

# Predictive value of soluble ST-2 for changes of cardiac function and structure in breast cancer patients receiving chemotherapy

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## Abstract

The current study was to evaluate soluble ST-2 level and left ventricular ejection fraction (LVEF) in patients with breast cancer receiving doxorubicin or trastuzumab treatment for 6 months and determine whether soluble ST-2 level can be used to predictive left ventricular function impairment.

Patients who were diagnosed as having breast cancer receiving doxorubicin or trastuzumab or combined therapy were enrolled. Demographic data, prior medical history and related medical therapy, and site and stage of breast cancer information were collected from electronic health record. Fasting blood was used to detect soluble ST-2 and brain natriuretic peptide (BNP) levels before and after 6 months doxorubicin or trastuzumab therapy. Echocardiography was performed before and after 6 months of doxorubicin or trastuzumab therapy.

Participants were divided into 3 groups based on tertiary soluble ST-2 level. Compared with 1st tertiary group, patients in the 3rd tertiary group had higher proportion receiving combined therapy (14.3% vs 4.7%,  $P < .05$ ). Baseline soluble ST-2 level was similar across groups. After 6 months' therapy, soluble ST-2 level was significantly higher in the 3rd tertiary group. Pearson correlation analysis showed that soluble ST-2 level was positively correlated with left ventricular volume and E/e' ratio while negatively correlated with LVEF. Doxorubicin, trastuzumab, combined therapy, soluble ST-2 level, and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker treatment were all independently associated with LVEF change.

In breast cancer patients receiving doxorubicin or trastuzumab therapy, soluble ST-2 level can be used to predict cardiac function and structure changes.

**Abbreviations:** ACEi/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, BNP = brain natriuretic peptide, CHF = congestive heart failure, ECG = echocardiography, LVEF = left ventricular ejection fraction, LVESD/LVEDD = left ventricular end systolic/diastolic diameter, LVESV/LVEDV = left ventricular end systolic/diastolic volume.

**Keywords:** breast cancer, cardiac function, soluble ST-2

## 1. Introduction

Doxorubicin and trastuzumab are commonly used to treat patients with breast cancer.<sup>[1-3]</sup> Nevertheless, prior studies have consistently demonstrated that both drugs are significantly associated with cardiomyocytes injury, which gradually leads to congestive heart failure (CHF), and the underlying mechanisms are due to oxidative stress elicited by doxorubicin treatment.<sup>[4,5]</sup> Trastuzumab is a monoclonal antibody that

targets the ErbB2 signaling pathway.<sup>[6]</sup> Notably, the ErbB2 signaling pathway is pivotal to protect cardiovascular system from injury induced by inflammation and oxidation.<sup>[7]</sup> Prior clinical studies have shown that approximately 9% to 26% of patients who had received doxorubicin treatment developed left ventricular dysfunction,<sup>[8,9]</sup> and around 13% of patients with trastuzumab therapy had incident left ventricular dysfunction.<sup>[10]</sup> In addition, the incidence of CHF with combined doxorubicin and trastuzumab therapy is up to 27%.<sup>[11]</sup> Both experimental and clinical data together strongly indicate that periodically assessing cardiac functional and structural change before and after doxorubicin or trastuzumab therapy could help detect and prevent CHF development in patients receiving doxorubicin or trastuzumab therapy.

ST-2, a member of the interleukin 1 receptor family, is a unique biomarker with pluripotent effects, which is believed to have effects on cell proliferation, inflammatory states, and oxidative stress.<sup>[12-14]</sup> Experimental studies also demonstrated that ST-2 is expressed by cardiac cells in response to myocardial stress. ST-2 that binds to interleukin-33 has been proved to be cardioprotective in experimental models, including reducing cardiomyocytes apoptosis, ameliorating cardiac fibrosis, and improving cardiac function.<sup>[12-14]</sup> Clinical studies have also shown that among patients presenting with acute dyspnea, baseline ST-2 level was positively associated with clinical markers of CHF severity, including left ventricular ejection fraction (LVEF) and NYHA functional classification.<sup>[15,16]</sup>

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Despite many studies that have demonstrated the independent association between doxorubicin and trastuzumab therapy and incident CHF, few studies have been conducted in the Chinese populations. In addition, whether the novel heart failure biomarker ST-2 can be used to predict cardiac functional and structural change post doxorubicin and trastuzumab therapy is unknown. Therefore, one may anticipate that assessing the soluble ST-2 in plasma may be helpful to identify minor injury of cardiac tissue in the initial stage, which in turn may help to prevent CHF development induced by doxorubicin and trastuzumab treatment.

Thus, the objective of current study was to evaluate the change of soluble ST-2 level and LVEF in patients with breast cancer receiving doxorubicin or trastuzumab treatment for 6 months and determine whether soluble ST-2 level can be used to predict left ventricular function impairment.

## 2. Methods

### 2.1. Studied design and participants enrollment

This was an observational and single-center study, and the present study was approved by the Clinical Research Ethical Committee of The First People's Hospital of Danzhou. Patients ( $\geq 18$  years old) who were diagnosed as having breast cancer receiving doxorubicin or trastuzumab or combined therapy were enrolled after informed consent was obtained. Those who were pregnant, had prior history of coronary heart disease, myocardial infarction, valvular heart disease, cardiomyopathy, baseline LVEF  $< 50\%$ , or symptomatic CHF was excluded.

### 2.2. Data collection

Demographic data, prior medical history and related medical therapy, and the site and stage of breast cancer information were collected from electronic health record by 2 independent investigators. Fasting blood was used to detect soluble ST-2 and brain natriuretic peptide (BNP) levels before and after 6 months doxorubicin or trastuzumab therapy. In brief, soluble ST-2 level was measured using a sandwich double monoclonal antibody ELISA method (Quantikine1 ELISA; R&D Systems, Minneapolis, MN) in accordance to manufacturer's instructions. The inter- and intra-assay variation was 6% and 5%, respectively. Echocardiography (ECG) was performed by an experienced cardiologist who was blinded to the patients' information before and after 6 months doxorubicin or trastuzumab therapy. Patients were placed in left lateral position, and left ventricular volumes from apical 4 and 2-chamber views were obtained through tracing the endocardia border of left ventricle using 2D transthoracic ECG and the machine automatically calculated LVEF using the biplane Simpson method.<sup>[17]</sup> Left ventricular end systolic/diastolic volume (LVESV/LVEDV), left ventricular end systolic/diastolic diameter (LVESD/LVEDD), and  $E/e'$  ratio were collected to evaluate structural change of left ventricle.

### 2.3. Studied endpoints

Studied endpoints of current study were used to evaluate the association of soluble ST-2 level and changes of LVEF. In addition, cardiac structures assessed by ECG were also compared before and after 6 months of doxorubicin or trastuzumab therapy.

### 2.4. Statistical analysis

Continuous variables were presented as mean  $\pm$  standard deviation (SD) if normal distribution otherwise presented as median (interquartile range), and categorical variables were presented as number (percentage) of cases. Differences between groups were analyzed for statistical significance with 1-way analysis of variance (ANOVA),  $\chi^2$  test, or Fisher exact test as appropriate. Correlations between soluble ST-2 level and left ventricular function and volume were assessed with Pearson correlation. Independent factors for LVEF change from baseline to 6 months' treatment were evaluated with the use of stepwise multiple linear regressions analysis. To be specific, we first used univariate regression analysis to evaluate the association between potential factors and LVEF change; thereafter, in the multivariate regression analysis, factors with  $P$  value  $< .2$  were entered into the model. Receiver operating characteristic curve (ROC) were performed to evaluate the sensitivity and specificity of soluble ST-2 in predicting LVEF change. All the statistical analyses were performed in the SPSS software (IBM 23.0 version, IBM. Co.) and a 2-sided  $P$  value  $< .05$  was considered as statistically significant.

## 3. Results

From July of 2016 to September 2017, a total of 175 patients diagnosed as having breast cancer were hospitalized and 146 patients agreed to participate in the current study. After exclusion of 20 patients, 126 patients were recruited in the current study and all of these patients finished 6 month's follow-up (Fig. 1).

### 3.1. Baseline characteristics comparison

All participants were divided into 3 groups on the basis of tertiary soluble ST-2 level at the 6th month follow-up. Baseline characteristics were compared between these 3 groups. As presented in the Table 1, compared with the 1st tertiary group, patients in the 3rd tertiary group had higher proportion receiving combined therapy (14.3% vs 4.7%,  $P < .05$ ) but had lower proportion receiving angiotensin-converting enzyme inhibitor/angiotensin receptor blocker [(ACEi/ARB), 16.7% vs 23.8%,  $P < .05$ ]. While no significant differences in other variables between these 3 groups were observed. Nearly 9.5% patients had bilateral breast cancer and around 50% patients had stage 3 and 4 breast cancer. In addition, more than 50% patients had radiotherapy in each group.

### 3.2. Comparison of cardiac function and structures

ECG was performed at baseline and 6 months follow-up to evaluate and compare the changes of cardiac function and structures. As presented in the Table 2, there was no significant difference in LVEF and cardiac structures and volume at baseline. However, after 6 months follow-up, compared with the 1st tertiary of soluble ST-2 level, LVEF was significantly reduced, while left ventricular structure and volume was significantly increased in the 3rd tertiary group ( $P < .05$ ). In addition,  $E/e'$  ratio, a marker of diastolic function,<sup>[18]</sup> was also significantly higher in the 3rd tertiary group, indicating that cardiac diastolic function in the 3rd tertiary group was significantly impaired.

### 3.3. Correlation of soluble ST-2 level and cardiac function and structures

As presented in the Table 2, baseline soluble ST-2 level in 3 groups was similar (1st tertiary group  $6.5 \pm 1.3$  ng/mL, 2nd tertiary group

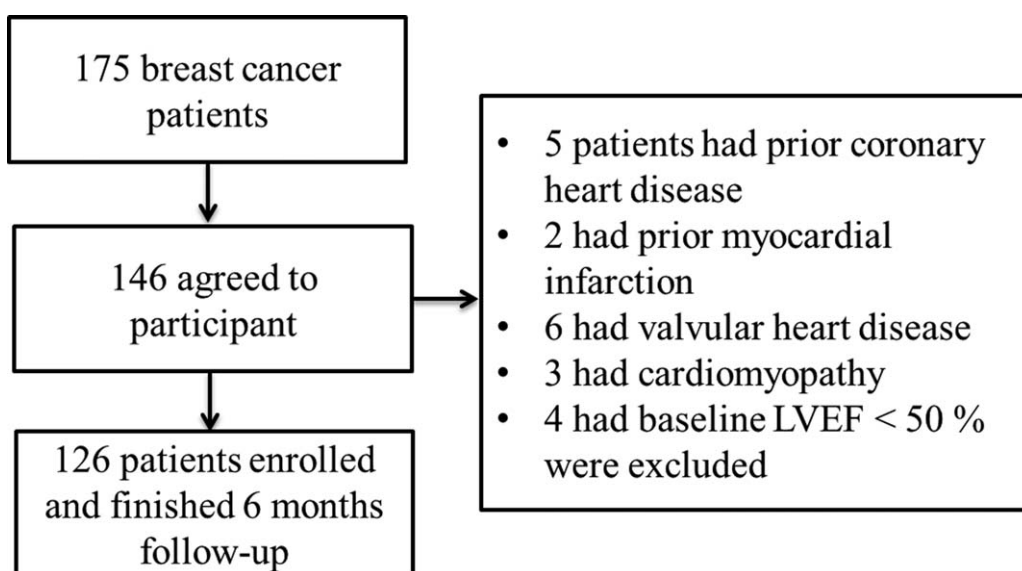


Figure 1. Schematic of study.

6.4±1.6ng/mL, 3rd tertiary group 6.5±1.1ng/mL,  $P=.978$ ). However, after 6 months therapy, compared with the 1st tertiary group, soluble ST-2 level was significantly higher in the 3<sup>rd</sup> tertiary

**Table 1**  
Baseline characteristics comparisons.

Variables	1st tertiary	2nd tertiary	3rd tertiary
N	42	42	42
Age, y	53.4±4.8	51.9±4.2	54.7±5.5
SBP, mm Hg	138±11	135±9	136±10
DBP, mm Hg	74±8	72±7	74±8
HR, bpm	79±10	81±8	79±12
BMI, kg/m <sup>2</sup>	23.5±6.3	24.7±6.0	23.8±6.7
Smoking, n (%)			
Never	39 (92.8%)	40 (95.2%)	40 (95.2%)
Prior	2 (4.8%)	2 (4.8%)	1 (2.4%)
Current	1 (2.4%)	0	1 (2.4%)
History of DM, n (%)	6 (14.3%)	5 (11.9%)	5 (11.9%)
History of HTN, n (%)	10 (23.8%)	11 (26.2%)	10 (23.8%)
History of HPL, n (%)	8 (19.0%)	7 (16.7%)	7 (16.7%)
ACEi/ARB, n (%)	10 (23.8%)	8 (19.0%)	7 (16.7%)*
Beta-blocker, n (%)	7 (16.7%)	6 (14.3%)	6 (14.3%)
Statins, n (%)	5 (11.9%)	5 (11.9%)	4 (9.6%)
Breast cancer site, n (%)			
Right	19 (45.2%)	18 (42.9%)	18 (42.9%)
Left	19 (45.2%)	20 (47.6%)	20 (47.6%)
Bilateral	4 (9.5%)	4 (9.5%)	4 (9.5%)
Breast cancer stage, n (%)			
1	6 (14.3%)	5 (11.9%)	5 (11.9%)
2	15 (35.7%)	15 (35.7%)	16 (38.1%)
3	17 (40.5%)	16 (38.1%)	17 (40.5%)
4	4 (9.6%)	6 (14.3%)	4 (9.6%)
Radiotherapy, n (%)	22 (52.4%)	22 (52.4%)	23 (54.8%)
Doxorubicin, n (%)	23 (54.8%)	22 (52.4%)	23 (54.7%)
Dosage (mg)	1225.4±96.6	1219.7±91.8	1222.5±92.4
Trastuzumab, n (%)	17 (40.5%)	15 (35.7%)	13 (31.0%)
Dosage (mg)	1576.8±106.3	1624.1±119.5	1507.2±104.9
Combined, n (%)	2 (4.7%)	5 (11.9%)	6 (14.3%)*

ACEi/ARB=angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, BMI=body mass index, bpm=beat per minute, DBP=diastolic blood pressure, DM=diabetes mellitus, HPL=hyperlipidemia, HR=heart rate, HTN=hypertension, SBP=systolic blood pressure.  
\*  $P<.05$  versus 1st tertiary.

group (1<sup>st</sup> tertiary group 9.6±3.0ng/mL, 2nd tertiary group 12.7±4.2ng/mL, 3rd tertiary group 16.8±3.8ng/mL,  $P<.05$ ). Pearson correlation analysis showed that soluble ST-2 level was positively correlated with LVESV, LVEDV, and E/e' ratio while negatively correlated with LVEF, with correlation efficient was 0.39, 0.41, 0.37, and -0.51, respectively [ $P<.05$ ], Fig. 2]. Although plasma BNP levels were also increased after 6 months therapy compared with BNP levels at baseline, no significant between-group differences were observed after 6 months therapy.

**3.4. Potential independent factors for LVEF change**

As presented in the Table 3, in the univariate regression analysis, hypertension, ACEi/ARB treatment, radiotherapy, doxorubicin, trastuzumab, combined therapy, soluble ST-2 level, and BNP

**Table 2**  
Comparison biomarker levels and cardiac function and structure.

Variables	1st tertiary	2nd tertiary	3rd tertiary
Baseline			
ST-2, ng/mL	6.5±1.3	6.4±1.6	6.5±1.1
BNP, pg/mL	30.8±8.5	32.4±10.3	31.6±9.7
LVEF (%)	61.2±3.4	62.4±3.9	60.9±3.7
LVESV, mL	51.7±2.8	50.4±2.0	52.1±2.2
LVEDV, mL	106.8±11.6	105.2±10.3	107.1±10.8
LVESD, cm	3.4±0.4	3.3±0.5	3.4±0.5
LVEDD, cm	4.8±0.7	4.9±0.6	4.8±0.6
E/e'	1.3±0.3	1.2±0.3	1.2±0.3
6 mo follow-up			
ST-2, ng/mL	9.6±3.0	12.7±4.2	16.8±3.8*
BNP, pg/mL	50.9±12.3	52.8±10.9	53.7±14.6
LVEF (%)	56.4±3.0	53.8±3.2	50.4±2.9*
LVESV, mL	54.5±3.6	56.2±3.1	58.9±4.3*
LVEDV, mL	109.3±10.5	112.7±11.6	115.6±12.4*
LVESD, cm	3.7±0.8	3.9±0.8	4.1±0.9*
LVEDD, cm	5.0±0.8	5.2±1.0	5.4±1.1*
E/e'	2.2±0.5	2.4±0.6	2.6±0.6*

BNP=brain natriuretic peptide, LVEDD=left ventricular end diastolic diameter, LVESD=left ventricular end diastolic volume, LVEF=left ventricular ejection fraction, LVESV=left ventricular end systolic volume.  
\*  $P<.05$  versus 1st tertiary.

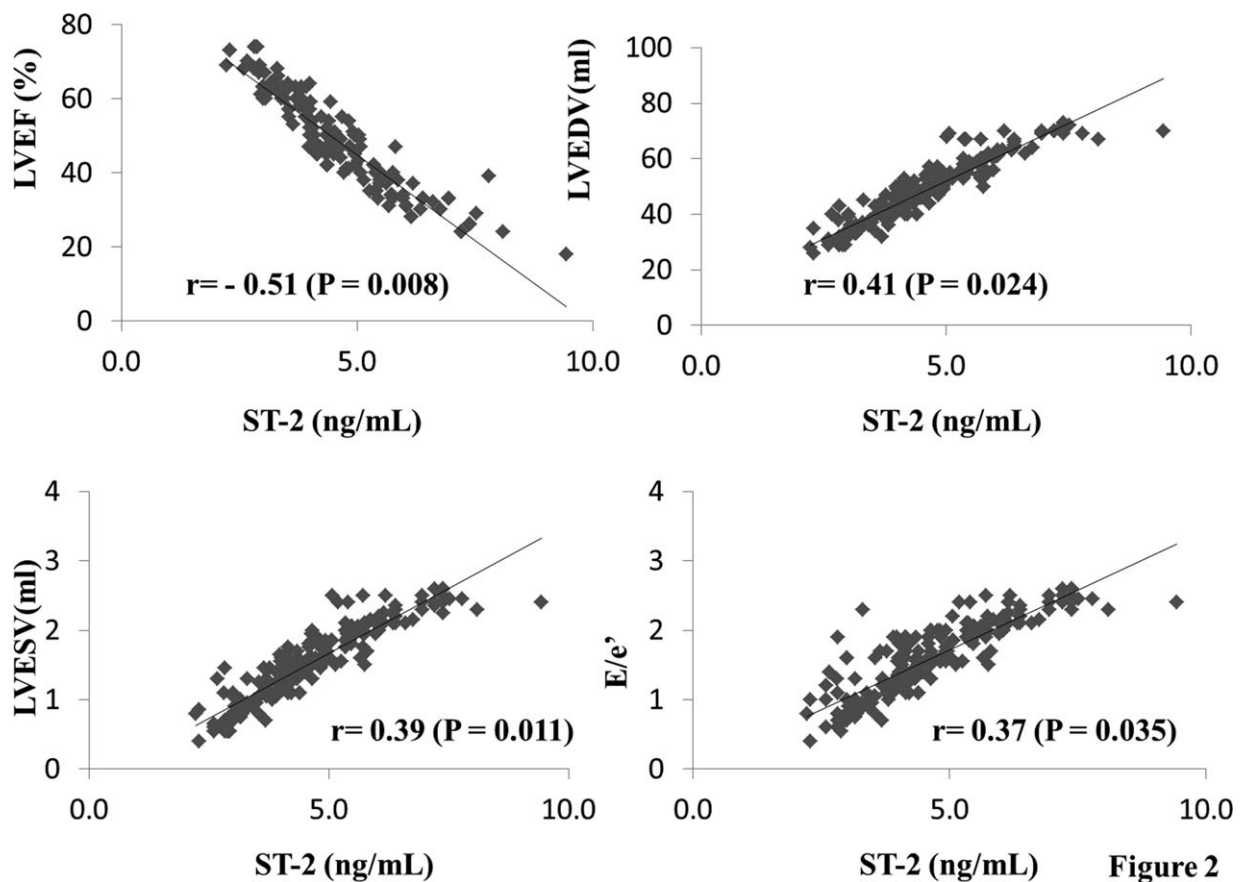


Figure 2. Correlation between soluble ST-2 and cardiac function and structure.

level were all independently associated with LVEF change. All these variables and age and diabetes mellitus were entered into the model of multivariate regression analysis. As summarized in the Table 3 that doxorubicin, trastuzumab, combined therapy, soluble ST-2 level, and ACEi/ARB treatment remained independently associated with LVEF change.

**3.5. Sensitivity and specificity of soluble ST-2 in predicting LVEF change**

The receiver operating characteristic curve was conducted to evaluate the sensitivity and specificity of soluble ST-2 in

predicting LVEF change. As revealed in Fig. 3, the area under the curve for soluble ST-2 to predict LVEF change was 0.74 ( $P = .002$ ), and the cutoff value of soluble ST-2 was 13.4 ng/mL, with sensitivity was 73% and specificity was 79%, respectively.

**4. Discussion**

Our current study indicates that in Chinese patients with breast cancer, doxorubicin and trastuzumab therapy have adverse effects on left ventricular structure and function, which is additive by combined therapy. Baseline soluble ST-2 level can be used to predict left ventricular structure and function change, with an

**Table 3**

**Independent factors for LVEF change from baseline to 6 months' follow-up.**

Independent variables	Univariate regression coefficient (SE)	P	Multivariate regression coefficient (SE)	P
Age, y	1.22 (0.70)	.13	1.09 (0.62)	.25
Diabetes mellitus	1.30 (0.64)	.09	1.17 (0.54)	.11
Hypertension	2.08 (0.39)	.008	1.25 (0.31)	.06
ACEi/ARB	-2.29 (0.65)	.001	-1.92 (0.49)	.02
Bilateral breast cancer	0.99 (0.16)	.23		
Stage 3/4 breast cancer	1.11 (0.25)	.35		
Radiotherapy	1.87 (0.44)	.01	1.19 (0.35)	.24
Doxorubicin	2.14 (0.52)	.003	1.77 (0.31)	.02
Trastuzumab	2.08 (0.41)	.007	1.63 (0.38)	.04
Combined therapy	3.35 (0.78)	< .001	2.85 (0.59)	.006
Soluble ST-2 level, ng/mL	2.26 (0.50)	.016	1.84 (0.42)	.03
BNP, pg/mL	1.87 (0.45)	.037	1.20 (0.35)	.19

ACEi/ARB=angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, BNP=brain natriuretic peptide, SE=standard error.

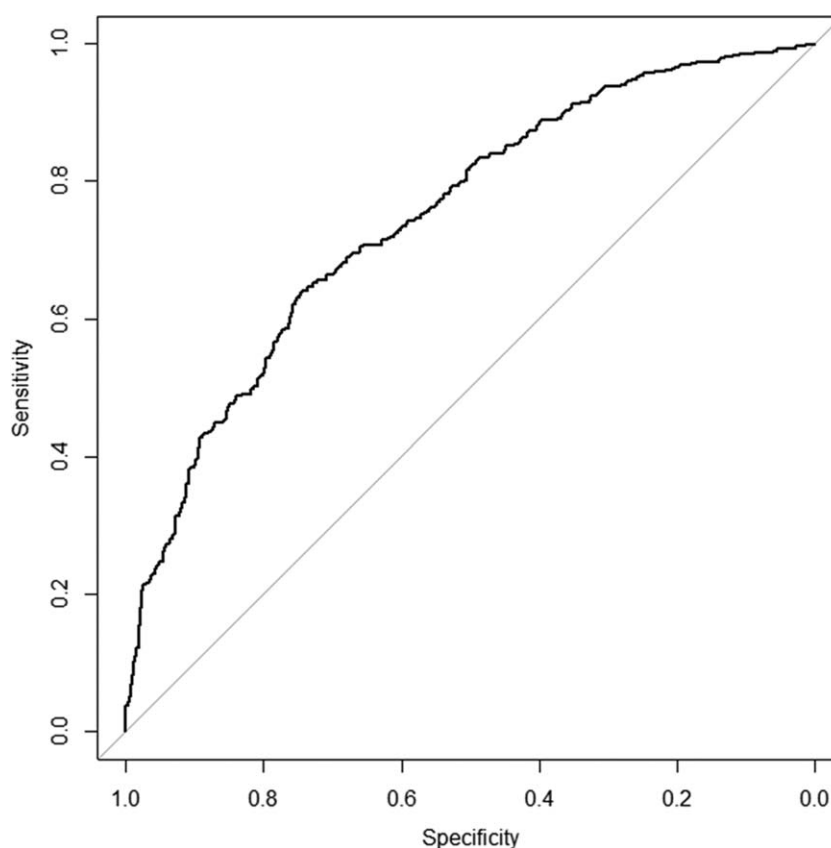


Figure 3. The ROC curve in predicting LVEF change.

acceptable sensitivity and specificity. Future studies are warranted to elucidate whether soluble ST-2 level can be used to predict long-term outcome in patients with breast cancer receiving doxorubicin or trastuzumab therapy.

Notably, breast cancer is a leading cause of morbidity and mortality in women around the world.<sup>[19,20]</sup> Doxorubicin and trastuzumab are the cornerstone regimen for breast cancer. However, many studies have shown the cardiotoxicity of these 2 medications. For example, Narayan et al<sup>[21]</sup> enrolled 277 breast cancer patients receiving doxorubicin, trastuzumab, or combined therapy. After 3 years' follow-up, they found that both doxorubicin and trastuzumab resulted in modest, persistent declines in LVEF. In addition, left ventricular volumes and diastolic function change was also significantly associated with LVEF decrease.<sup>[21]</sup> Consistent to prior study, our current study also observed that doxorubicin and trastuzumab therapy led to cardiac function and structure changes. Extending to the previous study, we found that even 6 months therapy could result in significant changes of cardiac function and structure. In addition, our current study has evaluated the change of serum soluble ST-2 and BNP levels, which had not been investigated in prior studies. To our best knowledge, this should be the first few studies to evaluate soluble ST-2 changes before and after doxorubicin and trastuzumab therapy. The clinical implication of these findings is that measurement of soluble ST-2 level may help to identify cardiotoxicity of doxorubicin or trastuzumab therapy in the early stage, which in turn help physician adjust medications doses and prevent CHF development.

Consistent to prior studies,<sup>[22,23]</sup> our current study also observed the additive adverse effects of combined therapy on

cardiac function and structure when compared with single therapy. Soluble ST-2 level was also significantly higher in combined group (combined  $14.2 \pm 6.0$  ng/mL, doxorubicin  $10.2 \pm 3.7$  ng/mL, trastuzumab  $9.6 \pm 3.1$  ng/mL,  $P < .05$ ), suggesting that physicians should be cautious of combined therapy in terms of their adverse effects on cardiac function and soluble ST-2 level might be useful for dosage adjustment.

Both our current study and prior studies have shown BNP elevation with doxorubicin and trastuzumab therapy compared with that at baseline.<sup>[24,25]</sup> However, in our current study, we did not find significant differences in BNP level between different groups, indicating that soluble ST-2 might be more sensitive than BNP in reflecting cardiac function and structure changes in an early stage. Furthermore, the ROC curve was 0.74, indicating that soluble ST-2 had a fair capacity to discriminate the change of LVEF. When the cutoff value of was 13.4 ng/mL, the soluble ST-2 had the best sensitivity and specificity to predict LVEF change. From clinical perspective, with a cutoff value, it was helpful and useful for physicians to guide therapy by monitoring soluble ST-2 change so as to predict LVEF change and prevent CHF development.

We observed that ACEi/ARB therapy appeared to have favorable effect on cardiac function. Many randomized clinical trials have demonstrated the cardioprotective effects of ACEi/ARB on preventing CHF development as well as improving cardiac function in patients with established CHF.<sup>[26,27]</sup> Our current study showed that ACEi/ARB therapy was beneficial to improve cardiac dysfunction induced by doxorubicin or trastuzumab. More clinical studies are needed to corroborate our current findings. In addition, experimental studies are needed to elucidate the underlying mechanisms.

There are some limitations of current study. First of all, this is a single center and observational study, and causal relationship could not be drawn. However, current study provides foundation for future study to corroborate our findings and elucidate the underlying mechanisms. Second, current study was subjected to a relative small sample size and short-term duration and future large sample size and long-term follow-up study is needed. Third, findings from current study should not extrapolate to other populations group. Last but not the least, although we have adjusted for potential confounding, observational design and unmeasured and undetected biases still exist.

## 5. Conclusion

In patients with breast cancer receiving doxorubicin or trastuzumab therapy, soluble ST-2 level can be used to predict cardiac function and structure changes.

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## Author contributions

**Conceptualization:** Guoding Huang, Jianfeng Zhai, Xiuzhu Huang, Dongdan Zheng.

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**Funding acquisition:** Guoding Huang.

**Methodology:** Xinting Huang.

**Supervision:** Dongdan Zheng.

**Validation:** Guoding Huang.

**Writing – original draft:** Guoding Huang.

**Writing – review & editing:** Guoding Huang.

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