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**Elevations of High-Sensitive Cardiac Troponin T and N-Terminal Pro-Hormone Brain
Natriuretic Peptide Levels in the Serum Can Predict the Development of Anthracyclines-Induced
Cardiomyopathy**

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Abstract

Background: Anthracyclines remain the cornerstone of the treatment in many cancers including lymphomas, leukemia and sarcomas, and breast cancer. The cardiomyopathy that develops from anthracyclines can lead to heart failure and decreased survival. Multiple mechanisms are involved the pathophysiology of anthracycline-induced heart failure.

Study Question: We hypothesise that anthracycline induced-cardiac (AIC) pathology can be monitored using a panel of blood biomarkers including High-Sensitive Cardiac Troponin T (hs-cTnT) for myocytes necrosis, and N-Terminal Pro-Hormone Brain Natriuretic Peptide (NT-proBNP) for parietal stress.

Study Design: A prospective, institutionally-approved study recruited all cancer patients scheduled to start anthracycline chemotherapy in the Transilvania University cancer clinics.

Measures and Outcomes: Transthoracic 2D echocardiography (2D-ETT) and the measurements of NT-proBNP and hs-cTnT plasma levels were performed at the beginning of the study, and 3 months and 6 months after anthracycline treatment initiation.

Results: The plasma levels of hs-cTnT at 3 months ($\rho = 0.439$, $p = 0.0001$) and 6 months ($\rho = 0.490$, $p = 0.0001$) are correlated with AIC occurrence. For a cut-off value of hs-cTnT at 3 months > 0.008 ng/ml we obtained 66.7% sensitivity, 67.9% specificity for developing AIC at 6 months, with a 54.5% positive predictive value and a 87.8% negative predictive value. The NT-proBNP serum levels at 3 months ($\rho = 0.495$, $p = 0.0001$) and 6 months ($\rho = 0.638$, $p = 0.0001$) are correlated with an AIC diagnosis at 6 months. For a cut-off value of NT-proBNP at 3 months > 118.5 pg/ml we obtained 80% sensitivity and 79.2% specificity for evolution to AIC at 6 months, with 52.2% positive predictive value and 93.3% negative predictive value.

Conclusions: In anthracycline-treated cancer patients, the increase in plasma levels of NT-proBNP and of hs-cTnT can predict the development of anthracycline-induced cardiomyopathy. Early identification of at-risk patients will potentially allow for targeted dose-reductions and will diminish the number of patients developing cardiac pathology.

Keywords: anthracycline-induced cardiomyopathy, high-sensitive cardiac troponin T (hs-cTnT), and N-terminal pro-hormone Brain Natriuretic Peptide (NT-proBNP)

ARTICLE

Background:

The recent reduction in cancer mortality and the constant increase in the number of cancer survivors represent a significant achievement. However, many of the cancer treatments have significant side-effects which can impact the quality and quantity of cancer survivorship. The quality of life depends equally by the established treatment, by its quality, as well as by the way in which it ensures the treatment compliance correlated to the communication of information about the disease.¹⁻³

Anthracycline chemotherapeutic drugs (doxorubicin, epirubicin, daunorubicin, idarubicin, etc) remain the cornerstone of treatment in many malignancies including lymphomas, leukemia and sarcomas, and breast cancer. However, the anthracycline treatment can cause cardiomyopathy, arrhythmias, heart failure and decreased survival.⁴⁻⁶ The cardiac dysfunction can occur acutely (during chemotherapy) and chronically with early-onset (during the first year of treatment) or late-onset (later than a year after the chemotherapy was completed).⁷⁻⁹

Clinical trials used various definitions for anthracycline-induced cardiomyopathy, which did not take into account subclinical myocardial impairment, as it can be detected by myocardial biopsy or advanced imaging techniques such as echocardiogram with myocardial deformation study and/or magnetic resonance. The ACC/AHA/ASE guide and The Task Force for Cancer Treatments and Cardiovascular Toxicity of the European Society of Cardiology defined anthracycline-induced cardiomyopathy as an impairment of the LV ejection fraction (LVEF) below 50%, or over 10% in comparison with the pre-treatment value.¹⁰⁻¹² The consensus of the American Society of Echocardiography and the European Association of Cardiovascular Imaging defined anthracycline-induced cardiomyopathy by a decrease in the LVEF of >10% or to a value < 53% in comparison with the pre-treatment value.¹³

Multiple mechanisms are involved the pathophysiology of anthracycline-induced heart failure including inflammation, ventricular remodeling, myocytes necrosis and parietal stress. These pathological processes can be monitored using a panel of blood biomarkers such as hs-cTnT for myocytes necrosis, NT-proBNP for parietal stress or growth/differentiation factor 15 (GDF 15) for inflammation.

Study Question:

The mechanisms of troponin release after chemotherapy are not fully elucidated. In patients with anthracycline-induced cardiomyopathy, the percentage of patients with increased serum level of troponin increases proportionally with the number of chemotherapy treatments performed and confirms the relationship between the cumulative anthracycline dose and the risk of cardiac toxicity.¹⁴ BNP and NT-proBNP are emerging as potential biomarkers for diagnosing and monitoring anthracyclines-induced cardiotoxicity and some oncological centers have recently started to include the natriuretic peptides in the cardiovascular monitoring protocols in patients treated with anthracyclines¹⁵. The utility of NT-proBNP and hs-cTnT to predict which patients will develop anthracycline-induced cardiomyopathy is not established, and constitute the topic of our current research.

Study Design:

This was a prospective study, which enrolled consecutive cancer patients that were prescribed anthracyclines as a treatment for their oncological disease. The local Ethics Committee has reviewed and approved the study protocol and each patient has signed the informed consent.¹⁶⁻¹⁸ Study eligibility criteria included: adult age (18 years or older), planned anthracycline treatment, no history of coronary disease, and a LVEF >50%. The anthracycline-induced cardiomyopathy was diagnosed using the recommended gold standard methodology (LVEF decrease below the value of 50% or with >10% units

in comparison with the initial value)¹⁰⁻¹², in absence of any other causes for the cardiac dysfunction except for anthracycline treatment.

We have collected demographic data, cardiovascular risk factors and personal medical history data during the enrolment visit. A transthoracic 2D echocardiography (2D-ETT) study and measurements of NT-proBNP and hs-cTnT plasma levels were performed at the initial visit and after 3 months and 6 months of treatment. The cardiovascular risk factor's treatment was prescribed in order to achieve and maintain the 'therapeutic targets' in conformity with the estimated cardiovascular risk for each patient on the SCORE risk charts.¹⁹

Measures and Outcomes:

Methods. LVEF was calculated by echocardiography using the Simpson modified biplane method which, although not as sensitive as MRI or myocardial scintigraphy, is a cost-effective, accessible and widely used method in current practice in many countries. The transthoracic 2D echocardiography has been performed on an ALOKA Prosound SSD-4000SV ultrasound machine. The NT-proBNP and hs-cTnT plasma levels were determined using an electro-chemiluminescence immunoassay (ECLIA) performed on a Roche Cobas e411 analyzer.

Statistical analysis. The statistical analysis was performed using the GraphPad InStat 3 and SPSS 20.0 softwares. The median value and the 25th and 75th percentiles for the variables with non-Gaussian distribution and the median value \pm standard deviation for those with Gaussian distribution are summarized. The nominal variables were expressed in percentage (%), and compared by Fisher test or X^2 . For the quantitative variables, the nonparametric Mann-Whitney test was applied for the variables with non Gaussian distribution and the t test with Welch correction was applied for those with Gaussian distribution. The assessment of the dynamics of LVEF values and of the plasmatic levels of

hs-cTnT and NT-proBNP at the start date, 3 and 6 months was performed with the Friedman nonparametric test. The Spearman correlation test was applied for the quantitative variables and the Chi-squared test for the nominal variables. Statistical significance was accepted as $p < 0.05$.

Results:

68 patients were enrolled in this prospective study, 27 men (39.7%) and 41 women (60.3%), with an average age 56.6 ± 10.2 years (limits of age 23 – 73 years). All the patients received doxorubicin, at a cumulative dose between 220 and 280 mg/m^2 up to 3 months and 420 – 500 mg/m^2 up to 6 months.

After 6 months of doxorubicin treatment, 15 patients (22.1%) were diagnosed with anthracycline-induced cardiomyopathy (group 1), and 53 patients (77.9%) (group 2) presented no LVEF decrease. There was no significant difference in the cumulative dose of doxorubicin between the two groups. The patients in group 1 were significantly older (62.5 ± 7.2 years versus 54.9 ± 10.4 years, $p = 0.009$). There was no significant difference in the estimated glomerular filtration rate between the patients in the two groups. The incidence of cardiovascular risk factors (arterial hypertension, diabetes mellitus, smoking, dyslipidaemia, obesity) and the medication use (angiotensin-converting-enzyme inhibitor/sartans, beta-blockers, diuretics, statins, and aspirin) did not differ between the two groups.

The LVEF values at baseline and at 3 and 6 months after the initiation of the anthracyclines treatment are summarized in Table 1. The plasma levels and the percentage increase of hs-cTnT during the 6 months follow up are shown in Table 2.

At enrolment, the plasma level of hs-cTnT has a median value of 0.0053 ng/ml in the whole study group (group 1 plus group 2, $n=68$ patients), 0.00713 ng/ml in group 1 and 0.00435 ng/ml in group 2 (no statistically difference between group 1 and group 2, $p = 0.0848$). After 3 months, the median value of hs-cTnT and respectively the percentage increase were significantly higher in the

group 1 versus group 2 [0.00998 ng/ml versus 0.00498 ng/ml ($p=0.0003$) respective 38.5% versus 0.6%, ($p=0.0001$)]. 6 months after the initiation of the anthracyclines treatment, the median value of hs-cTnT increased at 0.01006 ng/ml in the group 1 and at 0.00643 in the group 2 ($p = 0.0001$). The increase ratio of the hs-cTnT plasma level after 6 months as compared with the 3 months was 30% in the group 1 and 8.5% in the group 2 ($p = 0.0583$). The increase ratio hs-cTnT at 6 months in comparison with the baseline was 20% in the whole study group, and the increase in group 1 was significantly higher than in group 2 (107.5% vs. 17.3%, $p = 0.0001$). The plasma levels of hs-cTnT at baseline (before the anthracycline treatment) does not correlate to the occurrence of the anthracyclines-induced cardiomyopathy at 6 months ($\rho = 0.211$, $p = 0.083$). The plasma levels of hs-cTnT at 3 months ($\rho = 0.439$, $p = 0.0001$) and 6 months ($\rho = 0.490$, $p = 0.0001$) were correlated to the occurrence of the anthracyclines-induced cardiomyopathy.

The ROC curve analysis of the hs-cTnT values and the percentage increase during the 6 months of follow up is shown in Figure 1. Hs-cTnT levels at 3 months (AUC=0.806, 95% CI 0.665-0.946, $p=0.0001$) and 6 months (AUC=0.841, 95% CI 0.707-0.975, $p=0.0001$) as well as the percentage increase of hs-cTnT in the first 3 months (AUC=0.849, 95% CI 0.714-0.984, $p=0.0001$) and during 6 months (AUC=0.839, 95% CI 0.695-0.983, $p=0.0001$) are predictors for the occurrence of anthracyclines-induced cardiomyopathy. The increased ratio of hs-cTnT between 3 and 6 months in comparison with the increase percentage in the first 3 months has a lower predictive value for occurrence of the anthracyclines-induced cardiomyopathy at 6 months (AUC=0.670, 95% CI 0.507-0.832, $p=0.046$). For a cut-off value of hs-cTnT at 3 months > 0.008 ng/ml we obtained 66.7% sensitivity, 67.9% specificity for evolution with anthracyclines-induced cardiomyopathy at 6 months, with 54.5% positive predictive value and 87.8% negative predictive value. For one percentage of increase of hs-cTnT value in the first 3 months $> 20\%$, the sensitivity was 80%, the specificity 81%, the

predictive positive value 54.5% and negative predictive value 93.5% for evolution with asymptomatic anthracyclines-induced cardiomyopathy at 6 months.

The plasma levels and the percentage increase of NT-proBNP during the 6 months follow-up are shown in Table 3. At the start of anthracyclines therapy, the plasma level of NT-proBNP had a median value of 78.8 pg/ml in the whole study group, 88 pg/ml in group 1 and 79 pg/ml in group 2 ($p = 0.6626$). After 3 months, in group 1 the median value of NT-proBNP levels was 121 pg/ml, significantly higher than 97.7 pg/ml in group 2 ($p = 0.0001$). The percentage increase of the NT-proBNP levels in the first 3 months of treatment with anthracyclines was 49.2% in group 1, significantly higher than 16.1% in group 2 ($p = 0.0009$). After 6 months from the initiation of anthracyclines treatment, the median value of NT-proBNP increased to 198 pg/ml in group 1 and 110 pg/ml in group 2 ($p = 0.0001$). The percentage increase for the NT-proBNP level at 6 months were similar with the 3 months values, 55.7% in group 1 and 8.2% in group 2 ($p = 0.0001$).

The serum level of NT-proBNP at 3 months ($\rho = 0.495$, $p = 0.0001$) and 6 months ($\rho = 0.638$, $p = 0.0001$) correlated to the occurrence of anthracyclines-induced cardiomyopathy at 6 months. The percentage of increase of the NT-proBNP in the first 3 months ($\rho = 0.406$, $p = 0.001$) and between 3 months and 6 months ($\rho = 0.524$, $p = 0.0001$) was correlated with the occurrence of anthracyclines-induced cardiomyopathy.

The ROC curve analysis of the NT-proBNP values and the percentage increase in the 6 months follow up is shown in Figure 2. Our data show that the serum levels of NT-proBNP at 3 months (AUC=0.845, 95% CI 0.891-0.997, $p=0.0001$) and at 6 months (AUC=0.944, 95% CI 0.707-0.975, $p=0.0001$) and the percentage increase of NT-proBNP in the first 3 months (AUC=0.782, 95% CI 0.663-0.902, $p=0.001$), and between 3 and 6 months (AUC=0.865, 95% CI 0.785-0.971, $p=0.0001$) are predictors for anthracyclines-induced cardiomyopathy at 6 months. For a cut-off value of NT-proBNP at 3 months > 118.5 pg/ml we obtained 80% sensitivity and 79.2% specificity for evolution to

anthracyclines-induced cardiomyopathy at 6 months, with 52.2% positive predictive value and 93.3% negative predictive value. For a percentage increase of NT-proBNP in the first 3 months > 25.5%, the sensitivity was 66.7%, and the specificity 62.2%, with 33.3% positive predictive value and 86.7% negative predictive value.

Prediction models at 3 months for the occurrence of anthracyclines-induced cardiomyopathy at 6 months used a logistic regression model which included the following independent variables: for NT-proBNP: plasma level > 118.5 pg/ml, percentage increase > 25.5%, plasma level > 118.5 pg/ml associated with percentage increase > 25.5%; for hs-cTnT: plasma level > 0.008 ng/ml, percentage increase > 20%, plasma level > 0.0008 ng/ml associated with percentage increase > 20%. The independent predictors at 3 months for the occurrence of anthracyclines-induced cardiomyopathy at 6 months were plasma level of NT-proBNP > 118.5 pg/ml (SE=0.813, 95% CI 0.021-0.512, p=0.005) and a hs-cTnT value > 0.008 pg/ml associated with percentage increase > 20% (SE=0.884, 95% CI 0.012-0.376, p=0.002).

Discussion:

Carefully selected and validated plasma biomarkers can detect early myocardial impairment, and could represent an alternative diagnosis paradigm in order to predict and monitor left ventricle dysfunction.²⁰ Cardiac troponins are released in circulation when the myocytes membrane integrity is lost. In case of anthracyclines-induced cardiotoxicity, the increased troponins levels show myocardial injury without relation with myocardial ischemia.²¹ The plasma level of NT-proBNP is useful in differentiation of cardiac or non-cardiac causes of dyspnea²² and has prognosis value in patients with chronic heart failure.^{23,24}

In our study, at the enrolment time there were no significant differences of median values of hs-cTnT and respectively NT-proBNP between the patients that developed anthracyclines-induced cardiomyopathy (group 1) and the ones that did not (group 2). The plasma levels of hs-cTnT and NT-proBNP progressively increased in patients with anthracyclines-induced cardiomyopathy both 3 and 6 months after the start of anthracyclines treatment. The percentage increase of hs-cTnT and respectively NT-proBNP was significantly higher in the patients which developed anthracyclines-induced cardiomyopathy. The independent predictors at 3 months for the occurrence of asymptomatic anthracyclines-induced cardiomyopathy at 6 months were plasmatic level of NT-proBNP > 118.5 pg/ml and hs-cTnT value > 0.008 pg/ml associated with percentage increase > 20%.

The use of cardiac troponins as biomarkers of anthracycline cardiotoxicity was assessed in several clinical trials which included a total number of 1500 adult patients.²⁵⁻³⁴ Most of the clinical trials have reported that increased levels of cTnI are predictive for the occurrence of anthracyclines-induced cardiomyopathy.³⁵⁻³⁷ During last years, the clinical trials in which the cTnI was determined by ultrasensitive techniques, reconfirmed that cTnI is a biomarker of cardiotoxicity.^{35,38} The increase cTnI level in patients receiving anthracyclines treatment has proved to be predictive for occurrence of anthracyclines-induced cardiomyopathy²⁸, for clinically significant cardiovascular events²⁸ and is a useful indicator for starting the treatment of cardiac dysfunction with converting enzyme inhibitors and beta-blockers.^{39,40}

The use of new ultrasensitive techniques for determining extremely small amounts of cTnI has validated the value of hs-cTnI as a biomarker for anthracyclines cardiotoxicity.³⁵ The hs-cTnI levels can identify the patients with a low risk of occurrence of anthracyclines induced cardiomyopathy.²⁸ Quantification of cTnI levels by high sensitivity techniques concomitantly with advanced imaging measurements of cardiac dysfunction using modern echocardiography type 'spackle tracking'

techniques and tissue Doppler echocardiography demonstrated that the increase of hs-cTnI level and the decrease of longitudinal 'strain' $\leq 19\%$ at 3 months are predictors for LVEF decrease at 6 months.⁴¹

The previous published studies had a number of potential limitations, which limit their application in clinical practice. Despite the availability of several laboratory methods, the limit values of troponins is defined by the analytic precision at 99%.⁴² In addition, the collection protocol for the samples used in the previous studies was not homogenous⁴³, and the increase of troponin concentration was detected at different time intervals after the chemotherapy administration⁴⁴, which makes the data hard to generalize and implement. Finding an unequivocal cut-off value for the plasma troponins that detects the early myocardial injury induced by chemotherapy – as we did in our study- increases the clinical usefulness of blood cardiac markers in monitoring and adjusting the anthracyclines chemotherapy and prevents severe cardiac toxicity.

Based on our data (as well as on previous published research), we suggest that troponins must be included in both the dose-adjustment protocol for anthracyclines during the active treatment phase and the follow-up protocol for the cardiotoxicity effects of anthracyclines. Increased troponin levels predict the occurrence of the significant dysfunction of the left ventricle at least 3 months in advance²⁵⁻³⁴; and the early increase in troponins predicts the severity of ventricular dysfunction in the future^{35,39}; patients with persistent increased troponins for 1 months after the last series of chemotherapy have 85% probability of major cardiac events in the first year^{39,45} while patients with persistent decreased values of troponin have a low risk of cardiotoxicity in the first year after stopping the chemotherapy.^{39,45}

The utility of natriuretic peptides as markers for the anthracyclines-induced toxicity has been investigated in a limited number of trials. Some of these studies suggested that the natriuretic peptides could be valuable in predicting cardiotoxicity. A significant increase of BNP/NT-proBNP is measured after high doses of chemotherapy prior to bone marrow transplant, and the persistence of high levels

after chemotherapy has been associated with the development of cardiac dysfunction during the follow-up period.⁴⁶⁻⁵¹ On the other hand, studies that used the natriuretic peptides for anthracyclines-induced cardiomyopathy detection reported limited clinical utility.⁵²⁻⁵⁴ The published data are heterogeneous and often incomplete because important information are missing, such as: the percentage of patients with increased values of the natriuretic peptide, the laboratory methods used for determining the plasma levels and the cut-off values associated with the best diagnosis accuracy. In addition, only a few studies have evaluated the predictive value of the natriuretic peptides in detecting the anthracyclines-induced cardiac dysfunction. Although early promising data are becoming available, more research is needed in order to support routine use of the natriuretic peptides for the early detection of the cardiotoxicity.⁵⁵

In the '*Cardiovascular side effects of cancer therapies: a position statement from the Heart Failure Association of the European Society of Cardiology*' is stated that special attention should be paid prior to the initiation of cardiotoxic chemotherapy in patients with coronary disease and arterial hypertension, and these co-morbidities should be carefully managed prior to and during the anthracyclines treatment. Regular cardiovascular examinations should be part of routine care in patients receiving potentially cardiotoxic drugs, during and after chemotherapy. The identification and validation of reliable biomarkers for the prediction and detection of anthracycline cardiotoxicity remains an urgent, yet unfulfilled need.⁵⁶

Conclusions: In the early asymptomatic anthracycline-induced cardiomyopathy, the absolute plasma levels of NT-proBNP increased in association with the absolute plasma levels of hs-cTnT and preceded the pathognomonic left ventricular ejection fraction decrease. 3 months after anthracycline treatment initiation, the plasma levels of NT-proBNP and the plasma levels of hs-cTnT (absolute values and ratios) are predictors for developing anthracycline-induced cardiomyopathy at 6 months.

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Table 1: LVEF values (%)

LVEF (%)	Study group (n=68)	Group1 (n=15)	Group 2 (n=53)	p
Baseline (%)	60.1 (55;63)	61.5 (54.5;64.5)	60.1 (55.8;63)	0.8417
After 3 months of treatment (%)	57.9 (55.4;59.9)	54.3 (51.4;58.3)	58.2 (55.7;61)	0.0002
After 6 months of treatment (%)	55.6 (50.9;59)	49.1 (48.3;49.7)	56.2 (54.7;60.6)	0.0001
LVEF = left ventricle ejection fraction; data expressed as median and percentile 25 and 75				

Table 2: The plasma levels and the percentage increase of hs-cTnT during the 6 months follow up

Parameter	Study group (n=68)	Group 1 (n=15)	Group 2 (n=53)	p
hs-cTnT baseline (ng/ml)	0.00530 (0.00395;0.00748)	0.00713 (0.00430;0.00787)	0.00435 (0.00381;0.00748)	0.0848
hs-cTnT at 3 months (ng/ml)	0.00640 (0.00401;0.00937)	0.00998 (0.00737;0.01354)	0.00498 (0.00387;0.00830)	0.0003
Percentage increase of hs-cTnT at 3 months	6.7% (-3%; 30. 3%)	38.5% (27. 9%; 80. 8%)	0.6% (-8. 1%; 14. 5%)	0.0001
Hs-cTnT after 6 months (ng/ml)	0.00785 (0.00467; 0.01150)	0.01006 (0.01006; 0.01620)	0.00643 (0.00442; 0.00920)	0.0001
Increase percentage of hs-cTnT between 3 and 6 months	10.7% (2.5%; 32.1%)	30% (8.2; 54.6)	8.5% (1.4%; 27%)	0.0483
Increase percentage of hs-cTnT between baseline and 6 months	20% (10.3%; 77.6%)	107.5% (66.4%; 151.8%)	17.3% (6.85%; 41.7%)	0.0001
Hs-cTnT= T cardiac troponin evaluated through high sensitivity techniques. Data expressed as median and percentiles 25 and 75.				

Table 3: The plasma levels and the percentage increase of hs-cTnT during the 6 months follow- up

Parameter	Study group (n=68)	Group 1 (n=15)	Group 2 (n=53)	p
NT-proBNP level at baseline	78.8 (58.5; 96.4)	88 (56 – 100)	79 (60.5; 90.5)	0.6626
NT-proBNP level at 3 months (pg/ml)	99.6 (80.7;120.5)	121 (119.8;140.8)	97.7 (75.6; 111.8)	0.0001
Increase percentage of NT-proBNP in the first 3 months	20.8% (5.8%; 47.5%)	49.2% (20.3%; 116.5%)	16.1% (3.8%; 35.7%)	0.0009
NT-proBNP level at 6 months (pg/ml)	121.9 (89.4;134.9)	198 (132; 410)	110 (81.5; 125)	0.0001
Increase percentage of NT-proBNP between 3 – 6 months	11.4% (2.9%; 26.4%)	55.7% (21.3%; 232%)	8.2% (2%; 20.8%)	0.0001
Increase percentage of NT-proBNP between baseline and 6 months	35.1% (16.2%; 91.1%)	269.3% (79.7%; 396.2%)	23.5% (12.2%; 54.7%)	0.0001
NT-proBNP= N-terminal natriuretic peptide of type B .Data expressed as median and percentiles 25 and 75.				

Figure Legends

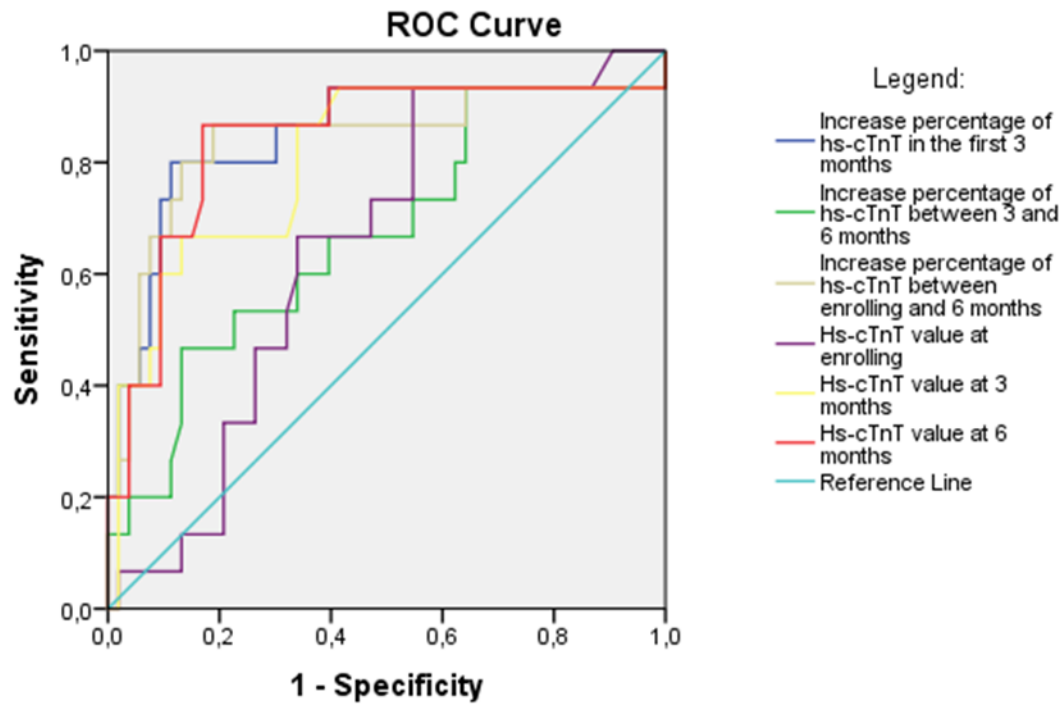


Figure 1: Receiver operating characteristic (ROC) curve analysis: Increased absolute levels and percentage increase of hs-cTnT can predict the development of anthracyclines-induced cardiomyopathy after 6 months of treatment.

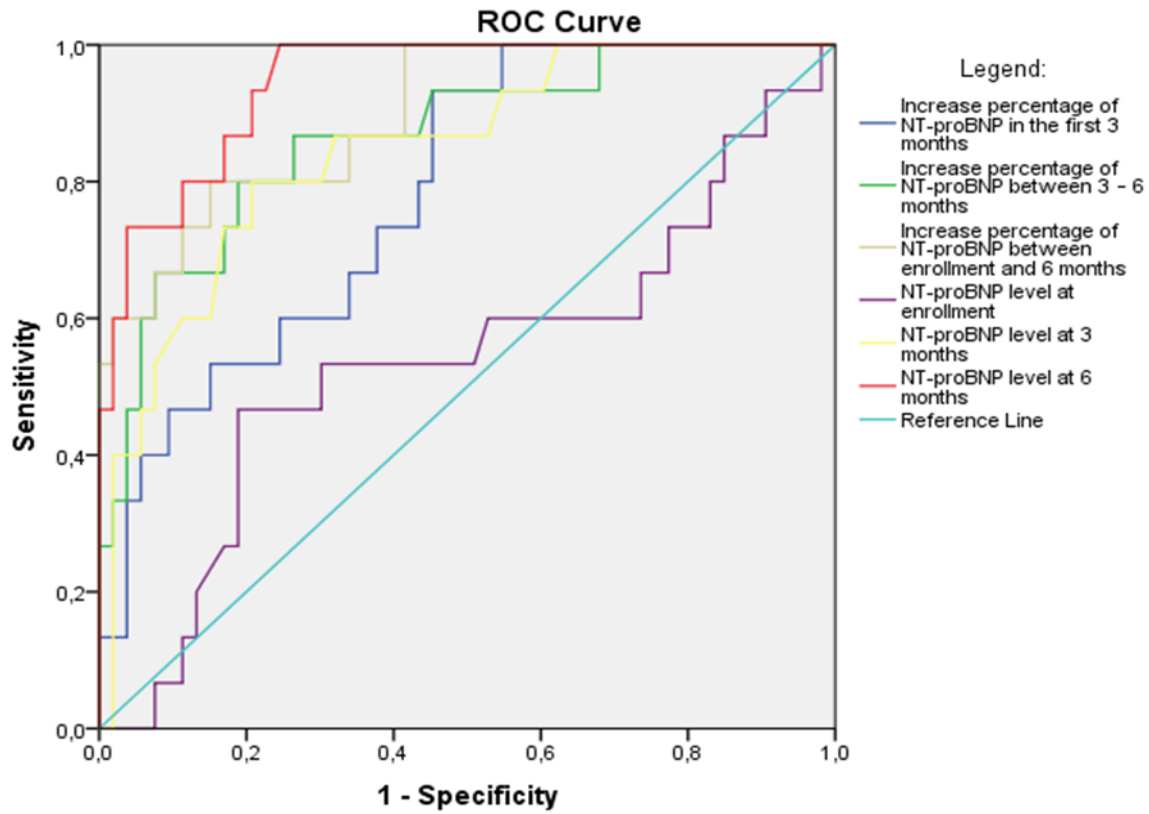


Figure 2: Receiver operating characteristic (ROC) curve analysis: Increased absolute levels and percentage increase of NT-proBNP can predict the development of anthracyclines-induced cardiomyopathy after 6 months of treatment.