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Research Article

Increased levels of high-sensitive Troponin-T after first dose of Adriamycin containing therapy may predict brain-type natriuretic rise after 6 months in patients with breast carcinoma

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Abstract

Objective: In this study, we aimed to investigate the usefulness of highly sensitive troponin-T (hs-TnT) levels for the early prediction of anthracycline-related cardiac stress and subclinical cardiac dysfunction.

Method: Patients newly diagnosed with breast cancer with normal cardiac function were randomized to our study. All patients had taken 240 mg/m2 adriamycin in 12 weeks. Brain-type natriuretic peptide (BNP) and hs-TnT levels were measured; echocardiography and tissue Doppler imaging was performed to all patients for 4 times: at baseline, 4-12 hours after first adriamycin dose, at 3 months and at 6 months.

Results: A total of 43 women (52.7±12.1 years) with breast cancer were included in our study. Brain natriuretic peptide elevation was observed in 8 patients, in which 2 of them showed symptoms and signs of overt heart failure. In the logistic regression analysis, hs-TnT levels (OR: 1.154; (0.974–1.336 in 95% CI) and BNP levels (OR: 1.009 (1.001-1.018 in 95 % CI) measured 12–24 hours after first adriamycin dose were independently associated with BNP rise at 6th month. Receiver operating curve analysis revealed a cut-off value of 12.85 ng/L for hs-TnT levels to predict BNP elevation at 6th month with 62.5% sensitivity and 85.7% specificity.

Conclusion: hs-TnT levels after first dose of adriamycin containing therapy higher than 18.65 ng/L was associated with BNP elevation at 6th month with a specificity of 97.1% in our patient group. Early hs-TnT elevation may represent a potential marker of chemotherapy-related cardiac dysfunction.

Keywords: Anthracycline, cardiotoxicity, highly sensitive troponin T, Breast Cancer

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INTRODUCTION

Breast cancer (BC) is the most frequently observed neoplasm in women. It also accounts for 15 % of all cancer deaths and is the second cause of death due to malignant diseases after lung cancer (1). Surgical excision, cytotoxic chemotherapy (CC), hormone blockade therapy, radiotherapy and molecular therapy are effective options in the treatment of BC. Cytotoxic chemotherapy as adjuvant therapy and for metastatic disease is the most important component of BC treatment and improves survival (2).

Anthracyclines are frequently used in adjuvant setting and also in metastatic disease. In case of her2/neu expression, trastuzumab is added to therapy and has been shown to decrease relapse rate (3,4). However, cardiovascular (CV) toxicity is seen with these drugs, with increased risk of mortality and morbidity. However, toxicity profiles of these two drugs are different: anthracyclines cause permanent myocardial damage, while trastuzumab causes transient/reversible cardiac dysfunction (5,6).

Early detection of patients developing myocardial dysfunction is of paramount importance in patients undergoing systemic chemotherapy (7). Sequential imaging with echocardiography and serial measurement of some biomarkers are the most frequently used methods for detecting CV toxicity (8-10). Cardiac troponins have been found to be useful in early detection of chemotherapy induced cardiomyopathy (CIC) (7,9,11-13). However, standard assays underestimate small troponin elevations and high-sensitive assays are much better for detecting subtle elevations (14). On the other hand, data about reliability of high-sensitive troponin assays for predicting CIC are limited. In this study, we aimed to investigate the predictability of subtle troponin alterations after first dose of anthracycline chemotherapy, detected by high-sensitive assays to detect CIC in patients with BC treated by anthracyclines and/or trastuzumab.

METHODS

The study protocol was approved by the Çukurova University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee at its meeting dated 23.08.2013 (Meeting No: 22, Decision No: 7). The study was conducted at Çukurova University Faculty of Medicine with the participation of the Departments of Oncology, Cardiology, and Biochemistry. All procedures performed during the study were in accordance with the ethical standards of the institutional research committee and with the Declaration of Helsinki (15).

Patient Selection

Chemo-naïve patients newly diagnosed with breast cancer (BC) and admitted to our Oncology Department for systemic chemotherapy were prospectively enrolled in the study. All participants had normal baseline cardiac function.

A total of 43 patients were included in the study. Among them, 20 patients had HER-2 positive tumors. Patients without HER-2 overexpression (n = 23) received anthracycline-based chemotherapy consisting of doxorubicin and cyclophosphamide (AC). Patients with HER-2 positive disease received the same anthracycline-based chemotherapy regimen followed by trastuzumab according to institutional treatment protocols. During the study period, pertuzumab was not routinely available at our institution; therefore, HER-2–targeted therapy in this cohort consisted exclusively of trastuzumab-based regimens.

All patients received a standardized anthracycline regimen consisting of doxorubicin 60 mg/m² administered for four cycles, corresponding to a fixed cumulative dose of 240 mg/m². No patient received additional anthracycline cycles beyond this protocol.

Endocrine therapy was not administered during the chemotherapy period evaluated in this study. According to institutional treatment practice, endocrine therapy (tamoxifen or aromatase inhibitors) was initiated only after the completion of chemotherapy. Radiotherapy was not administered during the chemotherapy period evaluated in this study. According to institutional treatment protocols,

radiotherapy was planned only after completion of systemic chemotherapy when indicated.

Patients with significant anemia (hemoglobin <11 g/dL) or hypoalbuminemia (serum albumin <3.5 g/dL) were not included in the study. The overall performance status of the study population was good, with patients generally having ECOG performance status of 0–1.

At baseline, patients were comprehensively evaluated regarding disease stage, cardiovascular history, and physical examination findings. The presence of diabetes mellitus (DM), hypertension (HT), and tumor characteristics including estrogen receptor, progesterone receptor, and HER-2 status were recorded. Patients receiving systemic chemotherapy for either adjuvant or metastatic indications were eligible.

Renal function parameters were evaluated at baseline. No patient had advanced renal dysfunction (eGFR < 60 mL/min/1.73 m^2).

Standard 12-lead electrocardiography (ECG) was performed at baseline. During follow-up, ECG evaluation was performed when clinically indicated. No clinically significant arrhythmic events were recorded.

Table 1. Timing of visits evaluating cardiovascular function

Visit	Timing of the Visit
Screening Visit (0)	Before initiation of SC
First Visit (1)	4-12 hours after administration of first dose of SC
Second Visit (2)	After administration of fourth dose of SC
Third Visit (3)	At the sixth month of SC

SC: Systemic chemotherapy

Patients with a history of other malignancies, prior systemic chemotherapy or chest radiotherapy, structural heart disease, previous exposure to cardiotoxic agents, or baseline BNP levels ≥200 ng/L at screening were excluded from the study. No participant had documented coronary artery disease.

A screening visit was done for CV evaluation before treatment, which was followed by 3 more visits. The timing of visits is listed on Table 1. Patients were monitored for symptoms and signs of heart failure in each visit accompanied by transthoracic echocardiography (TTE) evaluation and measurement of biochemical markers. A combination of Adriamycin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) therapy was administered to all patients and repeated for four times with 21-day intervals. Additional chemotherapy with trastuzumab was administered to HER-2 positive patients.

Transthoracic Echocardiographic Evaluation

Patients have undergone TTE in each visit. Echocardiography was performed by General Electric Vingmed US System Vivid S5 device. Standard chamber dimensions were measured to evaluate cardiac function. Ejection fraction (EF) was calculated according to modified Simpson's method (16). We also measured trans-mitral early atrial filling (E) and atrial contraction (A) waves by pulsed wave (PWD) Doppler at a sweep speed of 50 mm/sec. Mitral annular early atrial filling (e'), atrial contraction (a') and ventricular contraction (s') velocities at the mitral leaflet insertion points of septal and lateral left ventricular walls were measured by using tissue Doppler imaging (TDI) (17). All of the measurements were done by taking the average measurement of three consecutive beats. E/A, E/e' and e'/a' ratios were calculated in each patient.

Laboratory Tests

A 5 mL venous blood sample was obtained from each patient at every scheduled visit. Blood samples were centrifuged immediately and the resultant plasma was stored at -70°C. High-sensitive troponin T (hs-TnT), brain natriuretic peptide (BNP) and high-sensitive C-reactive protein (hs-CRP) markers were analyzed in these plasma samples. Plasma hs-TnT and BNP levels were measured by electrochemiluminescence immuno-assay (ECLIA) via Roche Cobas e411 system, whereas hs-CRP levels were measured by nephelometry via Beckman Coulter IMMAGE system.

Statistical Analysis

Statistical analysis was performed by IBM SPSS system (SPSS Inc, Chicago, IL). Patients were stratified according to 6-month BNP levels. Although the initial study design aimed to identify anthracycline-induced cardiomyopathy through comprehensive evaluation including echocardiography and tissue Doppler imaging, the low incidence of overt clinical cardiomyopathy led us to define patients with BNP levels ≥200 ng/L as having biomarker-defined cardiac stress, reflecting subclinical cardiac dysfunction (SCD group) rather than established cardiomyopathy; the remaining patients were considered as controls. Importantly, BNP elevation was not used to define overt cardiomyopathy but rather as a surrogate marker of increased ventricular wall stress and subclinical cardiac dysfunction. Numeric variables with normal distribution were compared by t-Test, whereas numeric variables without normal distribution were compared by Mann-Whitney-U (MWU) Test. Categorical variables were compared by chi-square test. Logistic regression analysis was performed to observe independent impact of variables on plasma BNP elevation. Receiver operating curve (ROC) analysis was performed to determine the cut-off values of hs-TnT levels for predicting 6th month BNP elevation. A p value less than 0.05 was considered as statistically significant.

RESULTS

A total of 43 women with BC were included in this study. All patients completed the planned four cycles of anthracycline therapy; therefore, the cumulative doxorubicin dose was identical (240 mg/m^2) across the study cohort. Of these patients, 8 of them had BNP levels higher than 200 ng/L at the 6th month follow-up visit and 2 of these 8 patients showed signs and symptoms of clinical heart failure. The demographic variables, baseline laboratory measurements and echocardiographic data of both groups are listed on Tables 2 and 3. The SCD group was significantly older than controls. Also, hs-TnT levels were significantly higher in the SCD group before CC; however, the measured hs-TnT levels in both groups were below cut-off values.

Table 2. Demographic variables of both groups

Variable	SCD Group N=8	Controls N=35	p value
Age (years)	63.3±8.0	50.3±11.7	**.006**
Diabetes mellitus (N, %)	3 (37.5)	5 (14.3)	.153
Hypertension (N, %)	3 (37.5)	5 (14.3)	.153
Metastatic disease (N, %)	4 (50.0)	14 (40.0)	.447
ER Positiveness (N, %) 8 (100)		27 (77.1)	.162
PR Positiveness (N, %)	7 (87.5)	24 (68.6)	.407
HER-2 Positiveness (N, %)	6 (75.0)	14 (40)	.100
Trastuzumab Use (N, %)	6 (75.0)	14 (40)	.100

SCD: Subclinical Cardiac Dysfunction, ER: Estrogen receptor, PR: Progesterone receptor

Table 3. Laboratory and echocardiographic variables at baseline

Variable	SCD Group N=8	Controls N=35	p value
hs-TnT$_0$ (ng/L)	9.81±3.70	6.27±3.01	**.022**
BNP$_0$ (ng/L)	110.95±64.39	73.78±51.95	.132
hs-CRP$_0$ (mg/L)	0.67±0.66	0.74±1.18	.748
EF$_0$ (%)	64.75±2.71	65.14±2.56	.963
E$_0$/A$_0$	1.92±0.54	1.10±0.34	.748
E$_0$/e$_0$'	7.27±1.94	7.81±1.40	.317
s$_0$' (cm/sec)	9.0±1.5	8.4±2.0	.317

SCD: Subclinical Cardiac Dysfunction, hs-TnT: high-sensitive Troponin-T, BNP: brain natriuretic peptide, hs-CRP: high-sensitive C-reactive protein, E/A: Early filling to left atrial contraction velocity ratio, E/e': Transmitral to annular early filling velocity ratio, s': annular systolic contraction velocity

Table 4. Laboratory and echocardiographic variables 4-12 hours after first dose of anthracycline chemotherapy

Variable	SCD Group N=8	Controls N=35	p value
hs-TnT$_1$ (ng/L)	28.72±39.76	9.00±4.51	**.013**
BNP$_1$ (ng/L)	211.8±168.5	67.6±61.27	**.020**
hs-CRP$_1$ (mg/L)	0.83±0.49	0.91±1.53	.317
EF$_1$ (%)	63.4±1.5	65.40±4.0	.140
E$_1$/A$_1$	1.06±0.32	0.93±0.97	.471
E$_1$/e$_1$'	7.57±2.10	7.65±2.10	.890
s$_1$' (cm/sec)	8.7±1.9	8.8±2.1	.863

SCD: Subclinical Cardiac Dysfunction, hs-TnT: high-sensitive Troponin-T, BNP: brain natriuretic peptide, hs-CRP: high-sensitive C-reactive protein, E/A: Early filling to left atrial contraction velocity ratio, E/e': Transmitral to annular early filling velocity ratio, s': annular systolic contraction velocity

The laboratory and echocardiographic parameters measured 4-12 hours just after first dose of anthracyclin containing chemotherapy are listed on Table 4. High-sensitive troponin-T and BNP levels were found to be higher in the SCD group when compared with control group. However, the echocardiographic parameters seemed similar in both groups.

Measurement of biochemical and echocardiographic variables after 4th dose of anthracycline containing chemotherapy and at 6th month of CC are listed on Tables 5&6. Brain natriuretic peptide levels were significantly higher in the SCD group as expected, however hs-TnT levels showed no significant alteration between groups. At 6th month follow-up, EF and systolic annular s' wave parameters were significantly impaired in the SCD group.

We have performed logistic regression analysis to see the independent influences of age, DM, HT, hs-TnT$_0$, hs-TnT$_1$ and BNP$_1$ variables on 6th month BNP elevation in women undergoing anthracycline containing chemotherapy (Hoshmer-Lemeshow goodness of fit p= 0.787). Only the parameters measured 4-12 hours after first dose of chemotherapy, hs-TnT$_1$ (OR: 1.154 (0.974-1.336 in 95 % CI) and BNP$_1$ (OR: 1.009 (1.001-1.018 in 95 % CI) showed a trend toward association with BNP elevation at 6 months. In the ROC analysis (Figure 1), hs-TnT$_1$ levels above 12.85 ng/L predicted 6th month BNP elevation with a sensitivity of 62.5 % and a specificity of 85.7 %. Furthermore, values higher than a cut-off value of 18.65 ng/L, predicted 6th month BNP elevation with a specificity of 97.1 %.

Table 5. Laboratory and echocardiographic parameters after 4th dose of anthracycline chemotherapy			
Variable	**SCD Group N=8**	**Controls N=35**	**p value**
hs-TnT$_2$ (ng/L)	13.23±9.58	14.64±6.08	.302
BNP$_2$ (ng/L)	1047.61±2080.53	64.81±49.60	**.000**
hs-CRP$_2$ (mg/L)	0.70±0.81	0.73±0.46	.364
EF$_2$ (%)	64.38±2.07	65.00±3.08	.679
E$_2$/A$_2$	1.13±0.58	1.04±0.34	.988
E$_2$/e$_2$'	8.39±2.61	7.61±2.57	.381
s$_2$' (cm/sec)	8.5±2.4	8.7±1.7	.240

SCD: Subclinical Cardiac Dysfunction, hs-TnT: high-sensitive Troponin-T, BNP: brain natriuretic peptide, hs-CRP: high-sensitive C-reactive protein, E/A: Early filling to left atrial contraction velocity ratio, E/e': Transmitral to annular early filling velocity ratio, s': annular systolic contraction velocity

Table 6. Laboratory and echocardiographic parameters at 6th month of systemic chemotherapy.			
Variable	**SCD Group N=8**	**Controls N=35**	**p value**
hs-TnT$_3$ (ng/L)	17.58±6.74	17.91±14.73	.274
BNP$_3$ (ng/L)	2304.91±3587.60	74.46±54.23	**.000**
hs-CRP$_3$ (mg/L)	2.29±3.94	0.76±1.28	.093
EF$_3$ (%)	58.75±5.42	64.59±3.55	**.004**
E$_3$/A$_3$	1.03±0.58	1.09±0.45	.433
E$_3$/e$_3$'	8.75±3.51	8.34±3.69	.550
s$_3$' (cm/sec)	7.7±3.1	8.9±1.8	**.028**

SCD: Subclinical Cardiac Dysfunction, hs-TnT: high-sensitive Troponin-T, BNP: brain natriuretic peptide, hs-CRP: high-sensitive C-reactive protein, E/A: Early filling to left atrial contraction velocity ratio, E/e': Transmitral to annular early filling velocity ratio, s': annular systolic contraction velocity

Given the limited number of HER2-positive patients receiving trastuzumab in our cohort, a subgroup analysis according to trastuzumab exposure was not statistically powered and therefore was not performed. This issue is acknowledged as a limitation of the study.

DISCUSSION

In this prospective study, we aimed to evaluate the predictive value of subtle troponin elevations for the development of cardiac dysfunction in 43 women with breast cancer undergoing systemic chemotherapy. Importantly, the cumulative anthracycline dose was standardized in the study (240 mg/m^2 for all patients), which eliminates cumulative dose variability as a potential confounding factor in the assessment of chemotherapy-related cardiac dysfunction. Although oestrogen receptor positivity was common in our cohort, endocrine therapy was not administered during the chemotherapy period evaluated in this study. Therefore, the potential cardiovascular effects of aromatase inhibitors or tamoxifen could not have influenced the cardiac biomarker measurements or the development of chemotherapy-related cardiac dysfunction in this cohort. Radiotherapy is a well-recognized contributor to long-term cardiac morbidity in breast cancer, particularly in patients receiving left-sided chest irradiation. However, none of the patients in the present cohort received radiotherapy during the study period in which cardiac biomarkers were assessed. Therefore, radiotherapy exposure could not have contributed to the observed cardiac outcomes. Potential confounding factors known to influence BNP levels, such as severe anaemia, hypoalbuminemia, or poor performance status, were minimized in the present cohort. Patients with haemoglobin levels below 11 g/dL or serum albumin

levels below 3.5 g/dL were excluded, and the overall performance status of the study population was ECOG 0–1.

Only two patients developed clinical signs of heart failure at 6 months. However, eight patients (18.6%) demonstrated a significant increase in BNP levels at the 6-month follow-up. We demonstrated that even subtle elevations of hs-TnT measured shortly after the first dose of anthracycline-containing therapy were associated with subsequent BNP elevation in this cohort. Moreover, hs-TnT levels measured 4–12 hours after the first chemotherapy dose predicted 6-month BNP rise with high specificity at a cut-off value of 18.65 ng/L. In the present study, early hs-TnT elevation showed a trend toward association with BNP elevation at 6 months in logistic regression analysis (OR: 1.154, 95% CI: 0.974–1.366). Although this association did not reach conventional statistical significance, hs-TnT demonstrated discriminatory capacity in the ROC analysis. This finding suggests that early myocardial injury detected by hs-TnT may precede later BNP elevation and subclinical cardiac dysfunction. The lack of statistical significance in regression analysis may be related to the relatively small sample size of the study cohort.

An important limitation of the present study is the relatively small number of cardiotoxicity events. With only eight SCD cases, the statistical power for multivariable logistic regression analysis is limited. Therefore, the regression results should be interpreted as exploratory and hypothesis-generating rather than definitive.

Importantly, BNP elevation does not by itself establish a diagnosis of cardiomyopathy; rather, it reflects increased ventricular wall stress and may represent early or subclinical cardiac dysfunction. In the present study, BNP was therefore used as a surrogate biochemical marker to identify patients at increased risk of developing chemotherapy-related cardiac impairment, particularly in a setting where overt clinical heart failure was infrequent. This biomarker-driven approach reflects a shift from late-stage cardiotoxicity detection toward early identification of myocardial stress, which is increasingly emphasized in contemporary cardio-oncology practice.

Cardiotoxicity is one of the most important complications of anthracyclines and trastuzumab, two drug classes widely used in breast cancer treatment (18). Cardiotoxic reactions may occur in acute, subacute, or chronic forms (6). Patients are traditionally monitored with transthoracic echocardiography (TTE) during and after chemotherapy. However, left ventricular ejection fraction (EF) is relatively insensitive for detecting early myocardial injury. Since systolic function is often preserved in the initial stages, acute and subacute cardiotoxicity may remain undetected by conventional TTE. A reduction in EF typically becomes evident only after structural myocardial damage has already occurred. In this context, biomarker-based approaches such as BNP and hs-TnT may provide earlier insight into evolving myocardial stress and injury before overt systolic dysfunction develops (18).

Adding Doppler and tissue Doppler measurements to TTE examination increases the probability of predicting the occurrence of SCD in the acute and subacute phases. Impairment of diastolic function is observed prior to systolic deterioration (19). A number of studies have shown that reduction of E/A wave ratio, an indicator of impaired diastolic function might be observed in early stages after CC administration and this impairment is a significant predictor of emerging CIC (20-22). Tissue Doppler measurements allow us to demonstrate subtle changes in diastolic functions. Annular to tissue early diastolic filling wave ratio (E/e') is a very good indicator of diastolic filling pressures and its increase might be associated with diastolic dysfunction (17,23). In this study, we have observed some alterations in diastolic functions in the follow-up period. There was no significant difference between SCD group and controls in terms of diastolic function measurements.

However, certain methodological limitations should be considered when interpreting these echocardiographic findings. One such limitation of

the present study is the absence of global longitudinal strain (GLS) assessment. Although GLS is currently recommended in cardio-oncology guidelines as a sensitive parameter for the early detection of subclinical cardiac dysfunction, the present study was conducted before strain imaging had become widely implemented in routine clinical echocardiographic practice in many centers. Therefore, cardiac function in our cohort was evaluated using conventional echocardiographic parameters, including LVEF and Doppler-derived indices.

There are a number of biomarkers useful for prediction, diagnosis and prognosis stratification of cardiac damage. Cardiac troponins are gold standard markers for demonstrating cardiac damage in almost all clinical conditions, including CIC (24). Lipshultz et al have shown that Troponin-T elevation has occurred in 30 % of patients receiving anthracycline containing regimen for lymphoblastic leukemia, which was correlated with increased mortality (25). Sawaya et al studied patients with BC and stated that detectable hs-TnT assay along with decrease in myocardial strain rate at 3rd month of chemotherapy were the most important predictors of SCD development at 6 months (7). Subtle elevations have been observed after first daunorubicin dose in an animal model searching high-sensitive troponin rise in daunorubicin administration; whereas more significant elevations have been demonstrated after 5th and 8th administrations. These elevations seemed to occur with a peak between 4-6 hours after drug administration and declined after 24 hours (26). On the other hand, in a study conducted in long-term survivors of childhood cancers, Pourier et al didn't find a significant relationship between high-sensitive troponin levels and development of SCD in children whom have undergone anthracycline treatment with an 8.3 years follow-up (27). However, they compared the values measured in routine follow-up visits, not in samples collected in true time intervals after drug administration. In our study, we found a significant relationship between 6th month BNP elevation and subtle elevations of hs-TnT levels measured 4-12 hours after the first dose of anthracycline containing therapy. On the other hand, high-sensitive troponin levels were almost similar between both groups in the samples collected at our 2nd and 3rd visits; just like results of Pourier's study.

Natriuretic peptides are important markers for diagnosis and risk stratification of heart failure (28). Various studies have demonstrated that persistent BNP elevation is associated with left ventricular dysfunction in patients receiving anthracyclines (29-31). In our study, BNP levels were significantly increased in the SCD groups in all visits performed after drug administration as expected. Another marker important for risk stratification in this patient population, hsCRP, didn't show any significant difference in both groups in our study.

The most important limiting factor in our study is low number of patient population. Since we had limited number of patients, clinical heart failure occurred in only 2 of our patients. Because of this, we set up the primary endpoint as 6th month BNP elevation. Eight of our patients showed progressive BNP elevation in 6 months; whereas the BNP levels were stable in the others.

Another point to consider is that dual HER-2 blockade with pertuzumab was not routinely available during the study period at our institution. Consequently, patients with HER-2 positive disease received trastuzumab-based therapy only. The absence of pertuzumab should therefore be taken into account when interpreting the cardiac outcomes of this cohort.

Although some patients in our cohort had metastatic breast cancer, these cases were limited to bone metastases and did not represent extensive visceral tumour burden. Additionally, none of the patients demonstrated severe anaemia or clinically significant hypoalbuminemia that could independently influence BNP levels. Nevertheless, the inclusion of patients with different treatment intents (adjuvant, neoadjuvant, and metastatic settings) represents a potential source of heterogenity. Due to the relatively small sample size, subgroup analyses according to treatment intent were not

feasible and this should be considered a limitation of the present study.

In conclusion, early hs-TnT elevation following the first dose of anthracycline chemotherapy may help identify patients at risk of subsequent ventricular stress, as reflected by persistent BNP elevation. These findings suggest that early biomarker surveillance could play a role in detecting subclinical cardiotoxicity before the development of measurable systolic dysfunction or overt clinical heart failure. However, given the exploratory nature and limited sample size of the present study, these results should be interpreted cautiously. Larger prospective studies integrating biomarker kinetics with advanced imaging parameters and clinical outcomes are needed to confirm these findings and to establish a more comprehensive risk prediction model for chemotherapy-related cardiac dysfunction.

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Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article..

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Ethical Declaration

The study protocol was approved by the Çukurova University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee at its meeting dated 23.08.2013 (Meeting No: 22, Decision No: 7).

Is previously presented?

Portions of the data presented in this manuscript have been previously presented in scientific meetings. Part of the study was presented as a poster at the ESC Congress 2015 (London, UK, August 29–September 2, 2015). Additionally, some of the data were presented as an oral presentation at the 18th International Eastern Mediterranean Family Medicine Congress (April 25–28, 2019).

These presentations represent preliminary dissemination of the data, and the current manuscript includes a more comprehensive analysis and full dataset

Is drived from thesis?

This manuscript is derived from the author's medical specialty thesis entitled "Prospective Evaluation of Cardiotoxicity Using Serological and Non-Invasive Methods in Patients Receiving Antineoplastic Chemotherapy", completed at Çukurova University Faculty of Medicine as a medical specialty thesis in 2015.

Authorship Contributions

Concept: CEC, SP, Design: OS, AIC, CEC, MD, Supervising: MD, SP, Financing and equipment: MBK, AC, Data collection and entry: OS, Analysis and interpretation: SM, AIC, MBK, AC, Literature search: SP, OS, CEC, Writing: OS, CEC, Critical review: OS, SP, CEC

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