, ms	1226.13 ± 39.74	1248.70 ± 41.07	**0.010**
T2 mapping value, ms	38.91 ± 2.14	38.53 ± 2.14	0.412

4. Discussion

In this prospective study, we aimed to evaluate subclinical changes in LV function, volumes, mass, and mainly in the myocardial tissue, with the help of CMR in a one-year period after HSCT, irrespective of the type of HSCT.

Our results showed no significant change in LV volumes, mass, systolic function, and T2 mapping, a marker of myocardial edema. T1 mapping had statistically significantly higher values in one year after HSCT. This could prompt an idea that the HSCT procedure is related to the increase in diffuse myocardial fibrosis.

T1 and T2 mapping techniques in cardiovascular magnetic resonance have been validated histologically in a study with rat models. Park et al. analyzed the myocardial injuries of rats that were injected with doxorubicin. T1 and T2 mapping and extracellular volume (ECV) values were calculated, and myocardial biopsy was performed. The study showed that T1 and T2 measures correlate to histopathologic changes that represent myocardial injury, in particular, the interstitial fibrosis, inflammation, and edema of myocardial biopsy with anthracycline-induced cardiotoxicity. T1 mapping and ECV showed the highest correlations with histopathologic changes [33].

In our study, LV EDV, LV EDVi, LV ESV, LV ESVi, and LV EF did not change statistically significantly in 12 months after HSCT. The results of our study are consistent with findings from other studies. Rotz and colleagues analyzed the echocardiographic parameters of 95 children and young adults. Echocardiography was performed before and 1–6 years after HSCT, and LV EF, as well as global longitudinal and global circumferential strains, were analyzed. The results of the study show that after HSCT, LV EF, as well as global longitudinal and global circumferential strains, remained unchanged from the baseline [34].

Despite the fact that LV EDV and EF did not change statistically significantly, our results show that T1 mapping values that could resemble the progress of a diffuse fibrosis increase. Changes in native T1 values in patients after HSCT compared to healthy individuals have also been revealed in several other studies. Paiman et al. analyzed the late effects of pediatric HSCT on LV function, aortic stiffness, and myocardial tissue characteristics. The study design was different—they analyzed 16 HSCT childhood survivors (14.8 ± 5 years after HSCT) and compared them to 16 healthy controls. They noticed a trend towards a lower LV EF in HSCT survivors compared to healthy controls, but the difference was not statistically significant (54 ± 6 vs. 58 ± 5%, $p = 0.055$). Native T1 (1211 ± 36 vs. 1227 ± 28 ms, $p = 0.158$) also tended to be higher in HSCT survivors than in healthy controls, but statistical significance was not reached. Moreover, the method of comparison was different—they compared the values to healthy controls and not to the baseline values. Also, the sample was very small [16].

There are more studies analyzing cardiotoxicity with the help of T1 mapping techniques. Most studies analyze anthracycline-induced cardiotoxicity. A study conducted by Jordan et al. concluded that the elevation in myocardial T1 mapping and ECV values

was noticed three years after anthracycline-based chemotherapy independently of the main underlying disease or cardiovascular comorbidities [35]. The other study analyzed changes in T1 mapping in childhood cancer survivors who received anthracycline-based chemotherapy and had normal systolic function. CMR evaluation was performed 2.5 to 26.9 years after anthracycline exposure. Pre-contrast T1 values were higher in childhood cancer survivors than in healthy controls, although the difference did not reach statistical significance [36].

In another study, T1 mapping and ECV were found to be early tissue markers of ventricular remodeling, representing diffuse fibrosis in children with normal LV EF post anthracycline therapy [37].

We did not identify a significant change in T2 mapping values. The increase in T2 mapping parameters resemble the features of edema. Our follow-up was conducted 12 months after the HSCT process, so active inflammation and edema in the myocardium were not expected at this time point.

The strength of our study is that it was performed prospectively. Therefore, we can compare baseline and follow-up values. The other studies mostly compared patients after HSCT or chemotherapy treatment to healthy controls. We did not notice any statistically significant impact of cardiovascular risk factors, main disease, and treatment regimens on T1 mapping, and the values increased in all patients. The biggest change was noticed in patients with diabetes mellitus (T mapping before HSCT was 1231.79 $\pm$ 11.35 ms, and it was 1277.14 $\pm$ 47.68 ms 12 months after HSCT) but the number of the patients was very small—only three patients. This could lead to a hypothesis that patients with diabetes mellitus tend to have more extensive diffuse myocardial fibrosis following HSCT, but further investigation and a bigger sample is needed.

Limitations

Due to the relatively small sample, the influence of different cardiovascular risk factors, main disease, and treatment regimens on diffuse myocardial fibrosis could not be defined. Further investigations with larger numbers of patients are needed.

5. Conclusions

Native T1 mapping values following HSCT increased compared to baseline values, which could resemble the progress of diffuse myocardial fibrosis and may reflect subclinical injury before clinical cardiovascular complications manifest. T2 mapping values remain the same and do not show edema or active inflammation processes at 12 months after HSCT.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Kaunas Regional Biomedical Research Ethics Committee of the Lithuanian University of Health Sciences (no. BE-2-96, 14 October 2021).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

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SUPPLEMENTS

No. 1

Kardiovaskulinės rizikos veiksnių anketa

1. Ar sergate kokia nors širdies liga? Jei taip, kokia?

   .....

2. Ar turite padidėjusį kraujospūdį (arterinė hipertenzija)
   Jei taip, kokius vaistus vartojate?

   .....

   .....

3. Ar dabar rūkote?
   Jei taip, kiek per dieną vidutiniškai surūkote cigarečių?

   .....

4. Ar anksčiau rūkėte?
   Jei taip, kiek metų rūkėte?

   .....
   Kiek metų neberūkote?

   .....

5. Ar sergate cukriniu diabetu?
   Jei taip, kiek metų?

   .....
   Kokius vaistus vartojate?

   .....

6. Ar jūsų šeimoje iš artimiausių giminaičių (tėvai, broliai seserys) buvo/yra sirgusių širdies ir kraujagyslių ligomis (miokardo infarktas, insultas)
   Jei taip, kokio amžiaus susirgo?

   .....

KAUNO REGIONINIS BIOMEDICININIŲ TYRIMŲ ETIKOS KOMITETAS

Lietuvos sveikatos mokslų universitetas, A. Mickevičiaus g. 9, LT 44307 Kaunas, tel. (+370) 37 32 68 89;el.paštas: kaunorbtek@lsmuni.lt

LEIDIMAS ATLIKTI BIOMEDICININĮ TYRIMĄ

2021-10-14 Nr. BE-2-96

Biomedicininio tyrimo pavadinimas: „Vaizdinių tyrimų vertė nustatant širdies pažaidą pacientams po kraujodaros kamieninų ląstelių transplantacijos“	
Protokolo Nr.:	**001**
Data:	**2021-09-17**
Versija:	**2.0**
Asmens informavimo forma:	**Versija: 01; data: 2021-05-17**
Pagrindinis tyrėjas:	**Prof. Gintarė Šakalytė**
Biomedicininio tyrimo vieta:	Lietuvos sveikatos mokslų universiteto ligoninė Kauno klinikos,
Įstaigos pavadinimas:	Kardiologijos klinika
Adresas:	Eivenių g. 2 LT-50161, Kaunas

Išvada:
Kauno regioninio biomedicininių tyrimų etikos komiteto posėdžio, įvykusio **2021 m. spalio mėn. 5 d.** (protokolo Nr. 2021-BE10-0012) sprendimu pritarta biomedicininio tyrimo vykdymui.

Mokslinio eksperimento vykdytojai įsipareigoja: (1) nedelsiant informuoti Kauno Regioninį biomedicininių Tyrimų Etikos komitetą apie visus nenumatytus atvejus, susijusius su studijos vykdymu, (2) iki sausio 15 dienos – pateikti metinį studijos vykdymo apibendrinimą bei, (3) per mėnesį po studijos užbaigimo, pateikti galutinį pranešimą apie eksperimentą.

Kauno regioninio biomedicininių tyrimų etikos komiteto nariai			
Nr.	Vardas, Pavardė	Veiklos sritis	Dalyvavo posėdyje
1.	Doc. dr. Gintautas Gumbrevičius	Klinikinė farmakologija	Taip
2.	Prof. dr. Kęstutis Petrikonis	Neurologija	Taip
3.	Dr. Saulius Raugelė	Chirurgija	Taip
4.	Dr. Lina Jankauskaitė	Pediatrija	Taip
5.	Prof. dr. Džilda Veličkienė	Endokrinologija	Ne
6.	Doc. dr. Eimantas Peičius	Visuomenės sveikata	Taip
7.	Aušra Degutytė	Visuomenės sveikata	Taip
8.	Dr. Žydrūnė Luneckaitė	Visuomenės sveikata	Taip
9.	Viktorija Bučinskaitė	Teisė	Taip

Kauno regioninis biomedicininių tyrimų etikos komitetas dirba vadovaudamasis etikos principais nustatytais biomedicininių tyrimų Etikos įstatyme, Helsinkio deklaracijoje, vaistų tyrinėjimo Geros klinikinės praktikos taisyklėmis.

Kauno RBTEK pirmininkas

Doc. dr. Gintautas Gumbrevičius

PATVIRTINTA
Lietuvos bioetikos komiteto
biomedicininių tyrimų ekspertų grupės
2016 m. lapkričio 15 d. sprendimu
PAKEISTA
Lietuvos bioetikos komiteto
biomedicininių tyrimų ekspertų grupės
2020 m. birželio 16 d. sprendimu

Informuoto asmens sutikimo forma, versija Nr. 02, data: 2021-09-17

INFORMUOTO ASMENS SUTIKIMO FORMA

Biomedicininio tyrimo pavadinimas: Vaizdinių tyrimų vertė nustatant širdies pažaidą pacientams po kraujodaros kamieninių ląstelių transplantacijos.

Protokolo Nr.: 001

Užsakovas: Lietuvos sveikatos mokslų universitetas
Adresas: A. Mickevičiaus g. 9, Kaunas 44307; Tel.: (+370 37) 327201.
El. paštas: komunikacija@lsmuni.lt

Užsakovo atstovas: prorektorė mokslui prof. habil. dr. V. Lesauskaitė

Atsakingas tyrėjas[1]: gydytoja kardiologė profesorė Gintarė Šakalytė, doktorantė gydytoja kardiologė Audronė Vaitiekienė, gydytojas hematologas doc. Rolandas Gerbutavičius, gydytojas hematologas dr. Domas Vaitiekus.

Tyrimo centro pavadinimas: Lietuvos sveikatos mokslų universiteto ligoninė Kauno klinikos Kardiologijos klinika ir Onkologijos ir hematologijos klinika

Adresas: : Eivenių g. 2, Kaunas; Tel.: (+370 37) 32 64 49.
El. paštas: kardiologijos.klinika@kaunoklinikos.lt

1. Kokia šio dokumento paskirtis?

Šioje formoje pateikiama Jums skirta informacija apie biomedicininį tyrimą, aptariamos tyrimo atlikimo priežastys, mokslinio tyrimo procedūros, nauda, rizika, galimi nepatogumai ir kita svarbi

[1] Atsakingas tyrėjas – tyrimo metu konkretų pacientą, pasirašantį Informuoto asmens sutikimo formą, prižiūrėsiantis tyrėjas.

informacija. Jei nuspręsite dalyvauti, prašysime Jūsų pasirašyti šią sutikimo formą, kuria sutinkate tyrimo metu vykdyti gydytojo tyrėjo ir tyrimo komandos nurodymus. Pasirašydami šį dokumentą, sutinkate dalyvauti moksliniame tyrime. Neskubėkite ir atidžiai perskaitykite šį dokumentą, jei nesupratote kokio nors žodžio ar teiginio, visus iškilusius klausimus būtinai užduokite tyrimo gydytojui ar kitiems tyrimo komandos nariams. Prieš priimdami sprendimą, galite pasitarti su šeimos nariais, draugais ar savo gydytoju.

2. Kodėl atliekami biomedicininiai/ klinikiniai vaistinio preparato tyrimai?

Svarbu suprasti, kad nors biomedicininio tyrimo metu Jums bus skiriami vaistiniai preparatai, atliekami sveikatos patikrinimai ar medicininės procedūros, biomedicininis tyrimas iš esmės skiriasi nuo įprastos (kasdienės) klinikinės praktikos. Įprastos (kasdienės) klinikinės praktikos tikslas yra Jus (t. y. konkretų asmenį, pacientą) išgydyti ir/ar pagerinti Jūsų sveikatos būklę. Pagrindinis biomedicininio (mokslinio) tyrimo tikslas – gauti naujų medicinos mokslo žinių, kurios ateityje padėtų kitų šia liga sergančių pacientų sveikatai. Kitaip tariant, pagrindinis šio tyrimo tikslas nėra tiesioginė nauda Jūsų sveikatai.

3.Kodėl atliekamas šis tyrimas?

Šio tyrimo tikslas – nustatyti ir įvertinti širdies magnetinio rezonanso tyrimo naudą vertinant širdies pokyčius po didelių dozių chemoterapijos taikant kraujodaros kamieninių ląstelių transplantaciją ir palyginti su standartiniu echokardiografijos tyrimu.

Kraujodaros kamieninių ląstelių transplantacija (KKLT) reikšmingai padidina pacientų išgyvenamumą daugelio piktybinių kraujo ligų atveju. Procedūra sudėtinga, galimos ankstyvosios ir vėlyvosios komplikacijos, tarp jų ir kardiovaskulinės: širdies nepakankamumas, perikarditas, aritmijos. Širdies pažaidos mechanizmas daugiaveiksmis: chemoterapijos toksiškumas, dimetilsulfoksido (konservantas) kardiotoksiškumas, sepsis, perkrova tūriu dėl gausios infuzoterapijos, trombotinė mikroangiopatija.

Literatūros duomenimis komplikacijų dažnis priklauso nuo daugybės faktorių – paciento amžiaus, gretutinių ligų, anksčiau skirtos kardiotoksinės chemoterapijos, KKLT tipo (autologinė ar alogeninė), kondicionavimo režimo (chemoterapija ir / arba spindulinės terapijos). Todėl kardiovaskulinės būklės įvertinimas prieš ir po KKLT tampa ypatingai svarbus. Literatūroje aprašomas reikšmingas širdies nepakankamumo žymenų padidėjimas po KKLT, taip pat elektrokardiogramos pokyčiai.

Širdies MRT išsiskiria unikaliomis galimybėmis vertinti miokardo audinio pokyčius, todėl galėtų būti reikšmingas vertinant ne tik klinikinę, bet ir besimptomę miokardo pažaidą. Tyrimuose, tiriančiuose kardiotoksinės chemoterapijos pažaidą, širdies MRT yra aprašomas kaip labai jautrus metodas. Tikimasi, kad nustačius širdies pažaidą po KKLT, bus galima užtikrinti paciento kardiovaskulinės

būklės intensyvesnį stebėjimą ir laiku skirti atitinkamą gydymą siekiant išvengti kliniškai reikšmingų komplikacijų

4. Kokie asmenys pasirenkami dalyvauti šiame tyrime?

Kviečiame Jus dalyvauti šiame tyrime, nes Jums planuojama atlikti kamieninių kraujodaros ląstelių transplantacija.

5. Kas atlieka/užsako šį biomedicininį / klinikinį vaistinio preparato tyrimą?

Šio biomedicininio tyrimo užsakovas yra Lietuvos sveikatos mokslų universitetas. Tyrimą atlieka: gyd. kardiologė profesorė Gintarė Šakalytė, gyd. kardiologė Audronė Vaitiekienė, gyd. hematologas doc. Rolandas Gerbutavičius, gyd. hematologas dr. Domas Vaitiekus.

6. Tikimybė patekti į skirtingas tiriamųjų grupes ir dalyvavimo šiose grupėse ypatybės.

Pacientai į grupes skirstomi nebus, visiems dalyviams bus taikomas vienodas ištyrimas. Jokio papildomo gydymo dėl šio tyrimo nebus skiriama (gydančio hematologo paskirtas optimalus medikamentinis gydymas nebus koreguojamas dėl įtraukimo į šį tyrimą).

7. Kiek truks Jūsų dalyvavimas šiame tyrime?

Bendra numatoma tyrimo trukmė – 3 metai. Jūs dalyvausite 12 mėn. - kai pasirašysite informuoto asmens sutikimo formą, turėsite apsilankyti pas gydytoją tyrėją dar 3 kartus, 2 kartus širdies magnetinio rezonanso tyrimo atlikimui ir vieną klinikinės būklės įvertinimui (bus atliekams po 12 mėn. įprastinio vizito pas gydytoją hematologą metu).

8. Kokiose šalyse bus vykdomas šis tyrimas?

Tyrimas bus atliekamas Lietuvoje.

9. Kiek tiriamųjų dalyvaus numatyta šiame tyrime?

Tikimasi, kad šiame biomedicininiame tyrime dalyvaus apie 100 žmonių.

10. Ką Jums reikės daryti?

Prašome leisti naudotis Jūsų medicininiais dokumentais (ligos istorija), kuriais remiantis bus renkami duomenys apie Jūsų širdies ir kraujagyslių sistemos būklę ir pagrindinę ligą.

Prieš pradedant gydymą (KKLT) prašysime užpildyti anketą, apie širdies ir kraujagyslių ligų rizikos veiksnius, Jums bus atliekama elektrokardiograma, slaugytoja iš venos paims kraujo tyrimams (Troponinas I, BNP, uždegiminio atsako baltymų tyrimai – iš viso 4 mėgintuvėliai kraujo – maždaug 4 valgomieji šaukštai), bus atliekama ramybės echokardiografija (įprastinis tyrimas atliekamas kiekvienam ligoniu prieš KKLT) ir širdies magnetinio rezonanso tyrimas (atskiras vizitas, trukmė iki 2 val). Šio tyrimo metu Jums teks ilgokai (apie 1val.) gulėti uždaroje patalpoje. Magnetinio širdies rezonanso tyrimo metu pacientas turi išgulėti nejudėdamas ant nugaros iki 1 val. laiko uždaroje patalpoje (specialiame magnetinio rezonanso aparate). Tyrimo metu naudojamas specialus

kontrastinis preparatas (pagrindinė sudedamoji medžiaga – gadolinis). Procedūros metu pro įvestą į veną kateterį radiologijos technologas arba bendros praktikos slaugytoja arba gydytojas radiologas specialiu injektoriumi sušvirkš reikiamą kiekį kontrastinės medžiagos. Po kraujodaros kamieninių ląstelių transplantacijos tyrimai bus kartojami praėjus 6-12 sav. (priklausomai nuo Jūsų būklės) – tie patys kaip prieš KKLT. Siekiant įvertinti subtilių miokardo pokyčių grįžtamumą, širdies MRT bus kartojamas praėjus 6 mėn. po transplantacijos (atskiras vizitas, trukmė iki 2 val.). Po 12 mėn. įprastinio vizito pas gydytoją hematologą metu Jūsų bus paklausta dėl klinikinių širdies pažaidos požymių.

11. Ar dalyvavimas biomedicininiame/ klinikiniame vaistinio preparato tyrime Jums bus naudingas? / Kokios naudos galite tikėtis dalyvaudami šiame tyrime?

Dalyvavimas tyrime tiesiogiai Jūsų sveikatos būklės nepakeis. Nustačius širdies pažaidą po KKLT, bus galima užtikrinti Jūsų kardiovaskulinės būklės intensyvesnį stebėjimą ir laiku skirti atitinkamą gydymą siekiant išvengti kliniškai reikšmingų komplikacijų. Tikimasi, jog tyrimo metu gauta informacija mokslininkams padės atrasti lengvai prieinamus tyrimo metodus, leidžiančius nustatyti ankstyvąją širdies pažaidą po KKLT bei sukurti naujus gydymo metodus, leidžiančius sumažinti komplikacijų riziką bei pagerinti artimosios bei tolimosios prognozės rodiklius.

12. Kokia su dalyvavimu šiame tyrime susijusi rizika ir nepatogumai?

Širdies magnetinio rezonanso tyrimas yra rutiniškai atliekamas klinikinėje praktikoje, todėl papildomos žalos Jums negali sukelti. Magnetinio rezonanso tyrimas nežalingas ir neturintis jonizuojančios spinduliuotės. Tyrimo metu gali jaustis įvairūs nepageidaujami pojūčiai, tokie kaip galvos skausmas, prakaitavimas, pykinimas, svaigulys, nuovargis, kurie praeina po tyrimo. Jūsų bus prašoma sulaikyti kvėpavimą. Tyrimo metu naudojamas specialus kontrastinis preparatas (gadolinis). Kontrastinės medžiagos švirkštimo metu galite jausti spaudimo ar diskomforto jausmą kateterio įvedimo vietoje, kartais karščio pojūtį. Apie 1 proc. atvejų gali pasitaikyti kontrastinės medžiagos ištekėjimas injekcijos vietoje, dėl to gali jaustis skausmas, atsirasti paraudimas, odos bėrimas, retai – skysčio sankaupa. Apie 1 proc. atvejų gali pasitaikyti alerginės reakcijos - bėrimai , pykinimas – vėmimas, svaigimas, sumišimas, dusulys, nemalonus jausmas krūtinėje, širdies plakimas, alerginis šokas. Šios komplikacijos dažniau pasitaiko pacientams, kuriems jau yra buvusios alerginės reakcijos į kontrastines medžiagas ar sergantiems alergine/nealergine astma. Ypač retais atvejais, gali įvykti embolija oru. Ypač retais atvejais, galima sisteminė nefrogeninė sklerozė. Tai dažniau pasitaiko pacientams, kuriems jau yra inkstų funkcijos sutrikimas. Dalyvaudami šiame tyrime galite patirti nepatogumų, tokių kaip sugaištas laikas vykstant į tyrimo vietą ar atliekant numatytus diagnostinius tyrimus. Remiantis Lietuvos Respublikos Sveikatos apsaugos ministro 2014-12-31 įsakymu planuojami atlikti tyrimai vertinami kaip nedidelį nepageidaujamą laikiną poveikį galinčios sukelti

procedūros. Jei dėl nenumatytų aplinkybių (force majore ar nenugalima jėga, trečiųjų asmenų nusikalstamos veikos ir pan.), kurios tyrėjui nėra žinomos ir kurioms įtakos tyrėjas negali daryti, konfidenciali informacija taptų prieinama tretiesiems asmenims, kuriems ją suteikti nebuvote davęs sutikimo, tyrėjas iš karto Jus apie tai informuos. Tačiau tyrėjas visais būdais stengsis užtikrinti, kad Jūsų asmens duomenys, tvarkomi šio biomedicininio tyrimo tikslu, nebūtų prieinami tretiesiems asmenims, kuriems jos suteikti nebuvote davęs sutikimo ir įgyvendins duomenų saugumo priemones, skirtas apsaugoti asmens duomenis nuo atsitiktinio ar neteisėto atskleidimo, taip pat nuo bet kokio kito neteisėto tvarkymo.

13. Jei atsitiktų kas nors negero? (Informacija apie draudimą)

Šio biomedicininio tyrimo metu bus papildomai taikomi tik nedidelį laikiną nepageidaujamą poveikį tiriamojo sveikatai sukelti galintys intervenciniai tyrimo metodai (periferinės venos punkcija ir kraujo paėmimas). Jei tyrimų metu reikšmingai keistųsi sveikatos būklė, nedelsiant būtų suteikiama adekvati reikalinga medicininė pagalba. Magnetinio rezonanso tyrimas nėra eksperimentinis. Šis tyrimas atliekamas daugeliui kitų pacientų, sergančių tokia liga kaip Jūsų, ir nedalyvaujantiems jokiuose tyrimuose, todėl biomedicininis tyrimas nėra apdraustas biomedicininio tyrimo užsakovų ir pagrindinių tyrėjų civilinės atsakomybės draudimu. Šio biomedicininio tyrimo metu bus taikomi tik neintervenciniai tyrimo metodai, kurie nekelia rizikos Jūsų sveikatai, todėl biomedicininis tyrimas nėra apdraustas biomedicininio tyrimo užsakovų ir pagrindinių tyrėjų civilinės atsakomybės draudimu.

14. Kokias pasirinkimo galimybes turėsite, jeigu nesutiksite dalyvauti šiame tyrime arba atšauksite sutikimą jame dalyvauti?

Tyrime dalyvaujate savanoriškai, todėl turite teisę atsisakyti, o pradėjęs galite bet kada iš jo pasitraukti. Jūsų sprendimas atsisakyti dalyvauti ar nutraukti dalyvavimą tyrime nedarys jokios įtakos teikiamai įprastinei sveikatos priežiūrai. Jei nuspręsite nedalyvauti šiame tyrime, gydytojas paskirs įprastą ligos gydymą, atsižvelgdamas į visas susijusias aplinkybes – Jūsų amžių, kitas ligas, bendrą sveikatos būklę ir kt.

15. Ar galėsite nutraukti dalyvavimą tyrime?

Jei nuspręsite pasitraukti iš tyrimo šiam nepasibaigus, tyrėjas pateiks ir paprašys parašyti laisvos formos atsisakymo prašymą.

Jūs turite teisę atsisakyti dalyvauti tyrime nenurodant priežasčių ir motyvų. Jūs gausite įprastinę sveikatos priežiūrą, jei Jūs atsisakysite dalyvauti biomedicininiame tyrime arba atšauksite sutikimą dalyvauti biomedicininiame tyrime. Biomedicininių tyrimų rezultatai, t. y. biomedicininio tyrimo dokumentuose iki sutikimo dalyvauti biomedicininiame tyrime atšaukimo įrašyti duomenys, jums pageidaujant, bus sunaikinami.

16. Jūsų dalyvavimo tyrime nutraukimo aplinkybės ir kriterijai

Tyrimo gydytojas ar užsakovas turi teisę bet kuriuo metu sustabdyti tyrimą ar Jūsų dalyvavimą jame. Asmenys, kurie turi teisę atšaukti sutikimą tiriamąjį pripažinus neveiksniu, apribojus jo veiksnumą ar kai jis dėl sveikatos būklės negali būti laikomas gebančiu protingai vertinti savo interesus bei tai, kad bus atsižvelgiama į tiriamojo, pripažinto neveiksniu, apribojus jo veiksnumą ar kai jis dėl sveikatos būklės negali būti laikomas gebančiu protingai vertinti savo interesus, norą atšaukti sutikimą, gali nutraukti Jūsų sutikimą dalyvauti tyrime.

17. Ar dalyvaudami šiame tyrime patirsite kokių nors išlaidų?

Dėl dalyvavimo šame biomedicininiame tyrime Jums galimos kelionės į gydymo įstaigą (į Lietuvos sveikatos mokslų universiteto ligoninės Kauno klinikas) išlaidos, kurios nebus kompensuojamos. Dalyvaudami šiame tyrime negausite finansinės naudos.

18. Ar Jūsų asmens duomenys bus konfidencialūs?

Biomedicininį tyrimą atliekant gauta sveikatos informacija, leidžianti nustatyti asmens tapatybę, yra konfidenciali ir gali būti teikiama tik pacientų teises ir asmens duomenų apsaugą reglamentuojančių įstatymų nustatyta tvarka. Duomenų valdytojai yra VšĮ Lietuvos sveikatos mokslų universiteto ligoninė Kauno klinikos, įmonės kodas: 135163499, adresas: Eivenių g. 2 LT-50161 Kaunas. Siekiant apsaugoti duomenų konfidencialumą, Jums bus suteiktas specialus kodas, kuris bus nurodomas visuose dokumentuose, išskyrus sutikimo Sąrašą, kuriame Jūsų vardas ir pavardė susiejami su kodu. Jūsų duomenis pagrindinis tyrėjas saugos seife, į kurį prieigą turės tik jis pats ir įgaliotas tyrėjas. Kompiuteriai, kuriuose bus saugomi elektroniniai tyrimo dokumentai ir duomenys, bus apsaugoti slaptažodžiu. Prisijungimo kodus žino tik tyrėjai, šie duomenys bus atnaujinami kas mėnesį. Dokumentai bus saugomi rakinamoje spintoje, kurios raktą turės tik tyrėjai. Jei sutiksite dalyvauti šiame tyrime, tyrėjai naudos tyrimui atlikti reikalingus Jūsų asmeninius duomenis. Duomenys bus renkami remiantis Jūsų pateikta informacija bei medicininių dokumentų įrašais. Atliekant šį tyrimą gauta sveikatos informacija nelaikoma konfidencialia ir gali būti paskelbta be Jūsų sutikimo, jeigu ją paskelbus nebus galima tiesiogiai ar netiesiogiai nustatyti Jūsų tapatybės. Surinkti duomenys bus skelbiami tik apibendrinti, jokiu būdu negalint identifikuoti Jūsų tapatybės.

19. Kas ir kokiu tikslu galės susipažinti su Jūsų asmens duomenimis?

Pasirašydami šią formą sutinkate, kad tyrimo centro tyrėjai, tyrimus kontroliuojančios institucijos (tokios kaip etikos komitetai) ir įgalioti tyrimą prižiūrintys asmenys galės susipažinti su visa šio tyrimo tikslais apie Jus surinkta informacija. Kitiems asmenims ar įmonėms bus teikiami tik užkoduoti sveikatos duomenys, neleidžiantys tiesiogiai nustatyti Jūsų tapatybės. („užkoduoti“ reiškia, kad dokumentuose bus nurodomas ne Jūsų vardas ir pavardė, o specialus numeris, kurį susieti su Jūsų asmeniu galės tik gydytojas tyrėjas). Surinktus duomenis tyrimo gydytojai naudos tik šio klinikinio

tyrimo tikslais. Jūs turite teisę sužinoti, kokie duomenys buvo surinkti, taip pat galite reikalauti ištaisyti, sunaikinti ar sustabdyti savo asmens duomenų tvarkymo veiksmus, jei nuspręsite pasitraukti iš tyrimo anksčiau numatyto laiko. Tada tyrėjai apie Jus neberinks naujos informacijos. Duomenys, kurie bus renkami apie Jus tyrimo metu: vardas, pavardė, adresas, telefonas, ligos istorijos numeris ir klinikiniai duomenys - amžius, lytis, ūgis, svoris, kardiologinė ir nekardiologinė anamnezė, ligos simptomų ir požymių atsiradimo laikas ir trukmė, rizikos veiksniai, objektyvaus tyrimo duomenys, įprastinių laboratoriniai tyrimų, kurie atliekami visiems, šia liga sergantiems pacientams LSMU Kauno klinikose, atsakymai. Širdies pažaidos žymenų ir uždegiminio atsako baltymų tyrimų atsakymai. Kardioechoskopijos duomenys. Širdies magnetinio rezonanso tyrimo duomenys. Širdies ir kraujagyslių komplikacijos 1 metų laikotarpyje.

20. Kiek laiko bus saugomi tyrimo metu surinkti duomenys ir kas už tai bus atsakingas?

Visa informacija bus užrašoma specialiai tyrimui sudaromuose elektroniniuose ir popieriniuose dokumentuose ir tyrimo centre saugoma 10 metų pasibaigus tyrimui. Tiek laiko saugoti duomenis įpareigoja teisės aktai/užsakovo nustatyta tvarka/ siekiant užtikrinti duomenų kokybę ir kontrolę. Vėliau Jūsų asmens duomenys bus sunaikinti tyrimo centro nustatyta tvarka. Už dokumentų saugojimą tyrimo centre bus atsakinga sveikatos priežiūros įstaiga kartu su pagrindiniu tyrėju.

21. Kas įvertino šį biomedicininį /klinikinį vaistinio preparato tyrimą? / Į ką kreiptis, jeigu iškiltų klausimų?

Dėl savo kaip tyrimo dalyvio teisių galite kreiptis į leidimą atlikti šį biomedicininį tyrimą išdavusį Kauno regioninį biomedicininių tyrimų etikos komitetą, Lietuvos Sveikatos mokslų universitetas, Mickevičiaus g. 9, LT-44307, Kaunas, tel. (8-37) 326889,el. paštas: kaunorbtek@lsmuni.lt. Iškilus klausimų galima kreiptis į įstaigą, kurioje bus vykdomas šis biomedicininis tyrimas- įmonės kodas - 13516399, Eivenių g. 2, LT-50161, Kaunas), tel.: (+370 37) 32 64 49. Faks.: (+370 37) 33 13 95, el. paštas: kardiologijos.klinika@kaunoklinikos.lt. Iškilus klausimų dėl asmens duomenų apsaugos, galite kreiptis į Valstybinę duomenų apsaugos inspekciją telefonu (8 5) 212 7535, el. paštu: ada@ada.lt, buveinės adresas: A. Juozapavičiaus g. 6, 09310 Vilnius

Jeigu turite klausimų dėl Jūsų asmens duomenų tvarkymo, kreipkitės į tyrėją. Tyrėjas Jūsų paklausimą gali perduoti asmeniui, atsakingam už asmens duomenų apsaugą (duomenų apsaugos pareigūnui).

22. Kita svarbi informacija, kuri gali turėti įtakos Jūsų apsisprendimui sutikti ar atsisakyti dalyvauti biomedicininiame/ klinikiniame vaistinio preparato tyrime.

Jūs turite teisę bet kuriuo metu užduoti su tyrimu susijusius klausimus – nedvejodami kreipkitės į gydytoją-tyrėją ar kitą tyrimo komandos narį. Gydytojui-tyrėjui galite paskambinti telefonu 8-37-326948

SUTIKIMAS DALYVAUTI BIOMEDICININIAME TYRIME

Aš perskaičiau šią Informuoto asmens sutikimo formą ir supratau man pateiktą informaciją.
Man buvo suteikta galimybė užduoti klausimus ir gavau mane tenkinančius atsakymus.
Supratau, kad galiu bet kada pasitraukti iš tyrimo, nenurodydama(s) priežasčių[2].
Supratau, kad asmuo, dėl kurio dalyvavimo biomedicininiame tyrime aš duodu sutikimą, gali bet kada pasitraukti iš tyrimo, nenurodydamas priežasčių.[3]
Supratau, kad norėdama(s) atšaukti sutikimą dalyvauti biomedicininiame tyrime, raštu turiu apie tai informuoti tyrėją/kitą jo įgaliotą biomedicininį tyrimą atliekantį asmenį.
Patvirtinu, kad turėjau užtektinai laiko apsvarstyti man suteiktą informaciją apie biomedicininį tyrimą.
Supratau, kad dalyvavimas šiame tyrime yra savanoriškas.
Patvirtinu, kad sutikimą dalyvauti šiame biomedicininiame tyrime duodu laisva valia.
Leidžiu naudoti asmens duomenis ta apimtimi ir būdu, kaip nurodyta Informuoto asmens sutikimo formoje.
Patvirtinu, kad gavau Informuoto asmens sutikimo formos egzempliorių, pasirašytą tyrėjo/ kito jo įgalioto biomedicininį tyrimą atliekančio asmens.

Asmuo (ar kitas sutikimą turintis teisę duoti asmuo)

_____	_____	_____	_____	_____	_:_
vardas	pavardė	atstovavimo pagrindas	parašas	pasirašymo data	pasirašymo laikas

Patvirtinu, kad suteikiau informaciją apie biomedicininį tyrimą aukščiau nurodytam asmeniui.
Patvirtinu, kad asmeniui (ar kitam sutikimą duoti turinčiam teisę asmeniui) buvo skirta pakankamai laiko apsispręsti dalyvauti biomedicininiame tyrime, atsižvelgiant į biomedicininio tyrimo pobūdį, taip pat įvertinus kitas aplinkybes, galinčias daryti įtaką priimamam sprendimui.
Aš skatinau asmenį (ar kitą sutikimą turintį teisę duoti asmenį) užduoti klausimus ir į juos atsakiau.

Tyrėjas ar kitas jo įgaliotą biomedicininį tyrimą atliekantis asmuo

_____	_____	_____	_____	_____	_:_
vardas	pavardė	pareigos tyrime	parašas	pasirašymo data	pasirašymo laikas

CURRICULUM VITAE

Name, Surname:	**Audronė Vaitiekienė**
Address:	The Hospital of Lithuanian University of Health Sciences, Department of Cardiology, Eivenių str. 2, LT-50161 Kaunas, Lithuania
E-mail:	audrone.vaitiekiene@lsmu.lt

Education:

2016–2023	Doctor of Philosophy (PhD) in Medicine, M 001, Lithuanian University of Health Sciences
2004–2010	Master of Science in Medicine. Kaunas University of Medicine.
1996–2004	Kaunas J. Jablonskis Gymnasium
1992–1996	Domeikava primary school

Professional experience:

2017 Apr till now	Cardiologist at the Hospital of Lithuanian University of Health Sciences, Cardiology department, Kaunas, Lithuania
2023 Sep till now	Assistant at the Department of Cardiology, Lithuanian University of Health Sciences, Kaunas, Lithuania
2018 Mar – 2018 May	Fellowship at Herzzentrum Leipzig in the field of cardiovascular magnetic resonance and computed tomography. Leipzig, Germany.
2010 Aug – 2017 Mar	Resident of Cardiology in the Department of Cardiology at the Hospital of Lithuanian University of Health Sciences, Kaunas, Lithuania
2012 Aug – 2013 Feb	Fellowship at Herzzentrum Leipzig in the field of cardiovascular magnetic resonance and computed tomography. Leipzig, Germany.

PADĖKA

Visų pirma dėkoju savo vadovei prof. Gintarei Šakalytei už pasitikėjimą ir kvietimą dirbti kartu. Ačiū už tikėjimą mano jėgomis, gerą nuotaiką ir pagalbą, kuomet jos reikia. Labai dėkoju konsultantei prof. Jolantai Justinai Vaškelytei už visą pagalbą, idėjų generavimą ir palaikymą. Esu be galo dėkinga doc. Monikai Biesevičienei už jos indėlį šiame darbe ir nuolatinį palaikymą bei draugystę. Ačiū klinikos vadovui prof. Remigijui Žaliūnui už įvertinimą ir suteiktą galimybę eiti mokslo keliu.

Esu dėkinga visam hematologijos skyriaus kolektyvui už indėlį įtraukiant ir kuruojant pacientus. Ačiū skyriaus vadovui prof. Rolandui Gerbutavičiui. Ypatingai dėkoju Miglei Kulbokei ir Ignui Gaidamavičiui už puikų komandinį darbą. Taip pat dėkoju radiologijos klinikos širdies ir kraujagyslių sektoriaus personalui, radiologijos technologams už puikų darbą kartu. Ačiū doc. Antanui Jankauskui už visą rūpestį ir pagalbą sudarant širdies magnetinio rezonanso tyrimo protokolą bei patarimus.

Dėkoju Agnei Bartnykaitei ir Irenai Nedzelskienei už pagalbą atliekant statistinius skaičiavimus. Taip pat dėkoju gyd. rezidentams Ignei Strazdienei, Justinui Žemaičiui, studentams Benui Kireiliui, Emilijai Lidžiūtei, Darijai Jankauskaitei už visą jų atliktą darbą, aktyvumą.

Noriu padėkoti visam širdies aritmijų skyriaus personalui už supratingumą, draugystę ir pagalbą kasdieniuose darbuose, galimybę skirti laiko ir moksliniam darbui. Ypač esu dėkinga prof. Arui Puodžiukynui, doc. Dianai Rinkūnienei ir Jurgitai Limbienei už kasdienę draugystę ir palaikymą. Taip pat dėkoju Laurai Zajančkauskienei už komandinį darbą pradedant doktorantūrą ir moralinį palaikymą.

Ačiū visiems pacientams, kurie net ir būdami ypatingai sunkios būklės, išvarginti daugybės tyrimų ir ilgalaikio gydymo, sutiko dalyvauti mūsų tyrime. Be jūsų šis mokslinis darbas nebūtų įvykęs.

Dėkoju draugams už nuolatinį moralinį palaikymą.

Labiausiai dėkoju savo šeimai – vaikams už supratingumą, kantrybę, meilę, tiesiog buvimą ir sugebėjimą pralinksminti šiuo įtemptu laikotarpiu, tėvams už tai, kas esu, už nuolatinę pagalbą kasdienybėje, meilę ir palaikymą, broliui už įkvėpimą judėti į priekį ir, žinoma, vyrui Domui už buvimą gera komanda ir partneriu ne tik gyvenime, šeimoje, bet taip pat ir šiame moksliniame kelyje – idėjų bendraautorystę ir besąlyginį palaikymą.