Positively association between novel cardiac biomarkers soluble ST2 and heart Dosimetry parameter in thoracic cancer chest radiation

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Research article

Keywords: radiation-induced heart disease, heart dosimetry parameter, sST2, cardiac biomarker, early detection

Posted Date: July 1st, 2019

DOI: https://doi.org/10.21203/rs.2.10896/v1

Abstract

Background Early screening and diagnosis of radiation-induced heart disease are difficult in patients with chest radiation exposure. sST2 involved in myocardial stress or injury. We aimed to evaluate short-term sST2, B-type natriuretic peptide (BNP) and the left ventricle ejection fraction (LVEF) changes and the relationship between sST2 and heart dose in patients who receive chest radiation. Methods We prospectively collected thoracic malignancy cancer patients from October 2016 to August 2018 who received chest radiotherapy. sST2 and BNP was measured before (recorded as preST2, preBNP), in the middle (recorded as midST2, midBNP) and after radiotherapy (recorded as postST2, postBNP). LVEF was detected using echocardiography before and after radiotherapy. BNP and sST2 among pre, mid, post groups were compared using nonparametric test. LVEF was compared using pair t-test. Standardized sST2 was calculated as postsST2/presST2. The correlation of standardized sST2 and heart dosimetry parameters were measured by Spearman's correlation test. Results Sixty patients were enrolled, including 37(61.67%) lung cancer, 18(30.00%) esophageal cancer and 5 (8.33%) thymoma patients. The median preST2, midST2, postST2 was 3.86 (IQR1.56-8.37), 6.33 (IQR 2.01-9.32) and 8.00 (IQR 4.2- 10.9) respectively. sST2 elevated with the progression of thoracic irradiation ($p<0.001$). The median preBNP, midBNP and postBNP was 22.56 (IQR 7.25-63.5), 32.25 (IQR 18.85-52.97) and 32.41 (IQR 17.23-55.97), respectively. The mean preLVEF and postLVEF was 64.36 and 62.76, respectively. There was no significant change in BNP and LVEF after radiotherapy. Standardized sST2 was correlation with V5Gy, V10Gy, V20Gy, V30Gy, mean heart dose and left anterior descending artery (LAD) (V5Gy rs = 0.541, p = 0.00; V10Gy rs = 0.504, p = 0.00; V20Gy rs = 0.437, p = 0.001; V30Gy, rs = 0.305, p = 0.026; mean heart dose rs = 0.395, p = 0.003 and mean heart dose of LAD rs = 0.414, p = 0.002). Conclusion BNP and LVEF were not changed after thoracic radiation. Serum sST2 levels were elevated during radiotherapy and associated with heart dose parameters in thoracic malignant tumor patients. sST2 would be regarded as a potential early diagnostic marker for RIHD.

Background

In view of the improvement of therapeutic effect and the growing number of long-term cancer survivors, RIHD in patients received thoracic radiotherapy has been much more concerned by oncologists [1]. RIHD often occurs in survivors of breast cancer, lymphoma or childhood cancer who undergo chest therapy after several years or decades [2-4]. There is no standard diagnostic method for RIHD. Myocardial markers (including BNP□pro-BNP and cTnI), echocardiography and cardiac magnetic resonance are common methods for diagnosing RIHD [4, 5]. Early screening and diagnosis of RIHD are difficult in patients with radiation exposure.

ST2 is a member of the interleukin-1 receptor family including transmembrane (ST2L) and soluble ST2 isoforms (sST2)[6]. IL-33 is a specific ligand of ST2L, forming the IL-33/ST2 signaling pathway, which is involved in myocardial stress or injury[7, 8]. Multiple researches revealed that elevated sST2 concentration involved in various heart diseases, such as heart failure[9-11], atrial fibrillation[12], heart transplant recipients[13, 14], chronic kidney disease-induced cardiac remodeling[15] and myocardial

infarction[7, 16]. The guidelines for heart failure management issued by ACCA/AHA in 2013 recommend soluble ST2 as an additional indicator of risk stratification in patients with acute and chronic heart failure [9].

Heart radiation exposure can lead to vascular endothelial cells damage and vascular inflammatory reaction, finally interstitial ischemic fibrosis caused by thrombosis or inflammatory reaction. A study demonstrated that the sST2 levels in workers from the nuclear industry were significantly higher (5 folds) than control group without exposure history [17]. When patients receive chest radiotherapy, the heart would be exposed to large doses x ray in a short time, especially in central lung tumors and esophageal cancer. However, the impact of chest radiation on sST2 is unclear and whether changes in sST2 are associated with cardiac doses is also unclear.

In this study, we examined levels of sST2, BNP, LVEF as well as heart dosimetry parameters in the serum of patients with receiving high-dose radiotherapy for thoracic malignancies. The study was aimed to evaluate the early changes of serum sST2 during thoracic radiotherapy and to find associations with heart dosimetry parameters.

Methods

Patients and Study Design

Patients receiving thoracic radiotherapy were enrolled from October 2016 to August 2018 in Department of thoracic Oncology, the second affiliated hospital of Nanchang University. Inclusion criteria：age >18 years, Eastern Cooperative Oncology Group performance status 0 to 2, adequate hematologic, hepatic and renal function. Exclusion criteria: an anther primary cancer (excluding skin cancer beyond 5 years)； thoracic radiation historically, malignant pericardial effusion, uncontrolled angina pectoris, myocardial infarction <3 months before enrollment, interstitial pneumonia active lung fibrosis or severe cachexia. The study was consented by all the enrolled patients and the Ethics Committee of the second affiliated hospital of Nanchang University.

Serum sST2 and BNP array

Blood samples were collected in tubes with EDTA and serum was separated by centrifugation for 10 min at 600 g/min. The serum samples were stored at -80℃ for later use. sST2 was determined using a high sensitivity enzyme-linked assay ELISA kit (Presage ST2 assay, Critical Diagnostics, San Diego, California) according to the manufacturer's procedures. sST2 levels were evaluated after determining the optical density of the samples at 450 nm (Thermo Scientific Microplate Reader, Varioskan LUX, Finland). BNP was detected in our clinical laboratory and collected in medical record system.

Cardiac echocardiography

Cardiac echocardiographic examinations were performed using GE Vivid (GE Healthcare, Vivid E9, USA) by experienced physicians blinded to all treatment data. LVEF was collected before and after radiotherapy.

Irradiation

All patients received intensity-modulated (IMRT) or volumetric-modulated radiotherapy (VMRT) using Elekta linear accelerator (Elekta Versa HD, Sweden) in a supine position fixed with mask or vacuum bag. The targets and organs at risk (OAR) including heart were contoured by the same physician and treatment plan was designed by specific physician. The dose of normal tissues was constrained (lung of V20<32%, V30<20%, heart of V40<30%). Dosimetry parameters of heart including mean dose of heart (MDH), mean dose of left anterior descending coronary artery (M-LAD), V_{5Gy}, V_{10Gy}, V_{20Gy}, V_{30Gy}, V_{40Gy} were extracted from Dose-Volume Histogram (DVH) curves in Monaco treatment planning system (Elekta Versa HD, Sweden).

Statistics

All values are presented as means ± standard deviation (SD) or median (interquartile range, IQR). Each variable was first characterized by Kolmogorov-Smirnov normality test for Gaussian distribution. According to the distribution, we used either two-tailed t-test/pair t-test or Wilcoxon rank-sum test for comparison of two groups. The relationships between more than two groups were analyzed by one-way ANOVA or Friedman test depending on the normality of the data distribution. Spearman's correlation coefficients were used for correlation analyses between dose parameters and sST2 level. The statistical software SPSS 20.0 (SPSS Inc., Chicago, IL) was used for all analysis. $P < 0.05$ (two sides) was considered statistically significant.

Results

Population characteristics

Demographic data in the study are shown in Table 1. A total of 60 patients received chest radiotherapy were enrolled. Lung cancer (61.67%), esophageal cancer (30.00%) and several thymoma (8.33%) patients were enrolled. The mean age was 61.5 years (range 30-84). Among them, 2 had history of coronary heart disease, 5 cases diabetes mellitus and 10 cases of hypertension. All the patients had received thoracic irradiation including radical radiotherapy, adjuvant radiotherapy or palliative radiotherapy.

sST2 elevated with the progression of thoracic irradiation, LVEF and BNP not changed

We evaluated the cardiac function changes using cardiac ultrasonography and serum cardiac biomarkers. Among the patients, the median preST2 midST2, postST2 was 3.86 (IQR1.56-8.37), 6.33 (IQR 2.01-9.32) and 8.00 (IQR 4.2- 10.9) respectively. The median preBNP, midBNP and postBNP was 22.56

(IQR 7.25-63.5), 32.25 (IQR 18.85-52.97) and 32.41 (IQR 17.23-55.97) respectively. The mean preLVEF and

postLVEF was 64.36 and 62.76 respectively. Compared to preST2, the midST2 and postST2 levels were higher in patients with thoracic radiotherapy, whereas no significant difference in BNP levels was observed between pre, mid and post radiotherapy patients (Figure1).

sST2 levels have no difference in baseline clinical parameters.

Table 2 showed sST2 levels after radiotherapy in subgroup of baseline clinical parameters. There was no difference in postST2 levels (Table2).

Standardized sST2 levels positively associated with heart dosimetry parameters

Mean V_{5Gy}, V_{10Gy}, V_{20Gy}, V_{30Gy}, V_{40Gy} and MHD was 60.93 (27.79), 51.43 (25.44), 39.17 (21.75), 28.07 (17.15),18.66 (12.18) ,18.60 (8.63), respectively. Median M-LAD was 11.31 (IQR 3.33-18.76). Standardized sST2 was correlated with heart dosimetry parameters was significant (V_{5Gy} r_s = 0.541, p = 0.00; V10 r_s = 0.504, p = 0.00; V_{20Gy} r_s = 0.437, p = 0.001; V_{30Gy}, r_s = 0.305, p = 0.026; MHD r_s = 0.395, p = 0.003 and M- LAD r_s = 0.414, p = 0.002) (Table3).

Discussion

This study firstly reported a novel biomarker, serum sST2 level, in thoracic malignant tumor patients is associated with heart dose parameters when they received chest radiotherapy. Our results showed that compared with before radiotherapy, sST2 increased during and after radiotherapy. Whereas, compared with before radiotherapy, postLVEF did not decrease and the traditional cardiac biomarker BNP was also not changed. Furthermore, an association between serum sST2 levels and heart dose was found.

Despite the rapid progress in cancer screening, diagnosis and treatment, treatment-related cardiovascular events including radiation-induced cardiac injury, remain unavoidable [1]. LVEF and blood markers (NT-proBNP/BNP, cTnI et) are still one of the classical methods in clinical practice for the for risk assessment, diagnosis and management of radiation induced heart disease[18]. In the small sample longitudinal study of cardiac Biomarkers in patients receiving thoracic radiotherapy, Gomez et al[19] showed that BNP increased during high doses of radiation to the heart in some patients. Recently, a long term retrospective study reported that median plasma BNP levels in 5-year breast cancer survivors after radiation therapy remained within the normal range, but the delta-BNP levels are positively related to the mean heart dose and mean left ventricular dose received[20]. However, the significance of BNP in the diagnosis and evaluation of radiation-induced cardiac disease is not fully understood. Our results showed that BNP had not changed after radiotherapy, compared with BNP in the baseline, indicated BNP would not increase in short -term post-radiation therapy.

LVEF plays an important role in detecting cardiac function changes. Nousiainen T et al. [21] demonstrated that early LVEF decline during doxorubicin therapy was associated with doxorubicin cardiotoxicity in lymphoma patients. However, Shelly X. Bian et al. [22] found that no acute changes in LVEF observed in breast cancer patients with concurrent trastuzumab and breast radiation. In this study, although the heart dose was higher than Shelly X. Bian's research, postLVEF was also not changed compared with baseline LVEF (preLVEF). Interestingly, we found that sST2 presented higher during radiotherapy. Then, sST2 might be useful in detecting acute or subclinical cardiotoxicity.

Accumulated results from clinical studies have shown that high cardiac radiation dose is directly associated with radiation-induced heart diseases [20, 23-25]. When make the radiotherapy regiment, oncologists must also consider tumor control rate and meanwhile the cardiac exposure dose. In childhood cancer survivors, a large sample case control study revealed heart failure was often occurred in patients with the median volume of the heart that received ≥ 30 Gy [26]. In stage III non-small-cell lung cancer, different cardiac events were associated with distinct heart volume doses, such as ischemic events were correlated with left ventricle and whole heart dose [23]. The mean V_{5Gy}, V_{10Gy}, V_{20Gy}, V_{30Gy}, V_{40Gy} and MHD in our study was 60.93%, 51.43%, 39.17%, 28.07%, 18.66 % and 18.60Gy. Our results demonstrated that standardized sST2 were related with V_{5Gy}, V_{10Gy}, V_{20Gy}, V_{30Gy} , MHD and M-LAD. Therefore, sST2 may be a potential for early detection of radiation induced cardiac damage.

We recognized that the study presents several limitations. First of all, this study is a longitudinal study of small samples. Moreover, our study only collected the serum samples during and after radiotherapy, which mainly reflects acute radiation-induced cardiac injury. Therefore, large sample of long-term follow-up studies should be warranted. Fortunately, a registered clinical study [27] on early detection of RIHD is under way.

Conclusions

In conclusion, we firstly reported serum sST2 levels were elevated during radiotherapy over time and associated with heart dose parameters in thoracic malignant tumor patients when they received chest radiotherapy. While the traditional biomarker and LVEF was not changed during thoracic radiation. This may indicated that sST2 may be a potential early diagnostic marker for RIHD. Further research is needed on the role of sST2 as an early detection, diagnose and prognostic marker in RIHD.

Abbreviations

RIHD: radiation-induced heart disease; BNP: B-type natriuretic peptide; LVEF: the left ventricle ejection fraction; IQR: interquartile range; sST2: soluble ST2;MHD: mean heart dose; M-LAD: mean dose of left anterior descending artery; IMRT: intensity-modulated radiotherapy; VMRT: volumetric-modulated radiotherapy; DVH: Dose-Volume Histogram.

Declarations

Ethics approval and consent to participate

The study was consented by the Ethics Committee of the second affiliated hospital of Nanchang University. All the enrolled patients were signed informed consent on admission.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed during the study are available from the corresponding author on reasonable request, except private information of participants.

Competing interests

The authors declare that they have no conflict of interest.

Funding

This study was supported by the National Nature Science Foundation (CN), grants No. 81560509 and 81760566 (to Liu Anwen)

Authors' contributions

Z-M Z, in charge of design of the work, analysis, and wrote the article. P X, S Z, helped with acquisition and analysis of the data. H-Y D helped to exam sST2. X-L J and J C helped to collect the serum samples. L H and A-W L, the Corresponding author, was in charge of guidance of the design and analysis the whole research. All authors read and approved the final manuscript.

Acknowledgements

We thank all the patients who participated in the study. We thank Bing Zou of the Radiotherapy Center for his help in collecting radiation heart dose parameters.

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Tables

Table 1. Characteristics of patients

Characteristic	Data Number (%)
AGE	61.50 (30.00- 84.00)
GENDER	
Male	52 (86.67%)
Female	8 (13.33%)
SMOKING	
No	33 (55.00%)
Yes	27 (45.00%)
HISTORY OF CORONARY DISEASE	
No	58 (96.67%)
Yes	2 (3.33%)
DIABETES MELLITUS	
Without	55 (91.67%)
With	5 (8.33%)
HYPERTENSION	
Without	50 (83.33%)
With	10 (16.67%)
CHEMOTHERAPY	
No	12 (20.00%)
Yes	48 (80.00%)
SURGERY	
No	34 (56.67%)
Yes	26 (43.33%)
TYPE OF PATHOLOGY	
Lung cancer	37 (61.67%)
Esophagus cancer	18 (30.00%)
Thymoma	5 (8.33%)

Table2. Subgroup analysis of ST2 levels in baseline clinical parameters.

Characteristic	postST2 Median (IQR)	P value
GENDER		
Male	8.08 (4.73-10.90)	0.128
Female	5.05 (1.54-9.23)	
SMOKING		
No	9.94 (5.59-10.95)	0.102
Yes	6.15 (2.06-9.57)	
HISTORY.OF.CORONARY.DISEASE		
No	8.04 (4.46-10.9)	0.226
Yes	1.46	
DIABETES.MELLITUS		
Without	7.70 (3.00-10.90)	0.668
With	8.08 (7.84-8.15)	
HYPERTENSION		
Without	8.15 (4.48-10.55)	0.633
With	7.62 (4.22-10.9)	
CHEMOTHERAPY		
No	8.15 (4.48-10.55)	0.956
Yes	7.62 (4.22-10.9)	
SURGERY		
No	7.7 (4.69-10.9)	0.964
Yes	8.15 (2.97-10.87)	
TYPE.OF.PATHOLOGY		
Lung cancer	6.38 (2.06-10.42)	0.197
Esophagus cancer	9.87 (7.7-10.95)	
Thymoma	10.8 (3.95-10.9)	

Table3. Correlation analysis between standard ST2 levels and cardiac dosimetry parameters.

Dose parameters of heart	Correlation Coefficient	p Value n=53
V_{5Gy}(%)	0.541	0.00
V_{10Gy} (%)	0.504	0.00
V_{20Gy} (%)	0.437	0.001
V_{30Gy} (%)	0.305	0.026
V_{40Gy} (%)	0.167	0.233
MHD	0.395	0.003
M-LAD	0.414	0.002

Figures

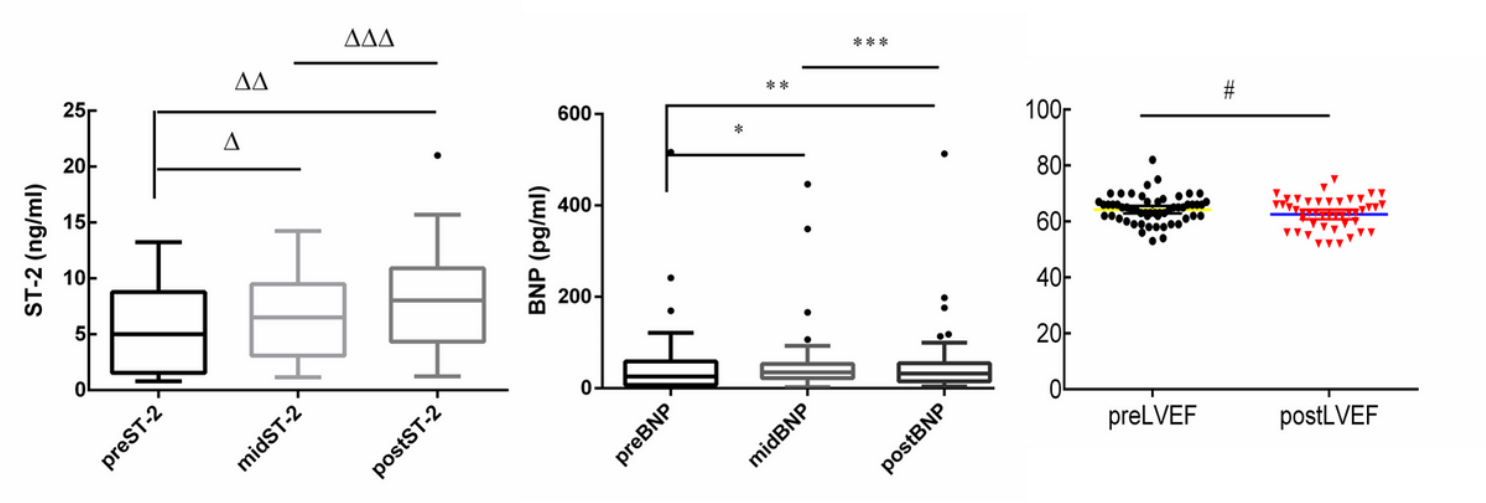

Figure 1

Serum cardiac biomarker and cardiac function changes in response to radiotherapy. (A) Comparison of ST2 levels in baseline (preST2), mid (midST2) and post radiotherapy (postST2) with Wilcoxon signed ranks test (Δp<0.001; ΔΔp<0.001; ΔΔΔp<0.001). (B) BNP levels in baseline (preBNP), mid (midBNP) and post radiotherapy (postBNP). Wilcoxon signed ranks test *p=0.074;**p=0.325; **p=0.727. (C) LVEF levels before and after chest radiotherapy (paired-samples T test, #p>0.05).