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CARDIOVASCULAR CHANGES INDUCED BY ANTITUMORAL TREATMENT IN NON-HODGKIN LYMPHOMAS

321.03 – CARDIOLOGY

Summary of the PhD thesis in medical sciences

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The thesis was developed within the Department of Internal Medicine, Cardiology Discipline, Nicolae Testemițanu State University of Medicine and Pharmacy of the founding consortium of the Doctoral School in Medical Sciences

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INTRODUCTION

Relevance and importance of the addressed issue

Cardiovascular diseases represent one of the leading causes of mortality among patients diagnosed with various types of malignancies. Recent studies suggest that the most significant changes in cardiovascular risk occur within the first year following the diagnosis of a malignant disease [1]. Although the majority of cancer patients ultimately die from the malignancy itself, cardiovascular complications represent the second most common cause of death [2]. This phenomenon has also been observed during the treatment of non-Hodgkin lymphomas (NHL). Nevertheless, the understanding and early detection of cardiovascular complications in NHL therapy remain unresolved challenges [3].

Non-Hodgkin lymphomas (NHL) are malignant tumors that originate from lymphoid tissue and are characterized by genetic, clinical, therapeutic, and prognostic heterogeneity. NHL encompasses a wide spectrum of clinical behavior, ranging from indolent to highly aggressive forms of the disease [4]. These lymphomas are among the most common hematologic malignancies, accounting for approximately 3.1–4.3% of all malignant tumors [5]. In the Republic of Moldova, the diagnosis of NHL is established at advanced stages of the disease in the majority of patients (87%) [6]. The 5-year survival rate has shown a significant increase, from 46% in 1975 to 72.7% during the 2010–2016 period. This improvement is largely attributed to the introduction and application of novel chemotherapeutic regimens and agents [7]. Currently, therapeutic options involve complex combinations of immunotherapy, chemotherapeutic agents, and radiotherapy. As a result of these treatments, many cancer survivors face an increased risk of developing cardiovascular complications [8]. Understanding the various cardiovascular adverse effects associated with NHL therapy is essential for their effective prevention and appropriate management. The severity of cardiotoxicity is influenced by several factors, including the mechanism of action of the specific therapeutic agents used, the initial and cumulative doses, the route of administration, the presence of cardiovascular risk factors, genetic predisposition, and the patient's age [9]. Antitumor therapy-related adverse cardiovascular effects may occur either acutely during treatment or may manifest months or even years after its completion. Among the most common cardiovascular complications associated with NHL treatment are cancer therapy-related cardiac dysfunction—which may range from asymptomatic forms to overt heart failure—arterial hypertension, venous thromboembolism, arrhythmias, and pericardial disorders [10].

Early diagnosis of cardiotoxicity induced by antitumor treatments is essential for preventing cardiovascular complications and ensuring the continuity of specific oncologic therapy. Assessment methods such as transthoracic echocardiography, cardiopulmonary exercise testing (CPET), 24-hour Holter ECG monitoring, and the use of cardiac biomarkers play a crucial role in the early detection of cardiovascular adverse effects. Early detection of cardiac dysfunction allows for prompt therapeutic interventions, reducing the risk of heart failure and other severe cardiovascular events. Transthoracic echocardiography is the reference method for evaluating left ventricular function, due to its widespread availability and cost-effectiveness. Advanced techniques, such as tissue Doppler and speckle tracking, enable the detection of subtle myocardial function changes before they become evident through conventional methods [11]. Cardiopulmonary exercise testing provides an integrated assessment of both cardiovascular and respiratory function; however, its role in evaluating cardiotoxicity remains not fully clarified. Peak VO_2 parameters and the ventilation slope in relation to carbon dioxide production (VE/VCO_2) are sensitive indicators of functional capacity and can predict the risk of heart failure [12]. In the

context of chemotherapy-induced cardiotoxicity, 24-hour Holter ECG monitoring can detect subtle changes in heart rate and electrical conduction, changes that precede the overt clinical manifestations of cardiac dysfunction. Holter ECG 24-hour analysis is useful in detecting episodes of silent myocardial ischemia and asymptomatic arrhythmias. This method contributes to risk stratification and personalized treatment planning for each patient [13]. However, the direct relationship between heart rhythm changes detected by 24-hour Holter ECG and the development of heart failure or other cardiovascular complications requires further studies. The analysis of cardiac biomarkers, such as troponin and natriuretic peptides, can provide valuable insights into subclinical myocardial injury. Elevated levels of these biomarkers can indicate cardiac impairment before the onset of clinical symptoms [14]. Although there is still no standardized protocol that includes all these monitoring modalities, the implementation of such an integrated monitoring tool, which includes periodic echocardiographic evaluations, cardiopulmonary exercise testing, 24-hour Holter ECG monitoring, and the analysis of cardiac biomarkers, could become standard practice for patients undergoing antitumor therapy with potential cardiotoxic effects. This multidisciplinary approach holds the potential to facilitate the early detection of cardiotoxicity, allowing for timely interventions and real-time treatment adjustments.

In the Republic of Moldova, there are few studies that have evaluated the cardiovascular status of patients undergoing antitumor treatment for NHL. Currently, there are no national, personalized cardiovascular monitoring protocols for patients with NHL. On the other hand, such a study would pave the way for the creation of specialized cardio-oncology programs in the Republic of Moldova. Specialized programs would encourage collaboration between hematologists and cardiologists to ensure an interdisciplinary approach to patient management

The aim of the study:

To identify changes in cardiovascular parameters and assess their role in the early diagnosis of complications associated with antitumor treatment in patients with non-Hodgkin lymphoma.

Study Objectives:

1. Estimation of the incidence and severity of rhythm disorders and arterial hypertension induced by antitumor treatment, as well as the assessment of their correlation with the specifics of antitumor therapy in patients with non-Hodgkin lymphomas.
2. Clarification of the importance of the cardiopulmonary exercise test in evaluating cardiovascular complications in patients with non-Hodgkin lymphomas undergoing antitumor treatment.
3. Highlighting the correlation between changes in cardiac function and cardiopulmonary capacity during antitumor treatment in patients with non-Hodgkin lymphomas.
4. Defining the risk factors and cardiovascular profile associated with cardiac dysfunction related to antitumor therapy in patients with non-Hodgkin lymphomas.
5. Development of a predictive model for antitumor treatment-induced cardiac dysfunction in patients with non-Hodgkin lymphomas by analyzing the relationship between changes in paraclinical parameters, the specifics of antineoplastic treatment, as well as cardiovascular and demographic risk factors.

This study complied with the Declaration of Helsinki of the World Medical Association from 1975, revised in 1983, and was approved by the Research Ethics Committee of "Nicolae Testemitanu" State University of Medicine and Pharmacy, being reviewed during the meeting held on December 28, 2021, and granted a favorable opinion under number 8.

Scientific novelty of this research:

1) Cardiovascular risk factors and those derived from the specific tumor profile associated with the onset of cardiotoxicity were identified; 2) The relationship between NHL treatment and the increase in blood pressure values was demonstrated, as well as its correlation with the increased incidence of cardiac arrhythmias; 3) The specifics of antitumor treatment associated with arrhythmic events during NHL therapy were identified; 4) Cardiopulmonary parameters with predictive value for the onset of cardiotoxicity were elucidated; 5) A model for predicting the risk of cardiotoxicity prior to the initiation of antitumor treatment was developed.

Theoretical significance of the research:

The study addressed the problem of early detection of cardiac dysfunction induced by antitumor therapy in patients with non-Hodgkin lymphoma, identifying predictive markers and developing a prediction model for cardiotoxicity. It demonstrated the impact of treatment on arrhythmias and blood pressure and provided opportunities for preventive intervention and optimized management.

Practical value of the work:

Based on the results obtained, it will be proposed to develop recommendations by integrating 24-hour Holter ECG monitoring, automatic ambulatory blood pressure monitoring, cardiopulmonary exercise testing, and serial echocardiography. The research suggests a multidisciplinary surveillance protocol that facilitates the early detection of arrhythmias and subclinical ventricular dysfunction, optimizes treatment to reduce cardiovascular risk, and adjusts the doses of antitumor therapy according to individual cardiac parameters. The implementation of the prediction model for cardiac dysfunction could reduce morbidity and mortality associated with antitumor therapy, thereby improving the prognosis and quality of life of patients.

Approval of the results obtained was carried out in accordance with the fundamental stages of the study. The main results were presented, discussed, and approved at the meetings of the Department of Internal Medicine, Cardiology Discipline at the Nicolae Testemițanu State University of Medicine and Pharmacy, Scientific Profile Seminar, as well as at:

- **National Conferences:**

Annual Scientific Conference of the USMF "Nicolae Testemițanu" (2021, 2022, 2023, Chișinău, Moldova). The 8th edition of the National Cardiology Symposium (2022, Chișinău, Moldova).

- **International Conferences:**

The 8th International Medical Congress for Students and young Doctors MedEspera (2020, Chișinău, Moldova). The VI International Black Sea Coastline Countries Scientific Research Symposium (2021, Giresun, Turcia). ESC Heart Failure Congress and World Congress on Acute Heart Failure (2022, Madrid, Spania). Congresul al 61-lea Național de Cardiologie (2022, Sinaia, Romania). ESC Heart Failure Congress and World Congress on Acute Heart Failure (2023, Praga, Cehia). The 37th Balkan Medical Week. The 8th congress on urology, dialysis and kidney transplanta from the Republic of Moldova „New Horizons in Urology" (2023, Chișinău, Moldova). ESC Heart Failure Congress and World Congress on Acute Heart Failure (2024, Lisabona, Portugalia). HFA Winter Research Meeting on Translational Heart Failure Research (2025, Viena, Austria), EUROINVENT 2025 17th Edition, ESC Heart Failure Congress and World Congress on Acute Heart Failure (2025, Belgrad, Serbia).

Keywords: heart failure, cardiotoxicity, chemotherapy-induced cardiac dysfunction, non-Hodgkin lymphomas.

1. GENERAL CHARACTERISTICS OF THE STUDY MATERIAL AND RESEARCH METHODS

1.1. General overview of the conducted study

The prospective analytical observational cohort study was conducted between 2021 and 2024 at the Institute of Oncology and the Institute of Cardiology in Chișinău, Republic of Moldova. Hematological patients were selected randomly and evaluated according to the study design. The research adhered to the Helsinki Declaration and was approved by the Ethics Committee of the Nicolae Testemițanu State University of Medicine and Pharmacy on December 28, 2021 (meeting Nr. 8).

To estimate the sample size, the McNemar test was used, which is suitable for the analysis of paired binary data, especially in studies with repeated measurements or "within-subjects" designs. The main parameters used in the sample size calculation included a significance level (α) of 0.05, a power of the test of 80% ($1 - \beta = 0.80$), and an odds ratio of 3, meaning that the post-treatment cardiotoxicity risk is three times higher (or lower) than the pre-treatment risk. The estimated proportion of discordant pairs, i.e., patients whose cardiotoxicity status changes between the two measurement points, was set at 0.3.

The results obtained from the sample size calculation indicate that to achieve 80% power, a total of 100 patients are required. It was also determined that between 9 and 21 discordant pairs are necessary to detect a statistically significant difference in terms of cardiotoxicity. Following the calculation, the actual power was found to be 80.34%, and the effective significance level achieved was 0.0428, which is lower than 0.05, thus ensuring proper control of Type I error.

Inclusion criteria for the study:

- Patients with a confirmed diagnosis of NHL.
- Patients aged ≥ 18 years.
- Ability to be monitored over time.
- Obtaining informed consent from the patient.

Exclusion criteria from the study:

- Presence of another oncological/hematological disease at the time of inclusion in the study.
- Patients with prior chemotherapy, immunotherapy, or radiotherapy treatment.
- Patients known to have heart failure NYHA III-IV.
- Left ventricular ejection fraction (assessed by echocardiography) < 50%.
- Known coronary/myocardial pathology.
- Moderate or severe valvulopathies.
- Pathologies of the pericardium.
- Suboptimal echographic window.

During the course of the study, patients were investigated across 3 visits. Visit 1 was the initial visit before the initiation of antitumoral treatment, visit 2 was conducted one month after the initiation of treatment, and visit 3 was held six months after the initiation of antitumoral treatment. Patients were investigated according to the design presented in Figure 1. The study design followed the "repeated measurements" type, a method in which the same subjects are investigated multiple times at different points in time. Since everyone included in the study acts as their own control, variations between participants are eliminated, which increases the statistical power. The repeated measurements design is more resource-efficient, requiring fewer participants.

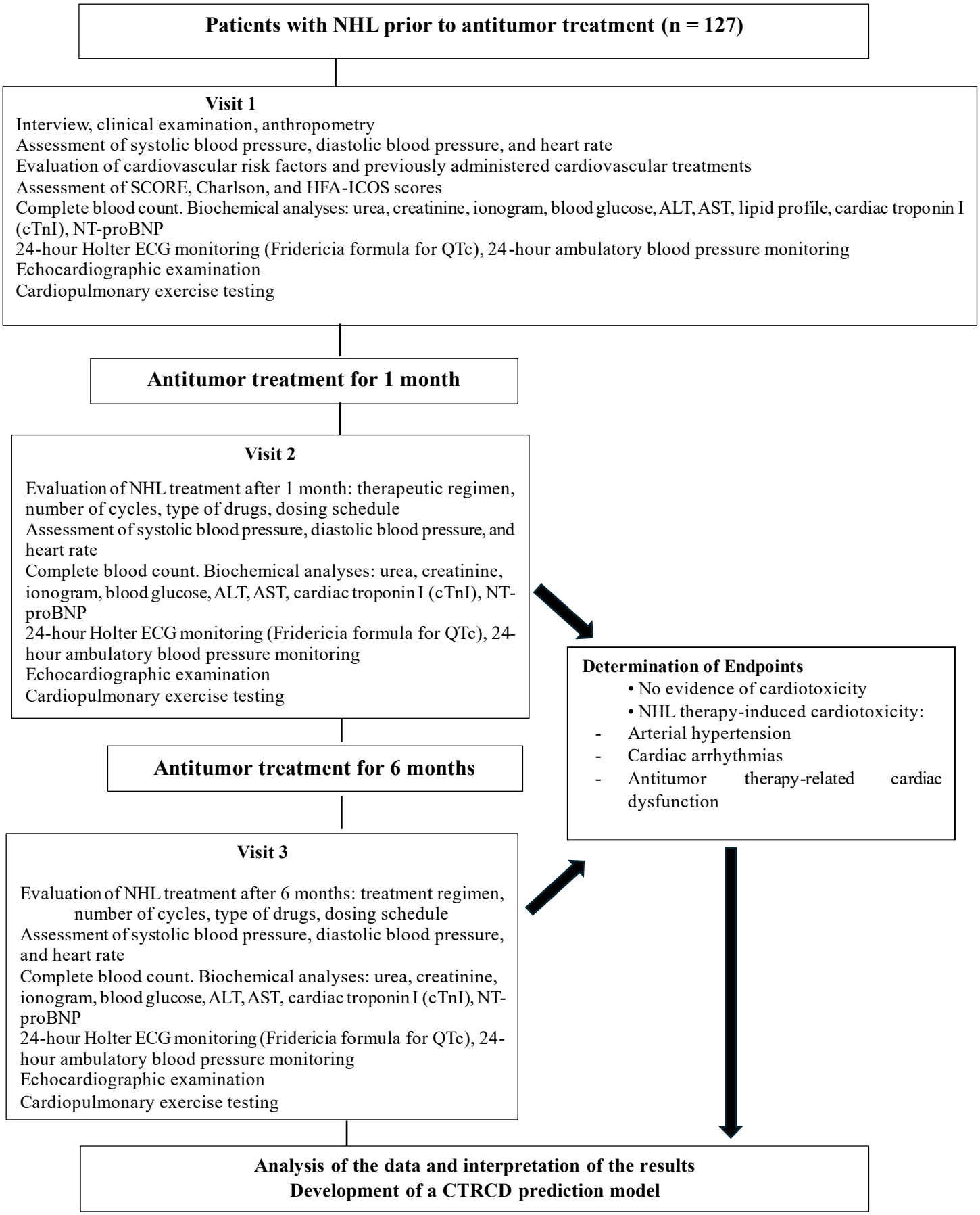

Figure 1. **Study design**

1.2. Applied methodology during the research

a) Clinical and laboratory methods

Throughout the study, patients were evaluated in three visits: prior to the initiation of antitumoral treatment, one month after the start of treatment, and six months later. Visit 1 (pre-treatment): general data were collected (age, gender, comorbidities, cardiovascular risk factors, type and stage of non-Hodgkin lymphoma), and the cardiovascular risk score (SCORE2/SCORE2-OP) was calculated. Visit 2 and 3: the therapeutic regimen, presence of complications, and adverse effects were analyzed. Additional at visit 3 (six months post-treatment): the treatment outcomes were evaluated. The clinical examination included system analysis, blood pressure measurement, anthropometric indices (BMI, waist circumference), and hemodynamic parameters. Laboratory investigations were conducted at all three visits and included: complete blood count, erythrocyte sedimentation rate, C-reactive protein, ionogram, renal function (eGFR according to CKD-EPI), lipid profile, fasting blood glucose. Anemia was classified according to CTCAE criteria, while metabolic syndrome was diagnosed according to ESC 2019 guidelines. Glomerular filtration rate (GFR) was assessed using the KDIGO 2020 classification.

b) Instrumental method

Ambulatory Blood Pressure Monitoring and Holter ECG – MATA were performed using the "ABPpro" monitor (2021). Blood pressure was measured every 30 minutes during the day and every 60 minutes at night, and patients completed a symptom journal. The obtained parameters included mean blood pressure values, blood pressure variability, and classification of the diurnal profile (dipper, non-dipper, over-dipper, night-picker). The 24-hour Holter ECG was performed with the "ECGpro Holter" monitor (2021), analyzing average heart rate, episodes of tachycardia, bradycardia, atrial fibrillation, and heart rate variability. QTc and PQ intervals, as well as ischemic changes in the ST-T segment, were also evaluated

Transthoracic Echocardiography was performed using the Vivid S5 ultrasound machine (GE Healthcare) according to international guidelines. Structural parameters of the atria and ventricles, myocardial mass, and types of ventricular remodeling were analyzed. Systolic and diastolic function of the left ventricle were evaluated, including ejection fraction, mitral flow velocities (E/A, e', TDE), Tei index of the right ventricle, and systolic pulmonary artery pressure.

Cardiopulmonary Exercise Testing was conducted using a cycle ergometer and 12-lead ECG monitoring (COSMED 2015, version 1.6.7). The protocol included four phases: rest, cycling without resistance, progressive effort (8-12 minutes, with a 5-25 W/min increase), and recovery. Ventilatory, metabolic, and cardiovascular parameters were measured.

c) Statistic methods

The primary data collected were processed automatically using open-source programs, RStudio version 2024.09.1+394 and Python version 3.12.3. Statistical analysis included the Mann-Whitney-Wilcoxon test for comparisons between independent groups and paired data, while correlations were evaluated using the Spearman coefficient. Categorical variables were analyzed using the Chi-square test (including the Monte Carlo version), with corrections for 2x2 tables, and the McNemar test for dynamic comparisons. The significance threshold was set at $\alpha = 0.05$. The study employed logistic regression to classify patients at risk for cardiotoxicity 6 months after treatment. The model was trained using stratified cross-validation, optimized with GridSearchCV (C=0.001–1000, L1/L2 penalties), and evaluated based on sensitivity. Performance was measured using the confusion matrix and the area under the ROC curve. The importance of variables was determined using SHAP methods and feature permutation.

2. RESULTS

2.1. General characteristics of the study group

The study cohort consisted of 127 patients with NHL, of whom 72 were male (56.7%, 95% CI: 48, 65) and 55 were female (43.3%, 95% CI: 35, 52). Geographically, 66 participants were from urban areas (52.0%, 95% CI: 43, 61), while 61 were from rural areas (48.0%, 95% CI: 39, 57). Regarding the age of the patients, they ranged from 34 to 83 years, with a median age of 62.0 years (IQR=14.0). The body mass index (BMI) had a median of 25.9 kg/m² (IQR=7.0), with a minimum of 18.6 kg/m² and a maximum of 48.7 kg/m². A total of 31 patients (24.4%, 95% CI: 17, 32) had a BMI > 30 kg/m². The abdominal circumference had a median of 78.0 cm (IQR=23.0). BMI analysis showed that 59 patients (46.5%, 95% CI: 38, 55) were normal weight, 37 (29.1%, 95% CI: 21, 37) were overweight, 21 (16.5%, 95% CI: 10, 23) had Grade I obesity, 7 patients (5.5%, 95% CI: 1.5, 9.5) had Grade II obesity, and 3 patients (2.4%, 95% CI: 0.0, 5.0) had Grade III obesity. Dyslipidemia was present in 84 patients (66.1%, 95% CI: 58, 74), and metabolic syndrome was found in 18 patients (14.2%, 95% CI: 8.1, 20). The most common comorbidity was hypertension, reported in about 50 patients (39.3%). A history of chronic obstructive pulmonary disease (COPD) was recorded in 27 cases (21.3%, 95% CI: 14, 28). The proportion of patients diagnosed with pre-existing chronic kidney disease was 14.9%. According to the severity of chronic kidney disease, 14 patients (11.0%, 95% CI: 5.6, 16) had CKD stages G1 and G2 according to KDIGO criteria, 2020. A total of 5 patients (3.9%, 95% CI: 0.55, 7.3) were diagnosed with CKD stage G3 (KDIGO). No patient included in the study had more severe stages of chronic kidney disease or other advanced/decompensated comorbidities.

The most frequent form of NHL was the indolent form, found in 78 patients (61.4%, 95% CI: 53, 70), presenting with a slow and less aggressive disease course. In the majority of cases, 123 patients (96.9%, 95% CI: 94, 100) were diagnosed with precursor B lymphoblastic lymphomas, a specific type of lymphoma involving immature B lymphocytes, known for their unique progression in hematologic malignancies. Based on disease stage, the most common stage was IV, found in 89 patients (70.1%, 95% CI: 62, 78), followed by stage III with 18 patients (14.2%, 95% CI: 8.1, 20), nearly equal to stage II, identified in 16 patients (12.6%, 95% CI: 6.8, 18), and stage I, found in only 4 patients (3.1%, 95% CI: 0.11, 6.2). Regarding the location of the primary tumor focus, the peripheral lymph nodes were the most common site, found in 94 patients (74.1%, 95% CI: 46, 98).

2.2. Impact of antitumor treatment on rhythm disturbances and blood pressure

All patients were evaluated through 24-hour blood pressure monitoring (MATA). The analysis of the results from monitoring during treatment revealed a statistically significant difference in the mean daytime blood pressure between the first and third visits, with a Mann-Whitney U test result of 1635.5, $p<0.001$. At the first visit, the mean daytime blood pressure was 124.8 mmHg (SD=12.1), while at the 6-month visit, it increased to 131.5 mmHg (SD=12.3). This difference was statistically confirmed, showing a clear trend of increased blood pressure throughout the treatment period. Additionally, the mean nighttime blood pressure also showed a significant increase. At the first visit, the mean nighttime blood pressure was 110.0 mmHg (SD=14.9), and by 6 months, it had risen to 117.0 mmHg (SD=13.1). These nocturnal changes were statistically significant, indicating a global increase in blood pressure during the night, alongside the ongoing treatment. Furthermore, the mean 24-hour blood pressure also exhibited a similar upward trend. At the beginning of the study, the mean 24-hour blood pressure was 118.7 mmHg (SD=11.7), and at the 6-month visit, it reached 125.0 mmHg (SD=12.3). These significant

differences were confirmed by a Mann-Whitney U test result of 1709.5, $p<0.001$, suggesting that the treatment had an impact on blood pressure over the analyzed period. Blood pressure phenotypes did not show significant statistical differences, with most patients remaining in the non-dipper phenotype.

24-hour Holter ECG monitoring showed a statistically significant increase in the mean heart rate (HR) over 24 hours after 6 months of treatment. Additionally, a decrease was observed in the cardiac rhythm variability indicators, including the standard deviation of RR intervals (SDNN) across the entire duration of the Holter recording, the mean standard deviation of RR intervals for each hour of recording (SDNNi), and the standard deviation of the means of RR intervals calculated over 5-minute periods (SDANN). The most pronounced change was observed for SDNN, which decreased from 64.1 ms to 59.6 ms (Mann-Whitney test value = 1573.5, $p<0.001$). The arrhythmic events detected at the end of the analysis that predominated included paroxysms of supraventricular tachycardia, ventricular and supraventricular premature beats. Paroxysms of supraventricular tachycardia were recorded in 16.5% of patients ($p=0.0014$). Supraventricular premature beats significantly increased in the mean number of events from 228.2 to 1052.8 after 6 months of follow-up ($p<0.001$). Ventricular premature beats also showed a significant increase in the mean number of events, from 47.9 to 300.5 events ($p<0.001$). The occurrence of these events was correlated with the doses of doxorubicin and high doses of cyclophosphamide. Following the idea of identifying proarrhythmic elements, we analyzed the dynamics of the PQ and QTc intervals, which play an essential role in arrhythmic risk stratification and in the early detection of a predisposition to malignant arrhythmias. Thus:

- The PQ interval did not show any changes throughout the course of the study. When analyzed independently in relation to the type of medication administered, we found a statistically significant influence of high doses of cyclophosphamide on the considerable increase in its duration: it was 196.6 ms (SD=36.8) in patients with high doses of cyclophosphamide, compared to 169.4 ms (SD=28.0), $p<0.001$. Doxorubicin did not influence the dynamics of the PQ interval.
- The QTc interval significantly increased from 403.2 ms to 432.8 ms, $p<0.001$. This increase moderately correlated with the dose of doxorubicin administered, and it also showed a significant statistical correlation with treatment regimens that included cyclophosphamide, $p<0.001$.
- Nearly 10% of patients developed a significant prolongation of the QTc interval $\geq$ 480 ms, $p=0.0026$, and a QTc interval between 450 ms and 480 ms for men and between 460 ms and 480 ms for women was identified in 17.4% of patients, $p=0.0001$. This highlights the need for careful monitoring and possibly adjusting the specific hematologic treatment. The changes were linked to high doses of cyclophosphamide, while no correlations were found with doxorubicin doses.

Through Spearman correlation (Figure 2), we found that there was no influence of doxorubicin doses on the mean 24-hour blood pressure values. The strongest correlation was observed with the number of supraventricular and ventricular premature beats (Spearman correlation coefficient 0.35 and 0.33). No correlations were found between doxorubicin doses and the QTc or PQ intervals. For supraventricular premature beats, it was found that there were significantly more events in individuals with high doses of cyclophosphamide (2296.8 events vs. 917.5).

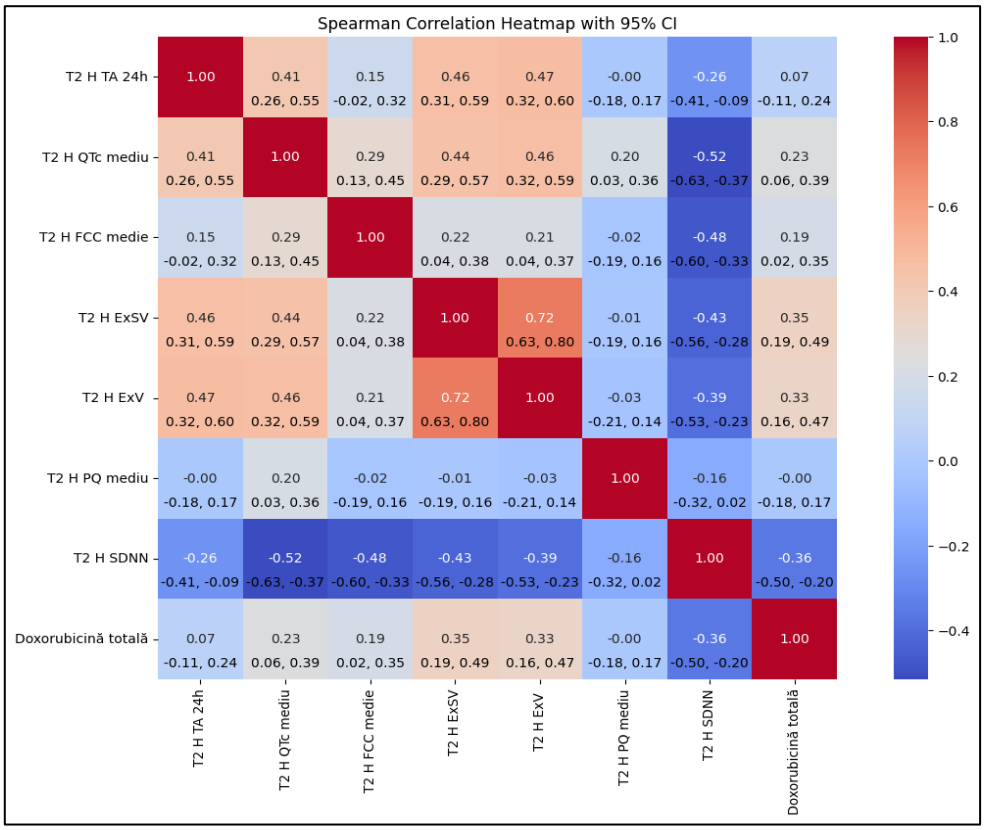

Figure 2. **Correlations between the administered dose of doxorubicin and the Holter ECG and MATA variables at the 6th month of treatment**

2.3. Dynamics of cardiopulmonary capacity and correlation with ventricular function

Table 1 presents the dynamics of metabolic gas exchange parameters, with the analysis performed using the Mann-Whitney test. Most parameters in this category showed a significant statistical decrease over time, including the peak VO_2, which is used as a prognostic factor for heart failure. The McNemar test showed that, at the end of the study, there was a significant increase in the number of patients with a peak $VO_2 < 14$ ml/kg/min. It was found that 48 patients who initially did not have this peak VO_2 value recorded it after 6 months of therapy.

Table 1. **Dynamics of metabolic gas exchange parameters at visits 1 and 3**

Metabolic gas exchange parameters	**Visit 1 Mean (SD)**	**Visit 3 Mean (SD)**	**U test Mann-Whitney (p)**
VO_2 initial, ml/kg/min	5.7 (1.2)	5.1 (1.3)	1153.5 **(p<0.001)**
VO_2 peak, ml/kg/min	16.0 (3.2)	13.0 (2.9)	241.0 **(p<0.001)**
VO_2 peak, % predicted	62.7 (13.2)	51.3 (13.9)	576.5 **(p<0.001)**
VO_2 at anaerobic threshold, ml/min	1089.3 (364.1)	890.4 (383.5)	1003.5 **(p<0.001)**
VO_2 / WR, ml/min/Watt	8.3 (1.3)	8.0 (3.5)	1811.5 **(p<0.001)**
Anaerobic threshold, % VO_2	48.8 (15.9)	44.7 (13.4)	1806.5 **(p<0.001)**
O_2 Consumption efficiency curve	2067.5 (463.7)	1782.5 (538.4)	1076.0 **(p<0.001)**
Respiratory exchange ratio	1.1 (0.2)	1.0 (0.1)	824.5 **(p<0.001)**

Applying the Mann-Whitney test to the dynamics of ventilatory performance parameters (Table 2), a significant increase was observed in the ventilatory equivalent of carbon dioxide, both

overall and at the anaerobic threshold, up to the third visit. To assess the significance of the changes recorded in the proportion of patients with a ventilatory equivalent of carbon dioxide ≥ 30, the McNemar test was applied. The results indicated that approximately 30 patients transitioned from normal values to $VE/VCO_2 \geq 30$ after 6 months, suggesting a deterioration in ventilatory efficiency (McNemar test = 5.95, p=0.0147).

Table 2. **Dynamics of ventilatory performance parameters at visits 1 and 3**

Ventilatory performance parameters	**Visit 1 Mean (SD)**	**Visit 3 Mean (SD)**	**U test Mann-Whitney (p)**
VE/ VCO_2	31.4 (5.9)	33.2 (5.8)	1984.5 **(p<0.001)**
VE/ VCO_2 at anaerobic threshold	32.4 (4.8)	34.4 (5.4)	1627.5 **(p<0.001)**
End-expiratory CO_2 pressure, mmHg	35.2 (4.4)	35.3 (5.4)	2469.5 (p=0.7188)

Subsequently, it was analyzed whether there were significant changes in the number of patients with a VE/VCO_2 ratio ≥ 30 over the course of treatment. This ratio, when exceeding 30, is considered in the literature as an indicator of reduced ventilatory incidence and is associated with an inappropriate ventilatory response in relation to carbon dioxide production, which may indicate cardiovascular or respiratory issues, as well as poor progression in individuals with heart failure. The dynamics of the VE/VCO_2 ratio ≥ 30 were analyzed at baseline and after 6 months of treatment. The McNemar test was used to evaluate the significance of the changes. Thus, 61 patients (53.0%, 95% CI: 43.5, 62.4) had an elevated VE/VCO_2 ratio (≥ 30) at both time points, indicating the persistence of this unfavorable parameter. Approximately 30 patients (26.1%, 95% CI: 18.3, 35.1) transitioned from normal values to $VE/VCO_2 \geq 30$ after 6 months, suggesting a deterioration in ventilatory efficiency. The McNemar test (5.95) and the p-value (0.0147) indicate a statistically significant change in this parameter over the 6 months. Among the cardiovascular parameters, we note that the O_2 consumption relative to the heartbeat decreased significantly by the third visit, Mann-Whitney test 917.5, p<0.001 (Figure 3).

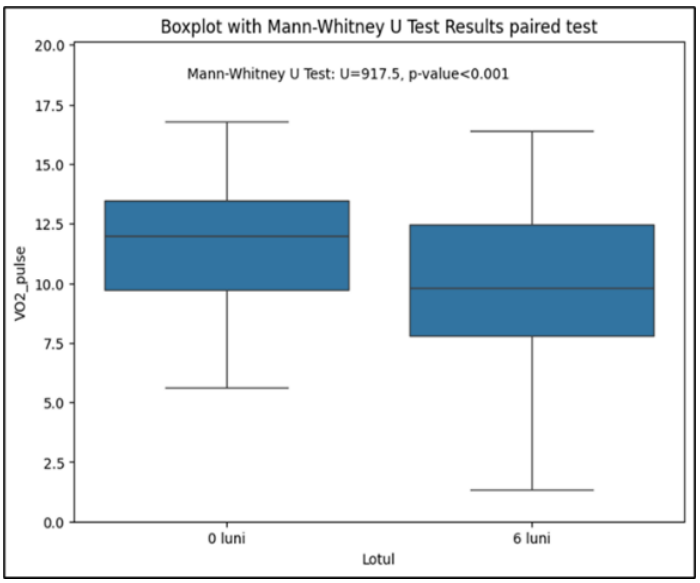

Figure 3. **Dynamics of oxygen consumption relative to heart rate**

Analyzing the study of the relationship between cardiopulmonary parameters and the evolution of left ventricular function (Figure 4), it was found that the parameter VO_2 peak has the strongest association with the left ventricular ejection fraction (LVEF) at 6 months (0.27), suggesting that a better functional response to CPET at baseline may predict a more favorable left ventricular function at the 3-month visit. The work rate (WR) showed a positive correlation (0.24), meaning that a higher exercise capacity at baseline is associated with a better ejection fraction at 6 months. Furthermore, a respiratory exchange ratio (RER) ≥ 1.10 also had a positive correlation (0.23) with LVEF

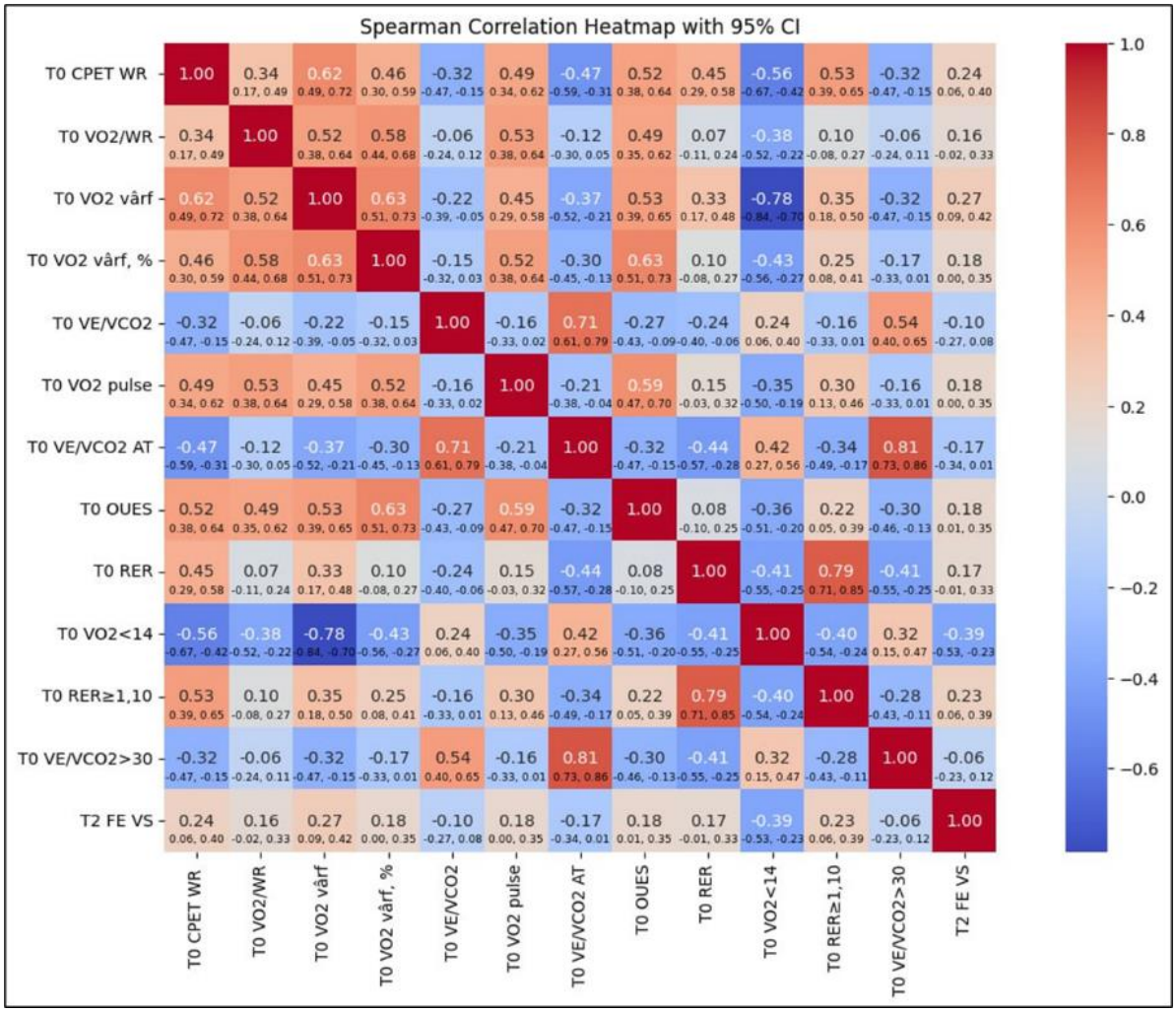

Figure 4. **Correlations between initial cardiopulmonary parameters and left ventricular function at 6 months of treatment**

2.4. Antitumor therapy-related cardiac dysfunction

At 6 months from the onset of anticancer therapy, chemotherapy-related cardiac dysfunction (CTRCD) was identified in 18 patients (14.2%). To address the formulated objectives, the general cohort was divided into two groups: Group I – 18 patients (14.2%) with CTRCD, and Group II – 109 patients (85.8%) without CTRCD. The methodological principles underlying the statistical analysis between the two groups included the use of appropriate non-parametric tests for small samples, such as the Mann-Whitney test and the Monte Carlo method, as well as reporting statistical confidence intervals. Identifying the factors associated with CTRCD will subsequently

allow the development of a predictive model, and significant factors will be integrated into a predictive model (discussed in the next subsection).

Analyzing the clinical profile of patients in the study groups, it was found that cardiovascular risk factors associated with CTRCD include: body mass index > 30 kg/m², the presence of hypertension, and a history of aggravated cardiac conditions. Among the comorbidities, chronic kidney disease, regardless of its stage, was associated with the subsequent development of therapy-induced cardiac dysfunction (Table 3).

Table 3. **General characteristics and clinical profile of patients with and without CTRCD**

	Group I (CTRCD, n = 18)[1]	**CI [2] 95%**	**Group II** (fără CTRCD, n = 109)[1]	**CI [2] 95%**	**Statistic test**	**p[3]**
Age (years)	65.3 (11.9) 69.5 (16.5) 35.0, 83.0	59, 71	60.9 (10.0) 62.0 (13.0) 34.0, 80.0	59, 63	1243	0.071
Sex					1.3	0.3
Male	8 (44.4)	21, 67	64 (58.7)	49, 68		
Female	10 (55.6)	33, 79	45 (41.3)	32, 51		
BMI (kg/m²)	28.2 (5.1) 28.7 (8.3) 18.6, 36.8	26, 31	26.6 (5.6) 25.2 (6.6) 19.2, 48.7	26, 28	1217	0.10
BMI > 30 kg/m²	8 (44.4)	21, 67	23 (21.1)	13, 29	4.6	**0.043**
AC (cm)	88.7 (20.7) 93.5 (33.8) 59.0, 124.0	78, 99	83.9 (17.8) 78.0 (20.0) 57.0, 139.0	80, 87	1108	0.4
Worsened anamnesis	7 (38.9)	16, 61	16 (14.7)	8.0, 21	6.1	**0.022**
Smoking	4 (22.2)	3.0, 41	26 (23.9)	16, 32	0.02	>0.9
Hypertension grade					24	**<0.001**
gr.I	2 (11.1)	-3.4, 26	2 (1.8)	-0.68, 4.4		
gr.II	6 (33.3)	12, 55	29 (26.6)	18, 35		
gr.III	6 (33.3)	12, 55	5 (4.6)	0.66, 8.5		
Diabetes mellites	5 (27.8)	7.1, 48	13 (11.9)	5.8 18	3.2	0.13
CKD					9.0	**0.029**
CKD G1/2	2 (11.1)	-3.4, 26	12 (11.0)	5.1, 17		
CKD G3	3 (16.7)	-0.55, 34	2 (1.8)	-0.68, 4.4		
Chronic bronchitis	5 (27.8)	7.1, 48	22 (20.2)	13, 28	0.53	0.5
Thyroid pathology	1 (5.6)	-5.0, 16	8 (7.3)	2.4, 12	0.07	>0.9

Note: *[1]mean (SD), median (IQR), minimum, maximum; n(%) [2]confidence interval; [3] Kruskal-Wallis test, Pearson Chi-Square test with the estimated p-value*

Regarding NHL pathology, no statistically significant differences were observed between the two analyzed groups. Thus, in Group I, the majority of patients had aggressive forms of non-Hodgkin lymphoma, with 10 cases (55.6%, 95% CI: 33, 79), while in Group II, indolent forms predominated, with 70 cases (64.2%, 95% CI: 55, 73), Monte Carlo test 2.5, p=0.12. Regarding the clinical stage of NHL, the results showed that in both patient groups, most patients were in stage IV of the disease, indicating an advanced form of the condition. In Group I, 10 patients (55.6%, 95% CI: 33, 79) were in stage IV, and in Group II, 79 patients (72.5%, 95% CI: 64-81) were at the same stage. The specificity of the treatment was analyzed in detail to identify a possible impact on the development of cardiotoxicity, given that certain treatment regimens may influence the risks of therapy-associated cardiac dysfunction. The predominant treatment regimen used in both patient groups was the R-CHOP regimen. In Group I, 13 patients (72.2%, 95% CI: 52, 93) followed this treatment regimen, while in Group II, the R-CHOP regimen was applied to 55 patients (50.5%, 95% CI: 41, 60), Monte Carlo test 3.9, p=0.4. The number of chemotherapy cycles performed showed statistically significant differences. For Group I, the average number of cycles was 6.3 (SD=1.0, 95% CI: 5.8, 6.8), while for Group II, the average number was 5.7 cycles (SD=1.2, 95% CI: 5.5, 6.0), Mann-Whitney test 1264, p=0.043. The total dose of doxorubicin administered showed statistically significant differences, with a higher dose used for the CTRCD group, Mann-Whitney test 1354, p=0.008. Thus, in Group I, the median dose of the drug was 510.0 mg/m² (IQR=522.5), while in Group II, it was 200.0 mg/m² (IQR=380.0).

All patients in the study groups underwent echocardiography, and significant statistical differences were identified between the groups regarding structural parameters. Statistically significant differences were recorded in patients who later developed cardiotoxicity, particularly concerning the dimensional parameters of the left atrium, such as the antero-posterior diameter, left atrial volume, and left atrial volume indexed to body surface area. The median value for Group I was 29.5 ml/m² (IQR=7.7), compared to 25.0 ml/m² (IQR=7.2) for Group II, Mann-Whitney test 1430, p=0.002. Regarding left ventricular parameters, a statistically significant difference was found for the left ventricular telediastolic volume, Mann-Whitney test 1516, p<0.001. In Group I, the median value for the left ventricular telediastolic volume was 150.5 ml (IQR=24.0), while for Group II, it was 128.0 ml (IQR=24.0). Concerning right ventricular parameters, significant statistical differences were found between groups in the basal diameter of the right ventricle and the right ventricular area during diastole, Mann-Whitney test 529, p<0.001. These values were significantly higher for patients in Group I compared to those in Group II. Among the left ventricular systolic parameters, the left ventricular ejection fraction at the pre-treatment baseline did not show statistically significant differences for the group that later developed cardiotoxicity, compared to those who did not develop it at 6 months of treatment. In Group I, the median left ventricular ejection fraction (LVEF) was 57.5% (IQR=5.3), while in Group II, it was 59.0% (IQR=5.0), Mann-Whitney test 767, p=0.14. Similarly, no statistically significant differences were reported for the left ventricular shortening fraction, Mann-Whitney test 794, p=0.2. Using pulsatile tissue Doppler, the maximum velocity of movement of the lateral and septal walls of the left ventricle was quantified in real-time. The maximum systolic velocity (S') at the lateral and/or septal mitral annulus is an indicator of longitudinal systolic function with independent prognostic value. The lateral S' value was significantly lower in Group I, with a median of 10.0 cm/sec (IQR=1.8), compared to Group II with a median of 12.0 cm/sec (IQR=3.0), Mann-Whitney test 404, p<0.001. Diastolic dysfunction at baseline was present in 5 patients (27.8%, 95% CI 7.1, 48%) in Group I, all of whom had Grade I diastolic dysfunction, while in Group II, 12 patients

(11.0%, 95% CI: 5.1, 17%) had Grade I diastolic dysfunction, and one patient (0.9%, 95% CI: 0, 27%) had Grade II diastolic dysfunction. Thus, the presence of left ventricular diastolic dysfunction did not show significant statistical differences between the groups, Monte Carlo test 3.9, p=0.2. On the other hand, several left ventricular diastolic function parameters were significantly different between the study groups. The E wave had a median value of 156.5 cm/sec (IQR=45.0) for Group I, compared to 164.0 cm/sec (IQR=27.0) for Group II, Mann-Whitney test 1310, p=0.023. The E/A ratio was significantly different for patients with CTRCD, with a median of 1.5 (IQR=1.0) for Group I, compared to a median of 1.2 (IQR=0.7) in Group II, Mann-Whitney test 1270, p=0.046. The E/A ratio ≥ 2, which is commonly associated with a restrictive filling pattern of the left ventricle, characterized by increased filling pressures and severely impaired diastolic function, predominated in Group I, Monte Carlo test 4.9, p=0.049. Another parameter that showed a significant statistical difference in patients who developed cardiotoxicity related to antitumor therapy after 6 months was the initial E/e' ratio. This parameter combines transmitral flow (E wave) and tissue Doppler motion of the mitral annulus (e') to estimate left ventricular filling pressures. For Group I, the E/e' ratio had a median of 8.6 (IQR=6.1), while for Group II, it was 5.5 (IQR=3.6), Mann-Whitney test 1397, p=0.004, indicating higher initial left ventricular filling pressures in Group I.

The analysis of the data obtained through 24-hour Holter ECG monitoring revealed that the average heart rate did not show significant statistical differences between the studied groups. The median for Group I was 72.5 bpm (IQR=13.8), while for Group II it was 73.0 bpm (IQR=13.0). Most patients were in sinus rhythm, with only 5 patients (4.6%, 95% CI: 0.66, 8.6) in Group II showing atrial fibrillation. There were no significant statistical differences in the maximum and minimum heart rate between the patients in the study. At the pre-treatment stage, supraventricular and ventricular extrasystoles were not frequent, and no paroxysms of ventricular tachycardia were recorded. Supraventricular tachycardia paroxysms were present in only 4 patients from Group II (3.7%, 95% CI: 0.14, 7.2), Monte Carlo test 0.68, p=0.6. Analysis of the average PQ interval and the corrected QT interval did not reveal any significant statistical differences between the study groups. All of these parameters showed significant statistical differences in the direction of reduction for patients who subsequently developed CTRCD. SDNNi had a median of 42.5 ms (IQR=15.0) for Group I, compared to a median of 64.0 ms (IQR=27.0) for Group II, Mann-Whitney test 395, p<0.001.

Subsequently, the data from the cardiopulmonary exercise test conducted by the patients during the first visit were analyzed. The aim was to assess whether there is any correlation between cardiopulmonary performance and the subsequent development of cardiac dysfunction induced by the treatment for non-Hodgkin lymphoma (NHL). The ability to reach a respiratory exchange ratio (RER) ≥ 1.10 showed a statistically significant incidence among patients who did not develop CTRCD, compared to those who developed this complication. In the group of patients who did not develop CTRCD, RER ≥ 1.10 was observed in 79 subjects (74.5%, 95% CI: 66, 83), compared to 8 patients (47.1%, 95% CI: 23, 71) in the group that developed CTRCD, Monte Carlo test 5.3, p=0.026. Thus, patients in Group II were more frequently able to reach maximum effort and the anaerobic threshold compared to those in Group I. Among the musculoskeletal parameters, a statistically significant difference was observed between the groups in terms of exercise performed. Patients in Group I performed exercise with a median of 115.0 Watts (IQR=23.0), while those in Group II had a median of 124.0 Watts (IQR=38.8), Mann-Whitney test 633, p=0.049. In the category of metabolic parameters, oxygen consumption and peak oxygen consumption did not

show a significant difference between the groups. Peak VO_2 had a median of 13.6 ml/kg/min (IQR=3.7) for Group I and 15.5 ml/kg/min (IQR=4.4) for Group II, Mann-Whitney test 697, p=0.14. On the other hand, more patients in Group I had a peak VO_2 < 14 ml/kg/min compared to those in Group II. In Group I, 9 patients (52.9%, 95% CI: 29, 77) had a peak VO2 < 14 ml/kg/min, compared to 27 patients (25.5%, 95% CI: 17, 34), Monte Carlo test 5.3, p=0.027 (figure 5).

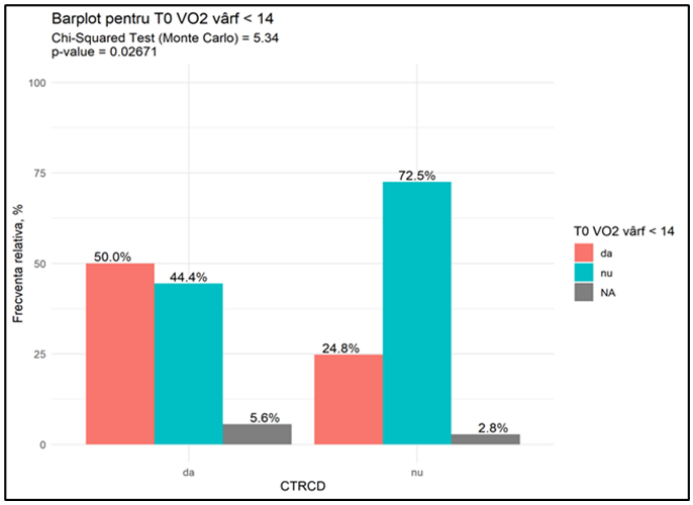

Figure 5. **Distribution of patients with peak VO_2 < 14 ml/kg/min in the analyzed groups**

To identify the predictors of cardiotoxicity, cardiovascular risk factors and comorbidities (age, BMI >30 kg/m², hypertension, type 2 diabetes, chronic kidney disease, dyslipidemia, smoking, SCORE risk, Charlson comorbidity score), serological parameters (hemoglobin, troponin I, NT-proBNP), echocardiographic parameters, Holter ECG, 24h MATA, and CPET were analyzed. Additionally, the characteristics of NHL and the antitumor treatment were considered. Analyzing the relative and absolute frequencies for developing the predictive model of CTRCD in terms of data imbalance, it was found that 14.2% of the studied patients developed the previously mentioned complication. This value is greater than 10%, which allows the use of standard methods for developing predictive classification models. The predictive model, developed based on data from 120 patients, was evaluated through the binary confusion matrix and achieved an accuracy of 94.2%. It correctly predicted cardiotoxicity in 11 patients and misclassified 6 cases. In the group of patients who did not develop cardiotoxicity, 102 were correctly identified, and only one case was misclassified (Figure 6).

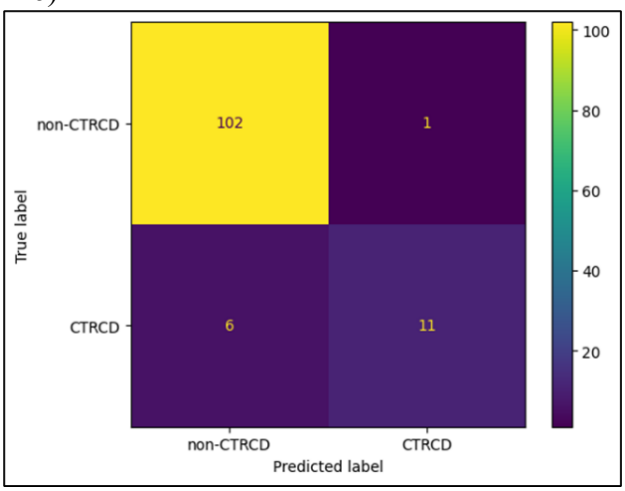

Figure 6**. Evaluation of the predictive model's performance for CTRCD**

The ROC curve presented in Figure 7 is constructed based on the relationship between the true positive rate (Y-axis) and the false positive rate (X-axis). The AUC value of 0.95, obtained in the analysis of the prediction model for the development of CTRCD, indicates a good performance in discriminating between patients who will later develop CTRCD and those who will not. Such a value suggests that the model is capable of correctly identifying 95% of positive cases (patients who will develop CTRCD) compared to the false positive rates, which is crucial in a clinical context. An AUC of 0.95 further indicates that, for a random selection of patients, the model has a 95% probability of assigning a higher risk of CTRCD to a patient who will actually develop this condition (Figure 7).

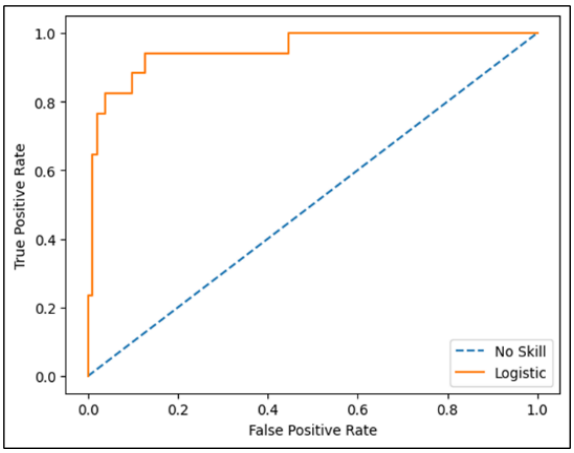

Figure 7. **Evaluation of the predictive model's efficiency for CTRCD using the ROC curve**

Following the initial analysis of the ROC curve for the prediction model of cardiotoxicity, we conducted a new evaluation based on precision and sensitivity metrics. This approach allowed us to examine the performance of the model from a different perspective, providing a more detailed understanding of the balance between correctly identifying positive cases and minimizing misclassifications. The ROC curve, obtained through the analysis of precision and sensitivity, generated an AUC of 0.824. This value indicates good discrimination ability, suggesting that the model is effective in identifying patients at risk of developing cardiotoxicity after 6 months of treatment. The AUC value of 0.824 suggests that, on average, there is a 82.4% probability that the model will correctly classify patients based on the occurrence of cardiotoxicity, compared to random classification (Figure 8).

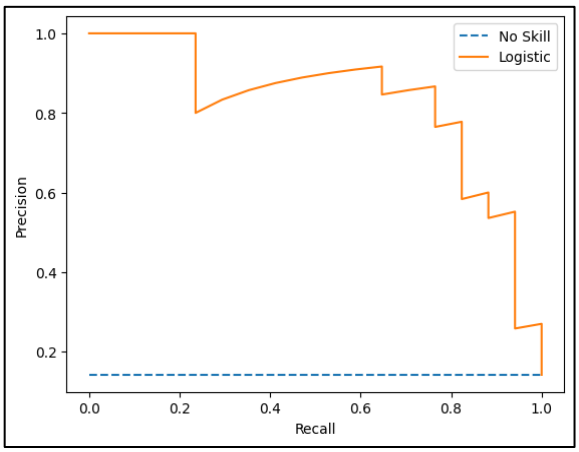

Figure 8. **Evaluation of the accuracy and sensitivity of the CTRCD prediction model**

The predictive model for cardiotoxicity was analyzed using ROC curves and interpreted through SHAP analysis (Figure 9), highlighting the contribution of variables to predictions. The most influential variables were SDNNi and average heart contractions (Holter ECG 24h), where higher values were associated with an increased risk. The cumulative dose of doxorubicin had a major impact, with higher values indicating a higher risk of adverse effects. Initial hemoglobin levels significantly influenced the prediction, with higher values correlating with a worse prognosis. Prolonged QTc interval and elevated NT-proBNP levels were important markers of CTRCD risk. Advanced patient age significantly contributed to increasing the risk. Among the echocardiographic parameters, the left atrial volume/body surface area ratio and the E/e' ratio had a moderate effect, with higher values associated with a higher risk. The E/A ratio had a lesser impact, but higher values indicated possible severe diastolic dysfunction. Exercise capacity (VO_2 < 14 ml/kg/min) was an important predictor of CTRCD, reflecting functional limitations. Additionally, an BMI >30 kg/m² had a significant impact, highlighting the role of metabolic factors in cardiovascular health.

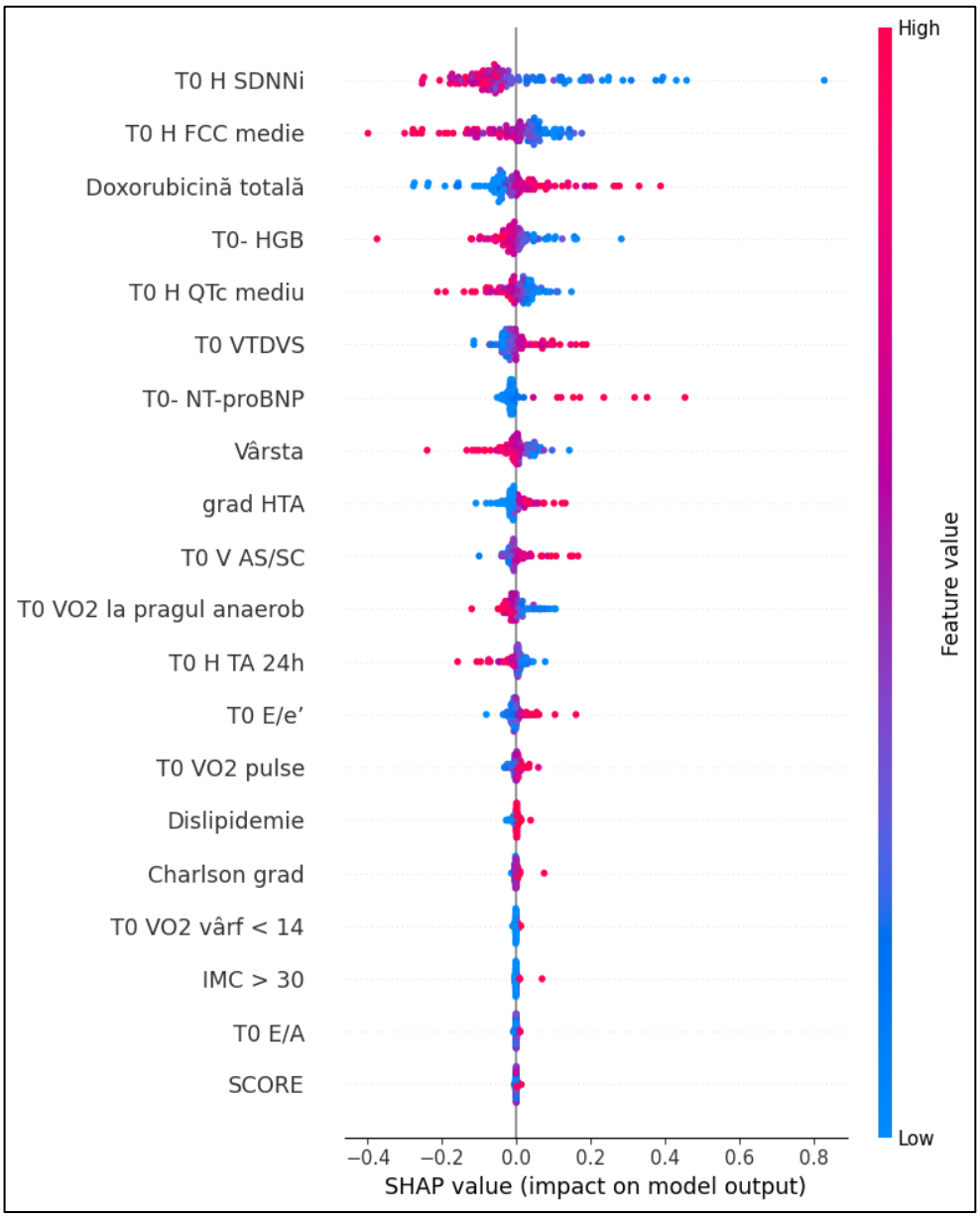

Figure 9. **Contribution of clinical variables in the CTRCD prediction model**

To elucidate the impact of each variable in the given prediction model, we used the permutation importance method (Figure 10). This analysis, compared to the previous one, represents a global aggregation of each component's contributions with a subsequent elucidation of its impact on the analyzed model. The major contribution (+0.12) of the SDNNi variable to the model confirms its importance in predicting the onset of cardiotoxicity. Variables with relatively similar importance were the average heart rate over 24 hours on Holter ECG and the total dose of doxorubicin (+0.07), suggesting a comparable influence on the model. The mean corrected QT/24h had a lower impact compared to the others mentioned above (+0.04), followed by hemoglobin value and initial NT-proBNP value with similar impacts (+0.03). The cumulative impact of the other variables (24 in total) had a contribution of +0.1 in total, suggesting that although each of these variables has a smaller impact individually, together they contribute substantially to the overall prediction.

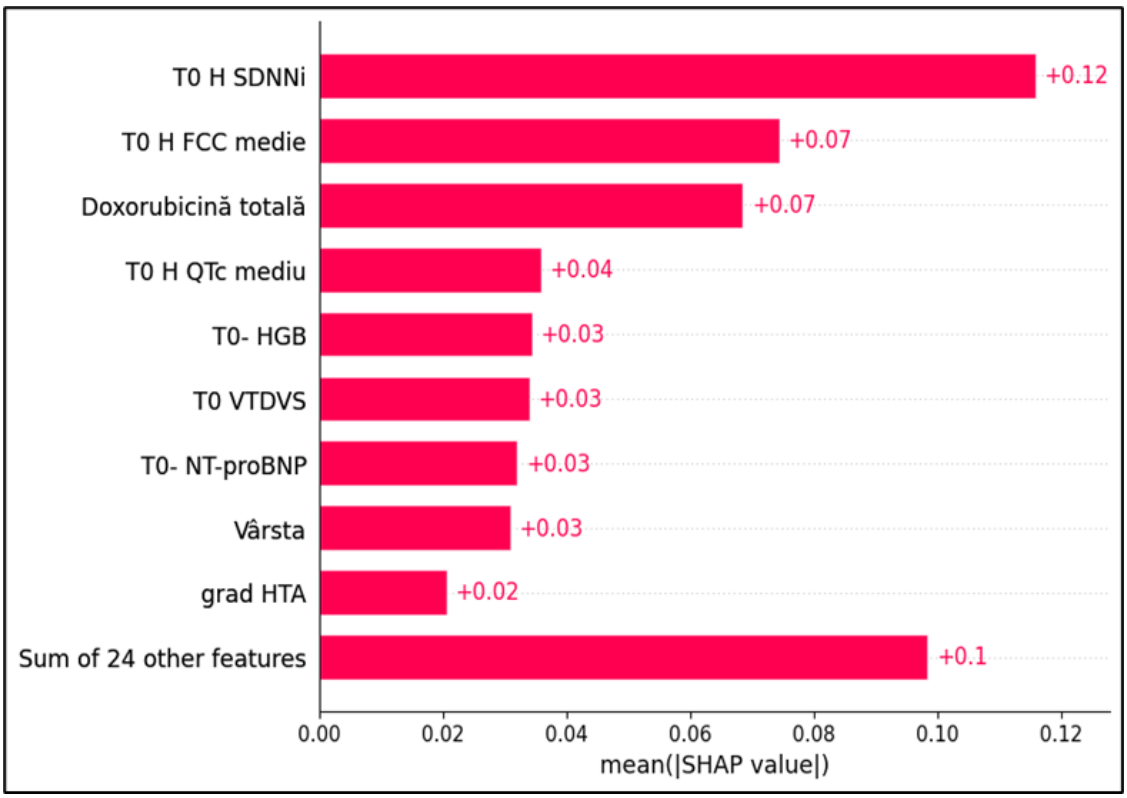

Figure 10. **Variable relevance in the CTRCD prediction model, mean SHAP values**

Additionally, the importance of each variable included in the model was analyzed based on the decrease in the model's accuracy score when the value of that variable is randomized or permuted. From this analysis, the greatest numerical contribution to the model's prediction comes from SDNNi with +0.12, where reduced heart rate variability is strongly associated with an increased risk of CTRCD. Following the impact on the prediction model, the next most influential factors are the increased average heart rate at 24-hour Holter ECG and the total dose of doxorubicin at 6 months of treatment, followed by the initial value of NT-proBNP, mean QTc/24h, and the initial hemoglobin value, with practically similar impacts. Variables such as the administration of rituximab, various treatment regimens (R-CHOP, COP, R-COP), have a lower influence on the model, suggesting that, although they may be relevant in certain clinical cases, they are not among the strongest predictors of CTRCD in this model.

DISCUSSIONS

Antitumor treatment for NHL can induce significant cardiovascular side effects, affecting the prognosis of patients. Early identification of at-risk patients, careful monitoring, and preventive strategies are essential. In the conducted study, the risk factors for cardiotoxicity at 6 months were hypertension, aggravated hereditary history, dyslipidemia, metabolic syndrome, and BMI > 30 kg/m². These results are supported by the literature, including a 2021 study that correlated hypertension, obesity, and diabetes with cardiotoxicity [15]. However, diabetes did not show the same association in this study. Age was not a significant risk factor, but dyslipidemia was correlated with cardiotoxicity, independent of triglyceride and HDL cholesterol levels. The SCORE score did not show significant differences. Among comorbidities, chronic kidney disease was associated with an increased risk of developing CTRCD.

Regarding serological biomarkers, NT-proBNP showed a correlation with cardiotoxicity, unlike troponin I. The dose of doxorubicin had a significant impact on cardiotoxicity, with doses ≥ 400 mg/m² being associated with an increased risk of cardiac dysfunction. Studies confirm the dose-dependent nature of cardiotoxicity, highlighting a higher incidence of heart failure at high cumulative doses [16].

Analysis of the initial echocardiographic parameters highlighted an association between cardiotoxicity and low s'lateral values, as well as an increased E/Vp ratio, suggesting early subclinical dysfunction. The diastolic function of the left ventricle revealed that the E/A and E/e' values were correlated with cardiotoxicity, although the literature data are contradictory [17]. Recent studies indicate a higher risk of systolic dysfunction in patients with initially elevated E/e' (>12.1), and some studies have associated an E/e' ratio >14 with a significant decrease in ejection fraction [18].

Studies regarding 24-hour Holter ECG evaluation have highlighted a significantly reduced heart rate variability in patients who later developed cardiotoxicity, while other parameters such as average FCC, PQ, or QTc did not show relevant correlations. These data support the inclusion of Holter ECG monitoring as a strategy for evaluating cardiac risk in cardiotoxic treatments. As for hypertension, most patients had grade II hypertension, with no significant changes in the degrees of hypertension over the 6 months of treatment. Although the average daytime and nighttime blood pressure for 24 hours increased significantly, the predominant phenotype was non-dipper. Ambulatory blood pressure monitoring highlighted a trend toward increasing blood pressure during chemotherapy, but without a significant impact from doxorubicin or cyclophosphamide on blood pressure values. Studies confirm that, unlike other chemotherapy agents (e.g., VEGF inhibitors), doxorubicin and cyclophosphamide are not directly associated with hypertension, although they may cause other forms of cardiotoxicity [19].

We evaluated cardiopulmonary functional capacity in patients with non-Hodgkin lymphoma throughout treatment, finding a significant decrease in peak VO_2, indicating deterioration of cardiorespiratory function and an increased risk of heart failure. Additionally, CPET highlighted a negative dynamic in VO_2 pulse, reflecting a decline in cardiovascular efficiency. Studies confirm the correlation between decreased peak VO_2 and chemotherapy-induced cardiotoxicity, and physical interventions may alleviate this decline. A decrease in peak VO_2 is correlated with chemotherapy progression and the subsequent appearance of cardiotoxicity [20]. Deterioration of cardiorespiratory function during treatment is further reinforced by the fact that peak VO_2 < 14 ml/kg/min is significantly higher in a number of individuals at the end of the

study compared to the initial stage. Studies investigating peak VO_2 < 14 ml/kg/min in the context of chemotherapy have shown that a peak VO_2 below this threshold is associated with reduced functional capacity and an unfavorable prognosis, especially in patients with cardiotoxicity induced by antitumoral treatment [21]. Ventilatory performance recorded a significant increase in the VE/VCO_2 ratio, with a higher number of patients exceeding the threshold of 30, suggesting progressive cardiopulmonary impairment. This parameter is associated with a reserved prognosis in the context of chemotherapy [22].

Early identification of patients at high risk for cancer therapy-related cardiac dysfunction (CTRCD) is essential for preventing irreversible impairment of cardiac function. In this context, several publications have proposed multimodal predictive models that integrate clinical, imaging, and biometric data, some assisted by artificial intelligence. One published study proposed a predictive model for CTRCD using clinical and echocardiographic variables [23]. Other analyses have focused on integrating data from electrocardiograms (ECG). One article demonstrated that artificial intelligence algorithms can analyze ECG data to anticipate subclinical cardiac changes before the onset of overt heart failure symptoms [24]. Similarly, another study highlighted the effectiveness of using baseline ECGs to predict the risk of CTRCD in patients treated with anthracyclines [25]. Thus, non-invasive methods are becoming promising tools in clinical practice. In HER2-positive breast cancer, treatment with trastuzumab has been frequently associated with cardiotoxicity. Another recent study proposed a personalized risk model based on demographic and echocardiographic factors, useful for guiding therapeutic decisions [26]. Furthermore, heart rate variability has been investigated as an early biomarker of cardiotoxicity. The data presented suggested that reduced heart rate variability may predict cardiac dysfunction before detectable changes in ejection fraction occur. All these studies highlight the significant potential of multimodal predictive models, especially those assisted by artificial intelligence, in the early detection of CTRCD and in the personalization of cardiac monitoring for oncology patients. In the model presented based on our study, we integrated variables from various fields, including clinical, serological, and instrumental diagnostic parameters. This model was developed using SHAP analysis. SHAP analysis is a procedure that ranks predictors according to their importance for the model's output and can be incorporated into existing medical systems, providing automated estimation of a patient's status regarding the potential onset of cardiac dysfunction related to antitumor therapy. This, in turn, implies possible early actions from medical personnel. The multivariate model successfully addressed a classification problem (according to artificial intelligence model development terminology), having only two possible outcome categories. This means that the developed tool, which adheres to all methodological standards, is capable of answering the question of whether or not the adverse effect in question will occur. Rapid implementation in clinical practice involves using the model for patients undergoing antitumor treatment to identify those who are likely to develop CTRCD as a result of therapy. This approach allows for early and targeted intervention, optimizing both medical supervision and resource allocation.

GENERAL CONCLUSIONS

1. During antitumor treatment, ambulatory blood pressure monitoring revealed a significant increase in daytime, nighttime, and average blood pressure values; however, this did not lead to a progression of hypertension to a more advanced stage. A high incidence of paroxysmal supraventricular tachycardia, supraventricular and ventricular extrasystoles was observed, which correlated with the administration of high doses of doxorubicin and cyclophosphamide. High doses of cyclophosphamide were associated with prolongation of the PQ interval, a significant increase in the QTc interval, and a higher incidence of QTc intervals ≥ 480 ms. Doxorubicin did not influence the duration of the PQ or QTc intervals.
2. The cardiopulmonary exercise test identified the early progressive decline in exercise performance, oxygen consumption, and ventilatory efficiency, along with impaired cardiac capacity to deliver oxygen during physical exertion, as adverse effects of antitumor therapy.
3. The cardiopulmonary profile of patients who developed cancer therapy-related cardiac dysfunction included a reduced ability to reach maximum effort, lower oxygen consumption at the anaerobic threshold, and a reduced slope of oxygen consumption efficiency. A peak VO_2 value below 14 ml/kg/min serves as an early prognostic factor for CTRCD. Better oxygen consumption efficiency was associated with preserved systolic function.
4. Predisposing factors for the development of cardiac dysfunction secondary to antitumor therapy include: arterial hypertension, obesity, dyslipidemia, metabolic syndrome, chronic kidney disease, and cumulative doxorubicin exposure exceeding 510 mg/m².
5. Clinical, echocardiographic, electrophysiological, cardiopulmonary, and serological parameters were identified as important determinants in the predictive model for antitumor treatment-induced cardiac dysfunction. Key parameters included: SDNNi, average 24-hour heart rate, cumulative dose of doxorubicin, NT-proBNP, QTc interval prolongation, E/e' ratio, VO_2 at the anaerobic threshold, and oxygen consumption relative to heart rate. This model represents a practical tool for the early identification of patients at high risk of developing cardiac dysfunction induced by antitumor treatment.

PRACTICAL RECOMMENDATIONS

For Hematologists:

1. Before starting antitumoral therapy, it is recommended to conduct a rigorous cardiovascular screening, including transthoracic echocardiography, automatic ambulatory blood pressure monitoring, 24-hour Holter ECG, and cardiopulmonary exercise testing. This approach aims to identify early cardiovascular comorbidities that could influence the safety of hematologic treatment.
2. Continuous monitoring of heart rhythm through 24-hour Holter ECG during treatment is essential to adjust chemotherapy doses based on electrocardiographic changes identified.

For Cardiologists:

1. Initiating and closely monitoring the treatment of hypertension, dyslipidemia, as well as other adverse reactions that may arise during antitumoral therapy. It is also crucial to evaluate and manage newly developed cardiac pathologies, including heart failure that occurs during antitumoral treatment.
2. Implementing a cardiopulmonary rehabilitation program alongside optimizing control of cardiovascular risk factors—such as hypertension, dyslipidemia, and obesity—especially in patients with peak VO_2 < 14 ml/kg/min or diastolic dysfunction. Additionally, it is recommended to consider including cardioprotective medications in the therapeutic regimen of patients at high risk for cardiotoxicity induced by antitumoral treatment.
3. Patients presenting with elevated NT-proBNP levels, prolonged QTc interval, or reduced oxygen consumption at the anaerobic threshold require continuous monitoring and periodic evaluations to prevent the deterioration of ventricular function. In this context, it is recommended to integrate the multimodal predictive model into existing healthcare systems to enable the automated assessment of a patient's status regarding the potential development of cancer therapy-related cardiac dysfunction (CTRCD).

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LISTA PUBLICAȚIILOR ȘI PARTICIPĂRILOR LA FORUMURI ȘTIINȚIFICE
ale dnei **Daniela Bursacovschi,** absolventă a doctoratului,
realizate la teza de doctor în științe medicale,
cu tema **„Modificări cardiovasculare induse de tratamentul antitumoral în limfoamele non-Hodgkin”**, 321.03 Cardiologie,
Universitatea de Stat de Medicină și Farmacie „Nicolae Testemițanu”
din Republica Moldova

LUCRĂRI ŞTIINŢIFICE

- **Articole în reviste științifice peste hotare:**
  - ✓ **Articole în reviste ISI, SCOPUS și alte baze de date internaționale:**
    1. Lund L. H., Crespo-Leiro M. G., Laroche C., Zaliaduonyte D., Saad A. M., Fonseca C., **Bursacovschi D.**, et al. Heart failure in Europe: Guideline-directed medical therapy use and decision making in chronic and acute, pre-existing and de novo, heart failure with reduced, mildly reduced, and preserved ejection fraction–the ESC EORP Heart Failure III Registry. In Appendix: *European Journal of Heart Failure.* 2024. ISSN:1879-0844; ISSN:1388-9842. doi: https://doi.org/10.1002/ejhf.3445 **(IF: 16.9).**
    2. Lyon A. R., Lopez-Fernandez T., Couch L. S., **Bursacovschi** D., et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). In Appendix: *European Heart Journal*. 2022; 43: 4229-4361. ISSN 0195-668X. doi: https://doi.org/10.1093/eurheartj/ehac244 **(IF: 38.1).**
    3. **Bursacovschi D**., Revenco V., Robu M., Arnaut O. Cardiopulmonary functional profiles in cancer therapy-related cardiac dysfunction among patients with non-Hodgkin lymphoma. In: *Diagnostics.* 15 (4); 417. doi: https://www.mdpi.com/2075-4418/15/4/417 **(IF: 3.0).**
    4. **Bursacovschi D.**, Revenco V., Robu M., Cazacu J., Arnaut O. Evolution of cardiopulmonary functional capacity in non-hodgkin lymphoma patients undergoing antitumoural treatment. In: *Arch. Balk. Med. Union.* 2024; 59(4): 365-372. doi: https://doi.org/10.31688/ABMU.2024.59.4.06 .
    5. **Bursacovschi D.**, Revenco V., Robu M., Arnaut O. Cardiac rhythm profile and heart rate variability in cancer therapy-related cardiac dysfunction among non-Hodgkin lymphoma patients. In: *Romanian Journal of Medical Practice.* 2024; 19(4): 428-436. doi: 10.37897/RJMP.2024.4.13.
    6. **Bursacvoschi D.**, Revenco V., Robu M., Arnaut O. Diastolic Function and Cancer Therapy-Related Cardiac Dysfunction in Non-Hodgkin Lymphoma Patients. In: *Arch. Balk. Med. Union*. 2025; 60 (2): 225-232. doi: https://doi.org/10.31688/ABMU.2025.60.2.07.

- **Articole în reviste științifice naționale acreditate:**
  - ✓ **Articole în reviste de categoria B:**
    7. **Bursacovschi D.**, Revenco V., Robu M. Evoluția funcției cardiace la pacienții cu limfom non-Hodgkin aflați sub tratament chimioterapic. În: *Buletinul Academiei de Ştiinţe a*

Moldovei. Ştiinţe Medicale. 2024; 1(78): 69-74. ISSN 1857-0011. doi: https://doi.org/10.52692/1857-0011.2024.1-78.08 .

8. **Bursacovschi D.** Rolul ecocardiografiei în prevenirea și monitorizarea cardiotoxității tratamentului antitumoral. În: *Buletinul Academiei de Ştiinţe a Moldovei. Ştiinţe Medicale*. 2023; 1(75): 133-139. ISSN 1857-0011. doi: https://doi.org/10.52692/1857-0011.2023.1-75.18 .
9. Lîsîi D., Cazacu J., **Bursacovschi D.,** Dogot M., Draganiuk A., Mucovozov V., Jucovschi C., Vataman E. Determinarea parametrilor prognostici pentru mortalitate la pacienții cu insuficiență cardiacă cronică după revascularizare coronariană. În: *Buletinul Academiei de Ştiinţe a Moldovei. Ştiinţe Medicale*.2020; 1(65): 215-222. ISSN 1857-0011.
10. **Bursacovschi D.,** Cazacu J., Lîsîi D., Vataman E. Evaluarea efectului reabilitării cardiace asupra funcției diastolice ventriculare stângi la pacienții ce au suportat revascularizare coronariana percutană. În: *Buletinul Academiei de Ştiinţe a Moldovei. Ştiinţe Medicale.* 2022; 1(72): 23-26. ISSN 1857-0011. doi: https://doi.org/10.52692/1857-0011.2022.1-72.04 .
11. **Bursacovschi D.**, Revenco V., Robu M, Arnaut O. Disfuncția cardiacă indusă de tratamentul antitumoral în limfoamele non-Hodgkin: influența comorbidităților și a factorilor de risc cardiovascular. În: *Buletinul Academiei de Ştiinţe a Moldovei. Ştiinţe Medicale.* 2025; 1 (81): 48-57. doi: https://doi.org/10.52692/1857-0011.2025.1-81.06.

- **Rezumate/abstracte/teze în lucrările conferinţelor ştiinţifice naţionale şi internaţionale:**

12. **Bursacovschi D.** Palliative care for a patient with heart failure. In: *Abstract Book of The 8th International Medical Congress for Students and Young Doctors MedEspera.* Chișinău: CEP „Medicina”, 2020, pp. 200-201. ISBN 978-9975-151-11-5.
13. **Bursacovschi D.,** Revenco V., Robu M. Evaluation of left ventricular function in patients with Non-Hodgkin's lymphoma undergoing chemotherapy. In: *Perspectives of the Balkan medicine in the post COVID-19 era: The 37th Balkan Medical Week. The 8th congress on urology, dialysis and kidney transplant from the Republic of Moldova „New Horizons in Urology"*, 2023, p. 40. ISSN Print: ISSN 1584-9244 ISSN-L 1584-9244. ISSN Online: 2558-815X.
14. **Bursacovschi D.,** Cazacu J., Lîsîi D., Vataman E. Impact of non-cardiac comorbidities on heart failure outcomes in patients after coronary revascularization therapy. În: *Cercetarea în biomedicină și sănătate: calitate, excelență și performanță*, 2021, p. 124. ISBN 978-9975-82-223-7.
15. Cazacu J., **Bursacovschi D.,** Dodu S., Moscalu V.V., Vataman E. The particularities of cardiopulmonary exercise testing in patients with pulmonary hypertension and heart failure in the early period after myocardial revascularization. In: *European Journal of Heart Failure*, 2023, 25(S2), p. 387. https://doi.org/10.1002/ejhf.2927 .
16. Cazacu J., **Bursacovschi D.,** Dodu S., Moscalu V.V., Vataman E. Peak oxygen uptake and ventilatory pattern in patients with heart failure with reduced ejection fraction in the early stage after myocardial revascularization by coronary artery bypass grafting. In: *European Journal of Heart Failure*, 2023, 25(S2), p. 64. https://doi.org/10.1002/ejhf.2927 .

17. **Bursacovschi D.,** Cazacu J., Cabac-Pogoreivici I., Robu M. Importanța indicelui de comorbiditate și prevalenței fragilității în evoluția limfoamelor non-Hodgkin cu celule B. În: *Revista de Ştiinţe ale Sănătăţii din Moldova*, 2022, 29(3), p. 165. ISSN 2345-1467.
18. **Bursacovschi D.,** Cazacu J., Cabac-Pogoreivici I., Robu M. The importance of comorbidity index and frailty prevalence in the evolution of large B-cell non-Hodgkin lymphoma. În: *Revista de Ştiinţe ale Sănătăţii din Moldova*, 2022, 29(3), p. 165. ISSN 2345-1467.
19. **Bursacovschi D.**, Revenco V. Multimodal predictive model for 6-month treatment-related cardiotoxicity in non-Hodgkin lymphoma patients. In *European Journal of Heart Failure, Supplement: HFA Winter Research Meeting on Translational Heart Failure 2025 In collaboration with the ESC Working Group on Myocardial Function,* 2025, 27 (1), p. 11-12. doi: https://doi.org/10.1002/ejhf.3616.
20. **Bursacovschi D**., Revenco V., Robu M., Arnaut O. Multimodal prediction model for cancer therapy-related cardiac dysfunction in non-Hodgkin's lymphoma patients. In *The 17'th edition of Euroinvent European Exhibition of creativity and innovation,* 2025, p.147-148. ISSN 260-4572.

- **Brevete de invenţii, patente, certificate de înregistrare, materiale la saloanele de invenţii:**
  - ✓ **Adeverințe privind înscrierea obiectelor dreptului de autor și a drepturilor conexe:**

21. **Bursacovschi Daniela**, Revenco Valeriu, Robu Maria, Arnaut Oleg. *Profilul clinic și paraclinic specific disfuncției cardiace legate de terapia antitumorală la pacienții cu limfom non-Hodgkin.* Nr. de înregistrare 2880 din 26.12.2024.
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23. **Bursacovschi Daniela**, Revenco Valeriu, Robu Maria, Arnaut Oleg. *Dinamica funcției cardiopulmonare și corelația cu funcția ventriculară stângă la pacienții cu limfom non-Hodgkin aflați sub tratamentul antitumoral.* Nr. de înregistrare 2882 din 26.12.2024.
24. **Bursacovschi Daniela**, Revenco Valeriu, Robu Maria, Arnaut Oleg. *Impactul tratamentului antitumoral asupra dereglărilor de ritm și hipertensiunii arteriale la pacienții cu limfom non-Hodgkin.* Nr. de înregistrare 2883 din 26.12.2024.

  - ✓ **Certificate de inovator:**

25. **Bursacovschi Daniela**, Revenco Valeriu, Robu Maria, Arnaut Oleg. *Testul cardiopulmonar pentru identificarea riscului de cardiotoxicitate la pacienții cu limfom non-Hodgkin aflați sub tratament antitumoral.* Certificat de inovator Nr. 6286 din 24.10.2024.
26. **Bursacovschi Daniela**, Revenco Valeriu, Robu Maria, Arnaut Oleg. *Definirea factorilor de risc și a profilului cardiovascular asociat cu cardiotoxicitatea tratamentului antitumoral la pacienții cu limfom non-Hodgkin.* Certificat de inovator Nr. 6287 din 24.10.2024.
27. **Bursacovschi Daniela**, Revenco Valeriu, Robu Maria, Arnaut Oleg. *Holter ECG 24h pentru monitorizarea cardiotoxicității și detectarea aritmiilor la pacienții cu limfom non-Hodgkin sub tratament oncologic.* Certificat de inovator Nr. 6288 din 24.10.2024.

✓ **Acte de implementare**

28. Vataman E., Lîsîi D., Priscu O., Cazacu J., **Bursacovschi D.,** Guțan I., Dodu S., Oprea C. *Insuficienţa cardiacă acută şi cronică la adult*: protocol clinic naţional PCN-82. Chișinău. 2023. URL: https://ms.gov.md/wp-content/uploads/2023/03/PCN-82-IC-cronica-si-acuta-la-adult-2023-final-MS.pdf .

- **Participări cu comunicări la forumuri ştiinţifice:**

✓ **Internaţionale**

29. **Bursacovschi D.,** Cazacu J., Cabac-Pogorevici I., Revenco V., Robu V. Evaluarea fezabilității testului de efort cardiopulmonar la pacienții cu limfom non-Hodgkin. *Congresul al 61-lea Național de Cardiologie*. Sinaia, România, 21-24 Septembrie 2022.
30. **Бурсаковски Д.** Опыт введения пациентов с ЛАГ в Молдове. Клинический случай. *Медицинское образовательное мероприятие Круглый стол „Опыт воздействия на простациклиновый путь в терапии ЛАГ”*. Астана, Республика Казахстан, 9 Декабря 2022.
31. **Bursacovschi D.** Evaluation of left ventricular function in patients with non-Hodgkin's lymphomas undergoing chemotherapy. *Perspectives of the Balkan medicine in the post COVID-19 era: The 37th Balkan Medical Week. The 8th congress on urology, dialysis and kidney transplant from the Republic of Moldova „New Horizons in Urology”*. Chișinău, 7-9 iunie 2023.
32. **Bursacovschi D.** Imaging modalities in cardiology. *Perspectives of the Balkan medicine in the post COVID-19 era: The 37th Balkan Medical Week. The 8th congress on urology, dialysis and kidney transplant from the Republic of Moldova „New Horizons in Urology”*. Chișinău, 7-9 iunie 2023.
33. **Bursacovschi D.**, Revenco V. Multimodal predictive model for 6-month treatment-related cardiotoxicity in non-Hodgkin lymphoma patients. *HFA Winter Research Meeting on Translational Heart Failure Research.* Vienna, Austria, 20-23 January 2025.

✓ **Naţionale**

34. **Bursacovschi D.,** Cazacu J., Cabac-Pogorevici I., Robu M. Importanța indicelui de comorbiditate și prevalenței fragilității în evoluția limfoamelor non-Hodgkin cu celule B. *Conferința Științifică Anuală ”Cercetarea în Biomedicină și Sănătate: Calitate, Excelență și Performanță”.* Chișinău, 19-21 Octombrie 2022.
35. Grosu A., **Bursacovschi D.** Optimizarea terapiei insuficienței cardiace cronice la etapa de ambulator. *Congresul al V-lea al medicilor de familie din Republica Moldova cu participare internațională. Simpozion Astra Zeneca.* Chișinău, 17-18 Mai 2024.
36. **Bursacovschi D.** Aptitudini esențiale în cardio-oncologie: stratificarea riscului, diagnosticul și managementul cardiotoxicității tratamentului antitumoral. *Simpozionul Național de Cardiologie „Actualități în cardiologie prin prisma ghidurilor noi ale Societății Europene de Cardiologie 2022”.* Chișinău, 20 Octombrie 2022.

- **Participări cu postere la forumuri științifice:**

✓ **Internaţionale**

37. **Bursacovschi D.**, Revenco V., Robu M. Safety and utility of cardiopulmonary exercise testing in non-Hodgkin lymphoma patients undergoing chemotherapy. *ESC Heart Failure Congress*. Prague, Czech Republic, 20-23 May 2023.

38. **Bursacovschi D.**, Revenco V., Robu M. Exercise capacity dynamics in non-hodgkin lymphoma patients. *ESC Heart Failure Congress*. Lisbon, Portugal, 11-14 May 2024.
39. **Bursacovschi D.**, Revenco V., Robu M. The impact of antitumor therapy on cardiac systolic function in patients with non-hodgkin lymphoma. *ESC Heart Failure Congress*. Lisbon, Portugal, 11-14 May 2024.
40. **Bursacovschi D.,** Revenco V. Multimodal predictive model for 6-month treatment-related cardiotoxicity in non-Hodgkin lymphoma patients. *ESC Heart Failure Congress*. Belgrade, Serbia, 17- 20 May 2024.
41. **Bursacovschi D.,** Revenco V., Robu M., Arnaut O. Multimodal prediction model for cancer therapy-related cardiac dysfunction in non-Hodgkin's lymphoma patients. In The *17'th edition of Euroinvent European Exhibition of creativity and innovation*, 8-10 May 2025.

✓ **Naţionale**

42. **Bursacovschi D.**, Cazacu J., Lisii D., Vataman E. Impact of non-cardiac comorbidities on Heart Failure outcomes in patients after coronary revascularization therapy. *Conferința Științifică Anuală „Cercetarea în Biomedicină și Sănătate: Calitate, Excelență și Performanță"*. Chișinău, 20-22 Octombrie 2021.

- **Awards received at national/international exhibitions or innovation fairs:**

43. Gold Medal – EUROINVENT 2025, 17th European Exhibition of Creativity and Innovation, May 8–10, 2025, Iași, Romania. "Multimodal Prediction Model for Cancer Therapy-Related Cardiac Dysfunction in Non-Hodgkin's Lymphoma Patients". Bursacovschi D., Revenco V., Robu M., Arnaut O.