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Efficacy of Novel Cardiac Biomarkers in Detecting Anthracycline-Induced Cardiac Toxicity

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ABSTRACT

Background: Anthracyclines can induce injuries to cardiac myocytes. Performance of echocardiography to detect Anthracycline Induced Cardiotoxicity (ACIC) for all patients under chemotherapeutic regimens is neither feasible nor cost-effective.
Objectives: This study aimed to investigate the changes in the serum levels of cardiac novel biomarkers after anthracycline usage to determine whether they are suitable candidates for screening or diagnosing ACIC.
Methods: In this pre-post study, patients without previous cardiovascular diseases who were candidates for chemotherapy with anthracyclines were recruited. The study was conducted on 30 patients selected through simple random sampling. Echocardiography and measurement of the serum levels of NT-pro Brain Natriuretic Peptide (BNP), soluble ST2, Galectin 3, and Growth Differentiation Factor-15 (GDF-15) were performed before chemotherapy and six months after the last session. ACIC was defined based on the echocardiographic criteria. Paired sample t-test was used to compare the biomarker levels. In addition, Receiver Operating Characteristic (ROC) curve was used to assess the specificity and sensitivity of the significant biomarkers in predicting the changes in Left Ventricular Ejection Fraction (LVEF).
Results: This study was conducted on 30 patients, 16 ones of whom had developed ACIC. The results revealed a significant increase in the serum levels of soluble ST2 (134.71 ± 60.46 vs. 137.49 ± 61.38, P = 0.011) and galectin 3 (6.82 ± 3.18 vs. 7.19 ± 3.29 ng/mL, P < 0.001) among the patients who had developed ACIC. ROC curve analysis showed that a soluble ST2 level ≥ 46.63 ng/ml could predict the occurrence of ACIC with 62.5% sensitivity and 100% specificity (AUC = 0.835, P < 0.001, NPV = 70%, PPV = 100%).
Conclusions: This was the first study, which simultaneously evaluated multiple biomarkers for the detection of ACIC. Among these biomarkers, only soluble ST2 demonstrated a promising ability for the detection of ACIC.

1. Background

Anthracyclines are frequently used for treatment of many malignancies (1), leading to an increase in survival rates. For instance, the 10-year survival rate for breast cancer increased from 40% in the 1970s to 78% in 2010 (2, 3). However, this family of antineoplastic agents has shown a serious side effect on cardiac myocytes. Anthracycline Induced Cardiotoxicity (ACIC) is dose-dependent and progressive (4). Although a cumulative dose of more than 300 mg/m2 has been found to be accompanied by the risk of ACIC, evidence has revealed that even a smaller dose could cause myocardial injury (1, 5). The Cardiac Review and Evaluation Committee (CREC) defined ACIC as a symptomatic decrease in the Left Ventricular Ejection Fraction (LVEF) more than 5% to lesser than 55% or a more than 10% decrease to lesser than 55% in asymptomatic patients (6, 7). However, the sensitivity of echocardiography is low for finding the early stages of cardiac damage, because cardiac remodeling can mask dysfunctional myocardial cells, causing the LVEF to stay within the normal range until the myocardial protecting mechanism fails to compensate (8).

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In the past decade, cardiac biomarkers were utilized to diagnose, monitor, and predict cardiac diseases (9). Accordingly, natriuretic peptides were found to be useful biomarkers to diagnose Heart Failure (HF), estimate the severity and prognosis, and possibly manage HF (10). In this context, the most commonly measured natriuretic peptides are B-type Natriuretic Peptide (BNP) and its amino-terminal cleavage pro-peptide equivalent, N-Terminal pro–B-type Natriuretic Peptide (NT-proBNP). Cardiomyocytes release these two biomarkers in response to wall stress (10). Soluble Suppression of Tumorigenicity-2 (sST-2) and Galectin-3 (gal-3) play an essential role in myocytes fibrosis, progressive cardiovascular dysfunction, remodeling, and death (11, 12). Wang et al. and de Boer et al. indicated that these biomarkers could predict future HF in asymptomatic patients with normal ranged BNP and EF (11, 12). The I myofibrillar component of troponin (TnI) has indicated cardiomyocyte damage and may be elevated in asymptomatic patients with early stages of HF (13)ÿþ. An elevated troponin level is an independent prognostic factor for the onset of HF and mortality rate in patients suffering from congestive HF (13). Growth Differentiation Factor-15 (GDF-15) is also an indicator of stress to the cardiac wall (12, 14). This biomarker can strongly predict the outcomes in patients with proven HF and even in asymptomatic patients with new-onset HF (12, 14).

2. Objective

Performance of echocardiography to detect ACIC for all patients under chemotherapeutic regimens is neither feasible nor cost-effective. Hence, the present study aims to investigate the changes in the serum levels of cardiac novel biomarkers after anthracycline usage to determine their suitability for screening or diagnosing ACIC.

3. Methods

3.1. Population

Patients suffering from breast cancer, lymphoma, leukemia, and other cancers who were candidate for receiving doxorubicin were recruited into this pre-post study using simple random sampling in 2018. These patients were referred by a hematologist to the cardiovascular clinic for baseline cardiovascular evaluation before starting the chemotherapy regimens. Patients with the history of previous cardiovascular diseases including coronary artery diseases, HF, and pulmonary hypertension as well as those who were unwilling or unable to participate were excluded, because these conditions could affect the serum levels of cardiac biomarkers (15-17). At first, a 24-subject sample size was estimated for the study. However, 30 patients were enrolled to compensate for the possible missed follow-up.

The survey was performed in compliance with the Declaration of Helsinki. In addition, all patients were required to sign written informed consent forms for taking part in the research and were ascertained about the confidentiality of their information. Ethical approval was also obtained from the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1399.166).

3.2. Echocardiography

A baseline Three-Dimensional Transthoracic Echocardiography (3D-TTE) was performed to evaluate the patients' cardiac structure, LVEF, and Global Longitudinal Strain (GLS). All patients were imaged in the left lateral decubitus position using the general electric E9 conventional echocardiography machine (GE, USA). In doing so, the transducer was placed in the left midclavicular line in the 4th to 5th intercostal spaces where the point of maximal impulses of the heart (PMI) was detected. All echocardiograms were analyzed by a specified reader. LVEF was calculated by the 3D-TTE probe from the apical 4-chamber view using an automated 3D protocol method. Speckle-tracking echocardiography was performed using the same machine. Displacement of the myocardial speckles in each spot was analyzed and tracked frame to frame. The longitudinal strain was assessed using Automated Functional Imaging (AFI). The global longitudinal peak strain was automatically calculated as an averaged value of the peak longitudinal strain in all 3-image planes (apical 2- and 4-chamber and long-axis views). The echocardiography was done by an authorized cardiologist who was blind to all other parts of the study. The TTE was repeated six months later immediately after the completion of the chemotherapy course.

3.3. Study Endpoint

Development of ACIC was considered as the endpoint and was defined based on the definition by the American Society of Echocardiography as more than 10% drop in LVEF, 15% drop in GLS, LVEF drop below 50%, GLS drop below -19%, or pathological rise in the troponin level.

3.3.1. Measurement of Biomarkers

Serum levels of NT-proBNP, sST2, gal-3, High-sensitive Troponin I (Hs-TnI), and GDF-15 were measured at baseline before chemotherapy and six months later immediately after the last chemotherapy session using Enzyme-Linked Immunosorbent Assay (ELISA) kits (bioassay technology laboratory, China).

3.4. Statistical Analysis

The normal distribution of the values was evaluated using Shapiro-Wilk test. Paired sample t-test was used to compare the biomarker levels. In addition, Receiver Operating Characteristic (ROC) curve was used to assess the specificity and sensitivity of the significant biomarkers in predicting LVEF changes. These tests were performed using the Statistical Package for Social Sciences (SPSS) software (IBM 23.0, SPSS Inc., Chicago, IL, USA), and $P < 0.05$ was considered statistically significant.

4. Results

4.1. Patients' Characteristics

This study was conducted on 30 patients aged 42.3 ± 10.6 years including five males (16.7%) and 25 females (83.3%). Among the patients, 20 (66.6%) were the new cases of breast cancer, four (13.4%) suffered from the new onset lymphoma, and six (20%) had other cancers. All patients received doxorubicin with a mean dose of 403.2 ± 101 mg/m2.

4.2. Echocardiography

The 3D-TTE revealed a significant drop in the mean LVEF from 58.78 ± 7.33% to 50.55 ± 7.07% after doxorubicin administration (P < 0.001) as well as a statistically significant decrease in GLS from 20.80 ± 1.79 to 19.04 ± 2.96 (P = 0.006). Totally, 16 individuals (group 1) met the CREC-ACIC definition and were classified as the ACIC group. Others did not meet the CREC-ACIC definition (control group).

4.3. Cardiac Biomarkers

According to the CREC-ACIC definition, 16 patients (26.7%) developed cardiotoxicity after doxorubicin administration (ACIC group). Paired sample t-test was used to compare the changes in the biomarkers before and after the chemotherapy regimen (Figure 1). The results revealed no significant changes in the levels of serum biomarkers before and after chemotherapy among the 14 patients without ACIC (control group). However, a significant increase was observed in the serum levels of sST2 (134.71 ± 60.46 vs. 137.49 ± 61.38, P = 0.011) and gal-3 (6.82 ± 3.18 vs. 7.19 ± 3.29 ng/mL, P < 0.0001) in the ACIC group. The changes in the serum levels of other biomarkers were not significant (Table 1).

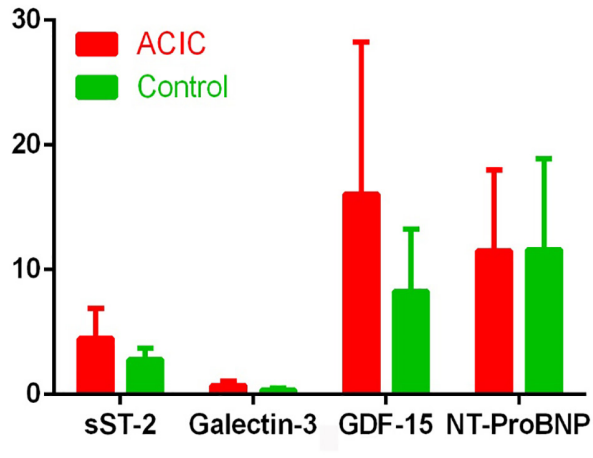
ROC curve analysis (Figure 2) for sST2 and gal-3 demonstrated that a gal-3 level ≥ 2.13 ng/mL could predict the occurrence of ACIC with 75% sensitivity and 57.12% specificity (AUC = 0.66, P = 0.11). An sST2 level ≥ 46.63 ng/mL could also predict the occurrence of ACIC with 62.5% sensitivity and 100% specificity (AUC = 0.835, P < 0.001, NPV = 70%, PPV = 100%).

5. Discussion

This was the first study evaluating multiple biomarkers for detection of ACIC. In this study, the behaviors of five novel cardiac biomarkers were investigated during treatment with anthracyclines. Among these biomarkers, only sST2 showed a promising ability for detection of ACIC.

ACIC is a growing problem; therefore, routine cardiac follow-ups and early detection are the cornerstones of avoiding irreversible complications (18). Although ACIC has been defined as a reduction in LVEF using echocardiography, this method lacks sensitivity to detect cardiotoxicity at early stages (8). Hence, the present study evaluated the changes in the serum levels of the five abovementioned biomarkers to determine whether they can detect ACIC.

Figure 1. Comparison of ACIC and Control Groups in Terms of Changes in Serum Biomarkers Revealed Significant Differences in all Biomarkers (P = 0.001), Except for NT-pro BNP.



ACIC, anthracycline-induced cardiomyopathy; sST-2, soluble suppression of tumorigenicity-2; Gal-3, galectin-3; GDF-15, growth differentiation factor-15; NT-proBNP, N-terminal pro brain natriuretic peptide.

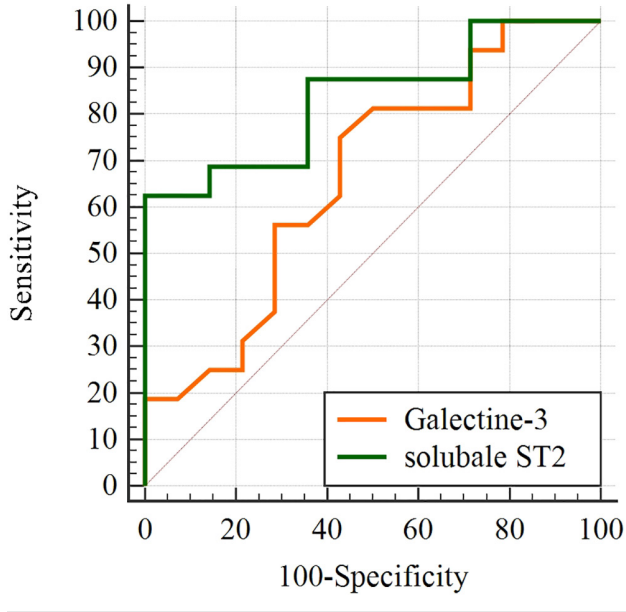


Figure 2. Receiver Operating Characteristic Curve Analysis Showing that an sST2 Level ≥ 46.63 ng/mL Could Predict the Occurrence of Anthracycline Induced Cardiotoxicity with 62.5% Sensitivity and 100% Specificity (AUC = 0.835, P < 0.001, NPV = 70%, PPV = 100%)

Table 1. Comparison of the Baseline and Final Values of the Serum Biomarkers in the Patinets Who Had Developed ACIC and Those Who Had Not

Group	Marker	Before	After	Change	P-value
ACIC	sST-2	42.72 ± 1.04	47.14 ± 1.05	4.48 ± 2.40	0.001*
ACIC	Galectin-3	1.61 ± 0.07	2.33 ± 0.1	0.72 ± 0.33	0.001*
ACIC	GDF-15	105.4 ± 5.85	121.69 ± 6.24	16.07 ± 12.17	0.002*
ACIC	NT-proBNP	299 ± 12.74	310.60 ± 11.23	11.50 ± 6.51	0.188
Control	sST-2	42.94 ± 0.368	43.76 ± 0.59	2.78 ± 0.93	0.023*
Control	Galectin-3	1.91 ± 0.07	2.11 ± 0.01	0.37 ± 0.11	0.020*
Control	GDF-15	108.64 ± 3.08	112.56 ± 3.39	8.26 ± 4.98	0.072
Control	NT-proBNP	305.75 ± 23.297	317.25 ± 24.93	11.60 ± 7.32	0.176

Abbreviations: ACIC, anthracycline-induced cardiomyopathy; sST-2, soluble suppression of tumorigenicity-2; Gal-3, galectin-3; GDF-15, growth differentiation factor-15; NT-proBNP, N-terminal pro brain natriuretic peptide. *P < 0.05

The prognostic effect of sST2 in different cardiovascular, pulmonary, liver, and other inflammatory and autoimmune diseases has been well established (19, 20). Multiple studies showed that increased serum levels of sST2 indicated more severe diseases and poorer outcomes in patients suffering from acute or chronic HF, regardless of the underlying causes (21-23). The present study findings also demonstrated that the mean serum level of sST2 significantly decreased in patients who fulfilled the CREC-ACIC definition. Up to now, a few studies have been conducted to specifically evaluate the effect of anthracycline on the serum level of sST2 (9). Yet, it is well known that other cardiac diseases leading to cardiac dysfunction may affect the serum level of this biomarker regardless of the cause. Thus, it lacks tissue and disease specificity (24). In contrast, the present study results showed that sST-2 had proper accuracy for diagnosis of ACIC (AUC = 0.835). Accordingly, the sST2 serum levels ≥ 46.63 ng/mL had 100% specificity and 62.5% sensitivity. Mueller et al. disclosed that an sST2 serum level ≥ 26.5 ng/mL had 76% sensitivity and 49% specificity in symptomatic patients (dyspnea) with HF (25). Hence, they believed that sST-2 did not have additive values in HF diagnosis in patients with dyspnea. These findings were inconsistent with those of the previous studies conducted by Gruson et al. and Pascual et al. who reported that sST-2 was associated with HF severity and outcome and had a higher discrimination power than NT-proBNP in the diagnosis of HF (26, 27). This heterogeneity might be due to different cut-off levels chosen for sST-2, sample size, differences in the underlying causes leading to HF, and whether the patients were symptomatic or not.

Multiple studies have confirmed the association between cardiomyocyte fibrosis and gal-3 serum level (9, 11). For instance, Tymińska et al. showed that gal-3 was an independent predictor of the development of HF after myocardial infarction (28). In a randomized controlled trial conducted by Felker et al., gal-3 could predict the long-term outcomes significantly and was associated with poor prognosis (29). However, these studies did not focus on the anthracyclines as the underlying cause of HF, and there is still controversy in the literature regarding the association between anthracyclines administration and HF development. The current study findings revealed a significant increase in the serum level of gal-3 in the group 1 participants who experienced a reduction in LVEF according to the CREC-ACIC definition. Therefore, this biomarker might play a role in the detection of ACIC. Similarly, Bulten et al. indicated that although there was a significant relationship between the serum level of gal-3 and abnormal echo features, this biomarker failed to predict early ACIC (30). Furthermore, Ky et al. and Feola et al. showed no significant relationship between the serum level of gal-3 and LVEF reduction in both short- and long-term follow-ups (6, 31). Although there was a significant increase in gal-3, the results of ROC curve analysis demonstrated that gal-3 did not have proper accuracy in the diagnosis of ACIC (AUC = 0.66, P = 0.11). To the best of our knowledge, few studies have been conducted to evaluate the diagnostic accuracy of gal-3 in ACIC. According to a study designed by Mueller et al., the diagnostic accuracy of gal-3 was low and it was not able to predict early ACIC (AUC = 0.57, P = 0.13) (25).

The changes in three other biomarkers (NT-proBNP, Hs-TnI, and GDF-15) were also assessed in the present study. The results revealed no significant relationships between these markers and changes in LVEF and GLS. There are still many controversies about the predictive values of these markers in ACIC and other causes of HF. Multiple studies have emphasized that NT-proBNP, Hs-TnI, and GDF-15 could be used to detect ACIC in early stages, while others have come to different conclusions (32-36).

This study had some limitations. Due to ethical considerations, cardiac biopsy as the gold standard was nor performed for detection of ACIC. Consequently, echocardiographic parameters were used for defining ACIC. This limited the power of the study to investigate whether these biomarkers could predict ACIC sooner than echocardiography. In addition, due to the used definition, there were a large number of cases with ACIC. Many studies have just used the criteria of more than 10% drop in LVEF. Considering only that criterion, only 14% of the patients in the control group could be defined as ACIC. Furthermore, an automated 4D echocardiographic method was employed to measure LVEF, which is the most accurate technique for performing this assessment. While numerous studies have only used 2D echocardiography, a more sensitive method was used in the present study for monitoring the changes in LVEF, which enhanced the researchers' ability to detect the ACIC cases.

5.1. Conclusion

In conclusion, this was the first study evaluating multiple biomarkers for detection of ACIC. Among these five markers, only sST-2 and gal-3 had a significant relationship with the changes in the echocardiographic parameters. According to the ROC curve analysis, just sST2 had the proper predictive accuracy for detecting ACIC within the first six months. This finding may raise the possibility of using this marker as a screening marker for ACIC. Yet, future studies are needed to determine whether this marker can help screen or even predict ACIC sooner than echocardiography.

5.2. Ethical Approval

The recent survey was performed in compliance with the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1399.166).

5.3. Informed Consent

All patients were required to sign written informed consent forms and were assured about the confidentiality of their information.

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Authors' Contribution

Study concept and design: A.A., acquisition of data: S.S.,

analysis and interpretation of data: S.S. and R.B., drafting of the manuscript: all authors, critical revision: all authors, statistical analysis: all authors, final approval: all authors.

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The authors have no financial interests related to the material in the manuscript.

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