

A prospective study of cardiac biomarkers in monitoring cardiac arrhythmia in Non-Hodgkin's lymphoma chemotherapy

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Abstract

Background

This study aims to evaluate serum biomarkers of cardiac arrhythmia in non-Hodgkin's lymphoma (NHL) patients undergoing Cyclophosphamide, Hydroxydaunorubicin, Oncovin and Prednisone (CHOP) chemotherapy regimen.

Methods

A prospective study was conducted involving 45 NHL patients from January 2022 to December 2023. Based on electrocardiogram, patients were categorized into arrhythmia group (24 cases) and normal group (21 cases). Serum levels of high-sensitivity troponin T (hs-TNT), N-terminal brain natriuretic peptide (NT-proBNP), soluble growth-stimulated expressed gene 2 (sST2), and myocardial-type fatty acid-binding protein (H-FABP) at baseline and before each chemotherapy cycle were analyzed. Logistic regression analyses and receiver operating characteristic (ROC) curves were employed to assess associations between biomarkers and cardiac arrhythmia.

Results

Hs-TNT levels exhibited significant increase from baseline to cycles C1-C4 ($P < 0.01$). sST2 levels showed a notable rise during cycle C2 compared to baseline ($P < 0.01$). Univariate logistic regression analysis indicated that interval changes in hs-TNT presented a greater risk for arrhythmia (with an odds ratio of OR:1.19; 95% CI: 1.02–1.37; $P = 0.024$), sST2 (OR:1.17; 95% CI: 1.01–1.36; $P = 0.042$), as well as in LVEF OR = 0.66 (0.462–0.943, $P < 0.05$). Consulting confounding factors, multivariate analysis revealed that Δ hs-TNT, Δ sST2 and Δ LVEF also predicted significant associations with arrhythmia. The ROC curve analysis demonstrated that Δ hs-TNT, Δ sST2, and Δ (sST2 + hs-TNT) provided good predictive values for arrhythmia, with areas under the curves measuring at 0.795, 0.683, and 0.866 respectively ($P < 0.05$).

Conclusions

Early detection of alterations in hs-TnT and sST2 may partially predict cardiac arrhythmia and changes of LVEF intensively associated with arrhythmia due to chemotherapy in NHL patients.

Introduction

Malignant lymphomas are classified into two main types: Hodgkin Lymphoma (HL), which accounts for approximately 10% of cases, and Non-Hodgkin Lymphoma (NHL), representing about 90% of cases. NHL is further categorized into various subtypes[1]. The diverse clinical manifestations of NHL pose

significant challenges for clinicians in terms of treatment [2]. The primary therapeutic options for NHL include chemotherapy, radiotherapy, and biologic therapy. Chemotherapy is the first-line treatment choice for NHL, with the CHOP regimen—comprising cyclophosphamide, doxorubicin, vincristine, and prednisone—being the standard initial approach [3]. However, the combination of multiple chemotherapeutic agents can lead to adverse side effects that may necessitate early discontinuation of therapy; one notable concern is cardiotoxicity[4]. Cardiovascular toxicity may arise from direct damage to cardiovascular tissues due to chemotherapy regimens or accelerated atherosclerosis, particularly in patients with pre-existing cardiovascular risk factors [5]. Cancer therapy-related cardiac dysfunction (CTRCD) can result in serious complications such as heart failure, valvular abnormalities, arrhythmias, or sudden cardiac death; notably, arrhythmias have been increasingly recognized as a significant issue within this context[6].CTRCD is characterized by its reversible nature and dynamic variability throughout the course of chemotherapy. Factors influencing CTRCD include age at diagnosis, cancer history, prior risk factors for cardiovascular dysfunctions as well as variations in treatment regimens regarding dosage and frequency [7].Consequently, CTRCD represents a critical concern for survivors of NHL who have undergone cancer treatment[8].

The echocardiographic measurement of left ventricular ejection fraction (LVEF) is recommended as the primary monitoring strategy by the European Society of Cardiology (ESC)[9]. However, LVEF is limited in its ability to capture the full spectrum of cardiac function. Cellular damage and subclinical symptoms may manifest prior to any functional impairment [10]. The assessment of cardiac biomarkers represents a critical approach for early diagnosis of myocardial damage before a decline in LVEF during chemotherapy for non-Hodgkin lymphoma (NHL)[11].

High sensitivity troponin T (hs-TnT), N-terminal pro-B-type natriuretic peptide (NT-proBNP), suppression of tumorigenicity 2 (ST2) protein, and H-FABP (heart fatty acid binding protein) are widely utilized cardiac biomarkers for assessing cardiac function[12]. A prospective study indicated that levels of hs-cTnT and NT-proBNP in breast cancer patients undergoing treatment with anthracycline drugs and/or trastuzumab were elevated, correlating with an increased risk of chemotherapy-induced left ventricular dysfunction (CTRCD)[13]. Furthermore, several studies have suggested that hs-TnT may hold potential value for the early diagnosis of CTRCD[14, 15]. The sST-2 levels exhibits higher sensitivity in predicting heart failure[16]. In anthracycline-related therapy, sST2 levels significantly increased by cycle 2 of treatment, mirroring the changes observed in cTnT and NT-proBNP[17]. Patients receiving anthracycline-containing chemotherapy exhibited elevations in hs-TnT, NT-proBNP, and sST2 levels, indicating that these biomarkers could provide distinct information regarding cardiac health.[18].

This research aimed to evaluate the potential significance of two established cardiac biomarkers hs-TnT and NT-proBNP, alongside two relatively novel biomarkers sST2 and H-FABP in relation to cardiotoxicity in non-Hodgkin lymphoma (NHL) patients undergoing chemotherapy. Serum levels were monitored at baseline and during the regimen, with a focus on analyzing their associations with the risk of cardiotoxicity.

Materials & Methods

Study population

A total of 45 NHL patients admitted to Fudan University Shanghai Cancer Center between August 2022 and December 2023 were selected for this prospective analysis. Inclusion criteria encompassed individuals aged 18 years or older, those newly diagnosed with NHL, and patients who had not received prior cancer treatment. Exclusion criteria included individuals who had undergone cardiac or vascular surgery, or who had experienced myocardial or vascular diseases within three months prior to enrollment; pregnant individuals; those receiving treatment for cancer recurrence; patients with concurrent malignancies; and individuals suffering from severe infections. Patient and tumor characteristics are summarized in Table 1. All participants received 4 to 6 cycles of CHOP-related chemotherapy. The study protocol adhered to the ethical standards outlined in the 1975 Declaration of Helsinki, as evidenced by prior approval from the Ethics Committee of Fudan University Shanghai Cancer Center, and the Institutional Review Board approval number is 050432-4-2307E.

Blood samples collection

Blood samples from the study population were collected at baseline and prior to the initiation of each cycle in the CHOP regimen. A 10 ml blood sample was obtained, with serum prepared within one hour and subsequently stored at -80°C.

Biomarker measurements

The serum levels of hs-TnT, NT-proBNP, sST2, and H-FABP were evaluated in all blood samples. Serum hs-TnT was measured using the fourth-generation Elecsys assay on the Cobas platform (Roche Diagnostics, USA). Serum NT-proBNP was also analyzed on the Cobas platform (Roche Diagnostics, USA). Additionally, serum levels of sST2 and H-FABP were quantified using an enhanced fluorescent immunoassay conducted on the Pylon 3D immune-analyzer (ET Healthcare, Suzhou, China).

Electrocardiogram Detection and Definition of Cardiotoxicity

Electrocardiograms were obtained using a digital work platform (SID Medical, Shanghai, China). In this study, cardiotoxicity was defined as cancer therapy-related arrhythmias, which were categorized into bradycardia or tachycardia, with atrial fibrillation (AF) identified as a significant complication[19]. The total cohort of 45 patients was classified into an arrhythmia group (n=24) and a normal group (n=21) based on the results of the electrocardiogram.

Echocardiography Detection

The echocardiography of patients was detected by GE Healthcare Vivid™ E90. Three indicators LVEF, Left Ventricular End Diastolic Diameter (LVEDD), and Left ventricular end systolic diameter (LVESD) were included in the study.

Statistical Analysis

Baseline characteristics were described using proportions for categorical variables, while medians with interquartile ranges were presented for continuous variables. Differences in categorical variables were compared using the Chi-Square test. Continuous variables were analyzed with the Mann-Whitney U test. The Wilcoxon signed-rank test was employed to assess changes in each biomarker concentration from baseline to C4.

According to previous references [7] and clinical significance, the adjusted variables closely related to chemotherapy-induced cardiac toxicity included age, gender, body mass index (BMI), systolic blood pressure, and diabetes. The associations between changes in biomarker values and cardiotoxicity were assessed using a logistic regression model. And the echocardiography results were also included for analysis. Receiver operating characteristic (ROC) curves were employed to evaluate the efficacy of the biomarker model. All tests were two-tailed, and a p-value of less than 0.05 indicated statistical significance. All analyses were conducted using SPSS 20.2 and MedCalc 20.0.

Results

Basic Clinical Characteristics of the Study Population

The baseline characteristics and biomarker levels are presented in Table 1. The timeline and analysis of blood draws according to cancer therapy regimen were shown in Figure 1. A total of 45 patients were enrolled in this prospective cohort and were divided into two groups based on their electrocardiogram results. The arrhythmia group consisted of 24 patients (n=24, median age=54.63 years, range=42.59-66.66 years), while the normal group comprised 21 patients (n=21, median age=51.62 years, range=40.39-62.85 years). At baseline, the level of hs-TNT in the overall population was 0.007ng/ml (range: 0.005-0.01 ng/ml), and the level of sST2 in total population was 11.1 ng/ml (range: 7.42-20.8 ng/ml). The baselines of LVEF, LVEDD and LVESD had no obvious differences between two groups ($P>0.05$). Meanwhile, there were no significant differences between the two groups in terms of age, BMI, chemotherapy regimen, hs-TNT, NT-proBNP, sST2, and H-FABP (all $P>0.05$).

Trajectories of Biomarkers During Cancer Chemotherapy.

Dynamic changes in serum biomarkers over time during the cancer chemotherapy process are illustrated in Figure 2. The hs-TnT level significantly increased early in C1 cycle compared to baseline ($P < 0.05$) in the arrhythmia group, reached a higher level in the second cycle (C2) ($P < 0.01$), and then declined during cycles three and four (C3-C4) ($P < 0.05$). In contrast, the hs-TnT levels in the normal group showed no significant changes throughout the chemotherapy regimen (Fig. 2A). No significant changes in NT-proBNP levels were observed in either group, except for a minor elevation in C2 in the arrhythmia group, which was not statistically significant (Fig. 2B). Additionally, sST2 levels exhibited a notable increase in C2 from baseline in the arrhythmia group, while the normal group showed no significant or only minor

elevations in sST2 levels during the chemotherapy process (Fig. 2C). The serum H-FABP levels showed no remarkable changes throughout the chemotherapy regimen (Fig. 2D).

Dynamic changes of echocardiography results during chemotherapy

The parallel analyses of echocardiography data across the CHOP cycles were performed. LVEF(%) results were analyzed in normal and arrhythmia groups at baseline and across the CHOP therapy cycles C1-C4 (Fig. 3A). The LVEF had no significant decrease in C1-C3 compared to baseline in arrhythmia group, but obvious decreased by $-4.095\% \pm 2.427$ ($P < 0.05$) in C4. LVEF(%) had no obvious change in normal group. LVEDD and LVESD levels had no significant changes from baseline to C1-C4 in both arrhythmia and normal groups (Fig. 3B,C).

Associations between Biomarker Level Changes and Arrhythmia

A total of 24 patients were identified as experiencing cardiotoxicity of arrhythmia. The findings from the univariate logistic regression analysis indicated that changes in levels of sST2 (Δ sST2) and hs-TNT (Δ hs-TNT) from baseline to cycle 2 (C2) served as independent predictors of cardiac arrhythmia in patients with NHL (refer to Table 2). Notably, the data for hs-TnT changes were scaled by a factor of 1000 for analytical purposes. Specifically, for each unit increase in hs-TNT, there was a 19% increase in the risk of arrhythmia (OR: 1.19; 95% CI: 1.02-1.37; $P = 0.024$). Similarly, for each increment of 1 ng/mL in sST2, the risk of arrhythmia increased by 17% (OR: 1.17; 95% CI: 1.01-1.36; $P = 0.042$). Meanwhile, the decline of LVEF(%) from baseline to post-treatment predict a risk of OR=0.66 (0.462-0.943), $P = 0.022$. However, upon conducting a multivariate regression analysis that accounted for confounding variables such as age, BMI, and diabetes, the changes in hs-TNT (Δ hs-TNT), sST2(Δ sST2) and LVEF(Δ LVEF) demonstrated significant predictive values for the arrhythmia group. Specifically, for each unit increase in hs-TNT and sST2, the risk of arrhythmia increased by 29% (OR: 1.29; 95% CI: 1.00-1.67; $P = 0.04$) and 26% (OR: 1.26; 95% CI: 1.01-1.58; $P = 0.038$) separately, as detailed in Table 2. And the risk of arrhythmia with the decline of LVEF increased by 43% (OR:0.57; 95% CI: 0.35-0.92; $P = 0.023$) (Table 2).

Predictive Value of Δ hs-TNT and Δ sST2 for arrhythmia

The receiver operating characteristic (ROC) curve analysis (Fig. 4) revealed that both Δ hs-TNT and Δ sST2 possess predictive value for cardiac arrhythmia, with areas under the curve (AUC) measuring 0.795 and 0.683, respectively ($P < 0.05$). Furthermore, the combination of Δ hs-TNT and Δ sST2 significantly enhanced the predictive capability for cardiac arrhythmia, yielding an AUC of 0.866 ($P < 0.001$). Among the 45 patients, 19 (42.2%) exhibited levels above the cutoff for Δ hs-TNT, with these elevations demonstrating a sensitivity of 75% and specificity of 84.21% for predicting cardiac arrhythmia; the positive predictive value (PPV) and negative predictive value (NPV) were 84.2% and 55.6%, respectively (Table 3). In contrast, 10 out of 45 patients (22.2%) exceeded the cutoff for Δ sST2, with these elevations showing a sensitivity of 40% and specificity of 94.74% for predicting cardiac arrhythmia, alongside PPV and NPV of 80% and 60.9%, respectively (Table 3). When combining Δ hs-TNT and

Δ sST2, sensitivity increased to 75% and specificity to 94.74%, with a notably higher PPV of 93.8% ($P=0.0001$) (Table 3).

Discussion

To the best of our knowledge, this study represents the inaugural examination of cardiac biomarkers at baseline and throughout the chemotherapy regimen for NHL. Blood samples from clinical subjects were collected as early as the first cycle post-treatment. The cardiac biomarkers analyzed included hs-TnT, NT-proBNP, sST2, and H-FABP, both prior to and during the chemotherapy cycles. The imaging results were also monitored. While it has been established that early monitoring for myocardial injury is beneficial, the majority of existing studies have initiated assessments 2–3 months following NHL chemotherapy[20]. Furthermore, there is a scarcity of research correlating cardiac biomarkers with cardiac toxicity resulting from (R)-CHOP chemotherapy.

The findings of this study indicate that in the arrhythmia group, hs-TnT levels significantly increased during the cycle C1 compared to baseline, peaked in the cycle C2, and subsequently declined in cycles C3-C4 relative to the normal group. Additionally, sST2 levels exhibited an increase in C2 from baseline within the arrhythmia group. No substantial changes in NT-proBNP and H-FABP levels were noted between the two groups, with the exception of a slight elevation in NT-proBNP during C2 in the arrhythmia group. Univariate logistic regression analysis revealed that the interval changes in sST2 and hs-TnT from baseline to C2 served as independent predictors of cardiac toxicity in NHL patients. When controlling for age, body mass index (BMI), and diabetes, the interval changes in hs-TnT demonstrated significant predictive value for the arrhythmia group. Specifically, each unit increase in hs-TnT was associated with a 29% heightened risk of cardiac arrhythmia.

In this investigation, electrocardiograms of NHL patients were continuously monitored, with cardiac toxicity identified as arrhythmia. The early detection and monitoring of arrhythmias induced by anthracycline agents are reversible[7][4]. This study found LVEF levels significantly decreased in C4 in arrhythmia group. And univariate and multivariate logistic regression analysis predicted the risk of arrhythmia with the decline of LVEF increased by 43%, $P < 0.05$. Cardiac injury can manifest upon the initial administration of anthracycline drugs, often presenting with subclinical symptoms that may lead to a decline in left ventricular ejection fraction (LVEF) or heart failure[21, 22]. The occurrence of arrhythmia as a consequence of cancer treatment has not been extensively studied[23]. The anthracycline agents included in the NHL chemotherapy regimen are closely associated with various arrhythmias, including potentially malignant forms. Notably, significantly prolonged ventricular repolarization indicators, such as QT and QTc intervals, may serve as early indicators of malignant arrhythmias[24, 25]. In clinical practice, the frequent and timely monitoring of echocardiography is often hindered by its complexity and cost; in contrast, electrocardiograms facilitate more frequent and timely assessments.

Hs-TnT serves as a highly sensitive biomarker for acute myocardial injury. Elevated levels of hs-TnT have been observed in patients undergoing high-dose chemotherapy, and the pattern of its release may serve

as a predictor of cardiac toxicity[26, 27]. In patients with NHL receiving CHOP chemotherapy, the variation in hs-TnT levels from baseline to post-fourth chemotherapy cycle exhibited a more pronounced difference compared to LVEF [20]. In the present study, hs-TnT levels increased significantly during cycle C1 of treatment in the arrhythmia group, indicating an early prediction of cardiac toxicity in NHL therapy. Notably, hs-TnT levels peaked during C2 and subsequently declined during C3 and C4 cycles, although they remained elevated compared to the normal group. Furthermore, the change in hs-TnT levels (Δ hs-TnT) from baseline to C2 emerged as an independent predictor of cardiac arrhythmia in NHL patients, even after adjusting for confounding factors such as age, BMI, and diabetes. Consistent with this study, only arrhythmia occurred in most clinical studies. The results showed that prior to heart functional impairment, damage at the cellular level might have occurred.

sST2L protects cardiac function through IL-33, while sST2 could bind to IL-33 and inhibit the protective effect of sST2L[28]. Additionally, sST2 has demonstrated potential utility in monitoring cardiac toxicity associated with cancer treatments[29]. However, research exploring the relationship between sST2 and chemotherapy in non-Hodgkin lymphoma (NHL) is limited. In the present study, sST2 levels obviously increased in C2 from baseline in arrhythmia group. The interval changes of Δ sST2 from baseline to C2 was an independent predictor of cardiac toxicity in NHL patients. Moreover, the combination of changes in Δ hs-TnT and Δ sST2 significantly enhanced the predictive accuracy for cardiac toxicity. The trend of initially increased and then declined in sST2 levels was similar to the changes observed in sST2 after anthracycline treatment in previous studies [30, 31]. Notably, sST2 is minimally affected by age and renal function, exhibiting lower individual variability [32]. Therefore, sST2 is deemed a suitable adjunctive biomarker for monitoring cardiac injury in the context of NHL chemotherapy.

In NHL patients, Prior to the functional damage, injury at cellular level may have occurred and early detecting of cardiac blood biomarkers was necessary. Cardiac biomarkers play a crucial role in the diagnosis of myocardial infarction [33]. Considering the pathophysiology associated with the CHOP regimen, which includes anthracycline-induced cardiotoxicity, it is plausible that cellular damage could be identified, thereby serving as an early detection method that complements LVEF measurements.

The study still had some limitations. The cohort enrolled in this investigation, while rigorously characterized, remains relatively modest in scale. This constrained sample size inherently restricts the statistical power of our analyses, potentially limiting the detection of subtle yet clinically significant effects. Furthermore, it may compromise the generalizability of our findings across broader or more diverse populations. Data collection was confined to baseline assessments and measurements obtained solely during the active treatment phase. The absence of comprehensive, longitudinal post-treatment follow-up data represents a significant gap. Consequently, this study cannot evaluate the long-term efficacy, sustainability of therapeutic benefits, or potential delayed adverse effects associated with the intervention. As longitudinal follow-up observations are currently in progress, critical questions regarding durability of response, relapse rates, and extended safety profiles remain unanswered within the present dataset. The current findings, while promising, necessitate further validation in larger, independent cohorts. The limited sample size also precluded robust internal validation strategies, such as splitting

the cohort into distinct training and test sets, which would have strengthened confidence in the model's predictive performance.

Conclusions

Early detection of alterations in hs-TnT and sST2 may partially predict cardiac arrhythmia and changes of LVEF intensively associated with arrhythmia due to chemotherapy in NHL patients.

Abbreviations

NHL non-Hodgkin's lymphoma

CHOP Cyclophosphamide, Hydroxydaunorubicin, Oncovin and Prednisone

hs-TnT high-sensitivity troponin T

NT-proBNP N-terminal brain natriuretic peptide

sST2 soluble growth-stimulated expressed gene 2

FABP myocardial-type fatty acid-binding protein

CTRCD Cancer therapy-related cardiac dysfunction

LVEF left ventricular ejection fraction

Declarations

Ethics approval and consent to participate

The study protocol adhered to the ethical standards outlined in the 1975 Declaration of Helsinki, as evidenced by prior approval from the Ethics Committee of Fudan University Shanghai Cancer Center.

Informed consent was obtained from all individual participants included in the study

Consent for publication

Not applicable.

Clinical trial number:

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors have no relevant financial or non-financial interests to disclose

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Authors' contributions

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Table 1 Basic clinical characteristics of overall cohort and stratified according to Arrhythmia

	All (n=45)	Normal (n=21)	Arrhythmia (n=24)	<i>P</i> value
Age, y	53.22(30.42-76.02)	51.62(40.39-62.85)	54.63(42.59-66.66)	0.393
BMI, kg/m2	24.20(16.88-31.15)	24.86(22.02-27.69)	23.62(19.27-27.97)	0.271
Family history of lymphoma, n(%)				0.811
No	35(77.8)	16(76.2)	19(79.2)	
Yes	10(22.2)	5(23.8)	5(20.8)	
Smoking, n(%)				1.010
No	38(84.4)	18(85.7)	20(83.3)	
Yes	7(15.6)	3(14.3)	4(16.7)	
Alcohol, n(%)				0.905
No	42(93.3)	19(90.5)	23(95.8)	
Yes	3(6.7)	2(9.5)	1(4.2)	
Hypertension, n(%)				0.701
No	41(91.7)	20(95.2)	21(87.5)	
Yes	4(8.9)	1(4.8)	3(12.5)	
Diabetes, n(%)				0.712
No	41(91.1)	20(95.2)	21(87.5)	
Yes	4(8.9)	1(4.8)	3(12.5)	
Chemotherapy regimen, n(%)				0.125
R-EPOCH	2(4.4)	0	2(8.3)	
R-CHOP	34(75.6)	16(76.2)	18(75)	
G-CHOP	2(4.4)	0	2(8.3)	
GB	3(6.7)	3(14.3)	0	
ZR-CHOP	1(2.2)	0	1(4.2)	
R-COP	1(2.2)	1(4.8)	0	
CHOP	2(4.4)	1(4.8)	1(4.2)	

Echocardiography (baseline)				
LVEF (%)	66.71(65.83-67.60)	66.33(64.99-67.68)	67.04(65.79-68.29)	0.515
LVEDD (mm)		48.48(47.36-49.59)		0.078
LVESD (mm)	47.73(46.97-48.50)	31.05(29.96-32.14)	47.08(46.02-48.15)	0.095
	30.29(29.59-30.99)		29.63(28.75-30.50)	
hs-TNT (baseline), ng/ml	0.007 (0.005-0.01)	0.006(0.0043-0.0088)	0.009 (0.005-0.001)	0.279
NT-proBNP(baseline), pmol/L	6.2 (2.94-12.8)	6.2 (2.84-13.3)	6.665 (2.888-13.03)	0.767
sST-2(baseline), ng/ml	11.1 (7.42-20.8)	17.45 (7.25-25.2)	8.42 (7.53-16.05)	0.234
H-FABP(baseline), ng/ml	1.965 (1.42-2.35)	1.8 (1.15-2.32)	2.0 (1,70-2.47)	0.336
Diagnose, n(%)				0.442
DLBCL				
⊠	5 (11.1)	2 (9.5)	3 (12.5)	
⊠	14 (31.1)	7 (33.3)	7 (29.2)	
⊠	5 (11.1)	4 (19)	1 (4.2)	
⊠	13 (28.9)	4 (19)	9 (37.5)	
FL+DLBCL	2 (2.2)	1 (4.8)	1 (4.2)	
FL				
⊠	1 (2.2)	0	1 (4.2)	
⊠-⊠	1 (2.2)	0	1 (4.2)	
⊠	1 (2.2)	1 (4.8)	0	
⊠	1 (2.2)	1 (4.8)	0	
ALCL ⊠	1 (2.2)	0	1 (4.2)	
MZBL ⊠	1 (2.2)	1 (4.8)	0	

BMI, Body Mass Index

R-EPOCH,Rituximab+Etoposide+Prednisolone+Oncovin+Cyclophosphamide+Hydroxydaunorubicn

R-CHOP, Rituximab+Prednisolone+Oncovin+Cyclophosphamide+Hydroxydaunorubicin

G-CHOP, Obinutuzumab+Prednisolone+Oncovin+Cyclophosphamide+Hydroxydaunorubicin

GB, Obinutuzumab+Bendamustine

ZR-CHOP, Zanubrutinib+Rituximab+Prednisolone+Oncovin+Cyclophosphamide+
Hydroxydaunorubicin

R-COP, Rituximab+Prednisolone+Oncovin+Cyclophosphamide

CHOP, Prednisolone+Oncovin+Cyclophosphamide+Hydroxydaunorubicin

DLBCL, Diffuse large B-cell lymphoma

FL, Follicular lymphoma

FL+DLBCL, Follicular lymphoma+Diffuse large B-cell lymphoma

ALCL, Anaplastic large cell lymphoma

MZBL, Marginal zone B-cell lymphomas

LVEF, left ventricular ejection fraction

LVEDD, Left Ventricular End Diastolic Diameter

LVESD, Left ventricular end systolic diameter

Data are median (interquartile range) or n (%). *P* value: Normal vs Arrhythmias.

Table 2 Associations between changes in biomarker values and arrhythmia

	Univariate			Multivariate		
	OR(95%CI)	β	<i>P</i> value	Adjusted OR(95%CI)	β	<i>P</i> value
Age	1.01(0.96-1.07)	0.01	0.62	1.02(0.94-1.11)	0.02	0.64
BMI	0.94(0.79-1.12)	-0.07	0.47	0.92(0.68-1.26)	-0.08	0.61
Diabetes	0.32(0.03-3.33)	-1.16	0.34	0.62(0.03-13.03)	-0.49	0.76
Δ hs-TNT	1.19(1.02-1.37)	0.17	0.024	1.29(1.00-1.67)	0.26	0.04
Δ sST2	1.17(1.01-1.36)	0.16	0.042	1.26(1.01-1.58)	0.24	0.038
Δ LVEF	0.66(0.462-0.943)	-0.415	0.022	0.57(0.35-0.92)	-0.57	0.023

Table 3 ROC Curves Analyses of the Predictive Performance of hs-TNT and sST2 for arrhythmia

Cutoff value	Sensitivity %	Specificity %	AUC	PPV%	NPV%	<i>P</i> value
Δ hs-TNT						
0.001	75	84.21	0.795	84.2	55.6	0.0001
Δ sST2						
2.055	40	94.74	0.683	80	60.9	0.033
Δ sST2+ Δ hs-TNT	75	94.74	0.866	93.8	78.5	0.0001

Figures

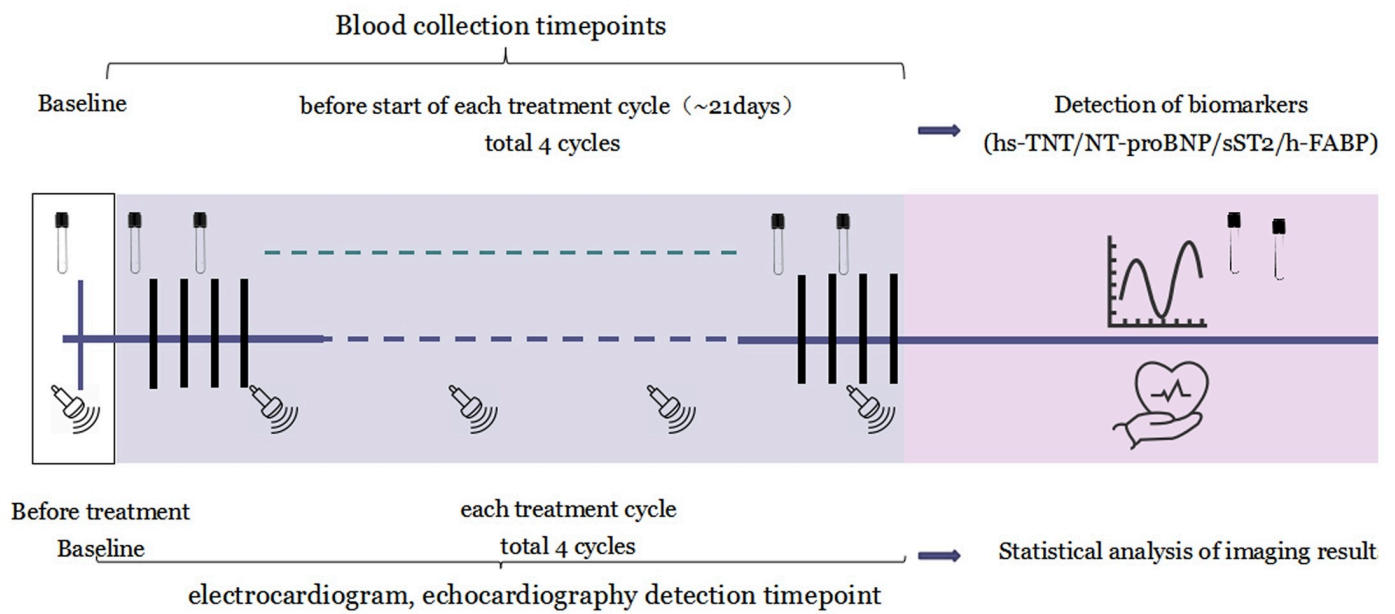


Figure 1

Timeline and analysis of blood draws according to cancer therapy regimen.

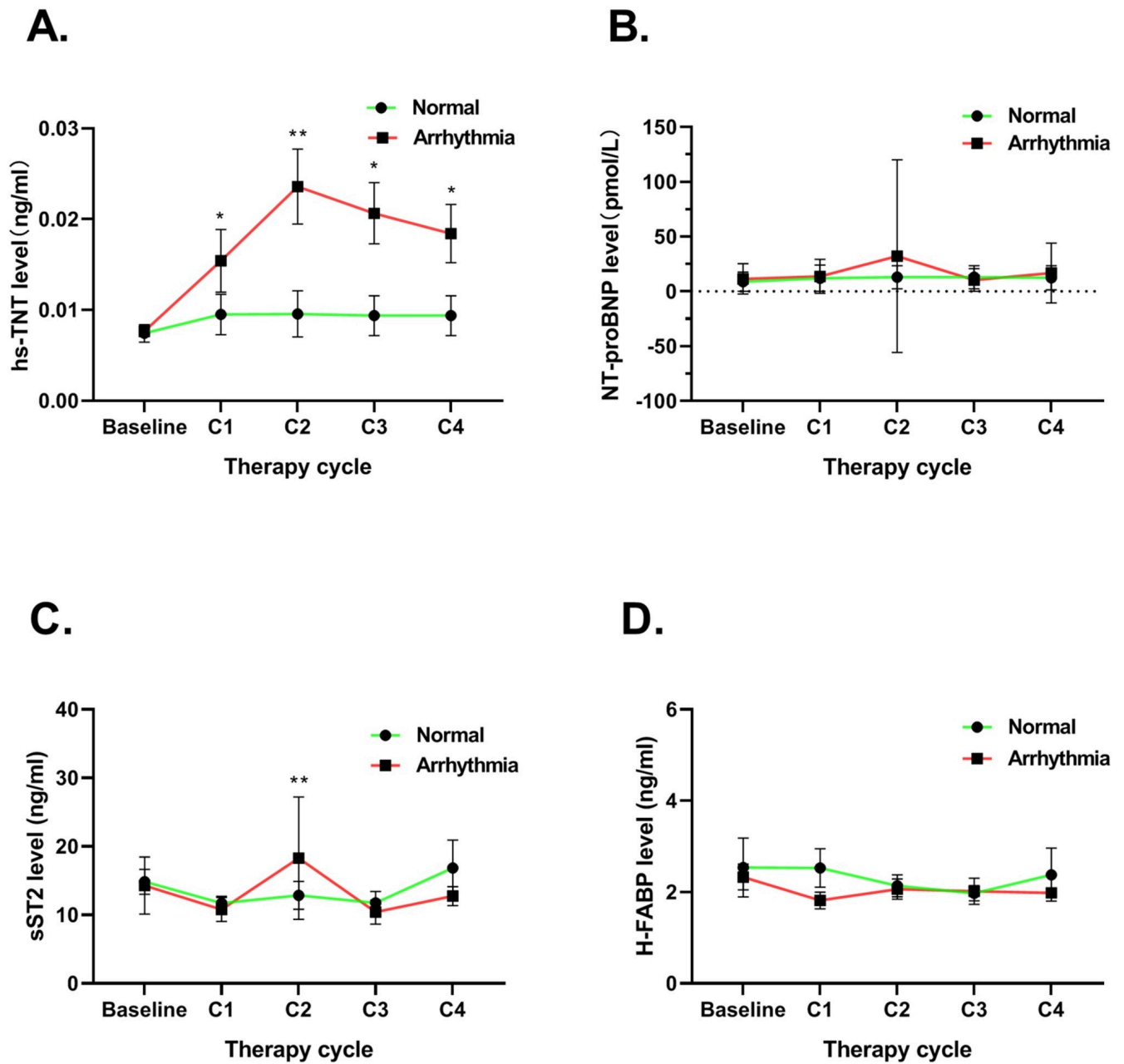


Figure 2

Mean estimated changes in biomarkers over time across the chemotherapy regimens. The red line represents mean estimated changes of biomarkers in arrhythmia group and the green line represents the changes of biomarkers in normal group; (A) high-sensitivity cardiac troponin T (hs-TNT), (B) N-terminal pro-B-type natriuretic peptide (NT-proBNP), (C) soluble suppression of tumorigenicity 2 (sST2), (D) heart-fatty acid binding protein (H-FABP). * $P < 0.05$; ** $P < 0.01$.

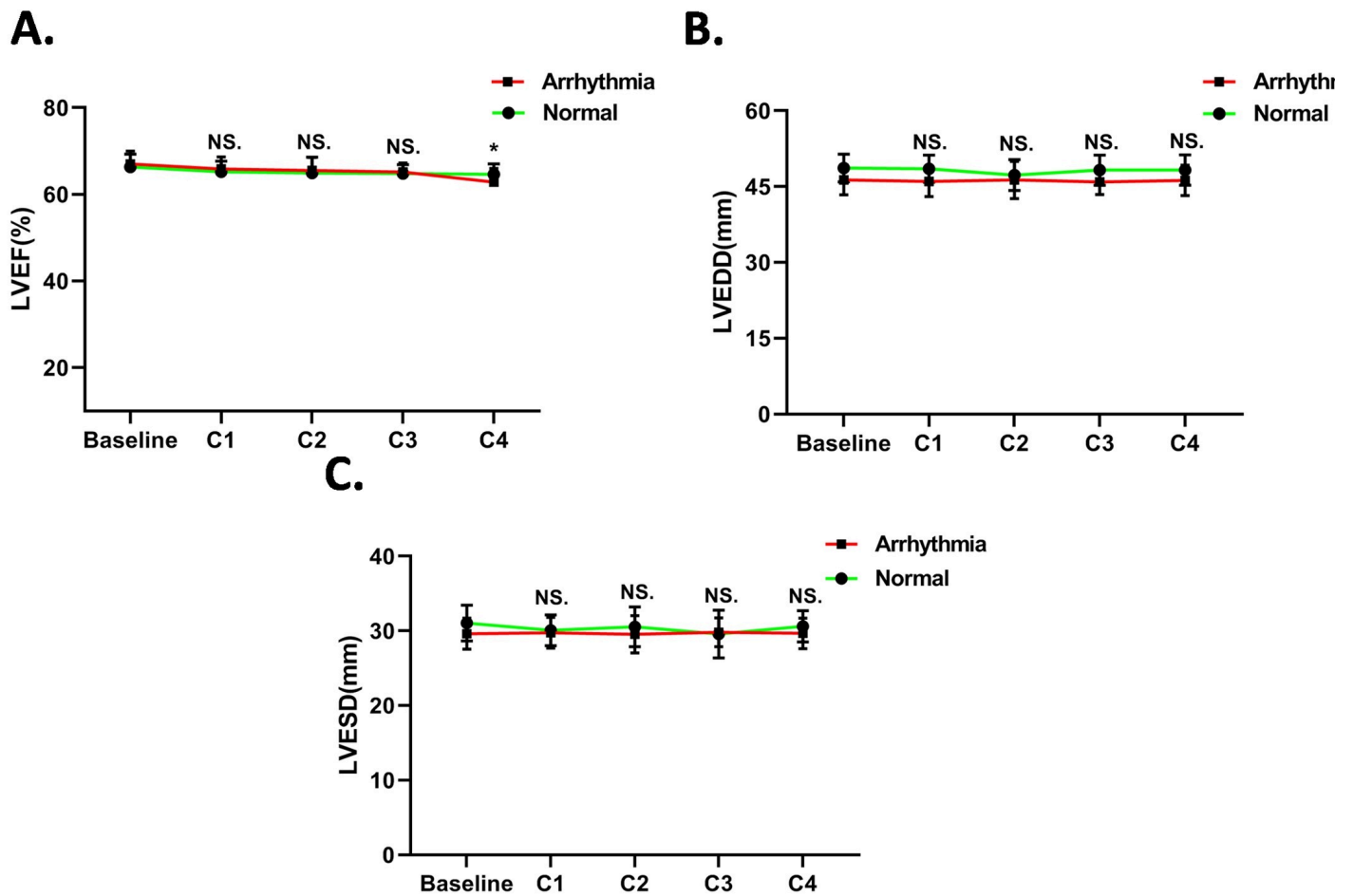


Figure 3

The parallel analyses of echocardiography data across the CHOP cycles. The LVEF(%) results of echocardiography at baseline and through the CHOP therapy cycles C1-C4 are monitored. (A) , LVEDD (mm) (B) and LVESD (mm) (C) results are analyzed .

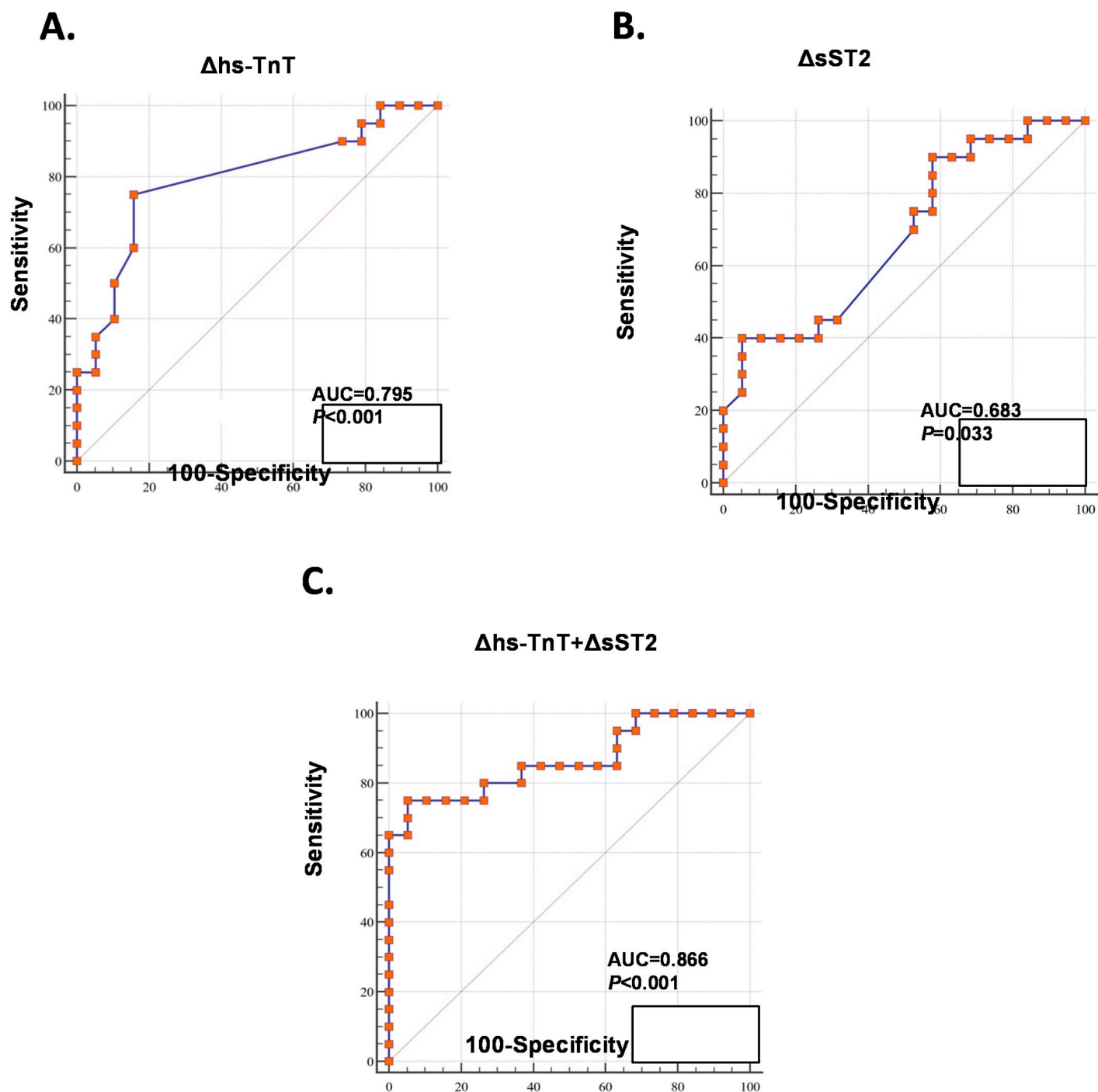


Figure 4

The area under the ROC curve (AUC) in predicting arrhythmia. ROC curve analysis of Δ hs-TNT/ Δ sST2 from baseline to C2 predicts the occurrence of arrhythmia. And the combining of Δ hs-TNT and Δ sST2 is also analyzed.