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CARDIOTOXICITY IN CONVENTIONAL AND CONTEMPORARY CANCER TREATMENT PROTOCOLS

THESIS SUMMARY

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CONTENT

ABBREVIATIONS

2D, 3D EchoCG – two-.three- dimensional echocardiography
5FU – 5-fluorouracil
BC- breast cancer
BMI- Body mass index
CI - Confidence Interval
CMP – cardiomyopathy
CT – chemotherapy
cTn - cardiac troponin
CTRCD – cancer therapy related cardiac dysfunction
CV - cardiovascular
Doxorubicin-ECD – doxorubicin equivalent cumulative dose
ECG – electrocardiogram
EF – ejection fraction
ESC - European society of cardiology
GEE - Generalized Estimating Equations for estimate generalized linear models
Gy – Gray - a unit of measurement for absorbed radiation
HF – heart failure
HFpEF – heart failure with preserved ejection fraction
HFrEF– heart failure with reduced ejection fraction
hsTnT - highly sensitive cardiac troponin T
IQR- Interquartile rangeт
IVRT - Isovolumic Relaxation Time
LV – left ventricle
LVEF – left ventricular ejection fraction
LVGLS - Left Ventricular Global Longitudinal Strain
LVMPI - Left Ventricular Myocardial Performance Index
LVe' – left ventricular early diastolic tissue velocity
OT – oncologic therapy
RT - radiotherapy
RV – right ventricle
RVEF – right ventricular ejection fraction
RVFAC - Right Ventricular Fractional Area Change
RVFWGLS- Right Ventricular Free Wall Longitudinal Strain
RVGLS - Right Ventricular Global Longitudinal Strain
RVMPI - Right Ventricular Myocardial Performance Index
RVS' – right ventricular systolic tissue velocity
RVe' – right ventricular early diastolic tissue velocity
TIC – trastuzumab-induced cardiotoxicity

1. INTRODUCTION

Cardiovascular (CV) diseases and cancer are the leading causes of mortality globally (World Health Organization, 2021 and 2022). Cardiovascular disorders affect patients with neoplasms during their therapy and for years thereafter, resulting in an elevated risk of CV mortality, heart failure (HF), stroke, pulmonary embolism, and myocardial infarction (Paterson et al., 2022). Cardio-oncology is a rapidly evolving subspecialty of cardiology that investigates all aspects of the relationship between CV diseases and malignancies. The objective is to enhance antitumor therapeutic efficacy while reducing cardiotoxicity and to implement long-term surveillance and management of cancer patients concerning CV comorbidities (Lyon et al., 2022). In the majority of cases, antitumor therapy is combined, which can result in a variety of adverse effects on the CV system, including myocardial dysfunction and heart failure, coronary artery disease, valvular involvement, arrhythmias, hypertension, thromboembolic complications, peripheral vascular damage and stroke, pulmonary hypertension, and pericardial involvement (Herrmann, 2020). Myocardial dysfunction and its clinical manifestation, heart failure, are significant cardiotoxic complications of oncological treatment (OT) (Zamorano et al., 2016). Scientific data offers insight into the molecular and cellular mechanisms underlying the initial cardiotoxic effects. Cardiomyocytes and the cells in their environment are directly damaged, resulting in early functional disorders in the myocardium that can persist and exacerbate over time. In addition to contractile dysfunction, pathophysiological mechanisms also elucidate potential disorders in diastolic myocardial function. Understanding the mechanisms of cardiac disorders associated with antitumor therapy is crucial for their early detection. Prompt identification of myocardial damage can avert its progression to HF.

Left ventricular (LV) systolic dysfunction, whether symptomatic or asymptomatic, together with early alterations in myocardial

deformation, are well recognized and constitute the foundation for diagnosis and management guidelines for patients receiving cancer therapy (Lyon et al., 2022). Monitoring right ventricular function in patients undergoing anticancer treatment is currently recommended, although it is not included in the definition of cardiac dysfunction induced by cancer therapy (CTRCD) (Lyon et al., 2022). In August 2024, a scientific statement was issued by the Heart Failure Association and the Cardio-Oncology Council of the European Society of Cardiology (ESC), which delineated OT-related injury to the right ventricle (RV), emphasizing the importance of deformation echocardiographic parameters for diagnosing its subclinical form (Keramida et al., 2024).

A variety of factors may contribute to changes in the structure and function of the RV in cancer patients, including previous right ventricular damage, neoplastic involvement, cardiotoxic effects of antitumor therapy directly on the right ventricle, as well as as a result of its burden after LV damage (Keramida et al., 2024). The RV possesses distinct anatomical, physiological, microstructural, and macrostructural characteristics that differentiate it from the left ventricle (LV). Some researchers assert that these features render it less vulnerable to cardiotoxic effects, while others believe that it is, conversely, more sensitive to OT (Barthur et al., 2017; Kelly et al., 2014; Lenčová-Popelová et al., 2014; Mortensen et al., 1986; Sanz et al., 2019). Right ventricular dysfunction is associated with an unfavorable clinical prognosis in a variety of conditions, including chronic HF with reduced and preserved EF, cardiac surgery, myocarditis, acute myocardial infarction, congenital heart malformations, and pulmonary hypertension (Konstam et al., 2018). The emergence of right ventricular dysfunction correlates with elevated mortality, deterioration of heart failure functional class, and the onset of multiorgan complications (Konstam et al., 2018; Sanders et al., 2020).

There is growing scientific interest in right ventricular dysfunction in the setting of OT. Clinical data indicates more pronounced metabolic alterations in the right ventricle's myocardium, compared to the LV, characterized by energetic remodeling of cardiomyocytes towards increased glucose utilization, a phenomenon observed in the myocardium of patients with heart failure (Kim et al., 2020) The INTERMACS registry for mechanical circulatory support indicates that 29% of patients with chemotherapy-induced cardiomyopathy exhibit a significant decrease in right ventricular ejection fraction (RVEF), with one-fifth necessitating assisted circulatory support (Oliveira et al., 2014). Research utilizing MRI corroborates right ventricular involvement by detecting myocardial edema and systolic failure. Numerous scientific groups (Krastev et al., 2010; Barthur et al., 2017; Belham et al., 2006; Boczar et al., 2016) have documented systolic and diastolic echocardiographic functional parameters anomalies. The accumulated clinical data are based on small and heterogeneous populations, and the results do not provide unambiguous information. The clinical significance of right ventricular injury remains unclear. Its prognostic value, the extent to which it can justify the inclusion of preventive treatment, and the methods for its treatment are still uncertain (Keramida et al., 2024).

Modern research concentrates on parameters that necessitate 3D and Speckle-tracking Echocardiography. These indicators can identify subclinical, early abnormalities in myocardial function. However, their reliance on specialized equipment and the cardiologists' expertise restricts their application to all oncology patients and every required follow-up assessment.

The present study was motivated by the necessity for further research on the functional changes of the RV under the influence of OT and for indicators that are both readily applicable in clinical practice and reliably capture these changes.

2. AIM AND TASKS OF THE STUDY

2.1. AIMS

The objective of the research is to investigate the changes in systolic and diastolic function of the RV in response to a variety of chemotherapy treatments and to suggest a user-friendly algorithm for echocardiographic evaluation of the right ventricle

2.2. ASSIGNMENT

2.2.1. To dynamically assess the echocardiographic parameters for systolic and diastolic function of the LV with 2D echocardiography and tissue Doppler in patients undergoing various systemic anticancer therapies.

2.2.2. To dynamically assess the echocardiographic parameters for systolic and diastolic function of the RV with 2D echocardiography and tissue Doppler in patients undergoing various systemic anticancer therapies.

2.2.3. To ascertain the relationships between alterations in echocardiographic parameters of right and left ventricular function and the variations in biochemical markers indicative of myocardial injury.

2.2.4. To examine the temporal, correlational, and predictive associations between the echocardiographic parameters of the right and left ventricles and clinical variables.

2.2.5. To create an algorithm for the early identification of myocardial injury and the risk assessment of patients.

3.MATERIALS

3.1. Clinical Cohort

The study was approved by the Medical University Hospital - Varna's Research Ethics Committee under No. 84/27.06.2019. The study was conducted at the First Cardiology Clinic in collaboration with the Clinic of Medical Oncology at the University Hospital "St. Marina" in Varna from June 2019 to February 2024. The trial comprised 60 patients aged over 18 who provided informed consent and received chemotherapy (CT) for breast and gastrointestinal malignancies (Table 1).

3.2. Exclusion criteria

- Persistent pulmonary conditions that cause pulmonary hypertension,
- History of pulmonary embolism,
- Hemodynamically relevant valvular disorders,
- Persistent atrial fibrillation,
- Heart failure, left ventricular systolic dysfunction, and established coronary artery disease
- A poor acoustic window.

4.METHODS

4.1. Clinical Methods

Patients underwent baseline assessments prior to commencing CT and were monitored for 18 months (on the 1st, 3rd, 6th, 9th, 12th, and 18th month). We evaluated the patients by gathering demographic and clinical indicators from their medical history, examination, and ECG, as detailed in Tables 1 and 2. The mean age of the patients was 53 years, with the youngest patient being 31 years old and the oldest 74 years old (Table 1). Women comprised 91.7% of the population. The mean body mass index (BMI) was 26.4 (SD 4.3) mg/m². Hypertension was present in 45% of the patients (n = 27), while ten percent of the

population (n = 6) had type 2 diabetes. Fifty percent (n = 30) of the patients were on ACE inhibitors or ARBs. Twenty-eight patients (45%) were administered beta blockers. Of these, 21 patients (35%) were receiving combination therapy that included beta blockers and RAAS inhibitors.

Table 1. *Population characteristics in terms of demographics, comorbidities, and cardioprotective therapy*

Population characteristics	**n = 60,** n (%)
Age, years	
• Mean, (SD)	53, (12)
• Min./Max.	31, 74
Gender	
• Female	55 (91.7%)
• Male	5 (8.3%)
Smoking	
• Smokers	19 (31.7%)
• Former smokers	4 (6.7%)
• Non-smokers	37 (61,6%)
BMI, mg/m2	
• Mean, (SD)	26.4, (4.3)
• Min./Max.	18.8, 35.1
Diabetes	6 (10%)
Hypertension	27 (45%)
Dyslipidemia	10 (17%)
Cardioprotective medications	
RAAS inhibitors	30 (50%)
• n = 21 (70%) – from baseline	
Beta blockers	28 (47%)
•n = 18 (64%) – from baseline	
RAAS inhibitors + beta blockers	21 (35%)
Statins	8 (13%)

Regarding the oncological disease, the majority of patients, 83.3% (n = 50), were diagnosed with breast cancer (BC), the remaining 10 patients (16.7%) had gastrointestinal neoplasms (Table 2). They were treated in 50% of cases with chemotherapy alone, in 48% with chemotherapy and targeted therapy, and one patient received chemotherapy and immunotherapy with pembrolizumab. The median duration of chemotherapy was 106 days (IQR 65, 114).

Table 2. *Population characteristics regarding cancer and cancer therapy*

Population characteristics	**n = 60,** n (%)
Type of cancer	
Breast cancer	50 (83.3%)
Colon cancer	4 (6.7%)
Rectal cancer	4 (6.7%)
Stomach cancer	1 (1.7%)
Pancreatic cancer	1 (1.7%)
Previous chemotherapy	5 (8.3%)
Previous chest radiotherapy	5 (8.3%)
Type of systemic cancer therapy	
• Chemotherapy	30 (50%)
• CT + targeted therapy	29 (48%)
• CT + immunotherapy	1 (1.7%)
• Hormone therapy	30 (50%)
Medicaments for systemic cancer therapy	
Anthracyclines	30 (50%)
Indexed Cumulative dose of Doxo, Mean (SD) (mg/m2)	128 (36)
5FU/Capecitabine	12 (20%)
Cyclophosphamide	34 (57%)
Taxane	49 (82%)
Platinum	12 (20%)
Target therapy/immunotherapy	
Trastuzumab ± Pertuzumab	24 (40 %)
Bevacizumab	3 (5%)
Lapatinib	1 (1.7%)
Ribociclib	2 (3.4%)
Pembrolizumab	1 (1.7%)
Anthracyclines ± trastuzumab	
• Anthracyclines	21 (35%)
• Trastuzumab	15 (25%)
• Anthracyclines + trastuzumab	9 (15%)
• Other	15 (25%)
Chest radiotherapy	27 (45%)
• > 50 Gy	22 (88.9%)
• Left-sided	13 (48%)
Radical surgery	53 (88%)
Duration of chemotherapy	
Median (IQR) (Days)	106 (65, 114)
Duration of targeted therapy (n = 29)	
Median (IQR) (Days)	447 (353, 630)

Fifty percent of the patients (n = 30) received anthracyclines (epirubicin), with a mean indexed equivalent cumulative dose (ECD) of doxorubicin of 128 (SD 36) mg/m2. Targeted therapy was provided to 29 (48%) of the patients, predominantly HER2-targeted therapy with trastuzumab and its variations (n = 24 (40%)). Trastuzumab was delivered sequentially to anthracycline treatment in 9 patients (15%). The median duration of trastuzumab therapy was 447 (IQR 353, 630) days. Radiation therapy (RT) was administered in 45% (n = 27) of the population for BC, with nearly half of them in the left thoracic region (Table 2).

The HFA-ICOS risk assessment instruments (Figure 1) were employed to evaluate the risk of CTRCD in patients (n = 45) who were treated with anthracyclines and/or trastuzumab (Lyon et al. 2022). Only seven patients were classified as high-risk, while sixteen patients (35.5%) were classified as moderate-risk. Due to the exclusion criteria, there were no patients at a very high risk.

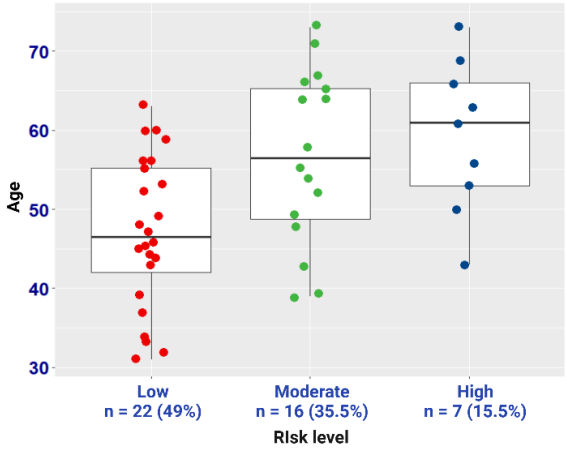

Figure 1. *Distribution of the patients treated with anthracyclines and/or trastuzumab (n = 45) based on the risk level for developing CTRCD.*

The patients were followed for a median of 446 (IQR 275, 720) days. The median number of visits was 5 (IQR 4, 6). Thirty-two (53%) patients were followed for 5 or more visits. Seventy percent (n = 42) of the population were followed for 12 or more months (Figure 2).

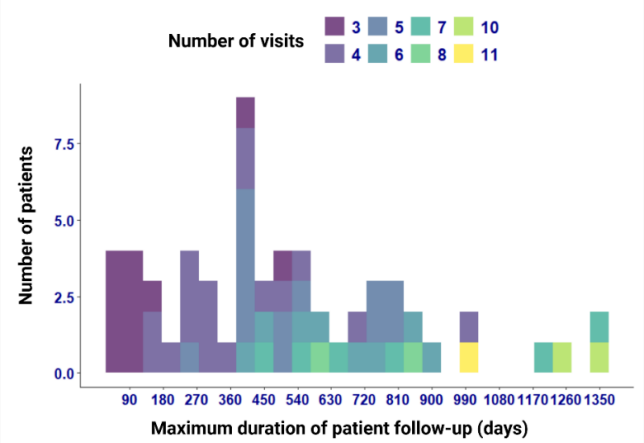

Figure 2. *Representation of the maximum number of visits in different colors and the maximum number of days of follow-up for individual patients*

4.1. Methods: echocardiographic assessment and troponin testing

Echocardiographic evaluation was conducted by a single cardiologist at baseline, 1, 3, 6, 9, 12, and 18 months. The assessment involved conventional the following parameters:

- For the LV assessment: indexed end-diastolic volume (EDVi), LVEF (biplane Simpson's method), MAPSE, E/A ratio, Tei index with PW and tissue Doppler (LVMPI-PW, LVMPI-TDI), IVRT, DecT, E/e' ratio, e' and S' velocities, valve assessment, left atrial area and volume (LAA and LAV).
- For the RV assessment: indexed RV end-diastolic area (RVAi), RVFAC, TAPSE, S' velocity of tricuspid annulus, Tei index with

PW and tissue Doppler (RVMPI-PW, RVMPI-TDI), E/A ratio, E/e' ratio, e' velocity, tricuspid regurgitation, systolic pulmonary artery pressure, right atrial area and volume (RAA and RAV).

Table 3 presents the baseline values of the 2D echocardiography parameters.

Table3. *Baseline values of the parameters of LV, RV, LA, RA from 2D echocardiography*

Parameters for LV and LA	**n = 60**	**Parameters for RV and RA**	**n = 60**
LV EDVi (ml/m2)		**RVAi** (cm2/m2)	
Mean, (SD)	41, (9)	Mean, (SD)	9.14, (1.72)
Min./ Max..	24, 64	Min./ Max..	4.65, 13.77
LVEF (%)		**RVFAC** (%)	
Mean, (SD)	64, (6)	Mean, (SD)	45.0, (6.3)
Min./ Max..	51, 75	Min./ Max..	31.0, 57.0
MAPSE (mm)		**TAPSE** (mm)	
Mean, (SD)	13.13, (1.83)	Mean, (SD)	19.4, (3.4)
Min./ Max..	10.00, 18.00	Min./ Max..	12.5, 29.0
Septal LVS' (cm/s)		**RVS'**	
Mean, (SD)	8.36, (1.56)	Mean, (SD)	12.78, (2.14)
Min./ Max..	4.50, 11.60	Min./ Max..	8.40, 17.50
Lateral LVS' (cm/s)		**Middle RV diameter** (mm)	
Mean, (SD)	9.72, (2.12)	Mean, (SD)	29.3, (4.0)
Min./ Max..	5.80, 14.50	Min./ Max..	18.0, 39.0
Average LVS'(cm/s)		**Basal RV diameter** (mm)	
Mean, (SD)	9.04, (1.62)	Mean, (SD)	36.4, (4.6)
Min./ Max..	5.25, 12.85	Min./ Max..	25.0, 47.0
LAVi (ml/m2)		**RAVi** (ml/m2)	
Mean, (SD)	31, (9)	Mean, (SD)	23, (8)
Min./ Max..	16, 55	Min./ Max..	10, 54
LVMPI-PW		**RVMPI-PW**	
Mean, (SD)	0.44, (0.11)	Mean, (SD)	0.31, (0.16)
Min./ Max..	0.22, 0.73	Min./ Max..	0.05, 0.77
LVMPI-TDI, septal		**RVMPI-TDI**	
Mean, (SD)	0.52, (0.11)	Mean, (SD)	0.42, (0.15)
Min./ Max..	0.29, 0.86	Min./ Max..	0.18, 0.96
LVMPI-TDI, laterat		**RVe', cm/s**	
Mean, (SD)	0.49, (-0.11)	Mean, (SD)	12.30, (2.71)
Min./ Max..	0.27, 0.81	Min./ Max..	6.60, 20.00
LVe', cm/s		**RV E/e'**	
Mean, (SD)	10.35, (2.33)	Mean, (SD)	4.51, (1.37)
Min./ Max..	6.20, 16.00	Min./ Max..	2.80, 7.70
LV E/e'			
Mean, (SD)	7.80, (2.28)		
Min./ Max..	4.80, 16.90		

The evaluation of echo parameters adhered to the guidelines of the American Society of Echocardiography and the European Society for Cardiovascular Imaging (Lang et al., 2015). The conclusive values of the indicators represent the mean derived from a minimum of three observations to mitigate intraobserver variability of the parameters

The biochemical marker hsTroponin T (hsTnT) was analyzed at baseline and prior to the chemotherapy courses at the 1st, 3rd, and later stages based on clinical judgment using the electrochemiluminescence immunoassay "ECLIA" method on the Cobas analyzers of the ROCHE company. The maximum threshold of the marker is 14 ng/L.

4.2.Statistical methods

- Descriptive statistics were used to determine the mean, median, standard deviation (SD), interquartile range (IQR), and proportions, depending on the type and distribution of the variables.;
- Paired" t-test for comparing correlated variables between two time-intervals;
- Correlation analysis for the relationship between variables, intraclass correlation analysis, and Bland-Altman test for assessing the variability of echocardiographic indicators;
- Generalized linear and logistic mixed-effects regression for single-factor and multifactor analysis employing generalized estimating equations (GEE) to monitor and compare correlated variables across time, as well as to ascertain the impact of factors on the variable; ROC analysis
- The "R" program, version 4.3.2 (31/10/23) was utilized.

5.RESULTS AND DISCUSSION

The 18-month follow-up results are presented as a consequence of the limited number of patients who were investigated after this time (Figure 2).

5.1.Assessment of the left ventricular function

5.1.1.Monitoring of the left ventricular ejection fraction

The examination of LV systolic function using the LVEF indicator revealed a decline up to 12 months following the commencement of OT, assessed using GEE regression analysis (Table 4).

Table 4. *Change in LVEF during and after OT, for a period of 18 months (GEE analysis)*

Time	LVEF change (%) Beta	95% CI	*p*
Baseline	—	—	
1st month	-1.0	-2.8, 0.71	0.2
3rd month	-3.3	-5.1, -1.5	**<0.001**
6th month	-4.3	-6.2, -2.3	**<0.001**
9th month	-1.8	-4.3, 0.74	0.2
12th month	-3.4	-5.7, -1.1	**0.004**
18th month	-2.7	-5.7, 0.28	0.075

A statistically significant reduction from baseline LVEF of 3.3% (95% CI -5.1, -1.5, p <0.001) was noted at the 3rd month, while a decrease of 4.3% (95% CI -6.2, -2.3, p <0.001) was recorded at the 6th month. The reduction in LVEF persisted until the twelfth month, after which the decline was maintained.

Analysis of the lowest LVEF for each patient relative to the baseline LVEF (Figure 3) revealed a decline in the majority of patients. In some patients, the maximal reduction in LVEF occurred prior to the conclusion of CT (red line), while in others, it occurred subsequent to the completion of CT. The mean difference between the baseline and

minimum LVEF was 6.7% (95% CI: 5.1, 8.3, p = 0.0000). All of these values, however, are within the error of this ultrasound method, as the inter- and intraobserver variability reported in the literature is 15% (Wood et al., 2014).

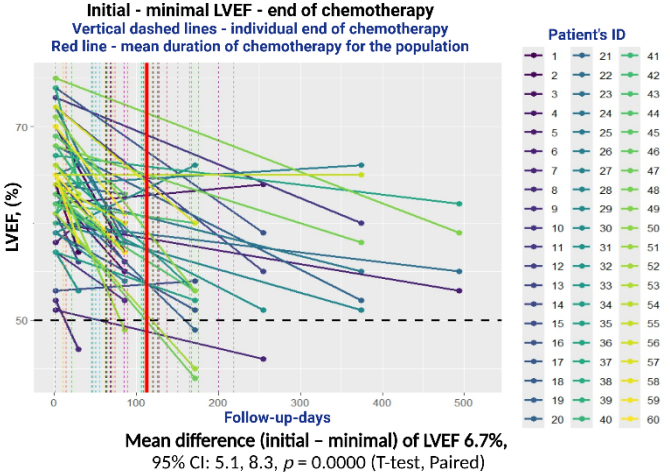

Figure 3. *Baseline and minimum LVEF in individual patients and mean difference in the entire population. The time to minimum LVEF is graphically presented against the mean duration of chemotherapy (red vertical line). The horizontal black dashed line points to the normal lower range for LVEF.*

The study by Gulati et al. (2016) demonstrated a lesser decrease in LVEF (measured by MRI) by 2.6% (95% CI 1.5, 3.8) following a combination of chemotherapy for breast cancer that was similar to our study. This chemotherapy included 5FU, anthracyclines, cyclophosphamide, taxanes, and trastuzumab. A meta-analysis of 26 randomized trials indicated a comparable reduction in LVEF of 4.5% (95% CI, 2.6, 6.4) associated with anthracycline-based regimens, with a gradual decline up to 6 months, after which no further changes were observed (Lee et al., 2023).

In six of our research participants, LVEF decreased below 50% (Figure 3 and Table 5).

Table 5. *Characteristics of patients (n = 6) with LVEF decline below 50%*

Parameter	**n = 6,** n (%)	**Parameter**	**n = 6,** n (%)
Min. LVEF, %	44 – 49%	**Female gender**	n = 6
•Δ LVEF > 10%	**n = 4**	**Non-smokers**	n = 4
•Δ LVEF ≤ 10%	n = 2	**BMI > 30 kg/m2**	n = 5
Time to occurrence, days	47 – 243	**Age, years**	**43 – 50 (n=5)**
•Between 3rd and 9th mo	n = 5		64 r. (n=1)
CT/Targeted therapy		**Hypertension**	n = 3
•Anthracycline	n = 2	**Diabetes**	n = 0
•Trastuzumab	n = 2	**Dyslipidemia**	n = 1
•Anthra + Trast.	n = 1	**Risk of CRTCD**	
•Other CT	n = 1	•Low	n = 1
Radiotherapy	n = 4	•Moderate	n = 3
Previous CT	n = 1	•High	n = 1
Previous RT	n = 1	•Not applicable	n = 1
Cardioprotection	n = 4	**Max. hsTnT (n = 3)**	9.8 ng/L
CV symptoms		**CV symptoms**	
•No	n = 1	•Palpitatins/VE	n = 3
•Hypertesive crisis	n = 1	•Dyspnea at exertion	n = 1

In **4 patients (6.7%),** there was a concurrent reduction in LVEF to between 44% and 49%, with a relative fall in LVEF exceeding 10%, without associated HF — **mild asymptomatic CRTCD**. Two patients experienced a decrease in LVEF that was less than 50%, but the percentage decline was less than 10%. In **one of these patients** with a relatively smaller decrease in LVEF, symptoms of dyspnea on exertion were reported, corresponding to NYHA class II HF (**mild symptomatic CTRCD**). Consequently, based on the current definition, the proportion of patients with **CTRCD in the examined sample was 8.3% (n = 5).** Five of the six patients were young, aged between 43 and 50, but had a BMI > 30 kg/m2. Treatment with RAAS inhibitors and beta blockers was prescribed to 4 patients. Three

patients were assessed to have a moderate risk of developing CRTCD, whereas only one patient was classified as high risk due to previous distant CT and chest RT (Table 5).

Prior to the standardization of the CTRCD definition by the ESC in 2022, and the introduction of deformation indices and biomarkers as diagnostic criteria, earlier research documented the incidence of CMP and HF resulting from oncologic treatment (OT). Bowles et al. (2012) reported that the incidence of HF/CMP in the first and second years following combined treatment with anthracyclines and trastuzumab was 6.2% and 9.8%, respectively, which aligns with our findings. Cardinale et al. (2015) identified LV systolic dysfunction (ΔLVEF > 10% to a value below 50%) in 9% of a substantial cohort (2600 patients) undergoing OT with anthracycline-based regimens. Our findings are further supported by a multicenter Italian study of 499 patients, which reported a 6% incidence of HF or asymptomatic decrease in LVEF below 50% during therapy with anthracyclines and/or trastuzumab (Tarantini et al., 2012).

Table 6. *Other echocardiographic parameters during the occurrence of a drop in LVEF below 50%*

Echocardiographic parameters during the occurrence of a drop in LVEF below 50%	**n = 6**
Septal LV S' velocity, cm/m2	
• Median (Min., Max.)	6.3 (5.5, 7.2)
Lateral LV S' velocity, cm/m2	
• Median (Min., Max.)	6.8 (6.0, 9.0)
Average LV S' velocity, cm/m2	
• Median (Min., Max.)	7.2 (5.75, 8.1)
RVFAC ≤35%	n = 3
RVS' velocity ≤ 10cm/s	n = 3
Minimum tissue LV systolic velocities in patients n = 2 with ΔLVEF ≤ 10%	
• **Septal LV S', cm/m2**	**5.0 и 6.5**
• **Lateral LV S', cm/m2**	**6.0 и 6.5**
• **Average LV S', cm/m2**	**5.5 и 6.5**
MAPSE < 12 mm (10.3 – 11.2)	**n = 3**
TAPSE < 16 mm	**n = 2**

The patients with a relative decrease in LVEF of ≤ 10% to below 50% did not undergo monitoring of hsTnT and LVGLS, thus precluding their classification as having CTRCD based on the current definition. Nevertheless, the minimum LV systolic tissue velocities were recorded at low values (Table 6). Upon diagnosis of minimum LVEF, the median LV septal tissue velocity S' measured 6.3 cm/s, while the lateral S' velocity was recorded at 6.8 cm/s (Table 6). Three patients demonstrated a concurrent reduction in RVFAC and RV systolic tissue velocity S'.

Considering the variability of the LVEF indicator, other criteria are needed in cases where it is not sufficient for diagnosis and for the appointment of cardioprotective therapy. According to the current definition, such are the parameters of myocardial deformation and cardiac biomarkers. In practice, their application is neither universal nor consistent. The systolic tissue velocities S' of the medial and lateral mitral annulus are alternatively considered to inform clinical decision-making.

5.1.2.Assessment of the left ventricular systolic tissue velocities

The examination of the alteration in LV systolic tissue velocities S' (at the septal and lateral mitral annulus and their average) over time following the start of oncological treatment indicated a steady decline until the 12th month (Tables 7 and 8, Figure 4).

Table 7. *Change in LV systolic S' velocities, septal and lateral, at each follow-up visit (GEE regression analysis)*

Time	S` ЛК септална			S`ЛК латерална		
	Beta	**95% CI**	**p**	**Beta**	**95% CI**[1]	**p**
Day 1	—	—		—	—	
1st mo	**-0.57**	**-0.92, -0.22**	**0.001**	-0.32	-0.78, 0.14	0.2
3rd mo	**-0.83**	**-1.2, -0.47**	**<0.001**	**-0.82**	**-1.3, -0.35**	**<0.001**
6th mo	**-0.99**	**-1.4, -0.59**	**<0.001**	**-0.75**	**-1.3, -0.23**	**0.005**
9th mo	**-0.62**	**-1.1, -0.11**	**0.017**	**-0.76**	**-1.4, -0.11**	**0.023**
12th mo	**-1.1**	**-1.5, -0.63**	**<0.001**	**-0.78**	**-1.3, -0.21**	**0.008**
18th mo	**-0.65**	**-1.3, -0.04**	**0.036**	-0.34	-1.1, 0.41	0.4

The decrease initiated within the first month for the LV septal and average S', with corresponding absolute values of -0.57 cm/s (95% CI -0.92, -0.22, p = 0.001) and 0.44 cm/s (95% CI -0.80, -0.09, p = 0.014), respectively. This observation may indicate the presence of early functional myocardial disorders resulting from the initiation of oncological treatment.

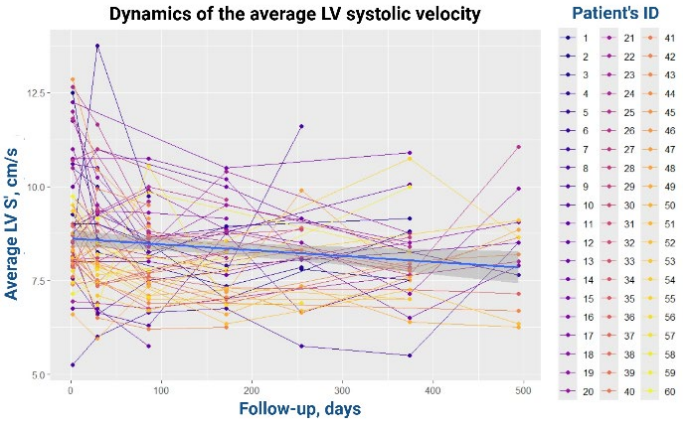

Figure 4. *Generalized linear mixed-effect regression analysis of the change in mean LV S' velocity during and after OT (blue line and 95%CI – gray area). Different colors – individual change.*

Table 8. *Change in the average LV S' during and after OT (GEE regression analysis)*

Time	Average LV S` Beta	95% CI	p
Day 1	—	—	
1st mo	**-0.44**	**-0.80, -0.09**	**0.014**
3rd mo	**-0.81**	**-1.2, -0.44**	**<0.001**
6th mo	**-0.87**	**-1.3, -0.47**	**<0.001**
9th mo	**-0.71**	**-1.2, -0.21**	**0.006**
12th mo	**-0.94**	**-1.4, -0.52**	**<0.001**
18th mo	-0.52	-1.1, 0.01	0.056

The reduction in the septal LVS` was sustained up to the 18th month, while the lateral and average LVS` velocities exhibited statistically significant decreases until the 12th month. The mean percentage relative decrease from baseline to minimum achieved for the septal LVS` was 16% (SD 13%); for the lateral LV S`, it was 14% (SD 11%); and for the average LVS`, it was 14% (SD 11%).

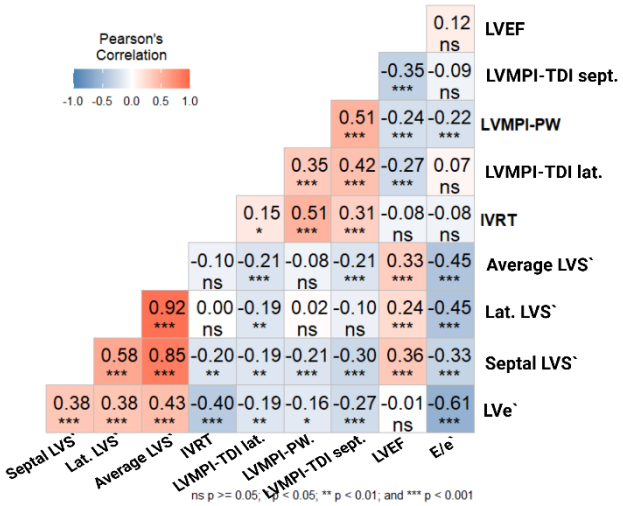

Figure 5. *Pearson correlation analysis of the relationship between systolic and diastolic LV parameters. Correlation coefficients and significance levels are shown (ns – not significant, * - p < 0.05, ** - p < 0.001 and *** - p < 0.001)*

Pearson correlation analysis showed a moderate positive, statistically significant correlation between LV systolic function indices from tissue Doppler (S' septal and average) and LVEF (R 0.36 and 0.33, respectively, $p < 0.001$). There was a weak correlation between lateral LVS' and LVEF (R 0.24, $p < 0.001$) (Figure 5).

The existing scientific literature on the alteration of mitral annulus tissue systolic velocities is limited, and the findings are not unequivocal. Some studies indicate that there is no significant reduction in LV systolic tissue velocities in the short term, specifically within 6 months following the initiation of OT. The findings encompass both anthracycline-based and targeted therapies (Boyd et al., 2017; Kaya et al., 2013; Cao et al., 2015). Song et al. (2017) observed a statistically significant reduction in the mitral annulus systolic tissue velocity following four cycles of an anthracycline-based regimen for diffuse B-cell non-Hodgkin lymphoma, decreasing from 11.5 ± 2.1 to 10.9 ± 1.6 cm/s; however, no significant change was noted after the eighth cycle (Song et al. 2017). Płońska-Gościniak et al. (2017) observed a significant decrease in the septal LVS' from 8.7 ± 1.73 cm/s to 7.0 ± 0.91 cm/s, $p < 0.0001$, and in the lateral LVS' from 10.24 ± 2.48 cm/s to 9.23 ± 1.12 cm/s, $p = 0.03$ at 12 months following the start of antimetabolite therapy (5FU and capecitabine).

The study by Ichikawa et al. (2024) supports the diagnostic value of the mitral annulus systolic velocities measured by tissue Doppler. A retrospective analysis of 256 breast cancer patients treated with anthracyclines, with or without trastuzumab, revealed that 56 patients (22%) experienced CTRCD. This group was characterized by a relative decrease of greater than 10% in LVEF to below 50%, or a relative decrease in LVGLS of at least 15%. In the CTRCD group, significant changes were observed in all three velocities, with baseline, 6-month, and 12-month values recorded as follows: for septal LVS` 7.5 ± 1.5, 6.5 ± 1.2, and 6.4 ± 1.0 cm/s; average LVS` 8.9 ± 2.6, 6.8 ± 1.7, and 6.6 ± 2.1 cm/s; and lateral LVS` 9.6 ± 2.2, 8.3 ± 2.1, and 8.7 ± 2.3 cm/s. A significant decrease was observed only for the septal LVS` in the group without CTRCD. Comparable dynamics were noted in LVGLS, which significantly declined in the CTRCD group at 6 and 12 months, while remaining stable in the group without CTRCD (Ichikawa et al., 2024). In a comparison of the diagnostic

value of the LV systolic tissue velocities and the global longitudinal strain, researchers performed a ROC analysis. The results indicated that a septal LVS' of ≤ 6.85 cm/s exhibited a sensitivity of 74% and a specificity of 73%, with an AUC of 0.81 for the diagnosis of CTRCD. The sensitivity and specificity of the lateral and average LVS` for detecting CTRCD were lower. The established optimal value of LVGLS for diagnosing CTRCD was 17.6%, exhibiting a sensitivity of 68% and a specificity of 88% (AUC 0.68) (Ichikawa et al., 2024). This study indicates that tissue velocity accuracy for diagnosing CTRCD surpasses that of LVGLS. Furthermore, in the CTRCD group, the reduction in the systolic tissue velocities was observed prior to or concurrently with the identification of the decrease in LVEF and LVGLS. The authors assert that patients exhibiting normal LVEF and LV septal systolic velocity exceeding the established threshold of 6.85 cm/s did not experience a significant reduction in LVGLS, suggesting that the latter study may be disregarded (Ichikawa et al., 2024). The proposed ultrasound follow-up algorithm during OT involves the initial assessment of LVEF and septal LV S' (Ichikawa et al., 2024).

The facts presented by Ichikawa et al. (2024) are also corroborated by the low systolic tissue velocities observed in our study in patients (n = 6) with a reduced LVEF < 50%. The median values for the septal, lateral, and average velocities were 6.3, 6.8, and 7.2, respectively (Table 6). Given the limited absolute number of patients with CMP (n = 5), it was inappropriate to separate groups with and without CTRCD, as done by Ichikawa et al. (2024), for the purpose of comparing tissue velocities. It is important to note that when comparing groups with a relative percentage decrease in LVEF above and below 10%, both groups exhibited a pathological decrease in LV tissue systolic velocities in a similar proportion of patients. Approximately 20% of each group demonstrated a decrease in the septal LVS' below 6 cm/s, while around 30% showed a decrease in the average LVS' below 7

cm/s (Table 9). This observation suggests that OT influences LV systolic tissue velocities while not significantly reducing LVEF.

Table 9. *Distribution of the minimum (maximum decreased) mitral annulus systolic velocities during follow-up according to the degree of relative percentage decrease in LVEF*

Parameter	Δ LVEF ≤ 10%, N = 29 (48%)	Δ LVEF > 10%, N = 31 (52 %)	*p*
Septal LV S` ≤ 6 cm/s	7 (24%)	6 (19%)	0.7
Septal LV S` ≤ 7 cm/s	20 (69%)	23 (74%)	0.7
Lateral LV S` ≤ 8 cm/s	19 (66%)	14 (45%)	0.11
Average LV S` ≤ 7 cm/s	9 (31%)	8 (26%)	0.7

5.1.3. Left ventricular systolic dysfunction

According to current guidelines, global longitudinal strain is used to identify asymptomatic LV systolic failure caused by OT. Left ventricular systolic dysfunction is defined by a relative percentage decrease in LVGLS exceeding 15% while the LVEF remains normal (> 50%) or when the LVEF is between 40-49% with a relative decrease of less than 10% (Lyon et al., 2022). Recommendations for echocardiographic assessment of LV suggest that when strain analysis is suboptimal or unavailable, LV longitudinal function should be evaluated using alternative indicators, such as MAPSE or mitral annulus systolic velocities via tissue Doppler (Lang et al., 2015). In a manner similar to the definition of asymptomatic CTRCD, we employ the average LV S' as a surrogate of LVGLS to evaluate longitudinal LV function and define LV systolic dysfunction, based on the aforementioned findings and reasoning. LV systolic dysfunction due to OT is defined as a relative reduction in LVEF exceeding 10% (ΔLVEF) to levels below 50%, and/or a relative reduction in average LV S' greater than 15% to values below 7 cm/s. **Twelve (20%) patient**s met the above criteria and were defined as having **LV systolic dysfunction resulting** from OT. Their characteristics are presented in

Table 10. Systolic left ventricular dysfunction was identified through decreased LVEF in two patients, decreased average LV S' in seven patients, and a combination of both parameters in three patients. Four patients exhibited symptoms consistent with heart failure. Patients were treated with different chemotherapeutic agents and had different risk factors and risk levels. Radiotherapy was provided to eight patients.Ten patients received treatment with cardioprotective medications, specifically RAAS inhibitors, either alone or in conjunction with beta blockers.

Table 10. *Characteristics of patients with LV systolic dysfunction, according to parameters: LVEF and LV S' (ΔLVEF >10% and LVEF < 50% /Δ mean LV S' > 15% and mean LV S' ≤ 7 cm/s)*

Parameters	**LV systolic dysfunction** n = 12
LVEF	n = 2
Average LVS`	n = 7
LVEF + LVS`	n = 3
Day of occurrence	
• Median (IQR)	128 (88, 256)
Symptoms of HF	n = 4
Age, years	
•Median (IQR)	57 (49, 64)
•Min., Max.	43, 73
Smokers	n = 4
BMI, kg/m2, mean (SD)	29.8, (4.3)
Hypertension	n = 8
Diabetes	n = 1
Dyslipidemia	n = 4
Risk of CTRCD	
•Low	n = 3
•Moderate	n = 4
•High	n = 4
Type of chemotherapy	
•Anthracycline	n = 6
•Trastuzumab	n = 3
•Anthra+ trastuzumab	n = 1
•Other	n = 2
Radiotherapy	n = 8
Total radiation dose ≥50 Gy	n = 6

Parameters	LV systolic dysfunction n = 12
Endocrine therapy	n = 9
Taxane	**n = 10**
Cyclophosphamide	n = 6
5 Fluorouracil	n = 1
Cardioprotection	n = 10

Table 11. *Echocardiographic parameters for systolic and diastolic function of the LV and RV in patients with LV systolic dysfunction,*

Parameters	LV systolic dysfunction (n = 12)	p
RVS', cm/s		
• Baseline • At the time of LV dysfunction • Minimum ≤ 9.5cm/s	12.25 (11.40, 13.65) 11.20 (10.10, 12.20) n = 3	p = 0.9
RVFAC, %		
• Baseline • At the time LV dysfunction • Minimum ≤ 35%	45.0 (41.5, 49.5) 39.0 (36.5, 43.5) n = 5	p = 0.1
TAPSE, mm		
• Baseline • At the time of LV dysfunction • Minimum ≤ 16 mm	18.6 (16.2, 23.0) 15.5 (14.6, 19.5) n = 7	**p = 0.007**
Septal LV S', cm/s		
• Baseline • At the time of LV dysfunction • Minimum ≤ 6 cm/s	7.90 (7.00, 8.50) 6.15 (6.00, 6.70) n = 8	**p < 0.001**
Lateral LV S', cm/s		
• Baseline • At the time of LV dysfunction • Minimum ≤ 8 cm/s	9.10 (8.15, 10.40) 7.15 (6.90, 7.90) n = 2	**p = 0.0037**
RVe', cm/s		
• Baseline • At the time of LV dysfunction	11.75 (10.15, 13.50) 11.30 (10.45, 12.25)	p = 0.79
RV E/e'		
• Baseline • On the time of LV dysfunction	4.70 (3.50, 5.20) 4.20 (3.40, 4.80)	p = 0.38
LVe', cm/s		
• Baseline • On the time of LV dysfunction	9.35 (8.00, 11.00) 8.63 (7.70, 9.55)	p = 0.077
LV E/e'		
• Baseline • On the time of LV dysfunction	7.85 (6.35, 9.35) 8.55 (7.45, 9.90)	p = 0.14

Parameters	LV systolic dysfunction (n = 12)	p
MAPSE, mm		
• Baseline	12.30 (11.00, 14.40)	
• On the time of LV dysfunction	11.30 (10.60, 13.40)	**p = 0.014**
hsTnT, ng/L		
• Baseline	8.3 (7.2, 9.8)	
• On the time of LV dysfunction	9.5 (7.6, 12.2)	

A statistically significant decrease in TAPSE ($p = 0.007$), septal ($p < 0.001$), and lateral tissue S' velocities ($p = 0.0037$), as well as MAPSE ($p = 0.0037$), was observed compared to baseline (Table 11). The hsTnT values in these patients were consistently within the normal range. At the time of LV systolic dysfunction, there was no significant decrease in RV systolic parameters (RVS' and RVFAC). However, at a subsequent follow-up stage, 5 patients experienced pathological RV S' and 3 patients had a decreased RVFAC of ≤ 35%.

The incidence of LV systolic dysfunction, defined in our study, can be compared with the incidence reported in studies using the parameter LVGLS. The SUCCOUR research, in which patients were treated with anthracyclines with or without trastuzumab, indicated that 24% had a relative decline in LVGLS of more than 12%, and 4.6% had a decrease in LVEF over a year. When using both criteria, the overall proportion of patients with myocardial dysfunction was 28.6% (Thavendiranathan et al., 2021). Ichikawa et al. (2024) reported a slightly lower incidence of 22% when both functional echographic indicators were utilized, comparable to the incidence of LV systolic dysfunction observed in our study. It is important to highlight that the criterion for a relative decline in LVGLS was set at above 15% according to the new guidelines. In contrast, the SUCCOUR study defined it with a lower threshold of above 12% (Thavendiranathan et al., 2024).

5.1.4.Assessment of MAPSE

Mitral Annular Plane Systolic Excursion (MAPSE) was assessed by calculating the average of the medial and lateral mitral annulus measurements. MAPSE analysis indicated a statistically significant reduction over time since the initiation of OT, corroborating the decline observed in other measures of LV systolic function. The maximum decrease of 1.1 mm (95% CI -1.6, -0.57, $p < 0.001$) was observed at the 6 month (Figure 6). This indicates that the mean baseline value of 13.13 mm declined to a mean of 12 mm. The sensitivity and specificity of this indicator for detecting CTRCD are, however, unsatisfactory, with an AUC of 0.68 at a threshold value of 11.7 mm and 79% and 45%, respectively (Ichikawa et al., 2024). The correlation between MAPSE and LVEF is weak, with a correlation coefficient $R = 0.17$, $p = 0.0072$. There exists a moderate correlation between MAPSE and the average and septal systolic LV S' velocities (respectively, $R = 0.36$ and $R = 0.34$, $p < 0.001$).

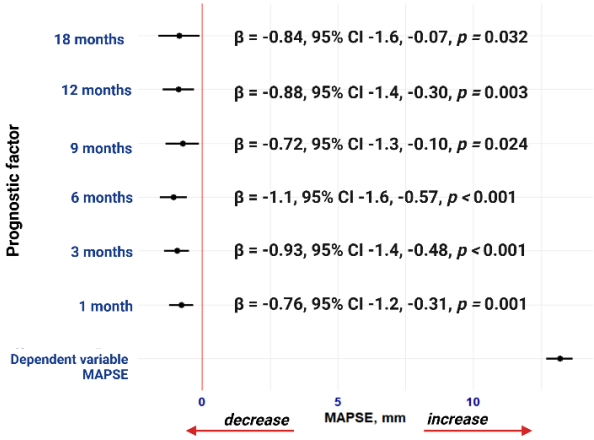

Figure 6. *Evaluation of MAPSE change over time from the start of OT by GEE regression analysis*

5.1.5.Left ventricular diastolic function

The interest of researchers in impaired LV diastolic function as an adverse consequence of OT has increased. Evidence indicates the presence of early diastolic dysfunction within weeks to months following the initiation of cancer treatment (Akpek et al., 2015; Avila et al., 2018; Boyd et al., 2017; Calabrese et al., 2018; Cao et al., 2015; Chang et al., 2016; Serrano et al., 2015; Stoodley et al., 2013; Upshaw et al., 2020). Some researchers have shown that abnormalities in left ventricular diastolic function are delayed in time from the onset of OT by 2-3 years to several decades (Barbosa et al., 2021; Bjerring et al., 2021; Moon et al., 2014; Palmer et al., 2023; Upshaw et al., 2020). The energy depletion of cardiomyocytes, along with microvascular and endothelial disorders, as well as fibrotic processes in the myocardium induced by various antitumor agents, contribute to both early and late disturbances in left ventricular diastolic function (Camilli et al., 2024; Hoffman et al., 2021; Lyle et al., 2018).

In our study, LV diastolic function was evaluated at each follow-up visit in accordance with the guidelines established by the European Association for Cardiovascular Imaging (EACVI) in 2016 (Nagueh et al., 2016).

Figure 7 and Table 12 illustrate the alterations in left ventricular diastolic function at each follow-up stage, expressed as proportions across various grades: normal, diastolic dysfunction grade I, II, and III. In a subset of the assessed patients, diastolic function could not be evaluated.

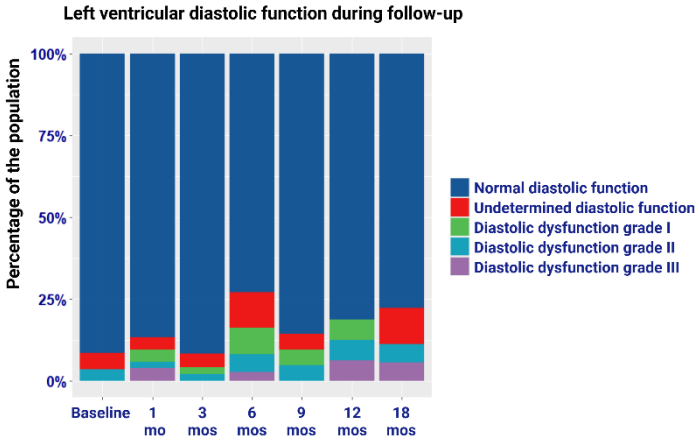

Figure 7. *Graphical depiction of the prevalence of LV diastolic dysfunction at each step of the follow-up.*

At baseline, 92% of the population exhibited normal diastolic function, while only two patients were initially classified with grade II diastolic dysfunction. It is noteworthy that the cases of normal left ventricular diastolic function predominated at each visit. Throughout the follow-up period, **7 patients (11.7%) exhibited** a decline **in LV diastolic function from a normal baseline** (Table 12). Three patients exhibited grade I diastolic dysfunction at the 1st, 6th, and 12th months. Two patients presented with grade II diastolic dysfunction at the 3rd and 6th months. Additionally, two patients were diagnosed with grade III diastolic dysfunction at the 1st and 12th months.

Table 12. *Left ventricular diastolic function at each patient visit*

LV diastolic function	**Day 1** n = 59	**1 mo** n = 53	**3 mos** n = 49	**6 mos** n = 37
Normal	54 (92%)	46 (87%)	45 (92%)	27 (73%)
Undetermined	3 (5.1%)	2 (3.8%)	2 (4.1%)	4 (11%)
Grade I	0 (0%)	**2 (3.8%)**	**1 (2.0%)**	**3 (8.1%)**
Grade II	2 (3.4%)	**1 (1.9%)**	**1 (2.0%)**	**2 (5.4%)**
Grade III	0 (0%)	**2 (3.8%)**	0 (0%)	**1 (2.7%)**

LV diastolic function	9 mos n = 21	12 mos n = 32	18 mos n = 18
Normal	18 (86%)	26 (81%)	14 (78%)
Undetermined	1 (4.8%)	0 (0%)	2 (11%)
Grade I	**1 (4.8%)**	**2 (6.3%)**	0 (0%)
Grade II	**1 (4.8%)**	**2 (6.3%)**	**1 (5.6%)**
Grade III	0 (0%)	**2 (6.3%)**	**1 (5.6%)**

Diastolic LV dysfunction persisted **in 5 patients (8.3%)** until the conclusion of their follow-up. Two patients experienced a concurrent reduction in LVEF to below 50% (46% and 49%).

Depending on the populations being studied, the frequency of diastolic dysfunction varies but can be classified as high, ranging from 16% to 36-42% (Calabrese et al., 2018; Cao et al., 2015; Honda et al., 2017; Palmer et al., 2023; Serrano, González et al. 2015). One study even claims it can reach 70% in the second year following OT (Upshaw et al., 2020). In contrast, other researchers did not observe significant deviations in echocardiographic diastolic parameters (Mincu et al., 2021). The results are challenging to compare because of varying criteria for diagnosing diastolic dysfunction, differences in oncological regimens, and discrepancies in patient follow-up duration. The proportion of patients with LV diastolic dysfunction in our study (11.7% (n=7)) is comparable to the 13% (n = 17) reported by Honda et al. (2017) in a similar population that was treated with trastuzumab with or without anthracyclines (Table 12). The diagnostic criterion for diastolic dysfunction in the study by Honda et al. (2017) is an E/e‘ ratio greater than 15. The researchers observed a concurrent reduction in LVEF in only 7 patients (40%) with confirmed diastolic disorders, whereas in our cohort, systolic left ventricular dysfunction was identified in two patients.

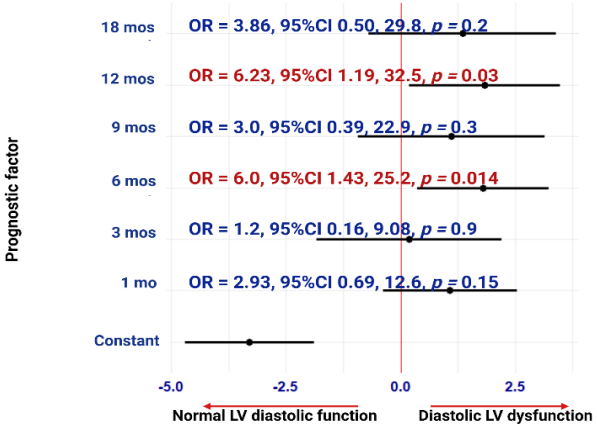

Figure 8. *Forest plot of the GEE logistic regression analysis for the influence of time from the start of OT on the dynamics of left ventricular diastolic function*

To analyze the onset time of diastolic left ventricular dysfunction, cases classified as diastolic dysfunction grades I, II, and III were aggregated into one group. Cases with undetermined diastolic function were excluded. Figure 8 illustrates the analysis of the effect of time from the onset of OT on diastolic left ventricular function.

At the 6th and 12th months of antitumor systemic treatment, the probability of developing LV diastolic dysfunction in our population increased, with odds ratios of 6.0 (95% CI 1.43, 25.2, p = 0.014) and 6.23 (95% CI 1.19, 32.5, p = 0.03), respectively.

This observation is partially aligned with the dynamics of different diastolic echocardiographic parameters. The diastolic parameters in our study exhibit deviations at a relatively early stage (Table 13).

Table 13. *Dynamics of the different parameters of LV diastolic function, assessed by GEE regression analysis*

Time	Beta	95% CI	*p*	Beta	95% CI	*p*
	E/e‘			e‘ (average)		
Day 1	—	—		—	—	
1 mo	0.15	-0.35, 0.66	0.6	-0.07	-0.51, 0.37	0.8
3 mos	**0.67**	**0.15, 1.2**	**0.012**	**-0.62**	**-1.1, -0.16**	**0.008**
6 mos	0.39	-0.19, 0.96	0.2	**-0.63**	**-1.1, -0.11**	**0.017**
9 mos	0.11	-0.61, 0.84	0.8	0.17	-0.48, 0.81	0.6
12 mos	0.51	-0.09, 1.1	0.094	-0.38	-0.96, 0.19	0.2
18 mos	-0.25	-1.0, 0.52	0.5	-0.42	-1.2, 0.36	0.3
	IVRT			DecT		
Day 1	—	—		—	—	
1 mo	1.0	-4.6, 6.6	0.7	2.8	-11, 16	0.7
3 mos	**5.7**	**-0.08, 11**	**0.053**	-3.2	-17, 10	0.6
6 mos	**6.8**	**0.34, 13**	**0.039**	11	-4.0, 26	0.15
9 mos	0.35	-7.6, 8.3	>0.9	1.9	-17, 21	0.8
12 mos	4.5	-2.1, 11	0.2	-0.18	-16, 16	>0.9
18 mos	3.4	-5.0, 12	0.4	6.1	-14, 27	0.6

A statistically significant increase in LV E/e' was observed at month 3 (β 0.67, 95% CI 0.15, 1.2, p = 0.012). Additionally, a decrease in LV e' was noted at months 3 and 6 (β -0.62, 95% CI -1.1, -0.16, p = 0.008 and β -0.63, 95% CI -1.1, -0.11, p = 0.017, respectively), along with a prolongation of IVRT at month 6 (β 6.8, 95% CI 0.34, 13, p = 0.039). Similar dynamics of distinct left ventricular (LV) diastolic parameters have been documented in previous studies (Avila et al., 2018; Barbosa et al., 2021; Boyd et al., 2017; Calabrese et al., 2018; Chang et al., 2016; Gąsior et al., 2024; Moon et al., 2014; Palmer et al., 2023; Serrano et al., 2015; Stoodley et al., 2013; Upshaw et al., 2020), which elucidate the heightened probability of developing LV diastolic dysfunction at 6th month (OR 6.0, p = 0.014).

5.1.6.Left Ventricular Myocardial Performance Index (LVMPI)

The LV Myocardial Performance Index (LVMPI), also known as the Tei index, is a comprehensive measure of the left ventricle's systolic and diastolic functions. It has been examined as a sensitive diagnostic marker in various cardiac conditions, including ischemic heart disease, heart failure, myocarditis, cardiac amyloidosis, diabetic cardiomyopathy, and Tako-Tsubo syndrome (Askin, Yuce, et al. 2023) (Mirna, Vogl, et al. 2023). Researchers are focusing on this parameter due to its ease of measurement, independence from variations in preload and afterload, insensitivity to heart rate variability, and the availability of a good echographic window. The index derived from PW Doppler interrogation of blood flow through the mitral valve and LV outflow tract (LVMPI-PW) is a validated method, with normal values of 0.39 ± 0.05. Values exceeding 0.49 are considered pathological (Flachskampf et al., 2021; Mirna et al., 2023). The evaluation of the dynamic alteration of the index assessed via tissue Doppler at the medial annulus (LVMPI-TDI septal) indicated a statistically significant increase of 0.03 in 3rd month (95% CI 0.00, 0.06, p = 0.041) (Table 14). LVMPI-PW exhibited a statistically significant increase in the 6th month from the initiation of OT, with a change of 0.04 (95% CI 0.00, 0.08, p = 0.045). In the 12th month, an increase was observed, approaching statistical significance. The LVMPI-TDI index assessed at the lateral annulus did not exhibit a statistically significant change (data not presented in the table).

Scientific data support the diagnostic utility of the parameter in identifying myocardial damage resulting from OT. Elalouani et al. (2012) observed an increase in LVMPI following the completion of anthracycline therapy courses, with values rising from 0.29 (0.22–0.39) to 0.57 (0.29–0.61), p = 0.04. Turan et al. (2017) reported an increase in LVMPI-TDI of the lateral mitral annulus from 0.37 ± 0.08 to 0.43 ± 0.07 (p < 0.001) following a single infusion of 5FU. Zhang

et al. (2017) found that an increase in LVMPI-PW by 0.095 predicts the occurrence of cardiotoxicity caused by anthracyclines. According to a meta-analysis of 13 studies on anthracycline OT, 11 of the studies demonstrated an increase in LVMPI. However, only five studies showed that this index could be more effective than LVEF in detecting myocardial dysfunction (Bennett et al., 2021). The authors state that there is not enough data to justify the application of the LVMPI in the standard evaluation of cardiotoxic cardiac damage.

***Table 14**. GEE linear regression analysis of the change over time of LVMPI measured with tissue Doppler at the septal annulus (left) and measured with PW Doppler (right)*

Time	LVMPI-TDI septal			LVMPI-PW		
	Beta	**95% CI**	***p***	**Beta**	**95% CI**	***p***
Day 1	—	—		—	—	
1 mo	0.01	-0.02, 0.03	0.7	0.02	0.00, 0.05	0.087
3 mos	**0.03**	**0.00, 0.06**	**0.041**	0.03	-0.01, 0.07	0.087
6 mos	0.02	-0.02, 0.05	0.3	**0.04**	**0.00, 0.08**	**0.045**
9 mos	-0.02	-0.06, 0.02	0.3	0.02	-0.04, 0.07	0.6
12 mos	0.01	-0.02, 0.04	0.4	**0.04**	**0.00, 0.08**	**0.055**
18 mos	0.01	-0.05, 0.07	0.8	0.04	-0.02, 0.10	0.2

The mean maximum value of LVMPI-PW in our population was 0.56 (SD 0.12), with a median time to its maximum increase of 108 days (IQR 45.8, 392.5). The maximal deviation of LVMPI-PW during the follow-up was available for 52 patients. Only 8 patients exhibited LVMPI-PW values within the normal range. In the remaining 44 patients, LVMPI-PW showed an increase at some point following the initiation of OT. In patients exhibiting maximum index values exceeding 0.6, there was a notable decrease in early diastolic tissue velocity LVe‘, as well as in septal and average LVS’, accompanied by prolongation of IVRT, consistent with the findings from the correlation analysis (Figure 5).

The greatest correlation observed was between LVMPI-PW and IVRT ($R = 0.51$, $p < 0.001$) (Figure 5). LVMPI-PW exhibited a weak

correlation with LVEF and septal LVS', with respective values of R = -0.24 ($p < 0.001$) and R = -0.21 ($p < 0.001$). LVMPI-TDI assessed at the medial mitral annulus demonstrated significant correlations with diastolic parameters IVRT (R 0.31, $p < 0.001$), LVe' (R = -0.27, $p < 0.001$), and septal LVS' (R -0.31, $p < 0.001$).

The relationships indicated demonstrate that an increase in LVMPI (PW and TDI) is associated with a prolongation of isovolumetric relaxation time and a reduction in the early diastolic tissue relaxation velocity e' of the left ventricle. Conversely, as myocardial performance indexes rise the septal S' of the left ventricle decreases.

5.2.Assessment of right ventricular function

Right ventricular systolic function is affected by various modalities of oncological therapy, including chemotherapy, targeted therapy, and radiotherapy (Chhikara et al., 2021; Shi et al., 2022; Sławiński et al., 2024; Theetha Kariyanna et al., 2023). From a clinical perspective, the questions posed include: What is the frequency of right ventricular involvement, the potential for reversibility of right ventricular disorders, the timing of their onset in relation to left ventricular disorders, and their prognostic significance?

5.2.1.Monitoring of the right ventricular fractional area change (RVFAC)

The follow-up analysis of RVFAC change post-initiation of OT indicated a statistically significant reduction as early as the first month, with a decrease of 2.3% (95% CI -3.9, -0.75, p = 0.004). This reduction was sustained until the 18th month, showing a decrease of 3.7% (95% CI -6.9, -0.43, p = 0.026) (Figure 9).

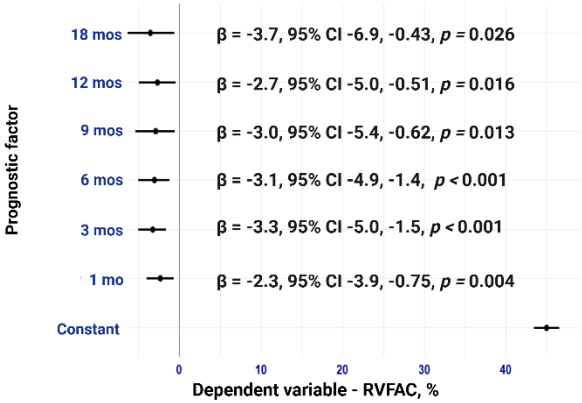

***Figure 9**. Foresplot of GEE regression analysis for the impact of time since OT onset on RVFAC change*

Following the initiation of oncological therapy, the earliest recorded minimal RVFAC was evaluated for each patient in comparison to baseline RVFAC and the conclusion of chemotherapy (Figure 10). The mean difference between the baseline and minimal RVFAC was 7.45% (95% CI 6.0, 8.9, p = 0.0000). The median percentage decrease in RVFAC for the overall population was 15% (IQR 10, 23).

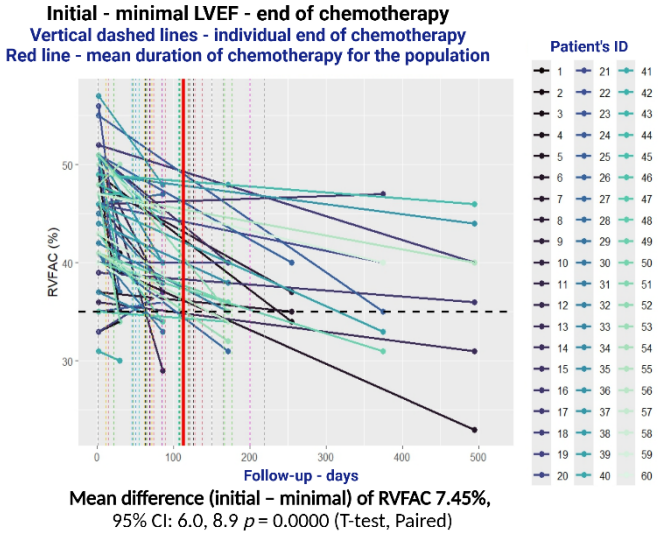

Figure 10. *Baseline and minimum RVFAC in individual patients and mean difference in the entire population. The time to minimum RVFAC is graphically presented against the mean duration of chemotherapy (red vertical line). The horizontal black dashed line points to the normal range for RVFAC*

There is scientific evidence of a decrease in RVFAC as a result of anthracycline-based CT and HER2-targeted therapy (Abdar Esfahani et al., 2016; Boczar et al., 2016; Calleja et al., 2015; Del Bene et al., 2023; Planek et al., 2020; Rossetto et al., 2024; Song et al., 2017; Tanindi et al., 2011) and at the same time some studies do not find a change in the parameter (Chang et al., 2016; Ferri et al., 2022;

Moustafa et al., 2016; Wang et al., 2021; Zhao et al., 2020). Similar to our study, Tanindi et al. (2011) reported a small (about 2%) but statistically significant decrease in RVFAC after two cycles of anthracycline-based chemotherapy (from 63.7+3.63% to 61.2+4.41%, $p < 0.001$). In a study conducted by Boczar et al. (2016), RVFAC decreased by an average of 6% from 48.3% (95% CI 44.8, 51.74) to 42.1% (95% CI 38.5, 45.6%) at month 3, following anthracycline chemotherapy ($p = 0.01$). Planek et al. (2020) found that after 6 months of anthracycline treatment, RVFAC fell from 47.3 ± 4.4% to 43.7 ± 3.9% ($p < 0.01$), with the degree of decline rising with the cumulative dose. Song et al. (2017) observed a 3% decrease in RVFAC at the conclusion of anthracycline-based therapy (from 44.3% to 41.2%, $p = 0.000$). A meta-analysis by Theetha Kariyanna et al. (2023) of 15 studies with a total population of 644 patients found that anthracycline and trastuzumab therapy resulted in a reduction in RVFAC of 3.74% (95% CI 1.33, 6.15, $p < 0.01$). The data from our study regarding the quantitative decline in RVFAC are close to the above-cited studies, according to which RVFAC declines by 3 to 6% over a different follow-up period – 3 to 6 months. By finding a persistent decrease in the parameter up to the 18th month, our data contradict those of Barthur et al. (2017), according to which the systolic function of the right ventricle is restored by the 18th month from the start of OT and are in confirmation of the findings of other scientific teams, which find a decrease in RVFAC at the 3rd, 6th, 9th and 12th months after OT (Abdar Esfahani et al., 2016; Boczar et al., 2016; Del Bene et al., 2023; El-Sherbeny et al., 2023; Planek et al., 2020; Rossetto et al., 2024; Song et al., 2017).

Twenty-one patients (35%) exhibited a minimal RVFAC of ≤35%, with 12 of these patients demonstrating a relative percentage decrease of more than 20% from baseline RVFAC. The relative reduction in RVFAC was chosen to surpass the mean percentage decrease observed in the population and address measurement variability.

Patients exhibiting a notable reduction in RVFAC were categorized into a distinct group and compared with the rest of the population, where the minimal RVFAC did not show a significant decrease (Table 15).

Table 15. *Comparative characteristics of patients exhibiting a minimum RVFAC ≤35% with a relative decrease ΔRVFAC > 20% versus the remainder of the population.*

Parameter	RVFAC ≤ 35%, ΔRVFAC> 20% N = 12	The rest of the population N = 48	p[1]
Minimum RVFAC			**<0.001**
•Mean, (SD)	32.2, (3.5)	40.9, (3.9)	
•Min./Max,	23.0, 35.0	36.0, 50.0	
Baseline RVFAC, mean (SD)	46.1, (5.1)	39.6, (4.8)	0.7
Previous CT, n (%)	3 (25%)	2 (4.2%)	**0.050**
Previous RT, n (%)	3 (25%)	2 (4.2%)	**0.050**
CT/ Targeted therapy , n (%)			**0.050**
•Anthracycline	2 (17%)	19 (40%)	
•Trastuzumab	1 (8.3%)	14 (29%)	
•Anthracycline + trastuzumab	**3 (25%)**	**6 (13%)**	
•Other	**6 (50%)**	**9 (19%)**	
Dispnea on exertion	1 (8.3%)	7 (14.6%)	0.3
Average. LVS', median (IQR), cm/s	7.55 (6.75, 8.13)	8.30 (7.65, 9.25)	0.068
Septal LVS', median (IQR), cm/s	7.00 (6.20, 7.80)	7.60 (6.90, 8.00)	0.14
Lateral LVS', median (IQR), cm/s	7.95 (7.15, 9.10)	8.95 (8.05, 10.00)	0.076
LVe', median (IQR), cm/s	8.58 (7.20, 11.00)	9.60 (8.30, 12.20)	0.2
RVS', cm/s			0.2
•Median (IQR)	10.55 (9.50, 12.9)	11.70 (11.0, 13.2)	
•≤ 9.5 cm/s	**3 (25%)**	**2 (4.3%)**	**0.052**
•≤ 9.5 cm/s + ΔRVS' > 10%	**1 (8.3%)**	1 (2.1%)	0.4
TAPSE, mm			0.6
•Median (IQR)	16.7 (15.9, 21.0)	18.7 (15.6, 21.0)	
•TAPSE ≤ 16 mm	**4 (40%)**	15 (33%)	0.7
•TAPSE ≤ 16mm+ΔTAPSE>15%	**1 (10%)**	9 (20%)	0.7
RVMPI-TDI			0.4
•Median (IQR)	0.40 (0.29, 0.61)	0.37 (0.30, 0.46)	
•RVMPI-TDI ≥ 0.55	3 (25%)	8 (17%)	0.7
•RVMPI-TDI≥ 0.55+Δ >15%	**1 (8.3%)**	5 (11%)	>0.9

1Wilcoxon rank sum exact test; Wilcoxon rank sum test; Fisher's exact test; Pearson's Chi-squared test

No significant differences were observed between the groups regarding demographics, comorbidities, risk of cardiotoxicity, type of OT, and utilization of cardioprotective therapy. Half of these patients received treatment with modalities other than anthracyclines and trastuzumab. These data indicate that direct myocardial injury may occur even with chemotherapeutic agents typically not associated with cardiac dysfunction. During the occurrence of minimal RVFAC, relatively low systolic and diastolic tissue velocities of the LV are observed: the median for the septal LVS' was 7.0 cm/s (IQR 6.2, 7.8), for the average LV S' is 7.55 cm/s (IQR 7.15, 9.1), and for LVe' it is 8.58 cm/s (IQR 7.2, 11.0). Three patients exhibited a low systolic tissue S' velocity of the RV $\leq$ 9.5 cm/s; four demonstrated a TAPSE of $\leq$ 16 mm and three had an RVMPI-TDI of $\geq$ 0.55. Right ventricular dysfunction is established through more than one parameter in these instances. On the other hand, these findings indicate that the diminished RVFAC may solely reflect RV systolic dysfunction or that the variability of this measure contributes to the overestimation of changes in RV systolic function. The analysis of the RVFAC parameter's variability revealed an intraclass correlation coefficient of 0.79 (95% CI 0.64, 0.89, $p < 0.001$), implying moderate agreement between repeated measurements. The Bland-Altman test indicates a slight mean difference of -0.78% between the measurements but with a wide confidence interval (-7.63 to 6.06%). The mean difference between the baseline and minimum RVFAC of the examined population is 7.45%, which exceeds the parameter's limits of agreement (Figures 10 and 11). The variability of the parameter is partially addressed in this study, as the final value of RVFAC at each follow-up visit represents the average of a minimum of three measurements. Contrary to our findings, the literature reports a higher reliability and interobserver correlation coefficient of 0.81 (Planek et al., 2020).

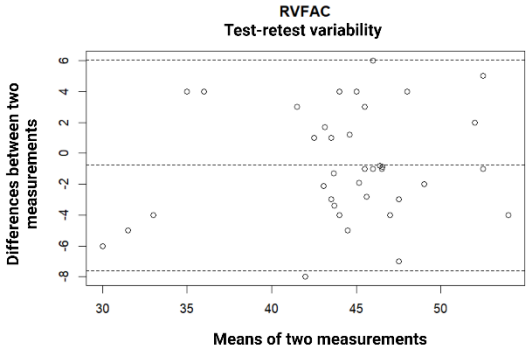

Figure 11. *Bland-Altman plot of the variability of the RVFAC parameter. The mean difference of the measurements is -0.782500 (limits of agreement of the measurements -7.63, 6.06)*

5.2.2. Surveillance of the systolic tissue velocity of the right ventricle (RVS')

In order to identify earlier myocardial disorders and surmount the variability and limitations of the RVFAC indicator, the systolic velocity indicator from tissue Doppler of the lateral tricuspid annulus (RVS`) was concurrently monitored. This metric has a strong intraclass correlation coefficient (0.98, 95% CI 0.96, 0.99, $p < 0.001$), indicating little intraobserver variability and excellent reliability in repeated exams. The parameter is, therefore, appropriate for monitoring the RV's functionality over time. The right ventricle contracts predominantly in a longitudinal direction due to its composition and the orientation of its subendocardial myofibers. Histological analysis indicates that the subendocardial myocardial layer is susceptible to the harmful effects of CT (Mortensen et al., 1986). Impairments in the longitudinal myocardial function of the RV cannot be compensated for because of the absence of a middle myocardial layer of circumferential fibers. These considerations imply that echocardiographic evaluation of RV longitudinal function may be indicative of early myocardial disorders. Such parameters are the

RVS` and the longitudinal strain of the right ventricular free wall (Liu, 2020).

The existing scientific findings are inconsistent concerning the time and magnitude of alterations in systolic S' tissue velocity of the RV. Several studies have demonstrated a reduction in the RVS` (Abdar Esfahani et al., 2016; Chang et al., 2016; Del Bene et al., 2023; Fawzy et al., 2024; Rossetto et al., 2024; Song et al., 2017; Tanindi et al., 2011; Wang et al., 2021), predominantly attributed to anthracycline-based treatment. Other studies have not observed any changes in this indicator (Anqi et al., 2019; Chen et al., 2019; El-Sherbeny et al., 2023; Xu et al., 2021). A meta-analysis of 21 studies involving 1355 patients revealed that RVS' diminished at the conclusion of OT, with a mean difference of −0.401 (95% CI −0.580, −0.222, p = 0.000) (Shi et al., 2022). A notable decrease in RVS` was observed after 3-6 cycles of CT and remained stable at 12 months, with no significant alteration in RVFAC (Shi et al., 2022). The existing research on RVS' as an indicator of functional alterations in the RV resulting from OT exhibit heterogeneity regarding oncological regimens, population size, and the frequency and duration of follow-up. It should be highlighted that there is confirmation of a decrease in RVS' under anthracycline-based regimens, and this assertion is supported not just by individual studies but also a major meta-analysis.

At the initial follow-up visit, our research demonstrates a statistically significant reduction in RVS' by 0.73 cm/s (95% CI -1.3, -0.17, p = 0.010). This reduction occurs after one or two cycles of CT, depending on the treatment regimen employed (Table 16). This finding aligns with the results of Tanindi et al. (2011), who reported an early reduction in RVS' from 11.35±1.85 cm/s to 11.0±1.82 cm/s (p = 0.002) following a single course of anthracycline-based CT.

Table 16. *GEE regression analysis of the change over time in RVS'*

Time	RVS` Beta	95% CI	p
Day 1	—	—	
1 month	**-0.73**	**-1.3, -0.17**	**0.010**
3 months	**-0.72**	**-1.2, -0.23**	**0.004**
6 months	**-0.62**	**-1.2, -0.05**	**0.032**
9 months	-0.06	-1.5, 1.4	>0.9
12 months	**-0.87**	**-1.4, -0.32**	**0.002**
18 months	-0.56	-1.7, 0.55	0.3

Data indicate a statistically significant decrease in RVS` by the sixth month (β -0.62, 95% CI -1.2, -0.05, p = 0.032). A significant decrease of 0.87 cm/s (95% CI -1.4, -0.32, p = 0.002) in tissue systolic RV velocity was seen one year after the beginning of OT. The findings align with the results reported by several researchers (Abdar Esfahani et al., 2016; Fawzy et al., 2024; Rossetto et al., 2024; Shi et al., 2022; Wang et al., 2021). At 18 months, there was no additional significant reduction in the parameter, which contradicts the long-term changes reported by Del Bene et al. (2023).

Figure 12 depicts a study of the earliest minimal RVS' for each patient in relation to the individual duration of CT (vertical dashed lines) and the average duration of CT (red line). The greatest parameter decrease occurred at different time points, including before the end of CT and in four patients at the conclusion of the 18-month follow-up period. The time for the reduction of RVS` is contingent upon the frequency of follow-up and the various modalities of OT: CT, a combination of CT and targeted therapy, and the presence or absence of RT. The conclusion is that RVS` monitoring must be conducted at each follow-up visit. The median time for decreasing RVS` to a minimum is 105 (IQR 30, 210) days. The mean difference between baseline and minimum reported RVS` was 1.88 cm/s (95% CI 1.42, 2.34, p = 0.0000) (Figure 12). The mean difference of 1.88 cm/s surpassed the concordance limits established by the Bland-Altman test, which were

-1.49 and 1.14 cm/s (Figure 13), reinforcing the follow-up indicator's reliability.

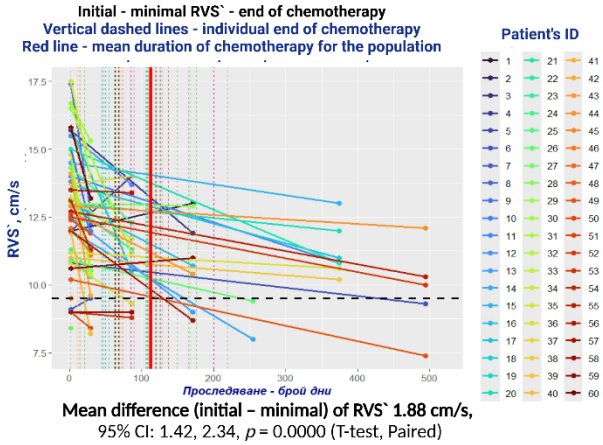

Figure 12. *Baseline and minimum RVS` in individual patients and the mean difference in the entire population. The time to minimum RVS` is graphically presented against the mean duration of chemotherapy (red vertical line). The horizontal black dashed line points to the normal lower range for RVS`*

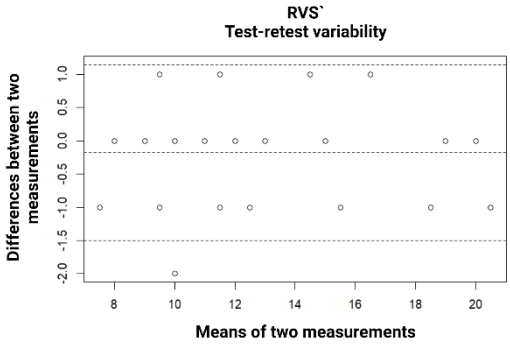

Figure 13. *Bland-Altman plot of the variability of the RVS`parameter. The mean difference of the measurements is -0.782500 (limits of agreement of the measurements -7.63, 6.06)*

In 12 patients (22%), RVS` reached pathological values of ≤ 9.5 cm/s. Among these, 5 patients (8.3%) exhibited a relative reduction of the indicator exceeding 15% compared to the baseline value. It means that in these patients, the parameter significantly deteriorated following the initiation of OT, suggesting the presence of systolic right ventricular dysfunction as a consequence of OT. Table 17 presents the characteristics of these patients.

Table 17. *Characteristics of patients (n = 5) with evidence of right ventricular systolic dysfunction, defined on the basis of a relative reduction of more than 15% in RVS' to ≤ 9.5 cm/s*

Echo parameters	**RVS' ≤ 9.5 Δ > 15%** n = 5	**Clinical parameters**	**RVS'≤ 9.5 Δ >15%** n = 5
Min. RVS', cm/s	7.40 - 9.00	**Risk of CTRCD**	
Baeline RVS', cm/s	10.20 - 12.50	•High	n = 1
Min. RVFAC, %	23.0 - 45.0	•Moderate	n = 1
•RVFAC ≤35%	n = 2	•Low	n = 1
•RVFAC ≤35% + Δ >20%	n = 0	**Age, years**	31 - 65
Min. septal LVS`, cm/s	5.00 - 7.00	**Smokers**	n = 2
•≤ 6 cm/s	n = 3	**Symptoms**	
Min. average LVS`, cm/s	5.95 - 8.25	Dispnea on exertion	n = 0
•≤ 7 cm/s	n = 3	**Type of OT**	
Min. lat. LVS`, cm/s	5.8 - 9.5	•Anthracycline	n = 2
Min. LVEF, %	54.0, 60.0	•Trastuzumab (Trz)	n = 1
TAPSE, mm	9.7 - 21.0	•Doocetaxel/Platine	n = 1
•≤16 mm + Δ > 15%	n = 3	•5Fluorouracil	n = 1
Max. RVMPI-TDI	0.31 - 0.64	•Anthra + Trz	n = 0
•>0.55 + Δ > 15%	**n = 1**	•Radiotherapy	n = 2
Max. RVMPI-PW	0.14 - 0.64	•Endocrine therapy	n = 2
		Max. hsTnT, ng/L	6.3 -16.8

The prevalence of pathological lowering of the parameter exceeds that discovered by Wang et al. (2021), despite the fact that in the population investigated, anthracyclines were supplied to all patients at greater doses. On the other hand, Wang et al. (2021) only followed participants for 10 months. Fawzy et al. (2024) identified a significantly elevated rate (39.4%) of pathological reduction in RVS`,

utilizing a higher threshold of 10 cm/s for definition. All patients received treatment with anthracyclines, and 50% were administered trastuzumab (Fawzy et al., 2024).

The our data showed that within the group with pathological decline of RVS`, the RV S' ranged from 7.4 to 9 cm/s, with only two patients exhibiting an RVFAC below 35% and none presenting an LVEF below 50%. The patients exhibited differing levels of risk for developing CTRCD and received treatment with multiple antitumor agents, including non-anthracycline therapies such as trastuzumab, 5FU, docetaxel, and cisplatin. No patient demonstrated symptoms consistent with HF. Nevertheless, low values of left ventricular systolic tissue velocities were observed. Left ventricular septal velocity S' attained minimum values ranging from 5 to 7 cm/s; in three patients, it was observed to be ≤ 6 cm/s. The minimum values of the average LVS' ranged from 5.95 to 8.25 cm/s, with three patients reached values below 7 cm/s. This demonstrates that a substantial reduction in the septal and average LVS' can be identified when diagnosing a pathologically decreased RVS' ≤ 9.5 cm/s. The other parameters could be within the normal limits. The correlation analysis further substantiates these findings. A moderate correlation exists between the septal S' of the LV and RVS' with $R = 0.44$ ($p < 0.0001$), and between the average LVS' and RVS' with $R = 0.31$ ($p < 0.0001$). The correlation between the lateral LV S' and RV S' is weak, with $R = 0.17$ and $p < 0.0001$ (Figure 22). The synchronized drop in the RV and LV systolic tissue velocities supports the vulnerable longitudinal myocardial layer theory, as these parameters indicate longitudinal myocardial systolic function (Liu et al., 2020).

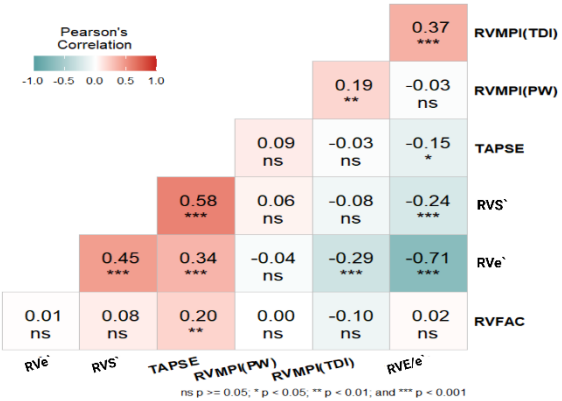

Figure 14. *Pearson correlation analysis of the relationship between systolic and diastolic RV parameters. Correlation coefficients and significance levels are shown (ns – not significant, * - $p < 0.05$, ** - $p < 0.001$ and *** - $p < 0.001$)*

The RVS` shows no correlation with the RVFAC parameter ($R = 0.08$); however, it exhibits a strong correlation with TAPSE ($R = 0.58$, $p < 0.001$) (Figure 14).

5.2.3.TAPSE monitoring

The TAPSE indicator measures the longitudinal systolic function of the RV and is affected by the heart's tracking motion (van den Bosch et al., 2017). The parameter's disadvantages include its reliance on preload and afterload, and the interrogation angle (Rudski et al., 2010). Numerous research teams have investigated the dynamics of the TAPSE following OT. Tanindi et al. (2011) reported an early decrease in TAPSE following one course of treatment with anthracyclines, cyclophosphamide, and 5FU for breast cancer, from 18.2 ± 2 mm to 17.8 ± 1.9 mm, $p = 0.002$. Chang et al. (2016) found a decrease in TAPSE following one cycle of anthracycline-based regimens, from 19.4 ± 4.7 mm to 15.7 ± 6.1 mm, with further reduction observed after three cycles ($p = 0.01$). Radiotherapy may induce early abnormalities

in the indicator, observed in the 4th week of treatment and one-month post-treatment, with mean values decreasing from 21.8 ± 2.5 mm to 21.2 ± 2.1 mm and subsequently to 20.9 ± 1.2 mm, p = 0.026 (Li et al., 2021). Sławiński et al. (2024) reported a notable reduction in TAPSE (from 22.1 mm to 20.3 mm, p = 0.021) as a result of combined treatment of chemotherapy and radiotherapy, whereas chemotherapy alone does not yield this effect. Other studies indicated a notable reduction in TAPSE within 6 to 12 months following the initiation of anthracycline-based chemotherapy, irrespective of alterations in other functional RV parameters, such as RVFAC and RVS' (Abdar Esfahani et al. (2016), Rossetto et al. (2024), Wang et al. (2021), Xu et al. (2021)). After a HER2-targeted or combined with anthracycline treatment, Kılıçaslan et al. (2015) also observed a decrease in TAPSE at 6 months. Data are available regarding long-term abnormalities in TAPSE following a 2-year follow-up in a population treated with anthracyclines ± trastuzumab ± RT (Del Bene et al., 2023). Long-term right ventricular damage, identifiable through various indicators such as TAPSE, persists even 13 years post-anthracycline-based therapy and RT (Murbraech et al., 2016).

Data from other research showed that TAPSE remained unchanged regardless of the chemotherapy and radiation treatments used (Krastev et al., 2010; Anqi et al., 2019; Chen et al., 2019; Cherata et al., 2019; Ferri et al., 2022; Keramida et al., 2019; Lange et al., 2012; Moustafa et al., 2016; Paraskevaidis et al., 2017; Zhao et al., 2020).

The current study did not observe a statistically significant reduction in TAPSE across various follow-up stages within the overall population. A decreasing trend in the indicator was observed in the 3rd, 6th, and 12th months (Figure 15).

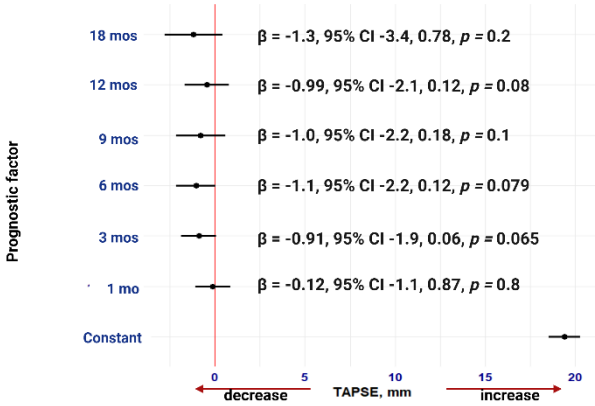

Figure 15. *Evaluation of TAPSE change over time from the start of OT by GEE regression analysis*

Despite the absence of significant changes in the TAPSE index during follow-up visits, an analysis of the individual minimum TAPSE values in 51 patients revealed that 25 patients exhibited a decline to pathological levels (≤ 16 mm) throughout the follow-up period, which averaged 168 days (Table 18). The reference value of 16 mm was selected, which is lower than the 17 mm specified in the guidelines, to enhance the reliability of detecting right ventricular dysfunction. At the point of maximum reduction in TAPSE, RVS' values were significantly lower at 10.51 cm/s (SD 1.43) compared to 12.55 cm/s (SD 2.03) in patients with a minimum TAPSE value exceeding 16 mm, $p < 0.001$ (Table 18). Nine patients (36%) with a TAPSE ≤ 16 mm attained an RVS' ≤ 9.5 cm/s, while 11 patients (44%) reached an RVFAC ≤ 35% throughout the follow-up period. Conversely, the group with a minimum TAPSE > 16 mm had only two patients (7.7%) who achieved a minimum RVS' of ≤ 9.5 cm/s ($p = 0.014$) and four patients (15%) who achieved a minimum RVFAC of ≤ 35% ($p = 0.025$).

Table 18. *Comparison of some indicators between patients with a decrease in TAPSE ≤ 16 mm and patients with a minimum value of TAPSE >16mm*

Parameters	TAPSE ≤ 16 N = 25	TAPSE > 16 N = 26	p[1]
BaselineTAPSE, mm (mean, (SD))	17.36, (2.86)	20.46, (2.63)	**<0.001**
Min. TAPSE, mm (mean, (SD))	14.14, (1.45)	19.01, (1.81)	**<0.001**
RVFAC at the time of min. TAPSE, %, (mean, (SD))	41.0, (5.9)	43.6, (5.2)	0.14
Achieved min. RVFAC ≤ 35%	n =11 (44%)	n = 4 (15%)	**0.025**
RVS‘ at the time of min. TAPSE, cm/s, (mean, (SD))	10.51, (1.43)	12.55, (2.03)	**<0.001**
Min. RVS’ ≤ 9.5 cm/s	n = 9 (36%)	n = 2 (7.7%)	**0.014**
Min. sept. LVS’ ≤ 6 cm/s	n = 8 (32%)	n = 2 (7.7%)	**0.038**
Time to min. TAPSE from the start of OT, median (IQR)	168 (65, 268)	108 (44, 255)	0.5

1Wilcoxon rank sum test; Pearson‘s Chi-squared test; Fisher‘s exact test

The correlations between TAPSE and RVFAC, as well as RVS`, further support these findings (Figure 14). A significant positive correlation exists between TAPSE and RVS ($R = 0.58$, $p < 0.001$), likely attributable to both parameters reflecting the longitudinal function of the right ventricle. A weak correlation exists with the RVFAC indicator ($R = 0.2$, $p = 0.001$). The proportion of patients exhibiting a minimum septal RVS’ ≤ 6 cm/s was significantly higher at 32% (n = 8) in the cohort with a minimum TAPSE ≤ 16 mm, compared to 7.7% (n = 2) in the cohort with a minimum TAPSE > 16 mm.16 mm.

5.2.4.Evaluation of right ventricular diastolic function

The evaluation of RV diastolic function was conducted following the algorithm outlined in the European Society of Cardiology guidelines for right ventricular assessment (Rudski et al., 2010). Figure 16 and Table 19 illustrate the distribution of individuals based on RV diastolic function.

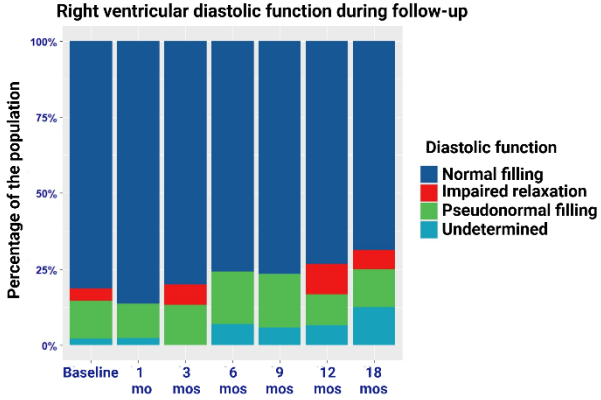

***Figure 16**. Graphical depiction of the proportions of RV diastolic dysfunction at each step of the follow-up*

***Table 19.** Diastolic function of the right ventricle at each of the patient visits*

RV diastolic function	**Day 1** N = 48	**1 mo,** N = 44	**3 mos,** N = 45	**6 mos,** N = 29	**9 mos,** N = 17	**12 mos,** N = 30	**18 mos,** N = 16
Normal	39 (81%)	38 (86%)	36 (80%)	22 (76%)	13 (76%)	22 (73%)	11 (69%)
Impaired relaxation	2 (4.2%)	0 (0%)	3 (6.7%) **2 new cases**	0 (0%)	0 (0%)	3 (10%) **3 new cases**	1 (6.3%) **1 new case**
Pseudonormal filling	6 (13%)	5 (11%) **1 new case**	6 (13%) **4 new cases**	5 (17%)	3 (18%) **2 new cases**	3 (10%)	2 (13%)
Undetermined	1 (2.1%)	1 (2.3%)	0 (0%)	2 (6.9%)	1 (5.9%)	2 (6.7%)	2 (13%)

Normal diastolic function of the RV is predominant at all stages of patient follow-up. No cases of restrictive filling of the RV have been registered. In the first month, one case of newly diagnosed RV diastolic dysfunction of the pseudonormal filling type was identified. In the third month, two cases of newly diagnosed impaired relaxation and four new cases of pseudonormal filling type were recorded. In the 9th month, two newly diagnosed cases of pseudonormal filling type of the RV occurred; in the 12th month, three new cases of impaired

relaxation were noted, and in the 18th month, one case of newly diagnosed impaired relaxation of the RV was identified.

The diastolic function of the RV was categorized into two binary states: pathological and normal diastolic function. In the group exhibiting RV diastolic dysfunction, cases of impaired relaxation and pseudonormal filling type were aggregated, while those with undetermined diastolic function were excluded. The impact of time since the onset of OT on alterations in diastolic right ventricular function was examined (Figure 17).

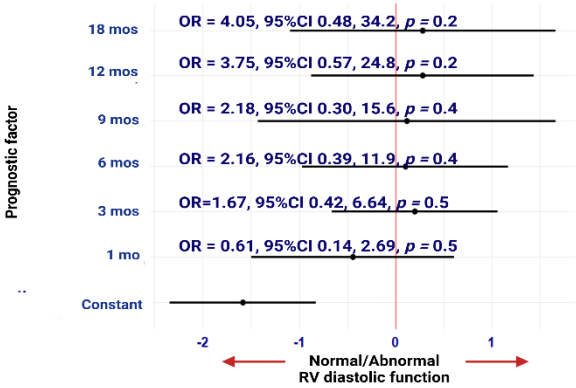

Figure 17*. Forest plot of GEE logistic regression analysis for the influence of time from the onset of OT on the dynamics of RV diastolic function*

No significant deterioration in the diastolic function of the right ventricle was observed from the onset of the OT at any follow-up stage.

Analysis of the individual parameters over time (Table 20) revealed that only the early diastolic e' velocity of the RV exhibited a statistically significant decrease at the 3rd month, with a reduction of 0.95 cm/s (95% CI -1.6, -0.2, p = 0.007), and at the 12th month, with a decrease of 1.2 cm/s (95% CI -2.2, -0.13, p = 0.027). The E/A

indicator showed a decreasing trend at the 3rd month (p = 0.062), while the E/e' indicator exhibited a tendency to increase (p = 0.075). The observed minimum value of RVe' after initiating OT was a median of 9.6 cm/s (IQR 8.15, 10.95), compared to a baseline median RVe' of 12.3 cm/s (IQR 10.4, 14.1), p < 0.001.

Table 20. *GEE regression analysis for the change in the RV indicators E/A, Deceleration time (DecT), E/e' and e'*

Time	RV E/A			RV DecT		
	Beta	95% CI	p	Beta	95% CI	p
Day 1	—	—		—	—	
1st mo	-0.02	-0.10, 0.07	0.7	14	-7.6, 35	0.2
3rd mo	**-0.09**	**-0.19, 0.00**	**0.062**	4.6	-15, 24	0.6
6th mo	0.07	-0.06, 0.21	0.3	6.7	-19, 32	0.6
9th mo	0.56	-0.48, 1.6	0.3	12	-20, 44	0.5
12th mo	-0.01	-0.15, 0.13	0.9	12	-12, 36	0.3
18th mo	-0.04	-0.26, 0.17	0.7	36	-6.7, 78	0.10
Time	**RV e'**			**RV E/e'**		
	Beta	**95% CI**	**p**	**Beta**	**95% CI**	**p**
Day 1	—	—		—	—	
1st mo	-0.39	-1.1, 0.35	0.3	0.10	-0.31, 0.51	0.6
3rd mo	**-0.95**	**-1.6, -0.26**	**0.007**	**0.29**	**-0.03, 0.61**	**0.075**
6th mo	-0.45	-1.5, 0.55	0.4	0.07	-0.37, 0.51	0.8
9th mo	-0.75	-2.1, 0.63	0.3	0.50	-0.45, 1.4	0.3
12th mo	**-1.2**	**-2.2, -0.13**	**0.027**	0.51	-0.15, 1.2	0.13
18th mo	-0.45	-1.8, 0.92	0.5	-0.04	-0.53, 0.46	0.9

The diastolic function of the right ventricle remains underexplored in patients undergoing OT. The existing scientific literature regarding diastolic right ventricular dysfunction in OT is limited, comprising a small number of studies with small sample sizes that examine various antitumor therapeutic regimens (Krastev et al., 2010; Abdar Esfahani et al., 2016; Chang et al., 2016; Kılıçaslan et al., 2015; Lange et al., 2012; Moustafa et al., 2016; Tanindi et al., 2011; Xu et al., 2021; Zhao et al., 2022). While the studies document the alteration of individual parameters, they do not examine the impact of the OT on the degree of diastolic dysfunction. Furthermore, the results presented exhibit

significant diversity. The research conducted by Xu et al. (2021) involved the largest patient population, comprising 95 patients with breast cancer who received four cycles of anthracycline-based regimens. The study did not show a significant change in the RV parameters, E/A and E/e', following the completion of CT and at the 12th month. Other researchers have reported similar findings, indicating that under anthracycline treatment conditions, no early changes were observed in the parameters RVE/A, RVE/e', and RVe' when monitoring patients during and immediately after CT (Chang et al., 2016; Zhao et al., 2020). Abdar Esfahani et al. (2016) observed a reduction in the indicators RVE, RVE/A, and RVe', while RVE/e' remained unchanged at the 6th month after anthracycline-based CT. One notable finding from their investigation was that there was no worsening in LV systolic and diastolic parameters (Abdar Esfahani et al., 2016). In populations that were treated with HER2-targeted therapy, certain scientists observed a reduction in RVe' at month 12 (Moustafa et al., 2016), while others reported an increase in RVE/e' without a change in RVe' (Kılıçaslan et al., 2015). Research examining the effects of RT revealed no significant short- or long-term alterations in right ventricular diastolic parameters (Tuohinen et al., 2015; Skyttä et al., 2019).

In our investigation of a mixed population with respect to OT, RVe' was the only indicator of RV diastolic function to exhibit a substantial decline in the third and 12th months (Table 20). No statistically significant changes were observed in the other parameters, consistent with the findings of Moustafa et al. (2016). In contrast to the aforementioned researchers, our study provides an evaluation of the degree of diastolic dysfunction employing the E/A RV, E/e' RV, DecT RV, and the algorithm recommended by ASE and ESC (Skyttä et al., 2019). No cases of restrictive filling type diastolic dysfunction were identified in the studied population (Figure 16, Table 19). During each follow-up stage, predominantly normal diastolic right ventricular

function was observed, alongside a few cases of diastolic dysfunction with impaired relaxation and pseudonormal filling patterns. **Thirteen RV diastolic dysfunction cases were newly diagnosed, accounting for 22% of the total.** Diastolic disorders persisted in only two patients until the conclusion of their follow-up. In the remaining patients, diastolic disorders were either temporary (n=6) or not followed up on (n=5).

5.2.5.Right Ventricular Myocardial Performance Index (RVMPI)

The RV myocardial performance index (RVMPI) reflects the global systolic and diastolic function of the right ventricle (RV). The index measurement can be conducted utilizing PW and tissue Doppler techniques. The issue with measuring RVMPI with PW Doppler is that it necessitates the sequential registration of the blood flow in the RV filling tract and the RV outflow tract in order to determine the emptying and filling times of the RV. These measurements are taken during distinct cardiac cycles, which can enhance the indicator's variability. Unlike RVMPI-PW, RVMPI-TDI is measured throughout the same cardiac cycle, which reduces technique error.

The RV myocardial performance index has been examined across multiple cardiovascular pathologies. Evidence indicates that the parameter possesses significant diagnostic and prognostic value in various forms of pulmonary hypertension, congenital heart anomalies, right ventricular infarction, and hypertrophic cardiomyopathy (Blanchard et al., 2009; Sebbag et al., 2001; Zhang et al., 2023). Limited research addresses the dynamics of RVMPI following antitumor treatment (Krustev et al., 2010; Abdar Esfahani et al., 2016; Belham et al., 2006; Chang et al., 2016; Kılıçaslan et al., 2015; Moustafa et al., 2016; Murbraech et al., 2016). Several exhibit a decline in RVMPI due to the effects of OT. Abdar Esfahani et al. (2016) found a deterioration of RVMPI from 0.31 to 0.37 after 6

months of anthracycline treatment ($p < 0.001$). Kılıçaslan et al. (2015) observed a significant change of approximately 20% in the parameter at the 6th month of HER2-targeted therapy. Krastev et al. (2010) reported an increase in the Tei index for both the LV and RV, from 0.50 ± 0.23 to 0.64 ± 0.24 ($p = 0.028$), six months following therapy with various chemotherapeutic agents. Chest radiotherapy influences the indicator, as noted by Li et al. (2021), who observed early deterioration occurring prior to the treatment's completion. Conversely, other researchers did not observe an increase in RVMPI associated with exposure to various types of OT (Belham et al., 2006; Chang et al., 2016; Moustafa et al., 2016)

Our study on a population treated with various chemotherapy regimens demonstrated a worsening in the tissue Doppler RV Tei index only at the 18th month from the commencement of oncological treatment, with borderline statistical significance (with 0.07, 95% CI 0.00, 0.13, p = 0.05). The RVMPI-PW indicator exhibited no significant change throughout the follow-up period (Table 21).

Table 21. *GEE regression analysis of tissue Doppler (left) and PW Doppler (right) RVMPI change over time.*

Time	RVMPI TDI Beta	95% CI	p	RVMPI PW Beta	95% CI	p
Day 1	—	—		—	—	
1st mo	-0.02	-0.04, 0.01	0.3	0.00	-0.05, 0.04	>0.9
3rd mo	0.00	-0.04, 0.04	>0.9	0.05	-0.01, 0.10	0.087
6th mo	-0.01	-0.05, 0.02	0.6	0.06	-0.01, 0.14	0.10
9th mo	-0.04	-0.09, 0.02	0.2	0.03	-0.03, 0.09	0.3
12th mo	-0.03	-0.07, 0.01	0.13	0.05	-0.02, 0.12	0.13
18th mo	**0.07**	**0.00, 0.13**	**0.051**	0.01	-0.06, 0.08	0.8

In 14 patients (23%), a relative increase in RVMPI-TDI of over 20% to a value > 0.55 was observed at some point during the follow-up (Table 22).

Table 22. *Comparative characteristics of the patients exhibiting a pathological increase in RVMPI-TDI > 0.55 with a relative increase exceeding 20% versus the remaining population.*

Parameters	**Δ RVMPI TDI>20% RVMPI TDI >0.55 N = 14**	**The rest of the population N = 45**	***P*[1]**
Max. RVMPI – TDI	0.66, (0.08)	0.43, (0.13)	**<0.001**
Min. RVe', cm/s	**7.81, (1.22)**	10.23, (2.17)	**<0.001**
Max. RVE/e'	**7.81, (2.15)**	5.09, (0.85)	**<0.001**
Min. RV S', cm/s	10.90, (1.80)	11.05, (1.72)	0.6
•RVS' ≤ 9.5 cm/s и Δ RVS' > 15%	**1 (7.1%)**	4 (8.9%)	>0.9
RVFAC (%)	44.9, (7.0)	45.2, (6.1)	0.7
• RVFAC ≤ 35%	5 (36%)	16 (36%)	>0.9
TAPSE, mm	19.6, (3.7)	19.3, (3.3)	0.4
Hypertension, n (%)	**11 (79%)**	**16 (36%)**	**0.005**
Diabetes, n (%)	**4 (29%)**	**2 (4.4%)**	**0.024**
Dyslipidemia, n (%)	**5 (36%)**	**5 (11%)**	**0.047**
Risk of CTRCD (N = 45), n (%)			**0.001**
• High	**5 (56%)**	**2 (5.7%)**	
• Moderate	3 (33%)	13 (37%)	
• Low	**1 (11%)**	**20 (57%)**	
Cardioprotection, n (%)	**12 (86%)**	**24 (53%)**	**0.030**
Time to max. RVMPI – TDI, days (Median (IQR))	117 (64, 445)	88 (29, 53)	0.13

1Wilcoxon rank sum exact test; Wilcoxon rank sum test; Fisher's exact test; Pearson's Chi-squared test

Our findings indicate that the RVMPI parameter is correlated with the diastolic function indicators of the RV: E/e '(R = 0.37, p < 0.001) and RVe '(R = -0.29, p < 0.001) (Figure 14). The RVMPI-TDI parameter shows no correlation with the systolic functional indicators RVS', TAPSE, and RVFAC. This is further corroborated by the analysis of patients (n = 14 (23%)), in whom RVMPI-TDI has a relative increase of over 20% to a value greater than 0.55 (Table 22). The E/e' ratio was significantly increased (7.81 (SD 2.15) vs. 5.09 (SD 0.85), p < 0.001), and the early diastolic tissue velocity RVe' was statistically significantly lower (7.8 (SD 1.22) cm/s vs. 10.23 (SD 2.17) cm/s, p < 0.001) in these patients compared to the remainder of the population.

No differences were observed between the groups concerning the functional parameters of left ventricular (LV) and right ventricular (RV) systolic function. The findings suggest that the RVMPI-TDI index, while global in nature, predominantly reflects the diastolic disorders of the right ventricle. The risk profile of patients exhibiting pathologically elevated RVMPI-TDI is significantly distinct from that of the general population, characterized by a higher prevalence of hypertension, type 2 diabetes mellitus, dyslipidemia, and an increased risk of CTRCD. These comorbidities are known risk factors for LV diastolic dysfunction and chronic heart failure (Obokata et al., 2020). In this line of thought, vascular endothelial changes caused by RT, which are related with the development of diastolic problems, may explain the indicator's deterioration soon after RT in the Li et al. (2021) study. In our study, RT was administered to a subset of patients (45%) following CT, potentially accounting for the observed delay in the RVMPI-TDI indicator changes.

With respect to the RVMPI-PW index, 10 patients were registered with a relative increase of over 20% to values exceeding 0.44 after the start of OT. No significant correlations were observed between this parameter and the other parameters of right ventricular systolic and diastolic function (Figure 14).

5.2.6.Definition of right ventricular dysfunction

The 2022 ESC Cardio-Oncology Guidelines do not offer any specific recommendations for diagnosing RV dysfunction attributable to OT. In August 2024, the Heart Failure Association and the ESC Cardio-Oncology Council released a scientific statement addressing right ventricular involvement in cancer patients (Keramida et al., 2024). The scientific statement presents a definition of right ventricular dysfunction. Asymptomatic right ventricular dysfunction is characterized by ultrasound findings that indicate subclinical

functional abnormalities without the presence of symptoms. Scientific organizations define subclinical RV functional impairment as a new relative decrease in RVFWLS of more than 15%, without any abnormalities in the standard echocardiographic parameters RVFAC, RVS', TAPSE, RVMPI, and RVEF. Symptomatic right ventricular failure is characterized by symptoms indicative of heart failure alongside structural and functional abnormalities of the right ventricle (Keramida et al., 2024).

At the time of our study, a definition of right ventricular damage as a consequence of OT was not established, and we also did not investigate deformation parameters. We adopted the methodology of Wang et al. (2021) to define RV dysfunction as the simultaneous pathological deviation of at least two functional indicators: Δ RVFAC > 20% and RVFAC ≤ 35%; Δ S' RV > 15% and S' RV ≤ 9.5 cm/s; Δ TAPSE > 15% and TAPSE ≤ 16 mm; Δ RVMPI-TDI > 15% and RVMPI-TDI > 0.55. The requirement of a specified relative percentage change for a particular parameter aimed to demonstrate the occurrence of pathological values after the initiation of OT. The selected degree of relative change exceeds the mean for a specific indicator, with a higher value assigned to the RVFAC parameter owing to its increased variability.

RV dysfunction associated with OT occurred in 7 patients, 11.7% of the population (Table 23). In four patients, the diagnosis was established through a significant decrease in RVS` in conjunction with the TAPSE or RVMPI-TDI parameters. In 3 patients, a simultaneous pathological decrease in RVFAC and a significant change in TAPSE or RVMPI-TDI were detected. The median time to onset of RV dysfunction was 257 days (about nine months) after the start of the OT with a wide IQR of 126 to 462 days. No patient showed symptoms of HF. Notably, 3 patients were treated with CT that did not contain anthracyclines or trastuzumab. All were administered chemotherapeutic agents from the taxane group. Radiotherapy was

performed in 4 patients. No patient had a decreased LVEF, but 6 reached low LV systolic tissue velocities – septal, lateral and average. Deterioration of LV and RV diastolic parameters was also recorded (Table 24).

Table 23. *Characteristics of patients with RV dysfunction*

Parameters	RV dysfunction n = 7	Parameters	RV dysfunction n = 7
RVFAC + RVMPI-TDI	n = 2	**Risk of CTRCD**	
RVFAC + TAPSE	n = 1	Low	n = 1
RVS' + TAPSE	n = 3	Moderate	n = 1
RVS' + RVMPI-TDI	n = 1	High	n = 2
Day of occurrence		**Type of CT**	
Median (IQR)	257 (126, 462)	Anthracycline	n = 3
Symptoms of HF	n = 0	Trastuzumab	n = 1
Age, years, Median (IQR)	63 (61, 65)	Anthra + trast.	n = 0
Smoking	n = 3	Other	**n = 3**
BMI, kg/m2, mean (SD)	26.3, (4.1)	**Radiotherapy**	n = 4
Hypertension	n = 5	**TCD ≥50 Gy**	n = 3
Diabetes	n = 2	**Taxane**	**n = 7**
Dyslipidemia	n = 1	**Cyclophosphamide**	n = 5
Cardioprotection	n = 6	**5 Fluorouracil**	n = 0

Table 24 presents the echocardiographic indicators at the point of RV dysfunction diagnosis, alongside baseline values for comparison and the minimum values recorded throughout the follow-up period. The data demonstrate that low LV systolic tissue velocities were observed - septal, lateral, and average. In six patients, the average LV S' attained a pathological value of less than 7 cm/s. A decrease was observed in the diastolic parameters RVe' and LVe', together with an increase in E/e' of the RV. No reduction in LVEF below 50% was detected in these patients, although a relative decrease was noted. There was only one patient with a pathological value of hsTnT; however, it was elevated at baseline.

Table 24. *Echocardiographic parameters in patients with RV dysfunction*

Parameters	RV dysfunction n = 7	Parameters	RV dysfunction n = 7
Septal LVS', cm/s		**Lateral LVS', cm/s**	
•Baseline	7.4 (7.00, 8.00)	•Baseline	7.5 (5.8, 10.5)
•During RV dysfunction	6.2 (5.7, 7.0)	•During RV dysfunction	8.0 (6.5, 10.9)
•Minimum ≤ 6cm/s	n = 6	•Minimum ≤ 8cm/s	n = 6
Average LVS', cm/s		**LVEF, %**	
•Baseline	7.75 (6.6, 8.75)	•Baseline	72 (61, 75)
•During RV dysfunction	6.85 (6.3, 8.85)	•During RV dysfunction	61 (60, 63)
•Minimum ≤ 7cm/s	n = 6	•Minimum < 50%	0 (0%)
RVe',cm/s		**RVE/e'**	
•Baseline	12.4 (8.5, 13.0)	•Baseline	4.6 (4.3, 5.6)
•During RV dysfunction	8.5 (7.0, 9.80)	•During RV dysfunction	5.8 (5.7, 5.8)
LVe', cm/s		**LVE/e'**	
•Baseline	8.6 (7.50, 9.3)	•Baseline	9.8 (9.2, 13.1)
•During RV dysfunction	7.2(5.80, 8.5)	•During RV dysfunction	10.1 (7.2, 14.6)
MAPSE, mm		**hsTnT, ng/L**	
•Baseline	12.15 (12.0, 12.8)	•Baseline	10.5 (10.3, 13.2)
•During RV dysfunction	10.5 (9.3, 11.5)	•Maximum	11.5 (10.9, 14.5)
LV systolic dysfunction	n = 2	**RV diastolic dysfunction**	n = 5

The precise definition of RV dysfunction by Wang et al. (2021) is a pathological change in ≥ 2 RV parameters – RVFAC < 35%, TAPSE < 17 mm, S' < 9.5 cm/s, RVMPI > 0.54, RVFWLS < 20% and 3D RVEF < 45%. Researchers observed RV dysfunction in 9 patients (14.8%) from a cohort (n = 61) undergoing anthracycline treatment for diffuse large B-cell lymphoma over a period of 10 months, a prevalence comparable to our findings. Four of these patients also exhibited LV systolic dysfunction (Wang et al., 2021). The data suggest that RV dysfunction may be an independent phenomenon. Comparable findings have been noted in our population. Among the patients with RV dysfunction (n = 7), LV systolic dysfunction was identified in only two cases, characterized by a notable reduction (> 15%) in the average LVS' to a value below 7 cm/s. However, it is important to mention that the other four patients with RV dysfunction exhibited a decrease in the average LV systolic S' < 7 cm/s, albeit with

a lesser relative change compared to the baseline value, suggesting some impairment in LV systolic function. A greater incidence of RV dysfunction was noted by other researchers. Rossetto et al. (2024) defined subclinical RV systolic impairment due to OT as a relative reduction in 3D RVEF by 10% and in RVFWLS by more than 15%. In a cohort of breast cancer patients (n = 83), researchers identified RV systolic dysfunction in 28% of those receiving anthracycline-based regimens and approximately in 19% of those treated with trastuzumab and radiotherapy. All patients exhibiting subclinical RV systolic dysfunction also demonstrated subclinical LV systolic dysfunction (Rossetto et al., 2024).

5.3.Relationships of echocardiographic indices of left and right ventricular function and biochemical markers of myocardial injury

Cardiac troponins (cTns) have been investigated in relation to anthracycline-based regimens, HER2-targeted therapies, anti-VEGF treatments, immunotherapy, and tyrosine kinase inhibitors. All studies indicated that cTns increase prior to the detection of functional damage by imaging methods (Ananthan & Lyon, 2020). The scientific evidence supporting the specificity and sensitivity of cardiac troponins (cTns) in detecting myocardial injury related to OT has led to their incorporation as a diagnostic criterion for asymptomatic CTRCD (Ananthan & Lyon, 2020; Lyon et al., 2022). Elevated cTns levels indicate a high risk and predict the onset of cardiac dysfunction in patients undergoing anthracycline-based and HER2-targeted therapies, demonstrating a sensitivity of 69% and a specificity of 87% (Cardinale et al., 2017; Michel et al., 2020). The absence of an elevation in cTns during OT suggests a minimal risk of cardiotoxicity, with a high negative predictive value of 93%. This finding is crucial for determining patients who do not necessitate cardiac function monitoring through imaging techniques (Cardinale et al., 2017;

Michel et al., 2020). The significance of these biomarkers in OT also encompasses the prediction of future CV events, including cardiac death, pulmonary edema, heart failure, and rhythm disorders (Cardinale et al., 2004). In the context of trastuzumab treatment, increased serum cTn levels are associated with a decreased probability of LV function recovery after CTRCD and cardioprotection administration (Cardinale et al., 2017; Zardavas et al., 2017).
We assessed high-sensitivity troponin T (hsTnT) levels in 41 patients at the onset of OT, as well as at the 1st and 3rd months, looking for early myocardial damage. In certain patients, the biomarker was assessed at the 6th, 9th, and 12th months. The analysis of hsTnT dynamics using GEE regression (Table 25) indicated a statistically significant increase in values at the 3rd and 6th months.

Table 25. *GEE regression analysis of hsTroponinT variation at each visit since the initiation of OT*

	Dynamics of hsTpononuнT, ng/L		
Time	**Beta**	**95% CI**	***p***
Day 1	—	—	
1st month	0.00	-1.3, 1.3	>0.9
3rd month	**1.2**	**0.35, 2.0**	**0.005**
6th month	**2.3**	**0.34, 4.3**	**0.021**
9th month	-0.48	-2.3, 1.4	0.6
12th month	2.1	-2.5, 6.6	0.4

Only 5 patients (12.2%) reached maximal values of hsTnt exceeding the upper limit of the norm of 14 ng/L, which was in the normal range at baseline (Figure 18). In one patient, the increase in hsTnT > 14 ng/L occurred after one cycle of chemotherapy, in two patients on the 106th day, and two on average over the first year.

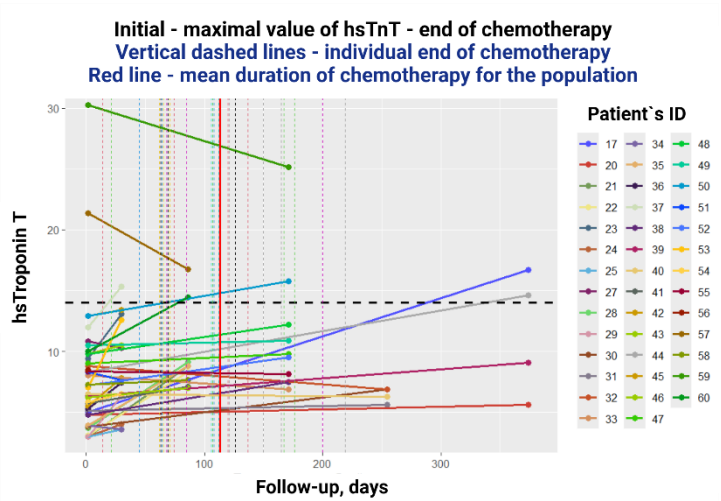

Figure 18. *Graphical representation of individual baseline and maximum hsTnT values compared to the end of CT (black dashed line – upper limit of the hsTnT norm, red vertical line – mean end of CT for the population, vertical dashed lines – end of CT individually for each patient)*

The median difference between the baseline and maximal hsTnT was 1.20 ng/L (IQR 0.39, 3.30). The median relative percentage increase in hsTnT was 23% (IQR 4%, 50%). None of the five patients exhibiting hsTnT levels exceeding the upper normal limit of 14 ng/L demonstrated LV systolic or RV dysfunction. Nevertheless, there was a reduction in the systolic parameters of the LV (LVEF, LV systolic tissue velocities) and the RV (RVFAC and S' RV). In a comparable cohort of 43 patients undergoing treatment with anthracyclines and/or trastuzumab, Sawaya et al. (2011) reported elevated hsTnI levels at 3 months in a greater proportion, precisely 28% of patients (Sawaya et al., 2011). Another study by Krastev et al. (2010) on a mixed population (n = 44) regarding OT did not find an increase in serum troponin I in the 6th month, measured with a standard analysis. Michel et al. (2019) performed a meta-analysis involving 5691 patients who

received various treatment regimens, including high-dose and low-dose CT and HER2-targeted therapy. The study found that 22% of patients experienced increased cardiac troponins (cTns). The disparity in the rate of increased cTn levels between our and the aforementioned research can be attributed to variations in the doses and types of oncological medications and the timing of sample collection. In numerous studies, blood samples were collected immediately following the corresponding chemotherapeutic cycle; thus, the troponin levels indicated acute cardiomyocyte damage (Pudil et al., 2020). In the present study, samples were collected before the respective cycle of OT, and the elevated troponin levels indicated persistent cardiomyocyte injury resulting from the prior CT dose (Pudil et al., 2020). Similar to our research, Bannister et al. (2023) investigated the serum levels of hsTnT in 64 patients before each cycle of anthracycline-based therapy. They discovered a gradual increase in the serum levels with each subsequent cycle. According to these scientists, baseline values of the indicator above 10.5 ng/L hold significant prognostic relevance for CTRCD, with an AUC of 0.75, 75% sensitivity, and 80% specificity (Bannister et al., 2023). Cardinale et al. (2017) emphasize that the timing of cardiac troponin sampling is crucial for the biomarker's informativeness. The Cardinale research team published recommendations in 2015 for conducting standard troponin tests at baseline, prior to, and following each cycle of CT, based on the kinetics of the biomarker in OT conditions. Although the study is financially justified due to its high negative predictive value, the necessity of serial cTns monitoring is a limiting factor in implementing this approach in actual clinical practice (Cardinale et al., 2017). Cardinale et al. (2017) indicate that additional research is necessary to determine the optimal timing for cardiac troponin measurements to enhance the utility of a single assessment.

In light of hsTns's predictive value, Sawaya et al. (2011) showed that the increase in the indicator may be prognostic for the development of

cardiotoxicity. Our findings indicated that hsTnT served as a predictor for reduction in the LV average, septal, and lateral S' velocities, with coefficients of β -0.07 (95% CI -0.12, -0.02, p = 0.008), β -0.06 (95% CI -0.11, -0.02, p = 0.005), and β -0.08 (95% CI -0.14, -0.01, p = 0.031), respectively (Figures 19 and 20). Interestingly, hsTnT showed no predictive value for a drop in the RV systolic indices RVFAC and RVS' (Figure 19). The paucity of information on biomarker values for the entire population has prevented the analysis of the relation with the more global indicators, such as left and right ventricular dysfunction.

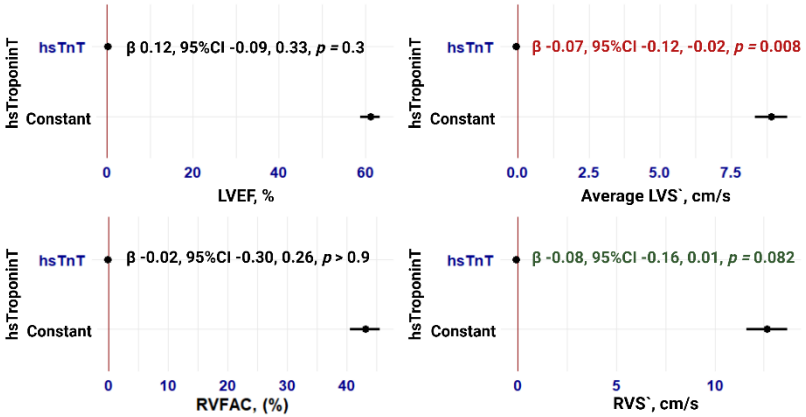

Figure 19. *Impact of hsTnT on echocardiographic indices of LV and RV systolic function, assessed by GEE regression analysis*

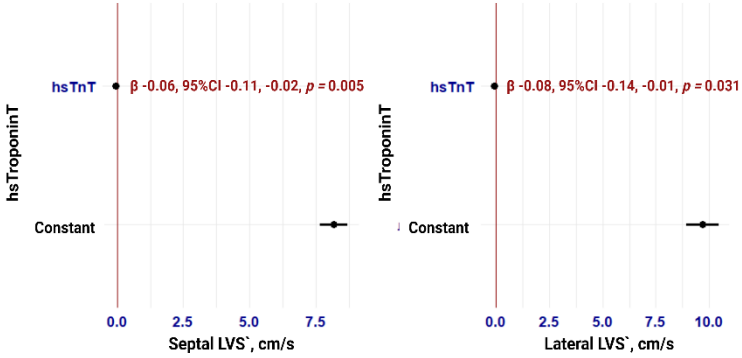

Figure 20. *Effect of hsTnT on the LV septal and lateral systolic tissue velocities assessed by GEE regression analysis*

In drawing an analogy between systolic myocardial tissue velocities and strain indices, the study conducted by Song et al. (2017) is interesting. Researchers discovered a correlation between hsTnT levels and 3D LVGLS ($R = 0.12$, $p = 0.03$) and 3D RVGLS ($R = 0.20$, $p < 0.01$) in their investigation of patients with anthracycline-based chemotherapy for diffuse large B-cell lymphoma. Specifically, the researchers identified a relationship between hsTnT levels and both LV and RV longitudinal systolic function. No additional scientific data regarding the relationship between right ventricular function and cardiac troponin levels were.

Utilizing hsTnT values and the 2022 ESC definition of CTRCD, we identified 17 patients (28.3% of the population) with CTRCD, including 12 patients exhibiting LV systolic dysfunction (refer to section 5.1.3.) and 5 patients with pathologically elevated hsTnT levels above 14 ng/L.

5.4. Relationships between left ventricular and right ventricular indices

5.4.1. Temporal relationships between left ventricular and right ventricular functional echocardiographic indices

Examining the temporal variations in LV and RV systolic and diastolic function indices is essential for determining the most sensitive markers of myocardial dysfunction. The parameter's capacity to predict future heart failure is crucial for justifying the timely administration of cardioprotective therapy.

Numerous scientific studies have demonstrated the presence of early myocardial abnormalities in the RV, either independently or concurrently with those in the left ventricle. These findings have been captured through conventional systolic and diastolic

echocardiographic parameters, as well as through 3D or deformation indices (Abdar Esfahani et al., 2016; Boczar et al., 2016; Chang et al., 2016; Ferri et al., 2022; Labib et al., 2021; Planek et al., 2020; Rossetto et al., 2024; Sławiński et al., 2024; Song et al., 2017; Tanindi et al., 2011; Tuohinen et al., 2015; Wang et al., 2021; Zhao et al., 2020). It is important to acknowledge that other researchers have reported that RV changes occur later than LV changes or that there are no changes in RV parameters at all as a result of OT (Anqi et al., 2019; Belham et al., 2006; Keramida et al., 2019; Lange et al., 2012; Nakano et al., 2016). The evidence is varied and complex to compare because of the differences in study populations, follow-up durations, oncological treatment regimens, and examined parameters.

The analysis of the time for maximum deviation in functional LV and RV parameters (Figure 21) demonstrates that certain indicators attained a peak of change earlier than others. It mainly occurred during the 3rd to 4th month, shortly following the conclusion of CT. This finding confirms the synchronous myocardial damage of the left ventricle and right ventricles. The RV systolic tissue velocity S' reached minimum values for a median duration of 105 days (IQR 30, 209.8 days) before the maximum deterioration of all LV systolic and diastolic parameters, except MAPSE. All RV parameters that underwent statistically significant deviations, including RVS', RVe', and RVFAC, reached minimum values prior to the corresponding LV parameters, such as systolic average, septal and lateral tissue velocities, e' of the LV, and LVEF. These observations provide a basis for investigating whether RV parameters can predict functional disorders of the LV.

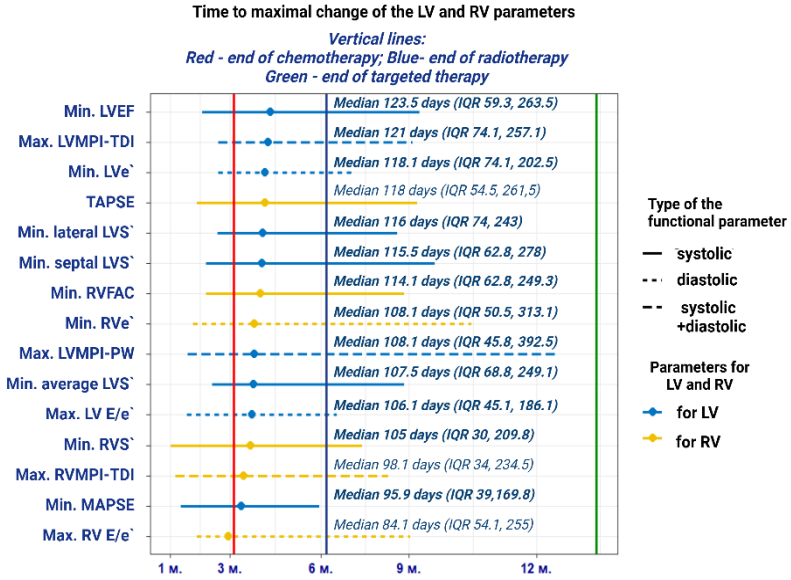

Figure 21. *Comparison of the times of the maximum change of some echocardiographic indicators for systolic and diastolic function of the LV and RV (point – median, line – interquartile range) The systolic, diastolic and combined functional indicators are distinguished by a different type of line. The indicators for LV and RV are marked with a different color. Vertical lines: red – end of CT, blue – end of RT, green - end of targeted therapy*

Moreover, it is notable that the tissue relaxation velocities of the right and left ventricles attained their minimum values before the maximum reduction in RVFAC and LVEF, respectively. This suggests an investigation into the prognostic significance of these diastolic parameters. The maximum deviations in all examined functional indicators for the LV and RV were observed at the conclusion or after the completion of chemotherapy, prior to the initiation of radiotherapy and targeted therapies.

5.4.2.Correlation and prognostic relationships between functional echocardiographic indices for LV, RV, and clinical factors

The correlation analysis of relationships between LV and RV indices shows that the most significant correlation exists between the systolic tissue velocity S' of the RV and the septal S' of the LV (R = 0.44, p < 0.001) and between the diastolic tissue relaxation velocities e' of the RV and e' of the LV (R = 0.45, p < 0.001) (Figure 22).

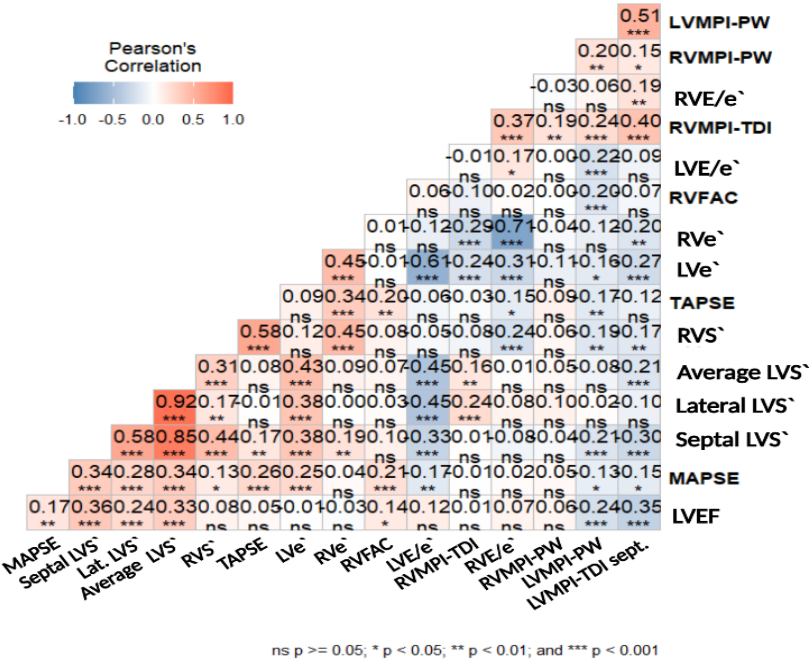

***Figure 22**. Correlations between the left and right ventricle's systolic and diastolic function parameters (Pearson method). The correlation coefficients for each pair of indicators and the level of significance are shown (ns – not significant, * - p < 0.05, ** - p < 0.001 and *** - p < 0.001)*

Regression analyses further corroborate these findings. The systolic tissue velocity S' of the RV serves as a prognostic indicator for alterations in the systolic average tissue velocity S' of the LV (β 0.18, 95% CI 0.11, 0.25; p < 0.001) and for left ventricular systolic dysfunction (OR 0.73, 95% CI 0.58, 0.91; p = 0.006) (Figures 26 and 27). Furthermore, the minimum value of S' RV precedes the time of achieving the minimum values of LV systolic tissue velocities (Figure 21). This necessitates the assessment of RV and LV tissue systolic velocities due to their predictive capacity regarding the onset of systolic dysfunction in the contralateral ventricle. An interesting observation is that in our population, there are correlational and prognostic relationships between diastolic and systolic functional parameters, both for the RV and for the LV. A moderate significant correlation was found between the tissue systolic velocity S' and the early diastolic tissue velocity e' of the RV (R = 0.45, p < 0.001) (Figures 14 and 22). At the same time, e' of the RV is a prognostic factor for the change in S' of the RV (β 0.34, 95%CI 0.1, 0.98, p = 0.005) (Figure 23).

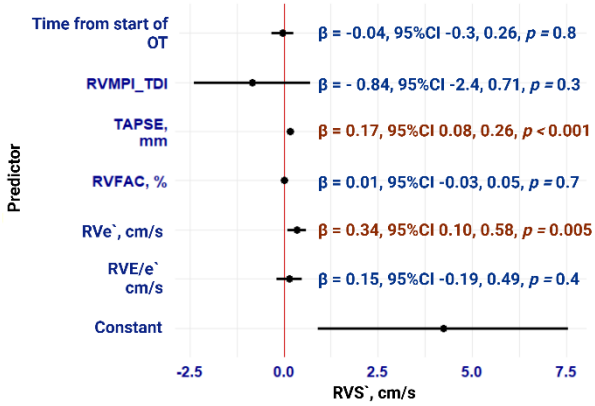

Figure 23. *GEE regression analysis for the prognostic value of time since onset of OT and functional RV indicators on the dependent variable RVS'. Predictors are TAPSE (β 0.17, 95%CI 0.09, 0.26, p =*

0.001) and e' of RV (β 0.34, 95%CI 0.1, 0.98, p = 0.005). The increase in both indicators is associated with an increase in RVS'.

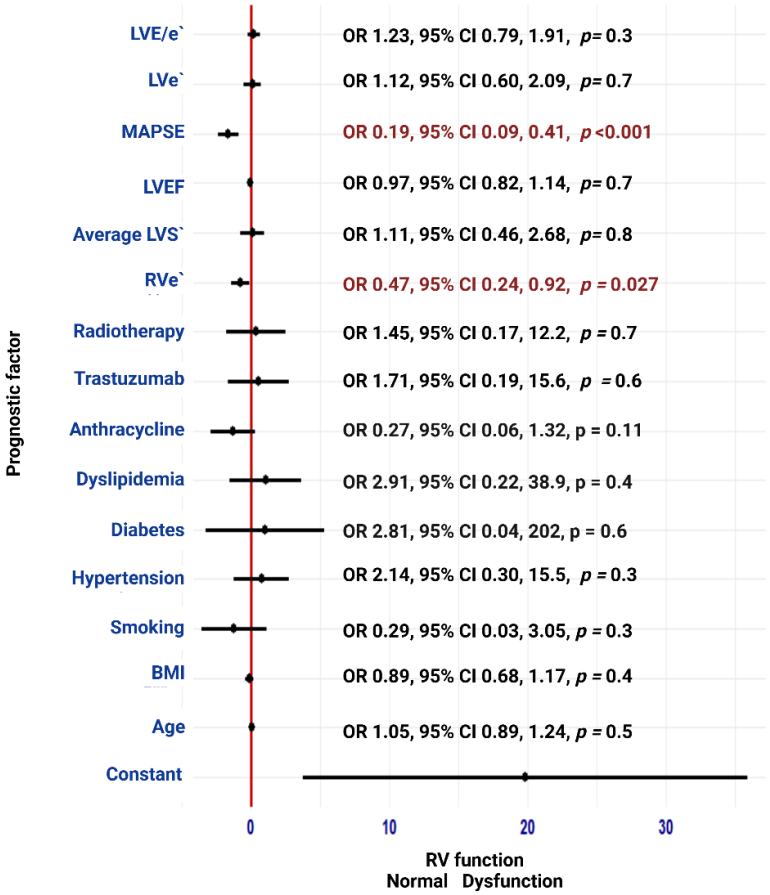

Figure 24. *Forest plot of GEE logistic regression analysis for the predictive value of clinical and echocardiographic indicators for the occurrence of RV dysfunction. The parameters MAPSE (OR 0.19, 95% CI 0.09, 0.41, p < 0.001) and RVe'(OR 0.47, 95%CI 0.24, 0.92, p = 0.027) are prognostic factors with statistical significance.*

In addition, early diastolic RVe‘ is an independent predictor of the RV dysfunction (OR 0.47, 95%CI 0.24, 0.92, p = 0.027) (Figure 24). The ROC analysis demonstrated that a value of 9.8 cm/s could independently predict RV dysfunction with a specificity of 76% and a sensitivity of 86% (AUC 0.83), despite the presence of multiple factors that influence myocardial function in the context of OT (Figure 25).

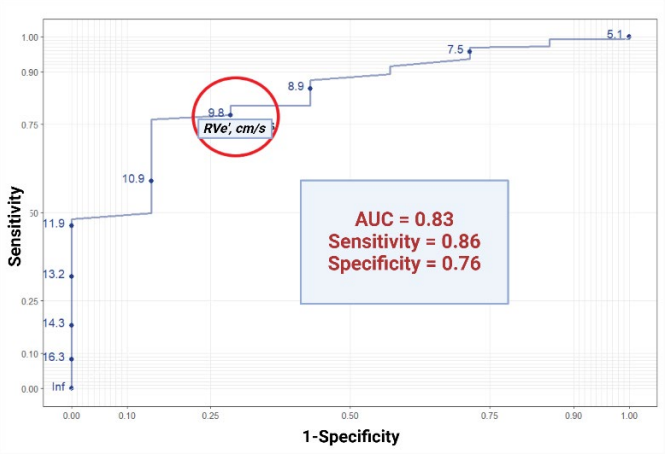

Figure 25. *ROC analysis of the right ventricular diastolic parameter e‘for prediction of RV dysfunction*

Correlation and prognostic relationships are also observed between the LV systolic and diastolic parameters. There is a moderate significant correlation between the LV average systolic tissue velocity S' and the LV early diastolic tissue velocity e' (R = 0.43, p < 0.001) (Figure 22). The LV diastolic index E/e' predicts a decrease in the average LV S' by 0.24 cm/s (95% CI -0.30, -0.19, p < 0.001). The LV tissue velocity e' (the average e' value of the medial and lateral mitral annulus) is a prognostic factor for LV systolic dysfunction (OR 0.69, 95% CI 0.53, 0.90, p = 0.006) and for CTRCD (OR 0.79, 95% CI 0.65, 0.97, p = 0.025) (Figures 26, 27, 28).

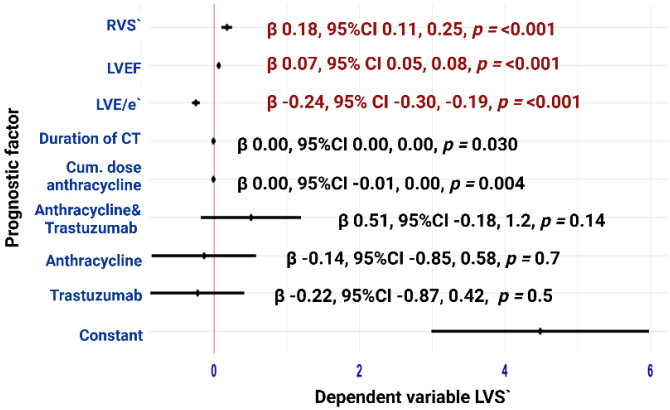

Figure 26. *Forest plot of GEE linear regression analysis for prediction of change in average LVS'.*

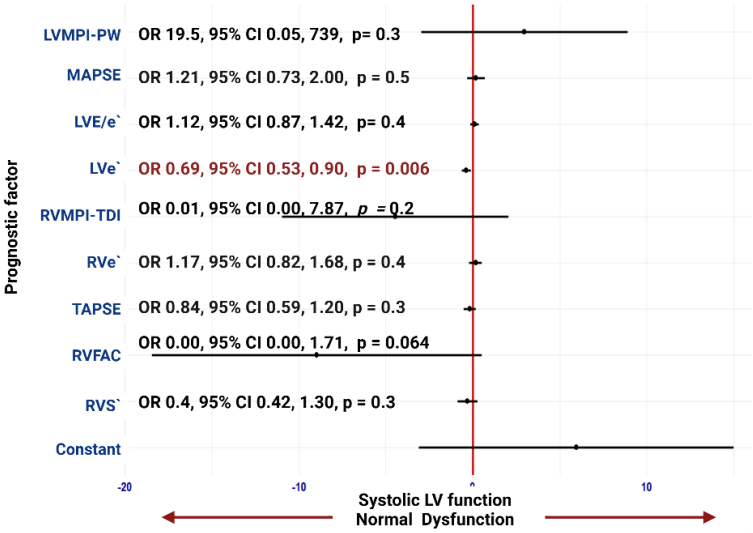

Figure 27. *Forest plot of GEE logistic regression analysis for the prognostic value of echocardiographic indicators for LV systolic dysfunction. A significant prognostic factor is LVe` (OR 0.69, 95%CI 0.53, 0.9, p = 0.006)*

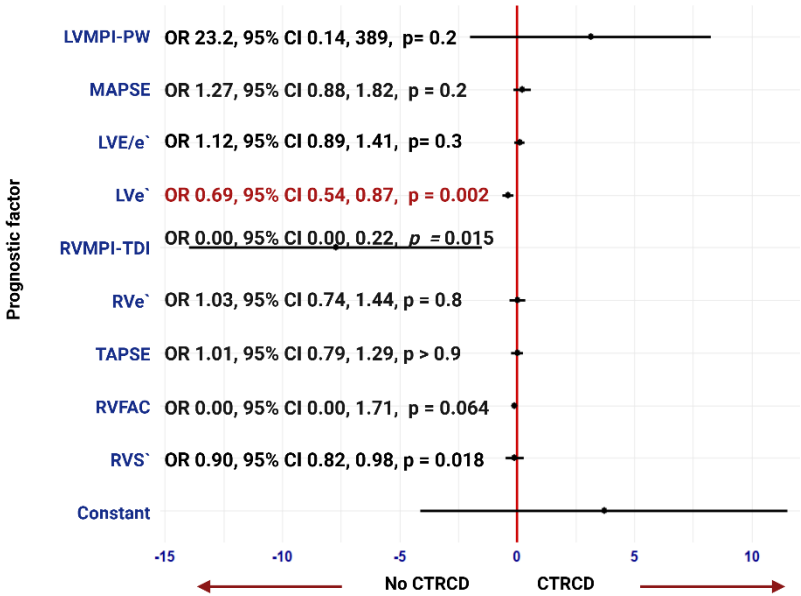

Figure 28. *Forest plot of GEE logistic regression analysis for the prognostic value of echocardiographic parameters for the occurrence of CTRCD. A significant prognostic factor is LVe'. A decrease is associated with an increased probability of the occurrence of CTRCD (OR 0.69, 95%CI 0.54, 0.87, p = 0.002).*

The interdependencies between diastolic and systolic disorders justify their evaluation in the follow-up of patients receiving OT. An analogy can be drawn between the correlation and predictive relationships of diastolic and systolic tissue velocities observed in our population and the association of diastolic dysfunction with myocardial mechanical disorders reported by Obokata et al. (2020). This dependence is attributed to microvascular disorders, which result in alterations in diastolic function and myocardial ischemia, consequently leading to systolic dysfunction (Obokata et al., 2020).

Analysis of the factors contributing to RV diastolic dysfunction indicated that moderate and high risk of CTRCD elevated the

probability of diastolic RV disorders by approximately fivefold (Figure 29). The risk assessment for CTRCD encompasses indicators including hypertension, diabetes mellitus, age, elevated BMI, and dyslipidemia, which are recognized risk factors for the onset of LV diastolic dysfunction and CHF (Obokata et al., 2020).

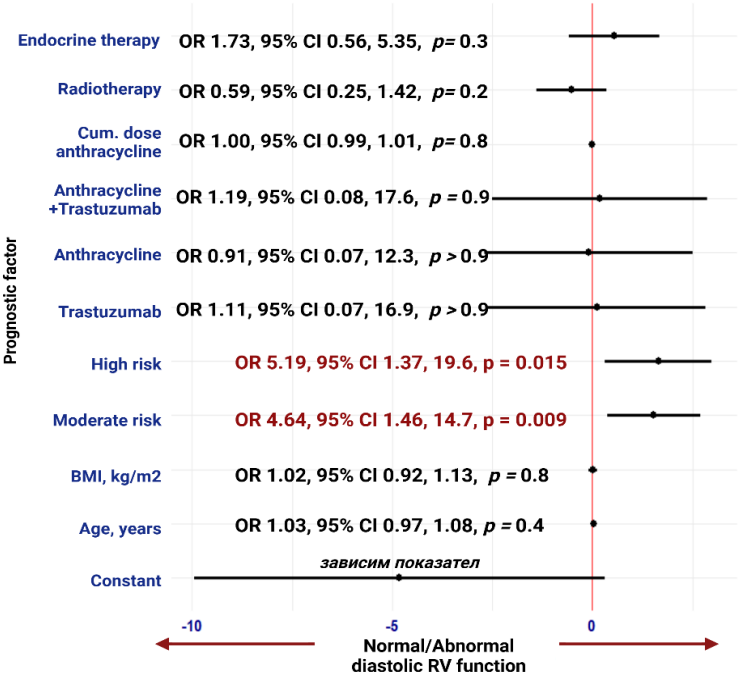

Figure 29. *Forest plot of GEE logistic regression analysis for the impact of clinical parameters on the occurrence of RV diastolic dysfunction (Area Under ROC Curve = 0.453, 95% CI (0.277, 0.629))*

A clinical prognostic factor for LV diastolic dysfunction in the studied population was RT (OR 10.4, 95% CI 1.75, 61.6, p = 0.01) (Figure 30). A correlation with the cumulative dose of anthracyclines was observed (OR 1.03, 95% CI 1.01, 1.05, p = 0.003). Moderate risk

of CTRCD and elevated BMI were identified as predictors of the development of LV diastolic disorders, with odds ratios of 11.1 (95% CI 3.37, 36.7, p < 0.001) and 1.23 (95% CI 1.06, 1.43, p = 0.006), respectively. It is noteworthy that systemic therapy with medications other than anthracyclines and trastuzumab is associated with a heightened probability of LV diastolic dysfunction (OR 108, 95% CI 5.65, 2048, p = 0.002) (Figure 30). This cohort of patients received treatment with fluoropyrimidines, platinum compounds, and taxanes. This observation supports the need for regular cardiological assessments of patients, even in the absence of treatment that is typically associated with CTRCD.

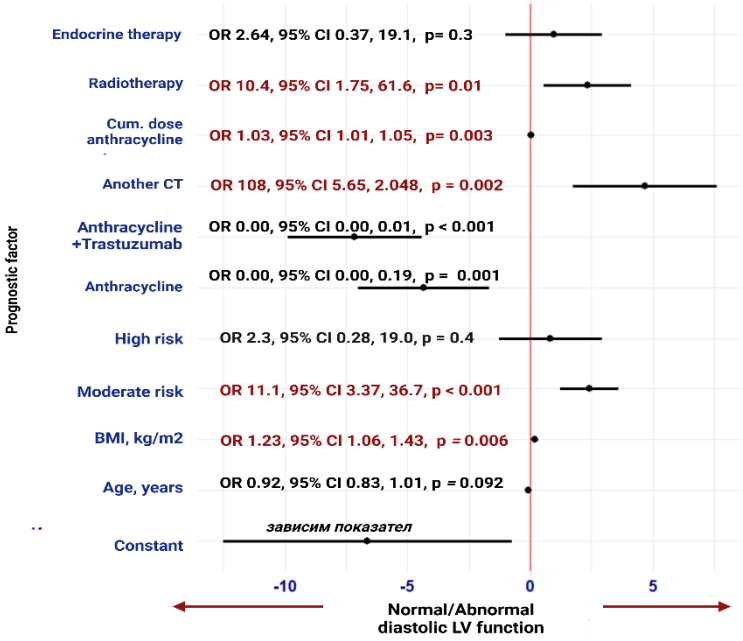

Figure 30. *Forest plot of GEE mixed logistic regression analysis for the impact of clinical parameters on the occurrence of LV diastolic dysfunction (Area Under ROC Curve = 0.851, 95% CI: (0.726, 0.975)*

Numerous studies have investigated LV and RV diastolic dysfunction in cancer patients (Abdar Esfahani et al., 2016; Camilli et al., 2024; Del Bene et al., 2023; Kılıçaslan et al., 2015; Xu et al., 2021; Zhao et al., 2022). Research on cancer-related RV diastolic dysfunction has identified alterations in specific parameters; however, it has not quantified the degree of diastolic impairment or established the prognostic relevance of diastolic indicators, nor their correlation with systolic abnormalities (Abdar Esfahani et al., 2016; Kılıçaslan et al., 2015; Moustafa et al., 2016).

Left ventricular diastolic impairment during OT is more thoroughly investigated, with evidence indicating its earlier onset relative to LV systolic dysfunction (Upshaw et al., 2020). Certain scientific studies suggest that diastolic LV disorders are more prevalent than systolic LV dysfunction, regardless of whether the treatment is anthracycline or HER2-targeted (Cao et al., 2015; Camilli et al., 2024; Honda et al., 2017; Klein et al., 2019; Rashid et al., 2024). Furthermore, some researchers assert that diastolic dysfunction is a more sensitive indicator of myocardial damage than deformation indices (Del Bene et al., 2023). Our study did not establish the prognostic value of diastolic right and left ventricular dysfunction for developing systolic functional impairment. Nevertheless, the prognostic significance of the early diastolic tissue velocity e' of the RV and LV for the manifestation of systolic dysfunction, respectively, of the right and left ventricle is consistent with the results of the studies above. The disturbances in myocardial relaxation observed early in systemic OT can be attributed to pathological intracellular processes, including impaired calcium homeostasis, disrupted calcium reuptake from the endoplasmic reticulum, dysfunction of titin, and endothelial microvascular disorders (Camilli et al., 2024). There is scientific evidence that diastolic myocardial disorders persist for years following OT and that HFpEF can develop (Camilli et al., 2024; Chang et al., 2021; Upshaw et al., 2020; Yu et al., 2020). The

evaluation of diastolic parameters should be incorporated into the regular echocardiographic assessment at each follow-up stage following OT. Insufficient evidence remains regarding the significance of diastolic dysfunction in initiating cardioprotective therapy (Camilli et al., 2024). Diastolic dysfunction is excluded from the definition of CTRCD, according to the 2022 guidelines on cardio-oncology (Lyon et al., 2022). One of the earliest cardio-oncology clinics in Europe set up in 2011 at Brompton Hospital in London, includes diastolic LV dysfunction as a diagnostic for subclinical cardiotoxicity in its protocols (Pareek et al., 2018).

Risk stratification of patients before and during the following courses of chemotherapy is an important component of cardiological evaluation. Many risk factors have been identified, particularly in systemic therapy with anthracyclines, HER2-targeted, and other targeted medications (Lyon et al.,2022). Traditional CV risk factors are associated with an elevated risk of CV events in cancer patients. Patients at very high risk include those with established cardiac conditions such as coronary artery disease, heart failure, cardiomyopathy, and valvular heart disease. Factors that increase the risk of cardiotoxicity encompass prior and ongoing anthracycline-based CT, elevated cumulative doses of anthracyclines, and prior left-sided RT (Lyon et al., 2022). The risk factors associated with RV dysfunction remain inadequately explored, although existing data indicate the impact of cumulative anthracycline dosage, RT, and certain types of targeted therapies (Keramida et al., 2024).

In our cohort, no clinical parameter related to patient risk, type, and duration of OT predicted deviation in the RV indicators RVFAC and RVS`, or the summarized indicator of RV dysfunction (Figure 24).

The multivariate regression analyses examined the influence of clinical indicators on the decline of LV functional parameters and identified prognostic factors that aligned with existing scientific literature. The clinical predictors of LVEF decline were OT with

anthracyclines (β = -8.3, 95% CI -15, -1.9, p = 0.011) and sequential therapy with anthracyclines and trastuzumab (β = -6.3, 95% CI -11, -1.3, p = 0.013). Additionally, the time since the start of cancer treatment encompassing its various modalities was a clinical predictor of LVEF decline (β = -2.8, 95% CI -4.6, -0.93, p = 0.003). Anthracycline therapy (β = -1.9, 95% CI -3.6, -0.28, p = 0.022) and the time since the beginning of OT (β = -0.40, 95% CI -0.76, -0.04, p = 0.028) were also independent prognostic factors for a decrease in the average LVS' (Figure 26). Prognostic factors for LV systolic dysfunction included a high risk of CTRCD (OR 14.1, 95% CI 3.01, 66.6, p < 0.001), BMI (OR 1.29, 95% CI 1.06, 1.56, p = 0.01), and the presence of dyslipidemia (OR 4.88, 95% CI 1.19, 20.00, p = 0.027). The degree of cardiotoxicity risk and BMI were independent prognostic factors in our population for CTRCD, as determined by our modification of the 2022 ESC definition (Figure 31).

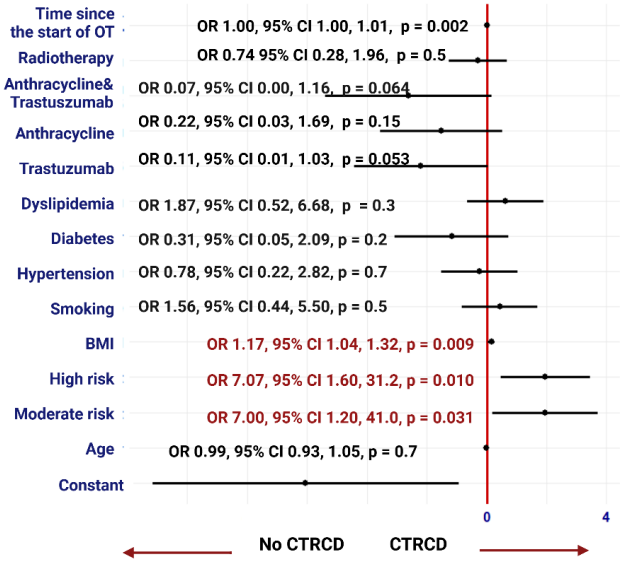

Figure 31. *GEE regression analysis assessing the predictive value of clinical indicators for the occurrence of CTRCD*

5.5.Algorithm for the early prediction of myocardial damage and the risk stratification of patients.

At the beginning of our study in June 2019, there were no established recommendations for managing and monitoring patients with oncological diseases. Additionally, various scientific communities employed differing criteria for CTRCD. The 2022 guidelines on cardio-oncology standardize the definition of CTRCD and outline specific protocols for risk stratification and patient monitoring (Lyon et al., 2022). The recommendations prioritize echocardiography for the initial assessment and monitoring of cardiac function due to its widespread availability and ability to provide rapid information. Three-dimensional Echo is recognized as a more accurate method for assessing LVEF and RVEF (Lyon et al., 2022). The right ventricle should be evaluated using the traditional systolic parameters (RVFAC, TAPSE, RVS') and the deformation index RVFWLS. The systolic and diastolic indicators, LVEF, E/e', and LA volume, serve to evaluate left ventricular function. The study of GLS of LV is recommended as it offers insights into subclinical early myocardial damage and forecasts the onset of clinically manifest CTRCD (Lyon et al., 2022).

While acknowledging the significance of deformation indicators, we suggest that routine monitoring should include the publication of systolic S' and early diastolic tissue velocities e' from the septal and lateral mitral annulus, as well as from the lateral tricuspid annulus, at baseline and during follow-up. Several arguments support this position: 1.) The study with tissue Doppler is simple and rapid to conduct, and it is associated with low variability in consecutive measurements. 2.) The interrogation with tissue Doppler provides simultaneous information on the systolic and diastolic tissue velocities and enables the acquisition of the myocardial performance indices of the left and right ventricles. 3.) It can assist in clinical decision-making in cases where the LVEF values are in the lower boundary. 4.) Our

study indicates that the tissue velocities, both systolic and diastolic, carry not only functional but also prognostic information for future CTRCD and RV dysfunction.

A stepwise assessment of various GEE regression models utilizing the variable selection criteria QIC (Quasi-likelihood under Independence model Criterion), AGPC (Akaike-type penalized Gaussian Pseudo-likelihood Criterion), SGPC (Schwarz-type penalized Gaussian Pseudo-likelihood Criterion), and the Wald test, determined that the RV and LV systolic tissue velocities, along with the early diastolic tissue velocities, had the highest prognostic significance. In our study, the prognostic factors for the reduction in RVS' include septal LVS' velocity and RVe', with respective coefficients of $\beta = 1.1$ cm/s (95% CI -1.9, -0.31, $p = 0.007$) and $\beta = 0.36$ (95% CI 0.25, 0.46, $p < 0.001$). In addition, RVS' served as a predictor of the decrease in the average LVS' (β 0.18, 95% CI 0.11, 0.25; $p < 0.001$), which subsequently acted as a prognostic factor for the decline in LVEF (average LV S' $\leq$7 cm/s - LVEF $\beta = -4.3$ (95% -6.6, -2.0; $p < 0.001$)). The systolic tissue RV S' velocity predicted LV systolic dysfunction (OR 0.7, 95% CI 0.53, 0.91, $p = 0.008$), which integrated the pathological deviations of LVEF and average LVS'. The left ventricular diastolic parameter LVe' was a predictor of LV systolic dysfunction and CTRCD, as defined by our study (OR 0.76, 95% CI 0.6, 0.97, $p = 0.025$ and OR 0.7, 95% CI 0.65, 0.95, $p = 0.025$, respectively). The RV diastolic parameter RVe` was a prognostic indicator for RV dysfunction (OR 0.56, 95% CI 0.41, 0.77, $p < 0.001$). The final regression models did not incorporate the degree of cardiotoxicity risk, age, comorbidities, radiotherapy, or endocrine therapy, which applies to the specific study population.

The strain indices of the LV and RV show numerous advantages. Nonetheless, a notable limitation is the requirement for a baseline value before initiating OT, which is only feasible for some patients. In patients undergoing mastectomy and radiotherapy in the chest region,

ultrasound imaging frequently fails to sufficiently visualize all segments of the LV and RV, hindering accurate assessment of GLS. The aforementioned circumstances serve as a constraint for assessing LVEF and RVFAC. Here again, the RV and LV systolic tissue velocities are considered.

Scientific research is focusing on diastolic disorders associated with OT, which are thought to manifest early in the course of OT or persist as late sequelae, potentially leading to HFpEF (Camilli et al., 2024; Chang et al., 2021; Palmer et al., 2023). This presents an additional rationale for monitoring the indicators LVe', RVe`, LVE/e', and RVE/e` in conjunction with other parameters related to diastolic function.

Our proposed algorithm for assessing and monitoring cardiac function during and after OT incorporates all recommendations from the 2022 cardio-oncology guidelines (Figure 32).

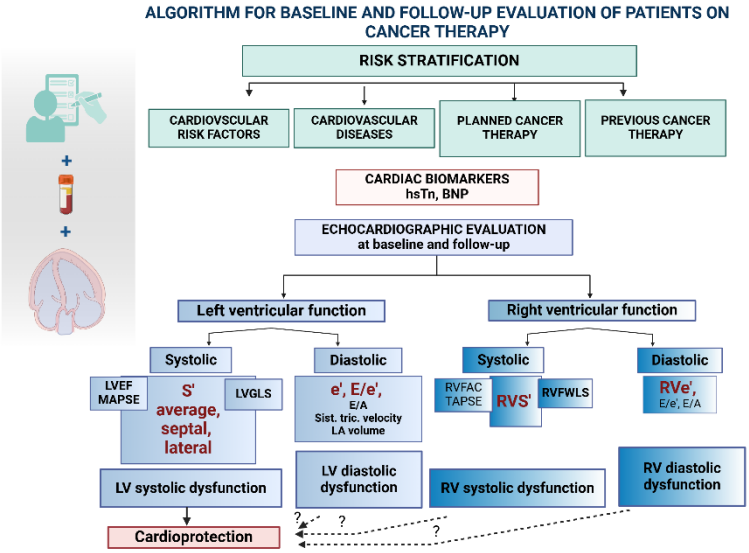

Figure 32. *Algorithm for assessing patients undergoing oncological treatment (created by Svetoslava Slavcheva with biorender.com)*

The assessment's integral component is the patients` risk stratification, which integrates anamnestic, laboratory, and echocardiographic data regarding CV risk factors, CV diseases, and the baseline functional status of the LV, RV, and heart valves. In the absence of the possibility or quality study of deformation indicators, essential components of the functional cardiac assessment include the systolic and diastolic parameters derived from tissue Doppler of the mitral and tricuspid annulus—S', e,' and the combined parameter E/e' for the LV and RV (Figure 32).

5.6.Limitations of the Study

The research was performed in a small sample that excluded patients at very high risk of CTRCD. The study population primarily consisted of female patients with no significant CV comorbidities. The follow-up period lasted 18 months; consequently, data on long-term cardiac function disturbances is unavailable. Seventy percent of the population was monitored for a duration of 12 months or longer, indicating that not all patients were observed for the entire study period. Therefore, findings regarding more acute early functional disturbances exhibit greater statistical significance. A direct comparison of the indicators of left and right ventricular longitudinal systolic function, specifically systolic tissue velocities and longitudinal strain, was not conducted. Subsequently, the investigation fails to determine the comparative evolution of these parameters over time. The dynamics of the monitored parameters result from the influence of OT and also reflect the effects of cardioprotective treatment administered to nearly half of the population.

6. CONCLUSIONS

1) The conventional echocardiographic parameters can detect LV systolic and diastolic function abnormalities due to OT as early as 1-3 months.

2) The right ventricular conventional functional echocardiographic parameters exhibit statistically significant deviations within the initial 1-3 months after the beginning of OT.

3) The RV systolic tissue velocity S' is a more appropriate parameter than RVFAC for assessing RV function, as it reflects early impairment and exhibits low variability.

4) The oncological therapy impacts RV systolic and diastolic function, which may be asymptomatic and not accompanied by LV damage.

5) High-sensitivity TnT testing may aid in diagnosing myocardial damage induced by OT.

6) The early alterations in conventional RV parameters, along with their functional and prognostic informativeness, strongly support the need to monitor them in patients undergoing OT.

7) The correlational and prognostic relationships between conventional echocardiographic indicators for RV and LV derived from tissue Doppler support their routine monitoring in OT conditions.

7. SUMMARY

The present study confirms the occurrence of cancer therapy-related biventricular impairments. Right ventricular damage as a result of OT is a reality and can be diagnosed with standard echocardiographic parameters. It can be an independent phenomenon or be accompanied by diastolic right ventricular disorders or left ventricular systolic dysfunction. The right ventricle differs from the left ventricle in many characteristics – cellular origin, myocardial structure, geometry, autonomic control, and lower oxygen demand with higher coronary reserve. According to some scientists, these qualities determine the reduced sensitivity to cardiotoxic effects (Lenčová-Popelová et al., 2014). Conversely, other authors suggest that the myocardial structure and the thin wall thickness of the right ventricle increase its vulnerability to damage following antitumor therapy (Barthur et al., 2017). Multiple clinical studies employing diverse imaging techniques validate right ventricular damage resulting from oncological treatment.

Identifying an accurate indicator for RV monitoring is crucial for assessing and comparing its functional state over time with the capabilities of most ultrasound devices, thereby circumventing a primary limitation of the method—the necessity for an optimal ultrasound window. Our study found that a mandatory minimum in echocardiographic cardiac assessment during and after OT is the measurement of RV tissue velocities. The systolic RV tissue velocity is a reliable and low-variance indicator of its functional state. RV shortening in the longitudinal direction accounts for 75% of the contraction (Sanz, Sánchez-Quintana et al. 2019). In this regard, evaluating the RV longitudinal function using the RVS parameter is imperative. In addition, the parameter also has a prognostic value for the deterioration of the longitudinal systolic function of the LV, measured with the septal systolic tissue velocity. Furthermore, from a practical perspective, assessing tissue PW Doppler at the lateral

tricuspid annulus provides insights into diastolic velocities and the overall RVMPI index of the right ventricle. In our studied population, early diastolic tissue velocity of the RV below 9.8 cm/s predicts RV dysfunction. The functional changes in the RV we found, as well as the correlation and prognostic dependencies with the functional disorders of the LV, confirm the need for regular echocardiographic assessment of the RV.

8. CONTRIBUTIONS

Original in nature:

1. For the first time in Bulgaria, conventional echocardiographic indicators were used to track changes in the systolic function of the right ventricle over an 18-month period in a population on systemic cancer therapy.
2. The right ventricle's diastolic function was evaluated during and after OT for a period of 18 months.
3. For the first time in Bulgaria, changes in the systolic and diastolic function of the left ventricle have been observed using conventional echocardiographic indicators over an 18-month period in a population undergoing systemic OT.
4. For the first time in Bulgaria, the predictive value of several echocardiographic measures for the onset of cardiac dysfunction (left and right ventricular) within 18 months following the initiation of cancer treatment was examined.
5. A follow-up of patients undergoing OT was conducted for the first time at the Medical University - Varna and the University Hospital "St. Marina," establishing the theoretical and practical foundations for future collaboration between oncologists and cardiologists.

Confirmatory in nature:

1. The echocardiographic systolic conventional parameters of the RV were found to deviate in a manner comparable to scientific data during cancer therapy.
2. Deviations in the echocardiographic diastolic conventional indicators of the right ventricle were observed due to oncologic treatment.
3. The incidence of right ventricular dysfunction in a population undergoing oncologic treatment was identified.

4. Systolic and diastolic left ventricular disorders influenced by cancer therapy were identified, aligning with existing scientific literature.

9.PUBLICATIONS AND REPORTS RELATED TO THE DISSERTATION

Publications:

1.Slavcheva S. Anthracycline-induced cardiotoxicity – primary preventive options. An overview. Bulgarian Cardiology. 2024; 30(1): 20-40. https://doi.org/10.3897/bgcardio.30.e120496

2. Bakalska S, Angelov A, **Slavcheva S** and R. Georgiev. Acute reversible heart failure induced by 5-fluorouracil chemotherapy. Bulgarian Cardiology. 2017; 23 (3), 58-63

Reports:

1. XVI National Congress of Cardiology, October 04-07, 2018; Albena, Bulgaria: **Slavcheva S**, Angelov A., Bakalska S. Acute cardiotoxicity after administration of 5-fluorouracil. Bulgarian Cardiology vol. XXII, 2018, Supplement 5 p. 29; UD-VI.1.

2. Seventh „Black Sea Symposium for Young Scientists in Biomedicine", November 22-24, 2019: Kalvachev NB, **Slavcheva S** , Vetkova M, Petrov P , Angelov A. Diagnostic tools for detection of cardiotoxicity – a methodological review. Scripta Scientifica Vox Studentium, vol. 3, suppl. 1, 2019.

3. Varna Cardiological Days, February 14–16, 2020.; Sts. Constantine and Helena Resort. **Slavcheva S.**, Angelov A. "Pericarditis and breast cancer. Clinical case".

4. XXVII Heart-Lung Association, 10 - 12 november 2023, Albena resort. Slavcheva S. „Trastuzumab, from the cardiologist's perspective: balancing risk against benefit".

5. XVIII National Cardiology Congress 2024, 10 - 13 October 2024; International fair Plovdiv, Bulgaria. **Slavcheva S**, Angelov A. Parameters of RV function in the course of systemic antitumor therapy.

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