Prediction of Cardiovascular Adverse Events in Patients Treated with R-CHOP Regimens by 3D Transthoracic Echocardiography

Yi-Hui Shen[1], Hui Zhang[1], Bo Yuan Zhang[1], YangYue Ni[1], Rui Zhao[2], Qunling Zhang[3], David Hsi[4], and Leilei Cheng[2]

[1]Zhongshan Hospital Fudan University
[2]Affiliation not available
[3]Fudan University Shanghai Cancer Center
[4]Stamford Hospital

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Abstract

Background: Patients treated for lymphoma are at risk of cardiovascular adverse events. Global longitudinal strain (GLS) and global circumferential strain (GCS) were reported for predicting cardiovascular adverse events in patients treated with doxorubicin. However, the prognostic value of RV ejection fraction by 3D transthoracic echocardiography (3D TTE) have not been elucidated yet. We hypothesized that RV echocardiography parameters increases the sensitivity for predicting the later CAE. Methods: In this retrospective study, ninety-six patients with diffuse large B-cell lymphoma with normal cardiac function treated with R-CHOP regimen were studied between January 2013 and January 2015 by 3D TTE. Basic demographic data, oncology and echocardiography parameters were measured. The main outcomes were the proportion of patients with grade 3–4 cardiovascular adverse events (CAE). The association of pre-chemotherapy and post-chemotherapy echocardiography parameters with CAEs was analyzed using proportional hazard analysis. Results: Over a median follow-up period of 6.1 years (range, 4.9-7.6 years) after the completion of chemotherapy, 18 of 96 patients (19%) experienced CAEs. Univariate predictors of CAE ($P < .05$) were LVGLS, LVGCS, RVEF, and RVESV. Multivariate analysis of all significant univariate variables showed that RVEF (hazard ratio, 0.848; 95% confidence interval,0.785–0.916; $P < .001$) were significantly and independently associated with CAE. Stepwise analysis of the multivariate associations showed an increase in the global x2 value after adding LVEF ($P < .001$) to significant clinical variables. Conclusion: LVGLS and RVEF were significantly and independently associated with CAE in patients. Adding RVEF to other clinical variables provided incremental prognostic information.

Title page

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Affiliations

[1]Department of Echocardiography, Zhongshan Hospital, Fudan University, Shanghai Institute of Cardiovascular Diseases, Shanghai Institute of Medical Imaging, 180 Fenglin Road, Shanghai, China

[2]Huangpu Branch, Shanghai Ninth People's Hospital Shanghai Jiao Tong University School of Medicine, Shanghai, China

[3]Department of Pathogen Biology, Jiangsu Province Key Laboratory of Modern Pathogen Biology, Center for Global Health, Nanjing Medical University, Nanjing, Jiangsu, China

[4]Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China.

[5]Department of Cardiology, Stamford Hospital, Columbia University College of Physicians & Surgeons, Stamford, USA

Corresponding authors:

Leilei Cheng, Department of Echocardiography, Zhongshan Hospital, Fudan University, Shanghai Institute of Cardiovascular Diseases, Shanghai Institute of Medical Imaging, 180 Fenglin Road, Shanghai 200032, China. Fax: +86-021-64038038; E-mail:*cheng.leilei@zs-hospital.sh.cn*

Or:

David H. Hsi, MD, FACC, FASE, Department of Cardiology, Stamford Hospital, One Hospital Plaza, Stamford, CT 06902, USA. Fax: +1-203-276-2324; E-mail:

dhsi@stamhealth.org

Or:

Zhang Qunling, Department of Medical Oncology, Fudan University Shanghai Cancer Center; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200032, China. E-mail: *zqldoc@163.com*

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Methods: In this retrospective study, ninety-six patients with diffuse large B-cell lymphoma with normal cardiac function treated with R-CHOP regimen were studied between January 2013 and January 2015 by 3D TTE. Basic demographic data, oncology and echocardiography parameters were measured. The main outcomes were the proportion of patients with grade 3–4 cardiovascular adverse events (CAE). The association of pre-chemotherapy and post-chemotherapy echocardiography parameters with CAEs was analyzed using proportional hazard analysis.

Results: Over a median follow-up period of 6.1 years (range, 4.9-7.6 years) after the completion of chemotherapy, 18 of 96 patients (19%) experienced CAEs. Univariate predictors of CAE ($P < .05$) were LVGLS, LVGCS, RVEF, and RVESV. Multivariate analysis of all significant univariate variables showed that RVEF (hazard ratio, 0.848; 95% confidence interval,0.785–0.916; $P < .001$) were significantly and independently associated with CAE. Stepwise analysis of the multivariate associations showed an increase in the global x^2 value after adding LVEF ($P < .001$) to significant clinical variables.

Conclusion: LVGLS and RVEF were significantly and independently associated with CAE in patients. Adding RVEF to other clinical variables provided incremental prognostic information.

Keywords: LV function, RV function, 3-D echocardiography, anthracycline cardiotoxicity, LV longitudinal strain, cardiovascular adverse events

Abbreviations

CAE = cardiovascular adverse event

GLS = Global longitudinal strain

GCS = Global circumferential strain

LV = Left ventricular

RV = Right ventricular

LVEF = Left ventricular ejection fraction

3DTTE= Three-dimensional transthoracic echocardiography

Introduction

Non-Hodgkin's lymphoma includes a variety of tumors originating from lymphoid tissues. With an estimated 500,000 new cases in 2018, non-Hodgkin's lymphoma accounts for approximately 3% of all cancer cases worldwide[1]. There is growing evidence that patients with cancer are at substantially increased risk of developing cardiovascular adverse event [2]. The reasons behind this observation are thought to be multifactorial, including the common risk factors between cancer and cardiovascular disease and the cardiovascular toxic effects of antineoplastic drugs[3, 4]. Even when impaired LVEF was diagnosed immediately after anthracycline therapy, 36% of patients failed to regain normal LV function despite therapeutic interventions[5]. Research into more sensitive markers of subclinical cardiac dysfunction or myocardial injury remains imminent.

Left ventricular ejection fraction (LVEF) has long been considered a key criterion for evaluating cardiotoxicity[6]. Left ventricular global longitudinal strain (GLS) has been shown to detect cardiac dysfunction earlier than LVEF and is an important predictor of chemotherapy-induced cardiotoxicity in patients with preserved LVEFs[7, 8]. LVEF and GLS are recognized as criteria for assessing cardiac function and monitoring chemotherapy-induced cardiotoxicity in most patients with heart disease and as per guidelines[9]. However, few data are available on right ventricular (RV) function in cancer survivors, especially in long-term cancer survivors. It is possible that measurements of RV function are more predictive of mortality than measures of left ventricular function in many cardiac diseases, e.g. late post-myocardial infarction, and chronic heart failure[10-12]. After treatment with anthracyclines, 27% of childhood cancer survivors had impaired right ventricular ejection fraction as assessed by cardiac magnetic resonance imaging[13]. However, the availability of cardiac magnetic resonance imaging (CMR) is limited in many areas, and echocardiography is the method of choice for screening cardiac toxicity after cancer treatment. Three-dimensional transthoracic echocardiography (3DTTE) has the advantage of full-volume acquisition of the entire right ventricle and can overcome the technical and clinical limitations of 2D transthoracic echocardiography[14]. The accuracy of 3D TTE in measuring RV volume and RVEF against CMR has been confirmed in recent studies, and it has been documented that RV volume measured by 3D TTE correlates well with the corresponding values obtained by CMR by using new RV analysis software[15-17]. Our previous study showed that subclinical changes in RV function and size by 3DE-derived RV volume occurred after the anthracycline-based chemotherapy[18]. However, the value of right ventricular function in predicting cardiovascular events in patients treated with anthracyclines remains to be investigated. Identifying patients at high risk for heart failure and cardiac death is particularly important in patients at high risk for clinical events, such as those with hematologic malignancies.

The purpose of this study was to assess the value of 3D echo right ventricular function measured during chemotherapy in identifying cardiovascular events in patients with hematologic malignancies treated with anthracyclines.

METHODS

Study Subjects

This study was approved by the Fudan University Shanghai Cancer Center (1212117-6) and Zhongshan Hospital Research Ethics Committee. We identified 149 consecutive patients with pathologically confirmed diffuse large B-cell lymphoma at Fudan University Shanghai Cancer Center who underwent echocardiography with strain measurements between January 2013 and January 2015. All patients received 4-8 cycles of R-CHOP therapy (cyclophosphamide 750 mg/m2; vincristine 1.4 mg/m2 up to a maximum dose of 2 mg/m2; doxorubicin 50 to 70 mg/m2 on day 1; prednisone 100 mg on days 1 to 5; and rituximab 375 mg/m2 every

21 days). We excluded patients with uncontrolled hypertension (n=1), renal or hepatic dysfunction(n=1), significant valvular disease (n=2), congenital disease(1), a widened QRS complex on surface ECG(n=1), arrhythmia (n=4), a previous history of heart failure and/or CAD (n=1) and noncardiac death (malignancy or complication linked to malignancy, n=25), patients with overall poorly tracking strain studies (n=17). The study population thus comprised 96 identified patients who underwent echocardiography examination before the commencement of chemotherapy and after the completion of chemotherapy (Figure 1).

Echocardiography Data Acquisition.

Transthoracic echocardiography was performed with a commercially available ultrasonography system (iE33, Philips Medical Systems, Andover Massachusetts) equipped with S5-1(1 to 5 MHz) and X3-1 (1 to 3 MHz). Standard three-dimensional (3D) images were acquired according to the recommendations of the American Society of Echocardiography. Six cardiac consecutive cycles for 3DE images were acquired for offline analysis. A wide sector was used to ensure that the entire LV cavity was included within the full-volume data set. Image parameters such as depth, sector size, angle, and focus were optimized to achieve a frame rate range of 60 to 80 fps for 2DE and 30 to 45 fps for 3DE analysis.

Offline analysis of the left and right ventricular three-dimensional (3D) image data was performed using the TomTec 4D RV analysis workstation (version 4.6.0.411, TomTec Imaging Systems, Unterschleißheim, Germany)[19]. Care was taken to include trabeculae during measurements. The endocardial borders were traced from the three apical views by an observer blinded to the clinical outcome. GLS and the average peak LV longitudinal systolic strain from the three apical windows were measured. GLS was calculated by measuring the entire endocardial line length at the end-diastole and end-systole (L1- L0/L0* 100%) in each view and averaging the results from the three views. RV end-diastolic volume (RVEDV); RV end-systolic volume (RVESV); RV ejection fraction (RVEF); LV end-diastolic volume (LVEDV); end-systolic volume (LVESV); and LVEF were measured. RV longitudinal free wall strain (RVLFS); RV longitudinal septal strain (RVLSS); LV global longitudinal strain (LVGLS); and LV global circumferential strain (LVGCS) were acquired simultaneously (Supplemental Figure 1). The intra-observer and interobserver variability values were calculated as the absolute differences between the corresponding 2 measurements in percentages of their mean and intraclass correlation.

Follow-up

Follow-up information was obtained regularly in an outpatient clinic. Telephone contacts to patients, physicians, and the next of kin were performed every 6 months. The follow-up time was started after completion of the treatment. The endpoint of the study was grade 3–4 cardiovascular adverse events (CAEs) including cardiac death, symptomatic heart failure, arrhythmia, Subclinical Cardiac dysfunction with the use of established toxicity grading system to quantify the severity of the adverse events (the Common Terminology Criteria for Adverse Events [CTCAE] of the US National Cancer Institute).

Intra-observer and interobserver variability analysis

Intra-observer and interobserver variability were assessed by randomly selecting 10 patients to be measured by one observer twice and by another independent observer, as detailed in Supplemental Table 2.

Statistical analysis

Continuous data are expressed as the mean ± SD. Categorical variables were expressed as counts (percentages). Kolmogorov-Smirnov Z tests were used to evaluate the normality of the data. Parametric tests were applied when normality was satisfied, otherwise, the Mann-Whitney U tests and chi-square tests were used for nonparametric data. Time to first CAE was defined as the number of days between the start of anthracycline therapy and the date of the first CAE and was considered for survival analysis. Patients who had not experienced CAEs as of their last visit date were censored at this date. Cox proportional hazard analysis was used to determine significant clinical and echocardiographic identifiers of time to CAEs. To perform a comparison of RVEF and LVGLS, we performed a proportional hazard analysis using these two terms in a

multivariate analysis. The incremental value of RVEF and LVGLS compared with RVEF in identifying subsequent CAEs was tested with chi-square tests. Receiver operating characteristic curve analysis was used to determine the relationship of LVGLS and RVEF value to the occurrence of CAEs. Survival without CAEs as a function of RVEF was analyzed using Kaplan-Meier analysis. All analyses were performed using a standard statistical software program (IBM SPSS Statistics for Windows version 23.0; IBM, Armonk, NY). P values $< .05$ were considered to indicate statistical significance.

RESULTS

Subjects Ninety-nine patients with diffuse large B-cell lymphoma were eligible. Of those, 3 patients were excluded from the analysis because of poor image quality (defined as >2 non-visualized segments). A total of 96 patients, 57 males, ranging in age from 24 to 78 years were finally included in the statistical analysis. All patients had received anthracycline-based regimens, and the median cumulative anthracycline dose was 380 mg/m^2 (range, 280-560 mg/m^2). Patients were studied a median of 6.1 years (range, 4.9-7.6 years) after the completion of chemotherapy (Figure 1). Fifteen patients had a history of hypertension and six had a history of diabetes, which were well controlled by medication. Twenty-nine patients had a history of smoking or were current smokers. Of the 18 patients with CAE, 8 developed arrhythmia (ventricular tachyarrhythmia-2 atrial fibrillation-6), heart failure-5, subclinical cardiac dysfunctions-3 and acute myocardial infarctions leading to death-2. No patients required acute treatment for dehydration or additional intravenous fluids beyond the standard chemotherapy. None of the patients received other cardiotoxic therapy, radiation therapy, or targeted therapy.

The comparison of the clinical characteristics of patients with and those without CAE is presented in Table 1. Patients with and without CAE had similar age, sex distribution, weights, and cumulative of doxorubicin.

Baseline Three-Dimensional Speckle-Tracking Echocardiographic Parameters

Baseline echocardiographic findings are listed in table 1. The mean LVEF of the patients before chemotherapy was 59.4±4.9% in those who did not develop CAE and 60.3±5.7% in those who did (p=0.527). Left ventricular volume and structure parameters were similar between the CAE and no CAE group. Left ventricular EF and strain parameters (GLS and GCS) were not significantly different between the two groups. The right ventricular parameters RVESV was statistically significant between the two groups (P=0.017).

Identifiers of CAE by Echocardiographic Parameters

Cox regression showed that among the significant univariate factors of 3D Echocardiography after the completion chemotherapy, LVEF, LVESV, LVGLS, LVGCS, RVEF, and RVESV had P values < 0.05 associated with CAEs. Neither RVEDV nor RV strains were associated with CAEs (Table 2).

Based on the receiver operating characteristic curve (Figure 2), a cutoff RVEF value of less than 46.33% (sensitivity, 72.2%; specificity, 82.1%; AUC=0.811; p¡0.001) after the completion anthracycline treatment would have correctly identified 13 of 18 of the study patients (72.2%) who developed CAE and 64 of 78 patients (82.1%) who did not have CAE. While LVGLS<17.29% (sensitivity, 66.7%; specificity, 82.1%; AUC=0.787; p¡0.001) was able to discriminate between patients with and without CAE (Figure 2A). When LVGLS and RVEF were combined, the sensitivity increased to 88.9%, the specificity was 82.1%, and the AUC increased to 0.882 (Figure 2B).

Figure 3 demonstrates the Kaplan-Meier survival curve comparing normal RVEF ([?]46.33%) with abnormal RVEF (<46.33%). Of note, 72% of the patients with abnormal RVEF (13 of 18) suffered from CAE during the follow-up, compared with only 18% of the group with normal RVEF (14 of 78).

A second multivariate analysis was done starting with the significant independent variable (GLS). RVEF was added via stepwise block analysis to these clinical parameters and was found to be significantly important (p<.001), as detailed in Figure 4.

Intraclass correlation coefficients (ICCs) showed interobserver and intra-observer reproducibility for our facility were 0.827 and 0.844 for LVGLS, respectively, and 0.939 and 0.859 for RVEF, respectively (Supplemental

Table 2).

DISCUSSION

In our study of 96 long-term survivors with diffuse large B-cell lymphoma treated with anthracyclines, we examined the role of left and right ventricular parameters before the start of anthracycline and after the completion chemotherapy in identifying the late occurrence of CAEs (cardiac death, symptomatic heart failure, arrhythmia, Subclinical Cardiac dysfunction). Although LVGLS had proven prognostic value, RVEF provided additional and independent information and added incremental value to a model including LVGLS. We found that by using a model combined LVGLS and RVEF could increase the sensitivity for predicting the late CAE. To our knowledge, this is the first study to evaluate the role of combining RV and LV function among patients with lymphoma for predicting late CAE in the context of R-CHOP regimen. Previous published studies mainly focused on the role of LVGLS in cardiovascular toxicity[20-22]. This study has the following novel findings: 1). We reported the proportion of patients with CAE caused by R-CHOP treatment; 2). We applied simultaneous 3-D LV and 3-D RV assessment 3). RVEF decreased during the chemotherapy was a strong predictor of CAE, and 4) combining LVGLS and RVEF may increase the sensitivity for estimating cardiovascular prognosis after chemotherapy.

The majority of CAE reported in our cohort were arrhythmia (8) including and heart failure (5) with an occurrence of 8.3% and 5.2%, respectively within a median of 6 years of follow-up. The pooled proportion of patients developing heart failure (5.2%) in our study is in line with previous studies reporting on the development of symptomatic heart failure, with a 4-5% incidence at a cumulative doxorubicin dose of 400mg/m^2[23, 24]. In our study, patients received concomitant treatment with cyclophosphamide, which complicated the interpretation of the association of doxorubicin and left ventricular dysfunction. A study that explored the association between cyclophosphamide doses and left ventricular dysfunction, found patients whose doses greater than 1.55 g/m^2 were associated with a low incidence of cardiotoxicity[25]. Little is known about right ventricular (RV) function in patients with lymphoma treated with R-CHOP, a small sample study found survivors had markedly increased risk (26%) of having impaired RV function (based on ejection fraction, and compared with normative values) [13]. The proportion of patients with impaired RV function (13%) in our data is quite high, and in many conditions, impaired RV function is associated with an increased risk of heart failure.

LVEF was one of the most important parameters for the assessment of cardiac function and for predicting CAE. However, many studies have proved that LVEF remained stable and within normal limits during the whole course of chemotherapy[20, 26, 27]. Anthracycline-induced cardiomyopathy can be a regional or diffuse pattern so the global LV function could remain normal by compensatory mechanism of healthy cardiomyocyte in the early stage[28]. Similarly, LVEF was not chosen in stepwise Cox proportional hazard analysis in our study. GLS is a sensitive measure of cardiac function and cardiac injury. Many studies have proved that patients with a reduction in GLS despite a preserved EF are at risk for cardiac injury and cardiac dysfunction [29, 30]. A previous study found GLS was associated with cardiac events while LVEF was within the normal range in patients treated with anthracyclines. In our data, LVGLS was also associated with the late CAE, and the threshold of GLS allowed us to identify patients who developed CAE with 66.7% sensitivity and 82.1% specificity. The use of GLS may allow the identification of a group of patients at risk of subsequent CAE and help to guide preventive medicine.

The assessment of RV function has become increasingly popular and been recognized as important to predict cardiac toxicity [31]. RV functional assessment with 2-dimensional and Doppler echocardiography has shortcomings due to the complex geometry of the right ventricle. Nagata et al validated the accuracy of RV volumes and RVEF measurements by 3D TTE against CMR. Although the manual editing of RV endocardial surface was required by 3D TTE, the 3D TTE was more widely adopted and convenient compared with CMR measurements. RV function by 3D TTE has emerging roles in future prognosis on chemotherapy patients [15]. RVEF<40% was a significant independent predictor of mortality after adjustments for age and LVEF. Gulati et al found that RVEF <45% was a powerful predictor of adverse cardiac events [32]. Some studies focused on the consistent impairment of RV function among in survivors of childhood cancer

after reaching adulthood[33, 34]. In the current study, we determined the prognostic value of 3D RVEF in R-CHOP treated patients without severe cardiac disease. We demonstrated that 3D RVEF is significantly associated with late CAE. Using variables selected by a stepwise forward procedure in Cox proportional hazard analysis, we established an incremental value of 3DRVEF over the LVGLS for predicting CAE. Our results clearly showed that 3DRVEF is an independent predictor of CAE.

Current guidelines on follow-up after chemotherapy focus on left ventricular function[9]. Many studies have started to explore and validate the important role of impaired RV function in prognosis in a wide range of diseases[10, 11, 35]. We feel that impaired RV function is a strong predictor of CAE in cancer survivors and a combination of LV and RV function parameters during chemotherapy can facilitate the prevention and treatment.

Finally, we want to emphasize the importance of the 3-D echo image quality for the meaningful analysis of the cardiovascular adverse event.

Limitations

There were limitations in the present study. Patients with severe cardiac diseases and noncardiac death were excluded from our study, which had some degree of selection bias. The 3D RV endocardial border identification may be of challenge as echo dropouts frequently occur. Due to the small size of our study, we did not confirm the finding in a separate independent "validation cohort". The development and validation of a multivariable prediction model for CAE after R-CHOP regimens treatment among patients with lymphoma is required in our future studies. Separate multivariable Cox analysis may be overfitted owing to the low incidence of adverse cardiac events induced by chemotherapy. Finally, our patients didn't undergo cardiac magnetic resonance (CMR) so our RV data sets measured by 3D transthoracic echocardiography were not tested for the correlation with CMR.

Conclusion

RVEF by 3D echo is an effective tool to stratify patients at high risk for CAE after chemotherapy. The RVEF helped identifying late CAE and added incremental value to the analysis of clinical variables and LVGLS. Therefore, in patients with lymphoma treated with R-CHOP regimens, a 3-D echo-based imaging for LV and RV could be used to help tailor oncologic and cardiac treatment and reduce CAE.

Data Availability

Most of the data used to support the findings of this study are included within the article. The supplementary data are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Figure Legends

Figure 1: Flowchart detailing patient selection.

Figure 2: ROC curves for 3D Echocardiographic Parameters in Predicting Later CAEs. (A) ROC curve analysis of LVGLS and RVEF respectively. The area under the curve (AUC) of LVGLS was 0.787 (95%

CI, 0.666-0.908; P < .0001) (blue line) and the AUC of RVEF was 0.811 (95% CI, 0.712-0.910; P < .0001) (green line). (B) ROC curve analysis of combined LVGLS and RVEF (curve). When LVGLS and RVEF were combined in the ROC curve analysis, the sensitivity increased to 88.9%, the specificity was 82.1%, and the AUC increased to 0.882.

Figure 3: CAEs-free survival according to RVEF. Kaplan-Meier curves depicting CAEs-free survival in patients with RVEF above or below the absolute value of 46.33 %. Patients. *P =0.007.

Figure 4: Stepwise addition of left ventricular RVEF to GLS. On multivariate stepwise block analysis, adding RVEF to GLS gives significant additional prognostic value.

Figure 1

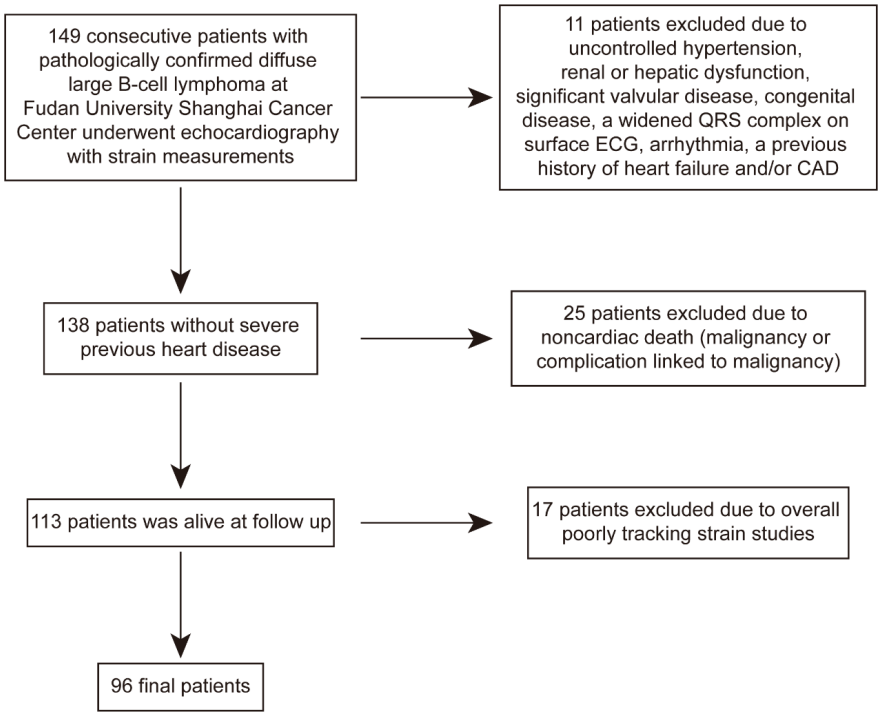

Figure 2

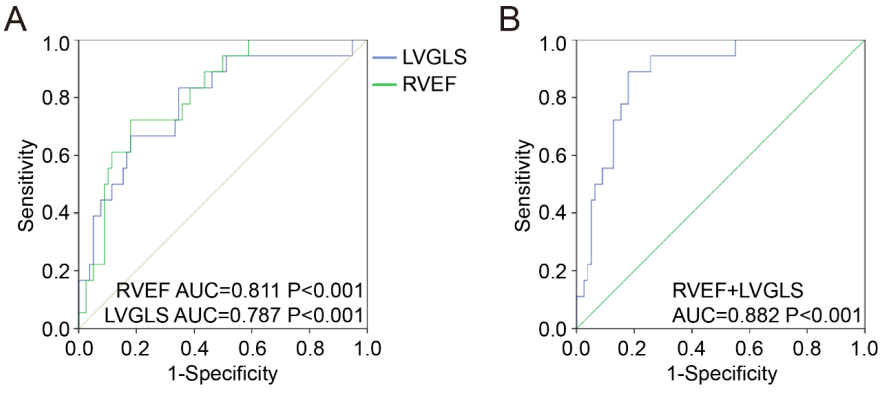

Figure 3

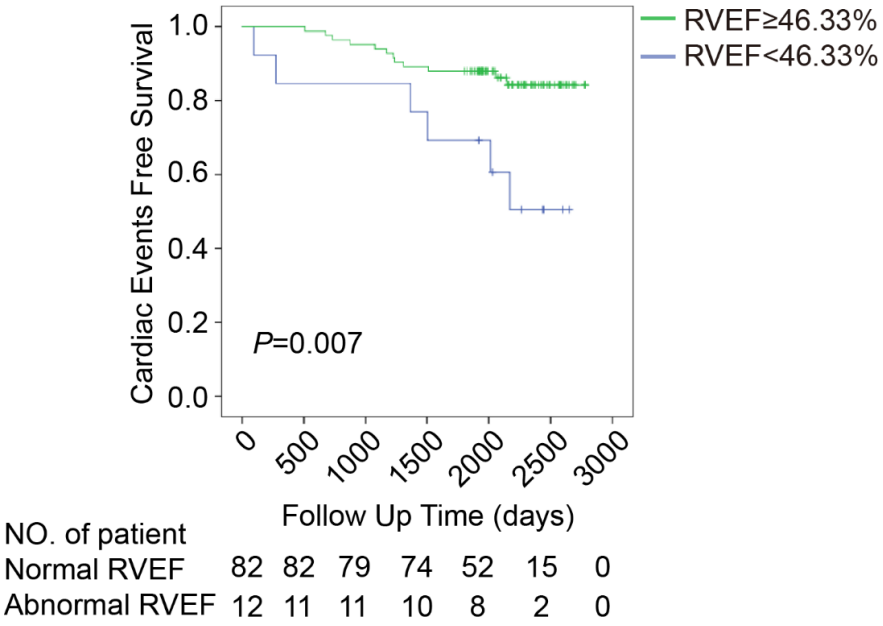

Figure 4

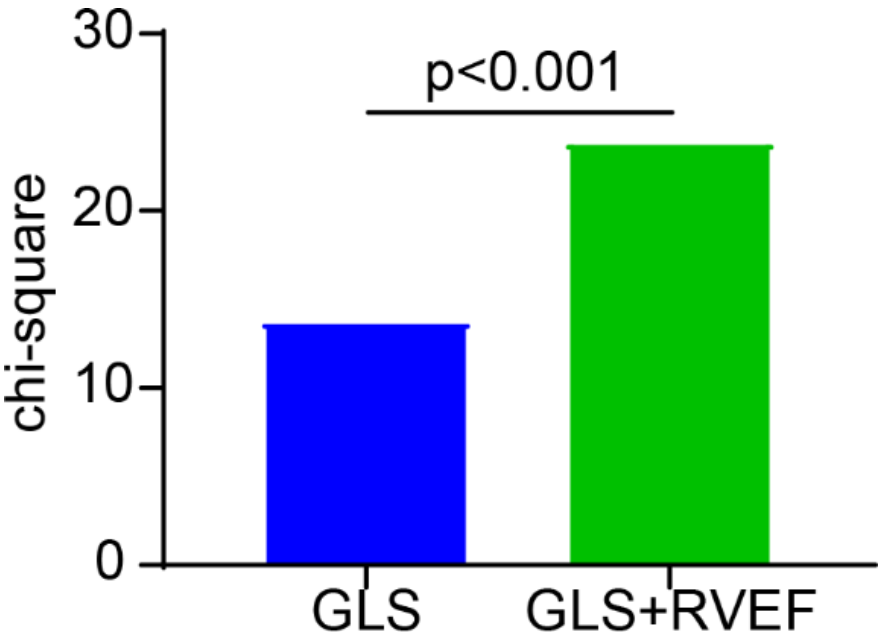

Table 1 Baseline characteristics of patients who did or did not develop CAEs

variable	Total(n=96)	No CAEs(n=7
Age(y)	49.7±11.8	49.4±11.3
Men	57(60%)	45(58%)
Weight(kg)	65±9.8	64±10
Follow-up period(d)	2242±281	2248±280

variable	Total(n=96)	No CAEs(n=7
Cycles of R-CHOP	5.4±1.3	5.4±1.4
Cumulative dose of doxorubin (mg/m^2)	379.9±94.0	378.7±94.7
Cardiac risk factors		
BP>140/90mm Hg	15(16%)	12(15%)
Diabetes mellitus	6(6%)	4(5%)
Smoking	29(30%)	23(29%)
Cancer		
I,II	78(81%)	58(74%)
III,IV	18(19%)	20(26%)
ECOGPS	0.49±0.54	0.46±0.55
Baseline 3D Echocardiography before chemotherapy	Baseline 3D Echocardiography before chemotherapy	Baseline 3D E
Left ventricular parameters		
LVEF(%)	59.6±5.0	59.4±4.9
LVEDV	73.7±13.0	72.9±12.0
LVESV	29.7±7.0	29.6±6.3
GLS	20.8±2.6	20.8±2.3
GCS	28.1±3.9	27.9±3.5
Right ventricular parameters		
RVEF(%)	50.7±4.2	50.9±4.1
RVEDV	63.2±13.1	61.8±11.2
RVESV	31.7±8.1	30.4±6.2

BP, blood pressure, ECOGPS, Eastern Cooperative Oncology Group performance status; EDV, end-diastolic volume; ESV, end-systolic volume. Other abbreviations as in Abbreviations.

Data are expressed as mean ± SD, or as number (percentage).

Table 2 Cox analysis of clinical and echocardiographic variables

variable	No CAE(n=78)	CAE(n=18)
Baseline characteristics	**Baseline characteristics**	**Baseline characteristics**
Age(y)	49.7±11.8	49.4±11.3
Men	57(60%)	45(58%)
Weight(kg)	65±9.8	64±10
Follow-up period(d)	2242±281	2248±280
Cumulative dose of doxorubin (mg/m^2)	379.9±94.0	378.7±94.7
Cardiac risk factors		
BP>140/90mm Hg	15(16%)	12(15%)
Diabetes mellitus	6(6%)	4(5%)
Smoking	29(30%)	23(29%)
3D Echocardiography after the completion chemotherapy	**3D Echocardiography after the completion chemotherapy**	**3D Echocardiography after the completion chemotherapy**
Left ventricular parameters		
LVEF(%)	57.0±5.2	54.3±7.7
LVEDV	73.9±13.3	76.7±15.3
LVESV	31.8±7.2	35.4±11.0
LVGLS	20.1±3.2	16.7±3.3
LVGCS	26.3±4.0	24.1±4.7
Right ventricular parameters		

RVEF(%)	49.2±4.4	44.3±4.4
RVEDV	66.6±13.6	68.0±16.0
RVESV	33.9±8.0	38.5±9.4
RVLFS	15.9±6.4	18.3±9.2
RVLSS	24.4±5.3	22.6±8.9

HR, hazard ratio, CI, Confidence interval; LFS, longitudinal free-wall strain, LSS, longitudinal septal strain. Other abbreviations as in Abbreviations.

*Using univariate predictors with P values $< .05$ as candidate variables.

+Multivariate significance defined as $P < .05$.

Data are expressed as mean ± SD, or as number (percentage).