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ORIGINAL ARTICLE

NT-proBNP and hs-cTnT in Predicting the Incidence and Prognosis of Anthracycline-Caused Cardiovascular Toxicities in Non-Hodgkin's Lymphoma

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SUMMARY

Background: **This study aimed to investigate the role of serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hs-cTnT) in predicting the occurrence and prognosis of symptomatic cardiovascular toxicities (CVTs) in non-Hodgkin's lymphoma (NHL) patients receiving anthracyclines (ATCs).**

Methods: **We conducted a retrospective analysis of serum NT-proBNP and hs-cTnT levels in 182 NHL patients undergoing anthracycline treatment. The post-treatment elevation ratio (ER) of NT-proBNP (NT-proBNP-ER) was calculated, and receiver operating characteristic curves (ROCs) were generated.**

Results: **The area under the curves (AUCs) of NT-proBNP-ER, hs-cTnT, and their combination for diagnosing symptomatic CVTs were 0.903, 0.811, and 0.9807, respectively. Serum NT-proBNP-ER ≥ 2.56 and hs-cTnT ≥ 11.68 ng/L were positively correlated with the occurrence of symptomatic CVTs. Patients with a post-treatment NT-proBNP-ER ≥ 2.56 had shorter progression-free survival (PFS) and overall survival (OS) than those with an NT-proBNP-ER < 2.56. Similarly, patients with post-treatment hs-cTnT ≥ 11.68 ng/L experienced markedly shorter PFS and OS compared to those with hs-cTnT < 11.68 ng/L.**

Conclusions: **An NT-proBNP-ER ≥ 2.56 or hs-cTnT ≥ 11.68 ng/L, individually or combined, are significant predictors of symptomatic CVTs. Exceeding these thresholds indicates a poor prognosis in NHL patients treated with anthracyclines.**

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INTRODUCTION

Non-Hodgkin's lymphoma (NHL) is a heterogenous group of lymphoproliferative neoplasms with diverse biological behaviors [1]. It originates in lymphoid tissues and proliferates through neoplastic lymphocytes, spreading throughout the body [2]. Despite considerable progress in treating NHL, some cases exhibit primary

chemotherapy resistance or relapse after brief remission, necessitating novel rescue therapies for managing tumor growth [3]. Anthracyclines, common first-line chemotherapeutic agents for many tumors, are associated with cardiotoxicity, a leading cause of mortality in cancer patients [4,5]. They induce cardiac damage by generating oxygen free radicals through both enzymatic and non-enzymatic pathways. This process involves the reduction of the anthraquinone group to semiquinone free radicals, which then interact with oxygen free radicals and other electrons, leading to an overload of oxygen free radicals. This excess overwhelms the detoxification capacity of the cardiac mitochondria and sarcoplasmic reticulum, causing heart damage [6,7]. Additionally, anthracyclines can form iron chelates through a non-enzymatic pathway, resulting in the production of oxygen radicals [8]. CVT, or drug-induced cardiac injury, encompasses various adverse effects as defined by the 2021 consensus of the Scientific Council of the International Cardio-Oncology Society (IC-OS) [9].

Anthracycline-related CVT is dose-dependent and can cause irreversible myocardial damage, primarily manifesting as cardiac insufficiency, heart failure, and arrhythmia [10]. This cardiac impairment begins with subclinical myocardial injury [11], leading to a decline in left ventricular ejection fraction (LVEF) and eventually symptomatic heart failure. Notably, myocardial damage may occur after the first dose of anthracycline therapy [12], indicating that there is no absolutely safe dose. Thus, identifying early diagnostic biomarkers or predictors of CVT during anthracycline therapy holds significant clinical importance.

Currently, ultrasound cardiography is the preferred method for assessing cardiac function before and after cancer treatment, with left ventricular ejection fraction (LVEF) being the most commonly used indicator. However, its sensitivity is relatively low, limiting the detection of subclinical myocardial injury, and measurement variability can reach up to 10% [13]. N-terminal pro-B-type natriuretic peptide (NT-proBNP) is secreted by ventricular muscles and varies with ventricular wall tension. Increased ventricular wall tension and NT-proBNP secretion occur during heart failure onset, with the level of increase indicating the severity of the heart failure [14]. Hs-cTnT is a myocardium-specific structural protein and a marker of cardiomyocyte injury, with its peak value indicating the extent of the injury [15]. According to the 2021 CSCO guidelines on the prevention of tumor treatment-related CVT, NT-proBNP and hs-cTnT are valuable for assessing baseline CVT risk and diagnosis. They assist in the early identification, monitoring, and prognosis of myocardial injury, although their optimal positive thresholds remain undefined [9]. Additionally, NT-proBNP levels are influenced by age, gender, renal function, body mass index (BMI), and other individual differences [16-18]. Given the undefined diagnostic thresholds of these cardiac biomarkers and their relationship with the occurrence and prognosis of anthracycline-induced CVTs, this retrospective study analyzed the clinical data of 182 NHL patients treated with anthracyclines. It focused on observing changes in NT-proBNP and hs-cTnT levels before and after treatment to ascertain their predictive value for symptomatic CVT events and patient prognosis. For the first time, clinical symptoms, LVEF, ECG changes, and the increased ratio of NT-proBNP and hs-cTnT before and after treatment were evaluated for their predictive value in symptomatic CVT events following anthracycline treatment and for prognosis assessment.

MATERIALS AND METHODS

Clinical data

Patient data from patients with NHL treated at Fujian Cancer Hospital between January 2017 and December 2019 were retrospectively collected from medical records. Inclusion criteria included patients aged over 18 years and an Eastern Cooperative Oncology Group (ECOG) score of 2 or less, starting epirubicin (EADM) treatment post-admission. Exclusion criteria encompassed a baseline left ventricular ejection fraction (LVEF) below 50%, congenital cardiovascular diseases, primary cardiac tumors, tumor-induced cardiac invasion, and prior chest radiotherapy or anthracycline use. Collected data encompassed gender, age, histopathological type, clinical stage [19], cumulative EADM dose, hypertension, diabetes, pre-treatment serum lactate dehydrogenase (LDH), white blood cells (WBCs), cholesterol (CHOL), and type of CV toxicity. A total of 182 NHL patients treated with EADM were enrolled (Figure 1), including 137 with diffuse large B-cell lymphoma, 21 with follicular lymphoma, 12 with mantle cell lymphoma, and 12 with other lymphoma types. Out of these, 16 patients experienced CV toxicity events: 9 with arrhythmia and 7 with symptomatic cardiac dysfunction. Detailed clinicopathological features are presented in Supplementary Table 1.

Determination of blood serum component levels

Written informed consent was obtained from patients prior to initial sample collection. The Ethics Committee of Fujian Cancer Hospital approved the use of human tissue samples (no. K2022-127-01). Intravenous blood samples (3 to 4 mL) were taken from the patients before and after each treatment course, or upon the emergence of symptoms, signs, and risk factors for myocardial injury. Samples were left at room temperature for 30 minutes and centrifuged at 3,000 r/minute for 5 minutes with a 15-cm radius centrifuge. Serum was extracted and stored at -80°C for analysis.

Serum NT-proBNP and hs-cTnT concentrations were determined by electrochemiluminescence immunoassay (Roche COBAS 411 electrochemiluminescence analyzer). LDH activity was measured using the standardized lactate substrate method (Beckman AU5800 Clinical Chemistry Analyzer). Total cholesterol (CHOL) levels were assessed via the cholesterol oxidase-peroxidase

enzymatic method (Beckman AU5800 Clinical Chemistry Analyzer), with established cutoff values of 250 U/L for LDH and 5.7 mmol/L for CHOL. Immediately after collection, 2 mL of blood were gently shaken for WBC measurement via flow cytometry (Sysmex XN-2000 Hematology Analyzer), with a cutoff value of 9.5 × 10^9/L.

Diagnostic standard for symptomatic cardiovascular toxicity (CVT) events

The classification and definition of CVT events were based on the 2021 consensus statement of the International Society of Cardiovascular Oncology (IC-OS) [20] and the Chinese Society of Clinical Oncology (CSCO) Guidelines for the prevention and treatment of cardiovascular toxicity in oncology. Briefly, cancer therapy-related cardiac dysfunction is categorized into asymptomatic and symptomatic types. Asymptomatic cardiac dysfunction is diagnosed through changes in cardiac serum biomarkers (e.g. cardiac troponin I [cTnI], hs-cTnT) and echocardiographic indicators (e.g. LVEF, global longitudinal strain [GLS]). Symptomatic cardiac dysfunction is diagnosed based on clinical manifestations such as chest tightness, palpitations, fatigue, weakness, reduced urine output, various degrees of dyspnea, exacerbated after exertion, and corroborated by LVEF or biomarker readings. CVT events, according to clinical symptoms, are classified as mild (no treatment required), moderate (diuretics needed for outpatient care), severe (hospitalization for heart failure), or extremely severe (mechanical circulatory support required). The grading for abnormal heart rate is as follows: level 1 (asymptomatic, no intervention necessary), level 2 (non-emergency medical intervention required), level 3 (emergency medical intervention required), and level 4 (life-threatening).

Clinical treatment and follow-up

Routine medical history, electrocardiogram (ECG), and serum tests for NT-proBNP, hs-cTnT, LDH, CHOL, and WBC were conducted before treatment. All 182 NHL patients received epirubicin as part of the R-CHOP/R-CHOEP/DA-EPOCH-R/R-miniCHOP chemotherapy regimens. The R-CHOP regimen includes Rituximab 375 mg/m^2 (intravenous) on day 1, Cyclophosphamide 750 mg/m^2 (intravenous), Epirubicin 40 - 50 mg/m^2 (intravenous), Vincristine 1.4 mg/m^2 (maximum of 2 mg/m^2) on day 2, and Prednisone 100 mg orally from day 2 - day 6 of each cycle. R-CHOEP adds Etoposide 100 mg/m^2 (intravenous) on days 2 - 4. DA-EPOCH-R consists of Rituximab 375 mg/m^2 (intravenous) on day 1, Etoposide 50 mg/m^2 (intravenous), Vincristine 0.4 mg/m^2, Epirubicin 10 mg/m^2 (intravenous) on days 2 - 5, Cyclophosphamide 750 mg/m^2 (intravenous) on day 6, and Prednisone 100 mg orally on days 2 - 6. Frail patients were administered R-miniCHOP at a reduced dosage.

These regimens were repeated every 21 days, typically over 6 cycles (range: 4 - 8). Dexrazoxane was utilized to mitigate cardiotoxicity before commencing chemotherapy.

Cardiovascular symptoms (chest tightness, palpitations, fatigue, weakness, reduced urine output, dyspnea of varying degrees, exacerbated post-exertion) were monitored throughout chemotherapy. If needed, additional NT-proBNP and hs-cTnT tests, electrocardiography, and color flow Doppler echocardiography were performed. Electrocardiography combined with NT-proBNP and hs-cTnT testing was routine after each chemotherapy cycle. The onset and duration of cardiovascular toxicity events, time of death, and data on patients' progression-free survival (PFS) and overall survival (OS) were compiled through medical records, correspondence, phone calls, and visits.

Follow-up continued until June 2022, spanning 66 months. Out of the 182 NHL patients, 5 were lost to follow-up, resulting in a follow-up rate of 97.3%. Among the 177 patients who attended follow-up visits, 35 experienced relapse or disease progression, accounting for a recurrence rate of 19.77%; 13 patients died, leading to a mortality rate of 7.34%. Progression-free survival (PFS) was calculated from the start of anthracycline treatment to the onset of relapse, progression, or death from any cause; overall survival (OS) was determined from the initiation of treatment to death from any cause.

Statistical analyses

Statistical analyses were conducted using SPSS 16.0 software (SPSS Inc, Chicago, IL, USA). Quantitative data were presented as mean ± standard deviation (SD), with medians (and interquartile ranges) for skewed distributions, and compared using independent or paired sample *t*-tests. The non-parametric test assessed variance heterogeneity, while the chi-squared (χ^2) or Fisher's exact test evaluated the incidence of CVT. The post-treatment NT-proBNP quantity divided by the pre-treatment baseline value was defined as the NT-proBNP elevation ratio (NT-proBNP-ER). Multivariable logistic regression analysis examined the association between each pathological feature. The prognostic significance of NT-proBNP-ER and hs-cTnT in patients with symptomatic CVT events, along with differences in PFS and OS, were analyzed using the Kaplan-Meier method. A p-value < 0.05 was considered statistically significant.

RESULTS

Symptomatic CVT events in patients with non-Hodgkin's lymphoma

Patient inclusion is illustrated in Figure 1. Among 182 NHL patients treated with anthracyclines, 132 exhibited no relevant abnormalities, while 34 experienced transient ECG abnormalities without associated symptoms, suggesting reversible damage not categorized as CVT in this study. Sixteen patients developed symptomatic CVT events: nine with grade 2 or higher arrhythmia (four with sinus tachycardia, three with atrial fibrilla-

Table 1. Multivariable logistic regression analysis of symptomatic CVT events.

	β value	SE value	Wald value	OR	95% CI	p-value
Age	1.005	0.910	1.220	3.787	0.459 - 16.265	0.269
Gender	-1.721	0.974	3.121	1.594	0.027 - 1.207	0.077
Diabetes mellitus	-0.362	1.955	0.034	0.497	0.015 - 32.111	0.853
Hypertension	-2.258	1.259	3.215	0.689	0.009 - 1.234	0.073
Clinical stage	1.040	0.940	1.225	1.452	0.449 - 17.852	0.268
EADM	-1.278	0.949	1.813	0.389	0.043 - 1.790	0.178
LDH	0.590	0.952	0.384	1.448	0.279 - 11.652	0.535
WBC	0.257	1.296	0.039	1.593	0.102 - 16.386	0.843
CHOL	0.340	0.977	0.121	1.452	0.207 - 9.534	0.728
NT-proBNP-ER	4.030	0.975	17.071	35.750	8.315 - 380.322	0.000
cTNT	3.126	1.059	8.712	21.389	2.858 - 181.596	0.003

Table 2. Comparative predictive value of absolute NT-proBNP and cTnT levels for cardiotoxicity.

Comparative analysis of related research in the field										
Source	Study design	Sample size	Cancer type	Markers	Detection platform	Cardiotoxicity prediction				Prognostic prediction
						Cutoff	Sensitivity	Specificity	AUC/OR	
Zhang et al. 2017 [28]	Retrospective	82	DLBCL	hs-cTnT	Cobas	+ 0.0075 ng/mL vs. baseline	69.2%	83.9%	0.79	/
Tzolos et al. 2020 [26]	Prospective	78	Breast cancer	hs-cTnT	Abbott	≥ 5 ng/L	69%	86%	0.84	/
Biniyam et al. 2020 [27]	Prospective	323	Breast cancer	hs-cTnT	Cobas	> 14 ng/L	60.3%	62.5%	/	/
				NT-proBNP	Cobas	> 300 ng/L	22.0%	94.2%	/	/
Daniel et al. 2021 [31]	Retrospective	930	Breast cancer and others	hs-cTnT	Cobas	≥ 7 ng/L	/	/	/	ACM (OR: 2.21, p = 0.0038)
				NT-proBNP	Siemens	≥ 141 ng/L	/	/	/	ACM (p = 0.4)
Romann et al. 2020 [32]	Retrospective	1,971	Breast cancer and others	hs-cTnT	Cobas	≥ 7 ng/L	/	/	OR 1.60, p = 0.006	ACM (OR 5.99 p < 0.001)
				Age-adjusted NT-proBNP	Siemens	≥ 450 pg/mL (< 50 years) ≥ 900 pg/mL (50 - 75 years) ≥ 1,800 pg/mL (> 75 years)	/	/	OR 4.00, p < 0.001	ACM (OR 4.51 p < 0.001)

DLBCL diffuse large B-cell lymphoma, ACM all-cause mortality.

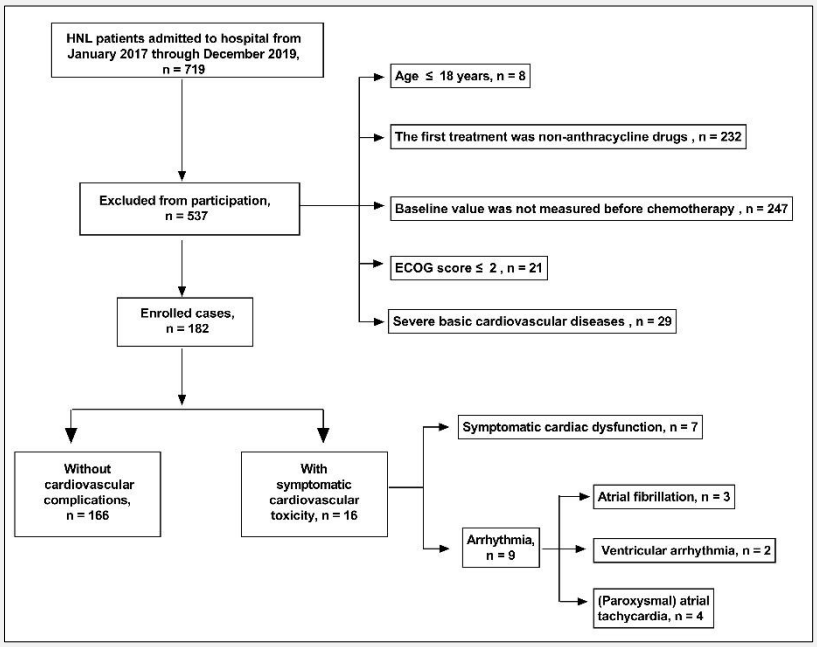

Figure 1. Flow diagram depicting the patient inclusion process in this study.

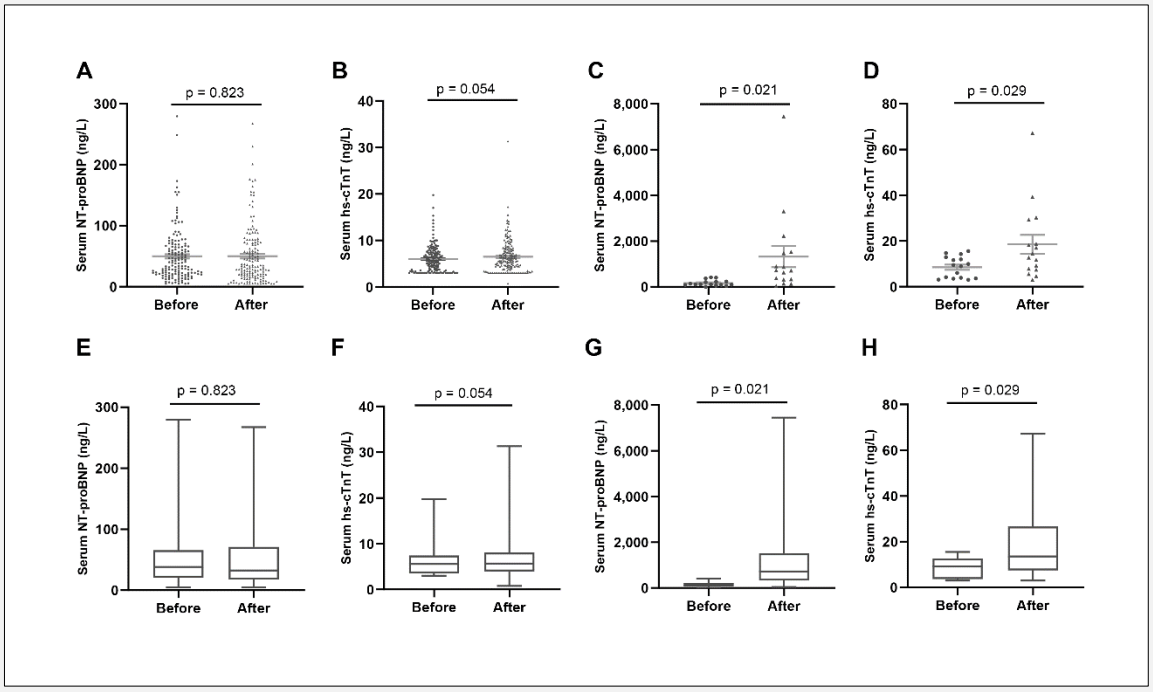

Figure 2. Serum NT-proBNP and hs-cTnT levels before and after ATC treatment.

Graphs depicting changes in NT-proBNP (A, B) and hs-cTnT (C, D) levels before and after treatment in patients without toxicity, and changes in NT-proBNP (E, F) and hs-cTnT (G, H) levels in patients with toxicity.

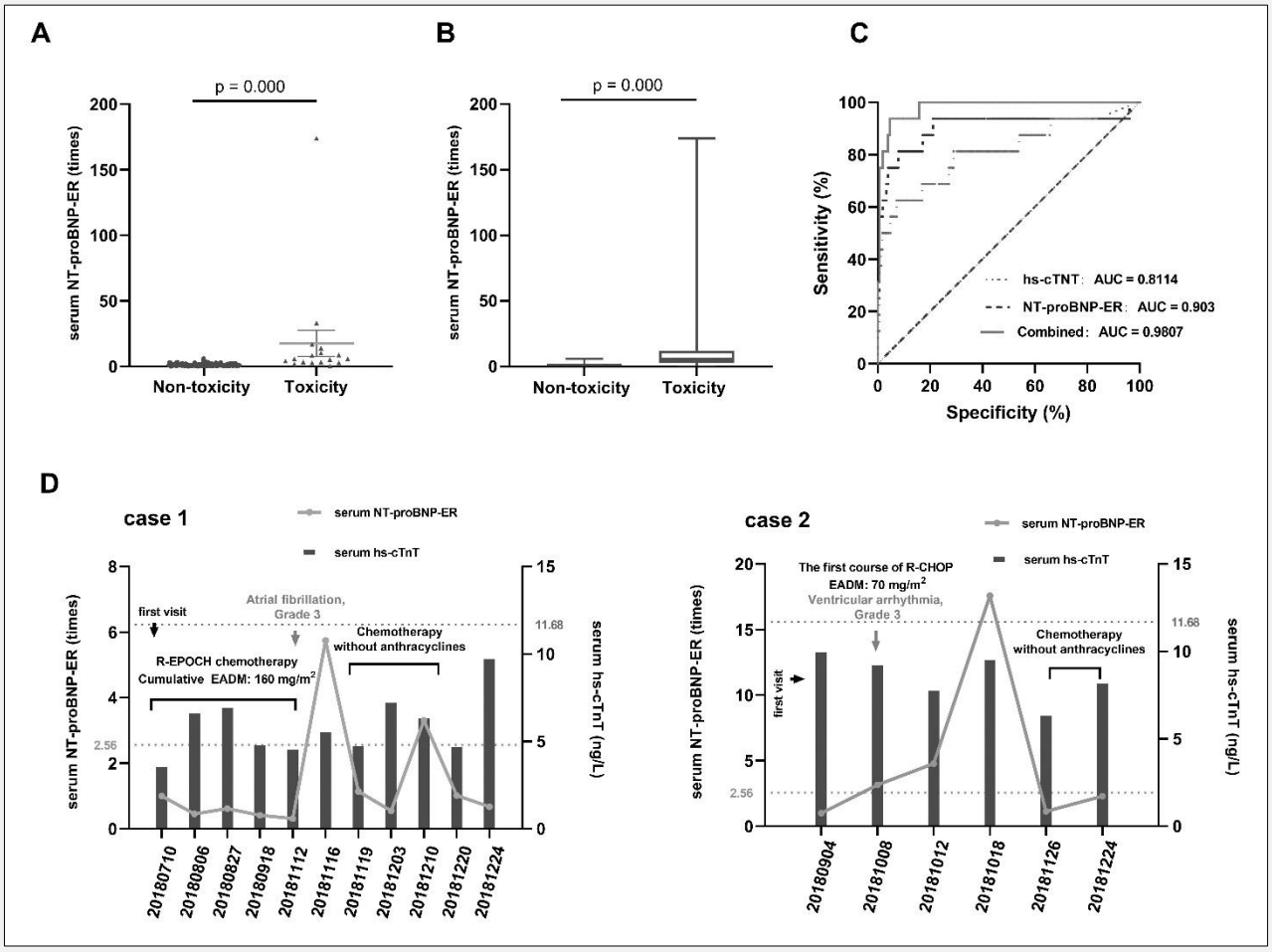

Figure 3. Post-therapeutic serum NT-proBNP-ER and hs-cTnT levels in predicting symptomatic CVT.

A, B Comparison of serum NT-proBNP-ER before and after ATC treatment in the toxic and non-toxic groups. C ROC curve analysis illustrating the predictive value of NT-proBNP-ER and hs-cTnT levels, and their combined use for symptomatic CVT. D Serum NT-proBNP-ER and hs-cTnT levels in two HNL patients during follow-up in the ATC treatment study.

tion, two with premature ventricular beats), and seven with symptomatic cardiac dysfunction (five mild to moderate, two severe). Cardiovascular toxicity was managed following the cessation of anthracycline chemotherapy and related therapy. The incidence of CVT events was 8.79%, with a median time to diagnosis of 37.5 (range: 6.0 to 116.5) days. Out of these, 11 patients over 60 years old showed an 18.03% (11/61) incidence rate, significantly higher than the 4.76% (5/105) rate in patients 60 years or younger (χ^2 = 6.251; p = 0.012) (Supplementary Table 1).

Changes in serum NT-proBNP and hs-cTnT levels before and after anthracycline treatment

In the 16 patients with CVT events, serum NT-proBNP and hs-cTnT levels significantly increased from 107.95 (85.85, 227.65) and 9.17 (3.14, 12.44) ng/L pre-treatment to 723.00 (326.35, 1,500.50) and 13.58 (7.06, 24.00) ng/L post-treatment. These increases were statistically significant in both unpaired (*t* = -2.579, p = 0.021) and paired sample *t*-tests (*t* = -2.422, p = 0.029) (Figures 2A to 2D). In contrast, patients without concurrent toxicities showed no significant change in NT-proBNP and hs-cTnT levels: pre-treatment levels were 38.21 (20.64, 65.52) and 5.56 (3.35, 7.43) ng/L, compared to post-treatment levels of 32.49 (17.52, 70.60) and 5.68 (3.99, 8.05) ng/L. These differences were non-

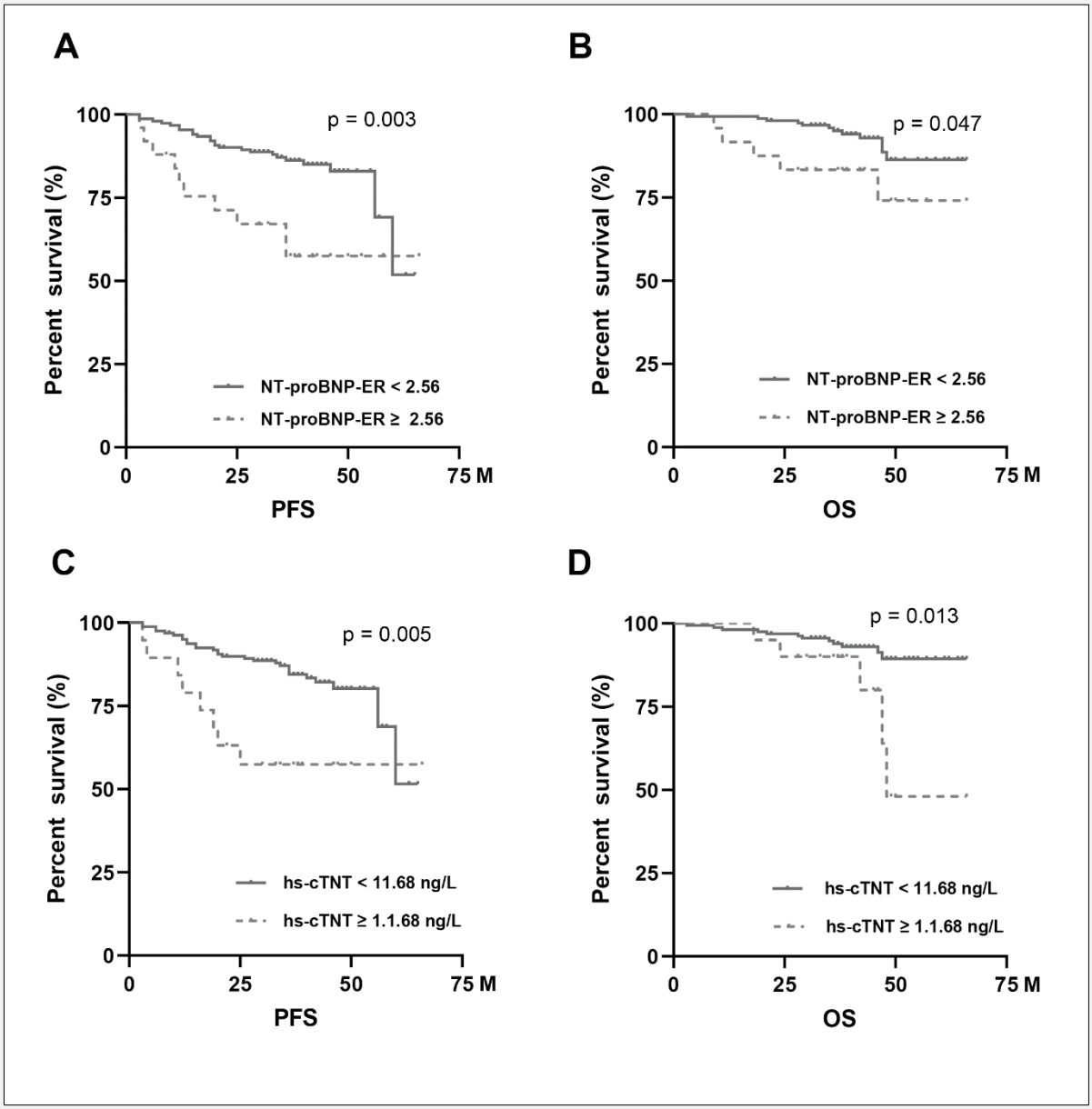

Figure 4. Prognostic implications of NT-proBNP-ER and hs-cTnT levels post-ATC treatment in NHL patients.

A, B Patients with an NT-proBNP increase ratio of 2.56-fold had poor PFS and OS. C, D Patients with a post-therapeutic hs-cTnT level of 11.68 pg/mL exhibited poor PFS and OS.

significant in unpaired (t = -0.224, p = 0.823) and paired sample t-tests (t = -1.938, p = 0.054) (Figures 2E to 2H). These findings indicate that increases in serum NT-proBNP and hs-cTnT levels following initial anthracycline treatment are associated with symptomatic CVT events in these patients.

Estimating predictive value of serum NT-proBNP elevation ratio and hs-cTnT after anthracycline treatment with ROC analysis

Evidence suggests that NT-proBNP levels are influenced by age, gender, renal function, and BMI. To account for these individual differences, we calculated the post-treatment increase in NT-proBNP as an elevation

ratio (ER), comparing post-first treatment values to baseline levels. In the 16 patients with concurrent toxicity events, the NT-proBNP elevation ratio (NT-proBNP-ER) was significantly higher at 5.74-fold (range: 3.16 to 10.26) compared to the 0.90-fold (range: 0.61 to 1.39) in patients without concurrent events ($Z = -5.301$, $p = 0.000$) (Figure 3A, 3B).

We assessed the predictive value of serum NT-proBNP-ER and hs-cTnT using ROC analysis. The area under the curve (AUC) for NT-proBNP-ER was 0.903 (95% CI, 0.789 - 1.018; $p < 0.001$), with an optimal diagnostic threshold of 2.56-fold, yielding a sensitivity of 81.25% and specificity of 92.11%. The AUC of hs-cTnT was 0.811 (95% CI, 0.676 - 0947; $p < 0.001$), with a diagnostic threshold of 11.68 ng/L, resulting in a sensitivity of 62.50% and specificity of 92.77%. Combining both biomarkers increased the AUC to 0.981 (95% CI, 0.959 - 1.000; $p < 0.001$) and improved sensitivity to 93.75% and specificity to 95.39% (Figure 3C).

Two patients were followed for up to 16 months during treatment (Figure 3D, 3E). They exhibited symptoms like chest tightness and palpitations during initial EADM treatment. While their LVEFs remained above 60%, post-treatment hs-cTnT levels were below 11.68 ng/L. However, NT-proBNP levels increased, with NT-proBNP-ER of 5.74-fold and 17.59-fold, respectively. ECGs indicated that atrial fibrillation and ventricular arrhythmia normalized immediately after stopping EADM treatment and implementing cardiac protection. These observations indicate that NT-proBNP-ER is a useful marker for identifying and predicting symptomatic CVTs in NHL patients undergoing anthracycline chemotherapy.

The relationship between serum NT-proBNP-ER, hs-cTnT, and symptomatic CVT events after anthracicline treatment

Using serum NT-proBNP-ER ≥ 2.56 and hs-cTnT ≥ 11.68 ng/L as cutoff values, along with using age, gender, clinical stage, and cumulative anthracycline dose (mg/m^2) as independent variables, we determined that NT-proBNP-ER ≥ 2.56-fold (OR [odds ratio] = 35.750, 95% CI, 8.315 - 380.322; $p = 0.000$) and hs-cTnT increase ≥ 11.68 ng/L (OR = 21.389, 95% CI, 2.858 - 181.596; $p = 0.003$) were significantly associated with the occurrence of symptomatic CVT events (Table 1). This suggests that serum NT-proBNP-ER and hs-cTnT are reliable predictors of symptomatic CVT events following anthracycline treatment.

Association between serum NT-proBNP-ER/hs-cTnT and PFS and OS after anthracycline treatment.

By June 2022, 5 of the 182 NHL patients were lost to follow-up, representing a 2.6% loss rate. For the remaining 177 patients, follow-up duration post-therapy initiation ranged from 3 to 66 months. There were 35 relapsed cases, yielding a recurrence rate of 19.77%. The median follow-up for OS was 42 months, with 13 deaths and a mortality rate of 7.34%.

Among the 177 patients, 25 had a post-treatment NT-proBNP-ER ≥ 2.56-fold, and 19 had hs-cTnT ≥ 11.68 ng/L. The 5-year recurrence and mortality rate for the 25 patients with an NT-proBNP-ER ≥ 2.56-fold were 40.0% (10/25) and 24.0% (6/25), respectively. In contrast, patients with an NT-proBNP-ER < 2.56-fold had lower 5-year recurrence rate (13.8%; 21/152) and 5-year mortality rate (7.2%; 11/152) (Figure 4A, 4B). The 19 patients with hs-cTnT ≥ 11.68 ng/L post-treatment had significantly higher 5-year recurrence (42.1%; 8/19) and mortality rates (21.1%; 4/19) than those with hs-cTnT < 11.68 ng/L, whose rates were 13.9% (22/158) and 7.6% (12/158), respectively (Figure 4C, 4D).

DISCUSSION

Anthracyclines are pivotal in the evolution of medical oncology, commonly used as first-line chemotherapy for NHL [7,21]. As outlined in the 2021 International Cardio-Oncology Society (IC-OS) consensus statement, CVTs are adverse events that can occur during anthracycline therapy. This treatment is often linked with type I cardiotoxicity, typically resulting in irreversible and permanent myocardial damage, manifesting as cardiac insufficiency, heart failure, and arrhythmia [10]. Early detection is crucial for preventing and managing CVTs and enhancing patient prognosis. Currently, echocardiography is the preferred method for monitoring cardiac function in tumor patients before and after treatment, with LVEF being the most widely-used index. However, its limited sensitivity impedes the detection of subclinical myocardial injury [13].

Key serum biomarkers of cardiac function include hs-cTnT and NT-proBNP. NT-proBNP, secreted by the ventricular muscle, varies with ventricular wall tension and plays a role in the negative feedback regulation of ventricular filling pressure. During heart failure, increased ventricular wall tension leads to a significant rise in NT-proBNP secretion, which is positively correlated with heart failure severity. Thus, NT-proBNP is a valuable biomarker for diagnosing, determining disease severity, and evaluating the prognosis of heart failure [14]. Cardiac troponins, specific structural proteins in cardiomyocytes, serve as indicators of cardiomyocyte injury; their serum levels reflect the extent of myocardial damage [15,22]. In the context of chemotherapy-related cardiotoxicity, NT-proBNP and hs-cTnT are more sensitive than echocardiography for early diagnosis [23-25]. The 2021 CSCO guidelines for preventing and treating cancer treatment-related CVT highlight the importance of these biomarkers in assessing baseline CVT risk and identifying risk factors, aiding in the early detection, monitoring, and prognosis of myocardial injury. However, the lack of defined optimal positive thresholds limits their diagnostic application [9].

Furthermore, NT-proBNP levels are significantly influenced by individual physiological factors, including age, gender, BMI, and renal function. For instance, NT-

proBNP levels tend to rise with age, possibly due to changes in cardiac structure/function, declining renal function, or increased heart weight in older individuals [17]. Additionally, NT-proBNP levels are generally higher in healthy women than in men [16] and show an inverse linear relationship with BMI, with higher BMI associated with lower NT-proBNP levels [18]. Consequently, the diagnostic and exclusion thresholds for heart failure using NT-proBNP should be adjusted based on these factors. Our retrospective study is unique in utilizing the NT-proBNP elevation ratio (NT-proBNP-ER, calculated by comparing biomarker values before and after initial anthracycline treatment) to account for individual variations and establish the optimal positive threshold for early diagnosis of symptomatic CVT events in NHL patients undergoing anthracycline therapy. This study also evaluates the efficacy of NT-proBNP and hs-cTnT in predicting the occurrence of symptomatic CVT events and patient outcomes. It found that an NT-proBNP-ER of 2.56-fold and a hs-cTnT level of 11.68 ng/L are significant indicators of symptomatic CVT events in patients with NHL treated with anthracyclines. Moreover, exceeding these thresholds is associated with a poorer prognosis.

Among the 182 NHL patients receiving anthracycline therapy, 16 experienced symptomatic CVT events. Out of these, 9 presented with arrhythmia, and 7 with symptomatic cardiac dysfunction. Notably, 11 patients were over 60 years old, exhibiting a higher incidence of toxicity events at 18.03% (11/61), compared to the 4.76% (5/105) in patients 60 years old or younger, indicating a higher risk of symptomatic CVTs with advancing age. Post-treatment serum NT-proBNP and hs-cTnT levels in these 16 patients significantly increased from baseline values of 107.95 (85.85, 227.65) and 9.17 (3.14, 12.44) ng/L to 723.00 (326.35, 1,500.50) and 13.58 (7.06, 24.00) ng/L, respectively. In patients without concurrent toxicities, a transient increase in NT-proBNP levels was observed post-chemotherapy, returning to baseline levels shortly thereafter and decreasing below baseline by the end of chemotherapy. This pattern was consistent with the findings in 34 patients who exhibited transient ECG abnormalities without related symptoms and returned to normal without treatment. The 16 patients with symptomatic CVTs after treatment demonstrated a significantly higher NT-proBNP increase ratio of 5.74-fold (3.16, 10.26), compared to a 0.90-fold (0.61, 1.39) increase in patients without concurrent events. Receiver operating characteristic (ROC) curve analysis of serum NT-proBNP-ER and hs-cTnT revealed an optimal diagnostic threshold of 2.56-fold for NT-proBNP-ER, with a sensitivity of 81.25%, specificity of 92.11%, and AUC of 0.903. For hs-cTnT, at a threshold of 11.68 ng/L, the sensitivity was 62.50%, specificity was 92.77%, and AUC was 0.811. Combined analysis of both biomarkers yielded a sensitivity of 93.75% and specificity of 95.39%, with an AUC of 0.981. Further multivariable logistic regression analysis showed that a serum NT-proBNP-ER of 2.56-fold and hs-cTnT level of 11.68 ng/L were significantly associated with the occurrence of symptomatic CVT. In the 16 patients with symptomatic CVT events, the absolute LVEF decrease of more than 10% during treatment was significant, with post-treatment values of 59.33% ± 2.96% and 59.25% ± 2.19%.

Tzolos et al. demonstrated that pre-treatment hs-cTnI concentrations in breast cancer patients prior to the second cycle of anthracycline therapy strongly predicted subsequent myocardial injury (sensitivity: 69%, specificity: 86%, ROC: 0.84) [26]. Other studies identified post-treatment hs-cTnT (> 14 ng/L) and NT-proBNP (> 300 ng/L) levels as significant predictors of CTRCD risk (HR 2.01; 95% CI 1.00 - 4.06 and HR 1.56; 95% CI 1.32 - 1.84, respectively) [27]. Zhang et al. proposed that hs-cTnT increase ≥ 0.0075 ng/mL from baseline showed superior predictive value (sensitivity: 96.2%, specificity: 83.9%, ROC: 0.79) [28] (Table 2). Our study innovatively introduced serum NT-proBNP elevation ratios to minimize interindividual variations from age, gender, obesity, and renal function, with combined hs-cTnT analysis significantly improving diagnostic performance over absolute values (sensitivity: 93.75%, specificity: 95.39%, AUC: 0.981). Notably, all 16 symptomatic cardiotoxicity cases maintained LVEF > 50% with < 10% absolute decline, suggesting NT-proBNP and hs-cTnT detect cardiovascular toxicity earlier than LVEF changes and may serve as predictive biomarkers for symptomatic cardiotoxicity in HNL patients receiving anthracyclines.

The cardiac biomarkers NT-proBNP and hs-cTnT are essential for early prediction of cardiac complications during chemotherapy and have significant value in forecasting patient mortality. Previous research has demonstrated a strong correlation between elevated post-chemotherapy NT-proBNP levels and one-year mortality in breast cancer patients [29]. Additionally, NT-proBNP is a reliable predictor for the occurrence and prognosis of heart failure in cancer patients receiving cardiotoxic chemotherapy [30]. Patients with pre-chemotherapy serum hs-cTnT ≥ 7 ng/L demonstrated significantly lower 5-year survival rates compared to those with lower levels ($p < 0.001$) [31]. Romann et al. further established that age-adjusted NT-proBNP effectively predicted both all-cause mortality (ACM) and cardiotoxicity occurrence [32] (Table 2). In line with these findings, our study followed 182 NHL patients undergoing anthracicline treatment and observed a 2.56-fold increase in NT-proBNP post-treatment. Furthermore, the PFS and OS in patients with post-treatment hs-cTnT levels ≥ 11.68 ng/L is significantly shorter than those patients without a 2.56-fold NT-proBNP increase or those whose post-treatment hs-cTnT levels were ≤ 11.68 ng/L. This suggests that these thresholds have clinical relevance in predicting post-treatment PFS and OS.

The detection and monitoring of serum cardiac function biomarkers hold practical and clinical importance. Since CVT induced by cancer treatment often initially manifests as abnormal cardiac function biomarkers, timely

and effective intervention during this early phase can prevent or reverse CVT events, thereby improving patients' progression-free and overall survival times. This reduces reliance on echocardiography and radionuclide imaging [20].

A limitation of this study is the small number of cases and the limited range of chemotherapeutic regimens examined. Future research should therefore focus on different chemotherapy drug combinations, expand the sample size, and utilize tracking methods beyond echocardiography to validate and further investigate optimal detection and management of CVT events.

CONCLUSION

Our study found that a serum NT-proBNP-ER of 2.56-fold and a hs-cTnT level of 11.68 ng/L are predictive of CVT complications and their prognosis in patients treated with anthracyclines, underlining their importance for the early clinical detection of symptomatic CVTs. However, as the detection of NT-proBNP and hs-cTnT is influenced by various factors, accurate diagnosis of CVT events induced by tumor treatment should not solely rely on serological markers but should also incorporate clinical symptoms and other relevant data.

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References:

1. Thandra KC, Barsouk A, Saginala K, Padala SA, Barsouk A, Rawla P. Epidemiology of Non-Hodgkin's Lymphoma. Med Sci (Basel) 2021;9(1):5. (PMID: 33573146)

2. Weniger MA, Küppers R. Molecular biology of Hodgkin lymphoma. Leukemia 2021;35(4):968-81. (PMID: 33686198)

3. Mozas P, Sorigué M, López-Guillermo A. Follicular lymphoma: an update on diagnosis, prognosis, and management. Med Clin (Barc) 2021;157(9):440-8. (PMID: 34210513)

4. Yeh ETH, Vejpongsa P. Subclinical Cardiotoxicity Associated With Cancer Therapy: Early Detection and Future Directions. J Am Coll Cardiol 2015;65(23):2523-5. (PMID: 26065991)

5. Miller KD, Nogueira L, Devasia T, et al. Cancer treatment and survivorship statistics, 2022. CA Cancer J Clin 2022;72(5):409-36. (PMID: 35736631)

6. Handa K, Sato S. Stimulation of microsomal NADPH oxidation by quinone group-containing anticancer chemicals. Gan 1976; 67(4):523-8. (PMID: 15920)

7. Minotti G, Cairo G, Monti E. Role of iron in anthracycline cardiotoxicity: new tunes for an old song? FASEB J 1999;13(2):199-212. Erratum in: FASEB J. 1999;13(3):594. (PMID: 9973309)

8. Kalyanaraman B, Morehouse KM, Mason RP. An electron paramagnetic resonance study of the interactions between the adriamycin semiquinone, hydrogen peroxide, iron-chelators, and radical scavengers. Arch Biochem Biophys 1991;286(1):164-70. (PMID: 1654778)

9. Armenian SH, Lacchetti C, Barac A, et al. Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2017;35(8):893-911. (PMID: 27918725)

10. Sheibani M, Azizi Y, Shayan M, et al. Doxorubicin-Induced Cardiotoxicity: An Overview on Pre-clinical Therapeutic Approaches. Cardiovasc Toxicol 2022;22(4):292-310. (PMID: 35061218)

11. Galán-Arriola C, Lobo M, Vílchez-Tschischke JP, et al. Serial Magnetic Resonance Imaging to Identify Early Stages of Anthracycline-Induced Cardiotoxicity. J Am Coll Cardiol 2019;73(7): 779-91. (PMID: 30784671)

12. Lipshultz SE, Rifai N, Sallan SE, et al. Predictive value of cardiac troponin T in pediatric patients at risk for myocardial injury. Circulation 1997;96(8):2641-8. (PMID: 9355905)

13. Lancellotti P, Nkomo VT, Badano LP, et al. Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. J Am Soc Echocardiogr 2013;26(9):1013-32. (PMID: 23998694)

14. Pudil R, Mueller C, Čelutkienė J, et al. Role of serum biomarkers in cancer patients receiving cardiotoxic cancer therapies: a position statement from the Cardio-Oncology Study Group of the Heart Failure Association and the Cardio-Oncology Council of the European Society of Cardiology. Eur J Heart Fail 2020; 22(11):1966-83. (PMID: 33006257)

15. Curigliano G, Cardinale D, Dent S, et al. Cardiotoxicity of anticancer treatments: Epidemiology, detection, and management. CA Cancer J Clin 2016;66(4):309-25. (PMID: 26919165)

16. Kavsak PA, Lam CSP, Saenger AK, et al. Educational Recommendations on Selected Analytical and Clinical Aspects of Natriuretic Peptides with a Focus on Heart Failure: A Report from the IFCC Committee on Clinical Applications of Cardiac Bio-Markers. Clin Chem 2019;65(10):1221-7. (PMID: 31387884)

17. Nishikimi T, Nakagawa Y. Potential pitfalls when interpreting plasma BNP levels in heart failure practice. J Cardiol 2021;78(4): 269-74. (PMID: 34088563)

18. Bayes-Genis A, Lloyd-Jones DM, van Kimmenade RRJ, et al. Effect of body mass index on diagnostic and prognostic usefulness of amino-terminal pro-brain natriuretic peptide in patients with acute dyspnea. Arch Intern Med 2007;167(4):400-7. (PMID: 17325303)

19. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32(27):3059-68. (PMID: 25113753)

20. Herrmann J, Lenihan D, Armenian S, et al. Defining cardiovascular toxicities of cancer therapies: an International Cardio-Oncology Society (IC-OS) consensus statement. Eur Heart J 2022;43(4): 280-99. (PMID: 34904661)

21. Jamal-Hanjani M, Pettengell R. Pharmacokinetic evaluation of pixantrone for the treatment of non-Hodgkin's lymphoma. Expert Opin Drug Metab Toxicol 2011;7(11):1441-8. (PMID: 21905966)

22. Daubert MA, Jeremias A. The utility of troponin measurement to detect myocardial infarction: review of the current findings. Vasc Health Risk Manag 2010;6:691-9. (PMID: 20859540)

23. Henri C, Heinonen T, Tardif J-C. The Role of Biomarkers in Decreasing Risk of Cardiac Toxicity after Cancer Therapy. Biomark Cancer 2016;8(Suppl 2):39-45. (PMID: 27257396)

24. Plana JC, Galderisi M, Barac A, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2014;27(9):911-39. (PMID: 25172399)

25. Sandri MT, Salvatici M, Cardinale D, et al. N-terminal pro-B-type natriuretic peptide after high-dose chemotherapy: a marker predictive of cardiac dysfunction? Clin Chem 2005;51(8):1405-10. (PMID: 15932966)

26. Tzolos E, Adamson PD, Hall PS, et al. Dynamic Changes in High-Sensitivity Cardiac Troponin I in Response to Anthracycline-Based Chemotherapy. Clin Oncol (R Coll Radiol) 2020; 32(5):292-7. (PMID: 31813662)

27. Demissei BG, Hubbard RA, Zhang L, et al. Changes in Cardiovascular Biomarkers With Breast Cancer Therapy and Associations With Cardiac Dysfunction. J Am Heart Assoc 2020;9(2): e014708. (PMID: 31959034)

28. Zhang C-J, Pei X-L, Song F-Y, et al. Early anthracycline-induced cardiotoxicity monitored by echocardiographic Doppler parameters combined with serum hs-cTnT. Echocardiography 2017; 34(11):1593-600. (PMID: 28942608)

29. De Iuliis F, Salerno G, Taglieri L, et al. Serum biomarkers evaluation to predict chemotherapy-induced cardiotoxicity in breast cancer patients. Tumour Biol 2016;37(3):3379-87. (PMID: 26449821)

30. Skovgaard D, Hasbak P, Kjaer A. BNP predicts chemotherapy-related cardiotoxicity and death: comparison with gated equilibrium radionuclide ventriculography. PLoS One 2014;9(5):e96736. (PMID: 24800827)

31. Finke D, Romann SW, Heckmann MB, et al. High-sensitivity cardiac troponin T determines all-cause mortality in cancer patients: a single-centre cohort study. ESC Heart Fail 2021;8(5):3709-19. (PMID: 34396713)

32. Romann SW, Finke D, Heckmann MB, et al. Cardiological parameters predict mortality and cardiotoxicity in oncological patients. ESC Heart Fail 2024;11(1):366-77. (PMID: 38012070)

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