Summed rest score in gated myocardial perfusion imaging is a good predicator for treatment-related cardiotoxicity after anthracycline chemotherapy in diffuse large B-cell lymphoma patients

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Abstract

Background: Anthracycline chemotherapy is commonly used in the treatment of diffuse large B-cell lymphoma (DLBCL) patients. Treatment-related cardiotoxicity (TRC) may be observed during treatment and may induce severe cardiac failure or cardiac arrhythmia as the main cause of death, even several years after chemotherapy implementation. Herein, we performed a study to investigate the prognostic value of gated myocardial perfusion imaging (G-MPI) summed rest score (SRS) for the early detection of TRC caused by anthracycline chemotherapy in DLBCL patients.

Methods: A total of 36 DLBCL patients were enrolled, and a series of parameters from the same individual patient were compared between baseline and after the end of the 6th R-CHOP chemotherapeutic regimen. According to whether TRC occurred during the observation period, the patients were divided into two groups, and parameters related to cardiac function were compared.

Results: SRS in G-MPI and QTc interval in electrocardiogram were significantly different before and after chemotherapy (P = 0.012 and P = 0.015, respectively).By comparing parameters related to cardiac function between the TRC group (n = 22) and the no-TRC group (n = 14), only SRS was significantly different (P = 0.012). Multivariate logistic regression analysis showed that the SRS level was the only independent predicator for TRC (P = 0.018, HR = 6.053, 95% CI: 1.364-26.869). Receiver operating characteristic curve analysis identified an optimal SRS cutoff of >1for predicting TRC after anthracycline chemotherapy (P 0.001).

Conclusion: The G-MPI SRS level was an early indicator for TRC surveillance in DLBCL patients after anthracycline chemotherapy, thus contributing to early treatment and a subsequent decrease in mortality caused by such cardiovascular complications.

Background

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma worldwide[1]. Although the use of anti-CD20 monoclonal antibodies has significantly improved the survival of DLBCL patients, traditional chemotherapy is still indispensable for the treatment of DLBCL. Because of high efficacy and broad spectrum of activity, anthracyclines, such as adriamycin and epirubicin, play an important role in first-line chemotherapeutic regimens for DLBCL[2].

Anthracyclines are commonly associated with cardiotoxicity, and the incidence is approximately 9%[3; 4]. The prognosis of anthracycline-induced heart failure is poor, with a 60% mortality rate at 2 years[5]. Clinical guidelines suggest limiting the maximum cumulative dose to reduce the incidence of cardiotoxicity while attempting to maintain the maximum antitumor effect[6].

Anthracycline-induced cardiotoxic damage occurs most often at the time of exposure, while the symptoms of cardiotoxicity related to heart failure might be masked for several years. Anticongestive treatment is usually not started until clinical manifestations show that the compensatory mechanism of

heart is no longer adequate and the prognosis is seriously deteriorated[7]. With the early recognition and treatment initiation, the prognosis of patients can be significantly improved [8]. Acute cardiotoxic side effects are rare and usually reversible. Late-onset cardiomyopathy is more common but it is difficult to treat and often along with a poor prognosis. Hence, it is of great importance to identify an appropriate and sensitive method for early detection of myocardial injury to improve the quality of life and prolong the survival of DLBCL patients.

Left ventricular ejection fraction (LVEF)refers to the ratio of stroke volume (SV) divided by the left ventricular end diastolic volume (LVEDV)[9].Notably, to date LVEF is still a classic index to evaluate systolic function, while it is highly dependent on preload and afterload conditions and it is a late marker of cardiotoxicity[10]. The activation of sympathetic nervous system in patients with heart failure maintains the normal left ventricular ejection fraction[7]. It may be a late finding to detect a decrease in LVEF after cancer treatment; therefore, earlier markers of myocardial dysfunction are required[11–13].

It may reduce the risk of cardiotoxicity that an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and/or β-blocker and/or statin can be administrated early[11]. In order to limit the risk of cardiotoxicity and enhance cardiac protection strategies, there is developing interest in findings pecific and sensitive markers of early left ventricle (LV) dysfunction, including cardiac biomarkers and advanced imaging modalities[14; 15].

Compared with other traditional methods, Gated myocardial perfusion imaging (G-MPI) is a novel sensitive method which can identify the small myocardial injury caused by chemotherapy[16]. The summed rest score (SRS) is a common parameter detected in G-MPI to evaluate the function of myocardial perfusion[17; 18]. Whether resting G-MPI quantitative analysis can detect myocardial injury in lymphoma patients after chemotherapy earlier than LVEF value has not been reported.

The aim of the current study was to investigate the prognostic value of G-MPI parameters in the early detection of impaired myocardial function in DLBCL patients receiving anthracycline chemotherapy.

Methods

Study design

Thirty-six patients newly diagnosed with DLBCL in the hematology department of the Third Affiliated Hospital of Soochow University were enrolled in the study between March 2016 and July 2019. Patients with any heart disease at baseline examination were excluded. All DLBCL diagnoses were made based on histological pathology. Clinical staging data were determined according to the Ann Arbor staging classification[19]. The study was designed to assess each patient's cardiac function by serum test, echocardiography and G-MPI at baseline and after the last cycle of chemotherapy (mean of 6 months).

All patients were administered 6 cycles of the chemotherapeutic regimen of R-CHOP (rituximab 375 mg/m^2; cyclophosphamide 750 mg/m^2, vincristine 1.4 mg/m^2, epirubicin, 70 mg/m^2 or pegylated

liposomal doxorubicin 25 mg/m^2, prednisone 100 mg for 5 days). The R-CHOP regimen was administered every 3 or 4 weeks according to hematopoietic recovery.

Cardiac function evaluation

Each patient's cardiac function was evaluated using a series of serum indicators, echocardiography and G-MPI. Treatment-related cardiotoxicity (TRC) was defined using similar criteria as described in the major adjuvant trials, including a decrease in LVEF > 15% from baseline, a decrease in LVEF > 10% to < 50%, symptomatic heart failure, arrhythmia, infarction or cardiac death[20; 21].

The serum indicators for cardiac function included brain natriuretic peptide (BNP), troponin, aspartate transaminase (AST), lactic dehydrogenase (LDH), creatine kinase (CK), creatine kinase-MB isoenzyme (CK-MB) and myoglobin. All of the indicator levels were measured using XE-2100 (Sysmex Co., Ltd., Kobe, Japan).

Echocardiographic examinations were performed using the ultrasonic diagnostic apparatus (Vivid E9; GE Healthcare, Waukesha, Wisconsin, USA) with a 3.5-MHz transducer. Reports were made according to the American Society of Echocardiography guidelines[22; 23].The indicators relevant to research included left atrial diameter (LAD), left ventricular posterior wall thickness (LVPWT), left ventricular end systolic diameter (LVSED), interventricular septal thickness (IVST), left ventricular end diastolic diameter (LVEDD) and LVEF.

Rest G-MPI was performed using a SPECT/CT scanner (Symbia T16, Siemens Medical Systems, Erlangen, Bavaria, Germany) which was equipped with a low-energy high-resolution collimator. The procedure was performed as follows: 1)The patient was intravenously injected of 740–925 MBq for rest studies and the radiochemical purity was > 95%; 2) 60 minutes after the injection, electrodes were placed upon the heart of patient with two detectors set at 90°; 3) images were acquired every 35 s and 6° clockwise from 45° at the right anterior oblique position to 45° at the left anterior oblique position with an acquisition matrix of 128 × 128 and a magnification of 1.45; 4) the gated acquisition was performed with electrocardiographic R-wave as the acquisition trigger signal and 8 frames/RR interval; and 5) the planar images were reconstructed by a Flash 3D iterative method (16 iterations and 2 subsets) and reoriented to obtain LV short-axis, horizontal long-axis, and vertical long-axis images. The LV was divided into 17 segments using QPS and QGS quantitative analysis software (QPS & QGS 2009, Cedars-Sinai Medical Center, Los Angeles, California, USA). The QPS was used to analyze myocardial perfusion. The segmental radiotracer activity in the rest and stress scans was scored according to a standard 5-point scale (0: normal; 1: mild; 2: moderate; 3: severe; 4: absent activity) and summed to generate an SRS[24].QGS was used to obtain the LVEF, summed motion score (SMS) and summed thickening score (STS).

Statistical analysis

SPSS Version 24.0 statistical software (SPSS Inc., Chicago, IL, USA) and MedCalc software version 15.11.4 were used for all statistical analyses in this study. Data which were normally distributed are shown as the mean ± standard error (SE), while data without a normal distribution are presented as the

median and interquartile range. We used paired t-tests, independent samples t-tests, and nonparametric tests to compare the mean or median between groups. Proportional differences were evaluated with the χ^2 test or Fisher's exact test. The optimal cutoff value for the association of the SRS level with TRC after anthracycline chemotherapy was determined on the basis of the result of receiver-operator characteristic (ROC) curve analysis. The initial univariate logistic regression analysis was followed by a multivariate logistic regression model using stepwise selection to identify univariate predictors of TRC. For all steps, $P < 0.05$ was considered statistically significant.

Results

Patients' baseline characteristics

From March 2016 to July 2019, 36 DLBCL patients were enrolled. The patients' baseline clinical characteristics are displayed in Table 1. Their mean age was 58 (27–72) years, and 20 patients were male. The body mass index (BMI) of these patients was 22.854 ± 0.636. At baseline all of the recruited patients had no comorbidity of heart disease, while 8 patients had hypertension, 5 patients had diabetes, and 10 patients also suffered from hypercholesteremia and hypertriglyceridemia. Ten patients (27.8%) were found in the early stage of lymphoma Ann Arbor classification (I-II), and 26 patients (72.2%) were found in the late stage of lymphoma Ann Arbor classification (III-IV). Ten patients (28%) were diagnosed with B symptoms.

Table 1
Baseline of the clinical characteristics of 36 diffuse large B cell lymphoma patients enrolled in this study

Characteristics	
Age, years [median (range)]	58 (27–82)
Gender [n (%)]	
male	20 (55.6%)
female	16 (44.4%)
BMI (mean ± SE)	22.854 ± 0.636
Comorbidity [n (%)]	
heart disease	0 (0%)
hypertension	8 (22.2%)
diabetes	5 (13.9%)
hypercholesteremia	10 27.8%)
hypertriglyceridemia	10 (27.8%)
Clinical stage [n (%)]	
I-II	10 (27.8%)
III-IV	26 (72.2%)
B-symptom [n (%)]	10 (28%)

Comparison of serum, echocardiography, electrocardiogram and gated myocardial perfusion imaging parameters at baseline and after chemotherapy

As listed in Table 2, by comparing the serum parameters of these patients before and after 6 courses of R-CHOP chemotherapeutic regimens, we found that fasting blood sugar (FBS, $P = 0.036$), total cholesterol (TC, $P = 0.03$) and low-density lipoprotein (LDL, $P = 0.001$) were significantly increased, and the hemoglobin level was significantly higher ($P = 0.034$) after chemotherapy.

Table 2
Comparison of Plasma markers before and after chemotherapy

Plasma markers	Before chemotherapy	After chemotherapy	*P*
FBS, mmol/L	4.98 (0.87)	5.3 (1.32)	0.0023
TC, mmol/L	4.287 ± 0.156	4.716 ± 0.159	0.03
HDL, mmol/L	1.076 ± 0.057	1.166 ± 0.053	0.073
LDL, mmol/L	2.521 ± 0.108	2.847 ± 0.134	0.001
TG, mmol/L	1.036(0.6)	1.475 (0.985)	0.155
ALT, U/L	18 (19.5)	18 (15)	0.665
creatinine, mmol/L	65.667 ± 1.709	68.273 ± 2.029	0.164
D-Dimer, mg/L	0.505 (0.74)	0.395 (0.398)	0.275
WBC, $\times 10^9$/L	5.06 (2.318)	4.51 (2.495)	0.139
hemoglobin, g/L	121.5 (24.25)	125.5 (25.5)	0.034
Platelet, $\times 10^9$/L	194.794 ± 11.824	187.147 ± 10.871	0.464
RDW (%)	13.1 (1.775)	13.5 (1.875)	0.174
β2-MG, mg/L	1.798 ± 0.125	1.854 ± 0.091	0.706
CRP, mg/L	7.25 (42.25)	4.95 (5.3)	0.177
PCT, ng/ml	0.053 (0.071)	0.069 (0.085)	0.655
BNP, pg/ml	67.5 (64.25)	36 (57.388)	0.06
AST, U/L	24 (11)	26 (11)	0.82
LDH, U/L	587.136 ± 51.855	557.136 ± 28.157	0.527
CK, U/L	49 (24.5)	55 (38)	0.509
CK-MB, ng/ml	0.7 (0.7)	0.9 (0.8)	0.149
troponin, μg/L	0.001 (0.003)	0.003(0.002)	0.142
myoglobin, ng/ml	15.1 (8.8)	15.8 (10.05)	0.765

FBS: fasting blood sugar; TC: total cholesterol; HDL: high density lipoprotein; LDL: low density lipoprotein; TG: triacylglycerol; ALT: alanine aminotransferase; WBC: white blood cells; RDW: red blood cell distribution width;β2-MG: β2-microglobulin; CRP: C-reactionprotein; PCT: procalcitonin; BNP: brain natriuretic peptide; AST: aspartate transaminase; LDH: lactic Dehydrogenase; CK: creatine kinase

Considering the cumulative cardiotoxicity of anthracyclines, we compared cardiac function-related serum indicators of these patients at the time of initial treatment and after the end of chemotherapy. There were

no significant differences, as listed in Table 2 ($P > 0.05$).

As listed in Table 3, we compared echocardiographic and electrocardiogram parameters of these patients at baseline and after chemotherapy, and we did not find any significant differences in these parameters in echocardiography, including LVEF ($P > 0.05$). Interestingly, we found that the QTc interval ($P = 0.015$) was significantly increased. By using the novel G-MPI method to evaluate cardiac function, we found that SRS, the indicator representing myocardial perfusion, was significantly higher after chemotherapy ($P = 0.012$) (Table 4 and Fig. 1).

Table 3
Comparison of markers in echocardiography and electrocardiogram before and after chemotherapy

	Before chemotherapy	After chemotherapy	*P*
Electrocardiogram			
LAD, mm	35.389 ± 1.462	34.5 ± 0.883	0.371
LVEDD, mm	46 ± 0.957	45.667 ± 0.886	0.674
LVESD, mm	31 (5)	30.5 (2.5)	0.754
IVST, mm	9 (1)	9 (1)	0.604
LVPWT, mm	9 (0.5)	9 (1.25)	0.964
LVEF, %	62.889 ± 0.593	62.5 ± 0.445	0.369
Electrocardiogram			
heart rate, bpm	73 (18)	79 (10.5)	0.102
PR interval, ms	153.5 (28)	174 (19.5)	0.475
QRS interval, ms	100 (10.5)	100 (13)	0.283
QT interval, ms	375.97 ± 5.607	372.636 ± 4.482	0.549
QTc interval, ms	421.25 ± 3.775	429.344 ± 3.349	0.015

LAD: left atrial diameter; LVEDD: left ventricular end diastolic diameter; LVSED: left ventricular end systolic diameter; IVST: interventricular septal thickness; LVPWT: left ventricular posterior wall thickness; LVEF: left ventricular ejection fraction

Table 4
Comparison of markers related to myocardial perfusion in gated myocardial perfusion imaging (G-MPI) before and after chemotherapy

markers	Before chemotherapy	After chemotherapy	*P*
SRS	2 (3)	3 (3)	0.012
SMS rest	0 (0)	0 (1)	0.9
STS rest	0 (0)	0 (0)	0.858
EF rest	65.514 ± 1.608	64.714 ± 1.746	0.582
SRS: summed rest score; SMS: summed stress score; STS: summed thickening score;			

Association of SRS with TRC

TRC was defined using similar criteria[20; 21] as a decrease in LVEF > 15% from baseline, a decrease in LVEF > 10% to < 50%, symptomatic heart failure, arrhythmia, infarction or cardiac death. According to these criteria and the characteristics of patients during observation, we divided all the patients into the TRC group (n = 22) and the no-TRC group (n = 14). In the TRC group, one patient had a myocardial infarction, one patient had a cardiac death, 20 patients had other kinds of arrhythmia,4 patients had a decrease in LVEF of > 15% from baseline or a decrease in LVEF of > 10% to < 50%, while none of them had symptomatic heart failure.

We compared the baseline characteristics of patients in these two groups. Then, we also compared the plasma markers and echocardiography, electrocardiogram and G-MPI parameters of patients after 6 courses of chemotherapy between these two groups (Tables 5–8). There was no significant difference in any of the parameters except SRS of G-MPI after chemotherapy: the median SRS levels of the TRC group and no-TRC group were 4 and 0, respectively ($P < 0.0001$).

Table 5
Comparison of baseline characteristics in no-TRC group and TRC group

Characteristics	**no-TRC (n = 14)**	**TRC (n = 22)**	***P***
Age, years [median (range)]	59 (29–76)	63(29–85)	0.797
Gender [n (%)]			
male	9(64.3%)	11(50%)	0.5007
female	5(35.7%)	11(50%)	
BMI (mean ± SD)	24.27 ± 1.198	23.49 ± 0.866	0.593
Comorbidity [n (%)]			
heart disease	0(0%)	0(0%)	> 0.9999
Hypertension	5 (29.4%)	3(15.8%)	0.2169
diabetes	2 (14.3%)	3(13.6%)	> 0.9999
hypercholesteremia	4(28.6%)	6(27.3%)	> 0.9999
hypertriglyceridemia	3(21.4%)	8(36.4%)	0.4672
Clinical stage [n (%)]			
I-II	5(35.7%)	5(22.7%)	0.4619
III-IV	9(64.3%)	17(77.3%)	
B-symptom [n (%)]	35.7%	22.7%	0.4619

Table 6
Comparison of Plasma markers in no-TRC group and TRC group after chemotherapy

Plasma markers	No-TRC (n = 14)	TRC (n = 22)	*P*
FBS, mmol/L	5.35(1.165)	5.285(1.55)	0.606
TC, mmol/L	4.67 ± 0.234	4.755 ± 0.197	0.786
HDL, mmol/L	1.077 ± 0.078	1.198 ± 0.065	0.248
LDL, mmol/L	2.854 ± 0.183	2.896 ± 0.176	0.879
TG, mmol/L	1.505(0.645)	1.38(1.802)	0.77
ALT, U/L	17(15.5)	19.5(15.75)	0.427
creatinine, mmol/L	62.675 ± 5.967	71.8 ± 3.11	0.148
D-Dimer, mg/L	0.41(4.055)	0.39(0.225)	0.733
WBC, $\times 10^9$/L	3.815(2.218)	5.056(2.19)	0.055
hemoglobin, g/L	127.714 ± 3.931	130.6 ± 3.975	0.621
Platelet, $\times 10^9$/L	166.286 ± 14.446	201.75 ± 14.891	0.109
RDW(%)	13.979 ± 0.399	13.58 ± 0.304	0.425
β2-MG, mg/L	1.982 ± 0.197	2.123 ± 0.188	0.608
CRP, mg/L	3.815(2.218)	5.075(2.21)	0.173
PCT, ng/ml	0.083 ± 0.0186	0.12 ± 0.05	0.469
BNP, pg/ml	20(38)	30(42)	0.058
AST, U/L	27(11.25)	26(9)	0.548
LDH, U/L	529.667 ± 28.374	551.514 ± 31.089	0.642
CK, U/L	55.5(38)	51(40.5)	0.94
CK-MB, ng/ml	1(1.3)	0.9(1)	0.599
troponin, μg/L	0.00235(0.003)	0.0026(0.00325)	0.33
myoglobin, ng/ml	16.65(8.075)	16.6(13.6)	0.822

FBS: fasting blood sugar; TC: total cholesterol; HDL: high density lipoprotein; LDL: low density lipoprotein; TG: triacylglycerol; ALT: alanine aminotransferase; BUN: blood urea nitrogen; WBC: white blood cells; RDW: red blood cell distribution width;β2-MG: β2-microglobulin; CRP: C-reactionprotein; PCT: procalcitonin; BNP: brain natriuretic peptide; AST: aspartate transaminase; LDH: lactic Dehydrogenase; CK: creatine kinase

Table 7
Comparison of markers in echocardiography and electrocardiogram in no-TCR group and TCR group after chemotherapy

	no-TRC (n = 14)	TRC (n = 22)	*P*
Echocardiography			
LAD, mm	36(5)	33.5(5.5)	0.07
LVEDD, mm	47 ± 1.388	46.778 ± 1.382	0.916
LVESD, mm	31(4)	30.5(6.25)	0.541
IVST, mm	9(1)	9(1.25)	0.16
LVPWT, mm	9(1)	9(1.25)	0.115
LVEF, %	62(4)	63(3.25)	0.82
Electrocardiogram			
heart rate, bpm	82 ± 4.414	79 ± 1.593	0.498
PR interval, ms	152.5(29.75)	157.5(31.75)	0.436
QRS interval, ms	98(10.5)	101(13.5)	0.294
QT interval, ms	357(33.75)	375(36.5)	0.432
QTc interval, ms	429.083 ± 4.728	429.5 ± 4.637	0.953

LAD: left atrial diameter; LVEDD: left ventricular end diastolic diameter; LVSED: left ventricular end systolic diameter; IVST: interventricular septal thickness; LVPWT: left ventricular posterior wall thickness; LVEF: left ventricular ejection fraction

Table 8
Comparison of markers in gated myocardial perfusion imaging (G-MPI) in no-TRC group and TRC group after chemotherapy

markers	No TRC	TRC	*P*
SRS	0(1)	4(3.25)	< 0.0001
SMS rest	0(0.25)	0(1.5)	0.375
STS rest	0(0)	0(0.5)	0.455
EF rest	61.357 ± 2.122	66.952 ± 2.463	0.118

SRS: summed rest score; SMS: summed stress score; STS: summed thickening score;

After adjusting for LVEF in echocardiography and QTc interval in electrocardiogram, multivariate logistic regression analysis showed that the SRS level was the only independent predictor for TRC (OR = 6.053, 95% CI: 1.364 to 26.869, *P* = 0.018, Table 9).

Table 9
Univariate and multivariate logistic regression analyses

Variables	P value	Multivariate analysis		
		OR	95%CI	P value
Clinical characteristics				
SRS	< 0.0001	6.503	1.709–24.738	0.006
QTc	0.953	0.982	0.888–1.086	0.721
EF rest	0.118	1.031	0.894–1.189	0.673
CI: confidence interval; OR: odds ratio. Other abbreviations as in Table 1.				

As shown in Fig. 2, by using ROC curve analysis, we identified an optimal SRS cutoff of > 1 for predicting TRC, with a sensitivity of 95.5%, specificity of 85.7%, and area under the curve of 0.964 ($P < 0.001$).

Discussion

To our knowledge, this is the first study to use rest gated myocardial perfusion imaging to evaluate abnormal changes in left ventricular myocardial perfusion in DLBCL patients before and after chemotherapies. The results showed that the SRS value detected after chemotherapy was significantly higher than that before chemotherapy, indicating that there was abnormal left ventricular perfusion after chemotherapy. Logistic multivariate analysis showed that SRS was an independent risk factor for TRC after chemotherapy in DLBCL patients. ROC curve analysis showed that when SRS was > 1, the possibility of TRC was especially high.

With anthracycline chemotherapy playing a prominent role in lymphoma treatment, DLBCL patients' prognoses continue to improve because of earlier detection and newer targeted therapeutic drugs. With longer survivorship, there will be a large number of DLBCL patients who will have to face the risk of cardiovascular morbidity and mortality which caused by long-term toxicity of anthracycline chemotherapy[25–28]. Cardiotoxicity caused by anthracycline is often progressive and irreversible, which severely affects the prognosis of DLBCL patients[14; 29; 30]. Serial echocardiographic evaluation of resting LVEF is still a classic index to monitor anthracycline-induced cardiac side effects. However, LVEF tests are limited by the low sensitivity. Normal LVEF does not mean there is no cardiotoxicity. The occurrence of irreversible cardiomyopathy often happen before observation of decreases in LVEF[4; 7]. It has been reported that at the early stage of cardiac function impairment, most patients present subclinical myocardial damage[31]. Early detection and treatment of cardiotoxicity can be critical for reduction in associated adverse cardiac events and for the cardiac function recovery. There was no significant change in left ventricular function, the electrocardiogram, or myocardial markers in the early stage of myocardial damage. Only when the myocardial function is severely damaged or overall heart function is impaired would there be detectable abnormal changes in indicators such as left ventricular

systolic function. In our study results, there was no significant difference in LVEF values before and after chemotherapy in DLBCL patients. According to the TRC criterion of LVEF value, only 4 DLBCL patients developed LVEF-related TRC after chemotherapy. Univariate and multivariate analyses of TRC showed that LVEF was not an independent risk factor for TRC. The results further confirmed that LVEF could not evaluate the cardiotoxicity caused by anthracycline drugs in the early stage.

The QTc interval on the electrocardiogram (ECG) refers to the QT interval corrected according to heart rate or RR interval[32]. Antineoplastic drugs open sodium and calcium channels by blocking potassium channels, resulting in cardiac repolarization abnormality and a prolonged QTc interval would be demonstrated on the ECG[33]. Drug-induced QTc interval prolongation has been considered to be a critical risk factor for cardiac toxicity and probably leads to palpitations, syncope, and sudden cardiac death caused by severe ventricular arrhythmias[30; 33; 34]. With a follow-up study of cardiac function in 147 adult surviving patients who had previously suffered from childhood tumors and received anthracycline chemotherapy, Markman TM et al. found that the prolonged QTc interval was related to the subsequent development of left ventricular dysfunction[14], suggesting that the QTc interval might be an earlier indicator for evaluating the impairment of cardiac function than LVEF. The normal range of the QTc interval is 350–450 ms in adult males and 360–460 ms in adult females[33]. Puppe J et al. pointed out that the risk of sudden cardiac death tripled when the QT interval was greater than 470 ms[33]. Porta-Sánchez A indicated that the patient should be evaluated carefully if he should discontinue the usage of all offending drugs when a prolonged QTc interval is detected (> 500 ms or an increase of > 60 ms longer than baseline)[31]. But when a patient's QTc interval fluctuates within the normal range, clinicians are prone to neglect the vigilance of patients with myocardial injury. In addition, considerable variation may be caused by differences in the technical circumstances and nonpathologic biologic variability. All the factors mentioned above have contributed to the uncertainty of using the ECG QTc interval as an indicator of cardiac toxicity monitoring. In this study, the mean QTc interval of patients after anthracycline chemotherapy was 429.344 ms. Although there was a significant difference before and after treatment, the mean QTc interval after anthracycline chemotherapy still did not reach the upper limit of the QTc interval of 450/460 ms. Moreover, the results of this study showed that the QTc interval was not an independent risk factor for TRC. Therefore, there are still limitations of using the QTc interval as an early indicator of cardiac toxicity.

The mechanisms of anthracycline-induced cardiomyopathies include endoplasmic reticulum stress, calcium dysregulation, activation of immune, impairment of progenitor cells, and some other parameters[35; 36]. To date, the most widely cited and accepted mechanism is oxidative stress caused by ROS production[37–40]. Koleini N et al. point out that cardiomyocytes need a large number of healthy-functioning mitochondria to product sufficient ATP to maintain contractile function and cell survival. Autophagic cell death and mitophagy have been proposed to be related to the cardiotoxicity of anthracycline[41]. Ichikawa Y et al found that anthracycline-dependent cardiotoxicity occurs through ROS production and possibly mitochondrial iron accumulation[42]. Mitochondria play a pivotal role in the metabolism and apoptosis of cardiomyocytes. ^{99m}Tc sestamibi(^{99m}Tc-MIBI) is a lipophilic cation

imaging tracer mainly localized in mitochondria. It is mainly sequestered within mitochondria by a huge negative transmembrane potential [43]. The distribution of ^{99m}Tc-MIBI in the myocardium is directly proportional to myocardial blood flow. When cardiomyocyte mitochondrial function is impaired, collapse of the mitochondrial membrane potential will lead toquick release of extracted ^{99m}Tc sestamibi. Therefore, G-MPI can show abnormal local myocardial perfusion, which can be used for early noninvasive evaluation of abnormal changes in mitochondrial function of cardiomyocytes[43–45].

SRS is an indicator of G-MPI for the quantitative evaluation of resting myocardial perfusion abnormalities. It can directly reflect changes in cardiomyocyte function. However, few studies have reported the application of G-MPI quantitative myocardial perfusion analysis in the early evaluation of myocardial damage caused by chemotherapy. In this study, ^{99m}Tc-MIBI G-MPI was used to quantitatively analyze the changes in myocardial perfusion before and after chemotherapy. The results showed that the resting perfusion SRS score in DLBCL patients after chemotherapy was significantly higher than that before chemotherapy. In addition, we applied logistic multivariate analysis in this study and found that SRS is an independent risk factor for predicting TRC in patients with DLBCL after chemotherapy. The results of ROC curve analysis indicated that an SRS > 1 has the highest efficiency in predicting TRC (area under the curve: 0.964, sensitivity: 95.5%, specificity: 85.7%). Namely, when SRS is > 1, prompt intervention is needed to prevent TRC. In this study, after 6 courses of anthracycline-containing chemotherapy, all of the DLBCL patients with TRC developed arrhythmia (22/22), and only a small portion of patients showed a significant decrease in LVEF (4/22). According to the results of this study, after anthracycline chemotherapy, the patients with DLBCL had abnormal regional myocardial perfusion, which was characterized by increased SRS. SRS is a much earlier indicator than LVEF and QTc interval and can be used to evaluate the cardiac toxicity not only associated with left ventricular dysfunction caused by chemotherapy (decreased LVEF) at an early stage but also caused by chemotherapy-induced arrhythmia at an early stage. The reason for this conclusion may be that abnormal perfusion is the pathological basis for left ventricular myocardial function impairment. The severity of perfusion abnormality is closely related to the decline in left ventricular function. The detection value of LVEF may still be in the normal range when slight myocardial perfusion abnormalities occur. Therefore, compared with LVEF, SRS can evaluate cardiotoxicity earlier. Cardiomyocyte damage can cause myocardial electrical conduction abnormalities and myocardial perfusion abnormalities at the same time, but the sequence and related mechanisms of the two are still unclear. In this study, the SRS abnormalities occurred earlier than QTc interval prolongation, indicating that myocardial mitochondrial damage after chemotherapy may first manifest as abnormal regional myocardial perfusion, which may be one of the factors causing arrhythmia. Studies have reported that patients with abnormal left ventricular myocardial perfusion had a significantly higher incidence of arrhythmia[46]. Therefore, compared with the QTc interval, SRS can predict the cardiac toxicity-associated arrhythmia caused by chemotherapy earlier.

Study limitations

Several limitations warrant mention. First, the enrolled sample size was relatively small: this study involved data on only 36 DLBCL patients. In the future, we will continue to expand the sample size and strive to obtain a larger sample and more convincing data. Second, the follow-up time was not long enough. In this study, we monitored and compared the cardiac function of patients with DLBCL only at the initial diagnosis and after 6 courses of R-CHOP chemotherapy. There may be some patients with delayed cardiac function that has not yet manifested. We will continue to follow up on the myocardial function of these patients and improve the follow-up results by rechecking G-MPI, color Doppler echocardiography, electrocardiogram and serum indexes related to myocardial function every six months. Third, due to the small sample size of this study, we did not compare cardiac function among subgroups of DLBCL patients with different prognosis stratifications. DLBCL is a kind of heterogeneous disease. Patients with different subtypes have very different prognoses. In the future, we will continue to expand the number of DLBCL patients enrolled and try to further refine the research. In this way, we would be able to compare cardiac function among different subgroups of DLBCL.

Conclusions

Anthracycline chemotherapy is closely related to the cardiotoxicity that occurs in patients with DLBCL, especially the abnormal electrical conduction of the myocardium. G-MPI SRS measurement provides a highly sensitive method for detecting early subclinical cardiac damage to myocardial electrical conduction in patients with DLBCL treated with anthracyclines, which may be helpful for hematologists to monitor and treat DLBCL patients' cardiac dysfunction in a timelier and more convenient manner.

Abbreviations

DLBCL: diffuse large B-cell lymphoma; TRC: treatment-related cardiotoxicity; G-MPI: gated myocardial perfusion imaging; SRS: summed rest score; LVEF: left ventricular ejection fraction; SV: stroke volume; LVEDV: left ventricular end diastolic volume; LV: left ventricle; BNP: brain natriuretic peptide; AST: aspartate transaminase; LDH: lactic dehydrogenase; CK: creatine kinase; CK-MB: creatine kinase-MB isoenzyme; LAD: left atrial diameter; LVPWT: left ventricular posterior wall thickness; LVSED: left ventricular end systolic diameter; IVST: interventricular septal thickness; LVEDD: left ventricular end diastolic diameter; SMS: summed motion score; STS: summed thickening score; SE: standard error; ROC: receiver-operator characteristic; FBS: fasting blood sugar; TC: total cholesterol; TG: triacylglycerol; HDL:high density lipoprotein; LDL: low-density lipoprotein; ALT: alanine aminotransferase; BUN: blood urea nitrogen; WBC: white blood cells; RDW: red blood cell distribution width;β2-MG: β2-microglobulin; CRP: C-reactionprotein; PCT: procalcitonin; ECG: electrocardiogram; CI: confidence interval; OR: odds ratio

Declarations

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Authors' contribution

YL, JW and MX designed the study and selected the study methodology. CQ, PX, LS, BH, FW, YY, YG and FL collected the data. YL and PX performed the statistical analysis and wrote the manuscript. JW and WD analyzed and interpreted the data. XX, YW and WG edited the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Written informed consent was obtained from each participant before the sample collection. This study was approved by the ethics committee of the Third Affiliated Hospital of Soochow University. All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration.

Consent for publication

Not applicable.

Competing Interests

There are no conflicts of interest in this study.

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Figures

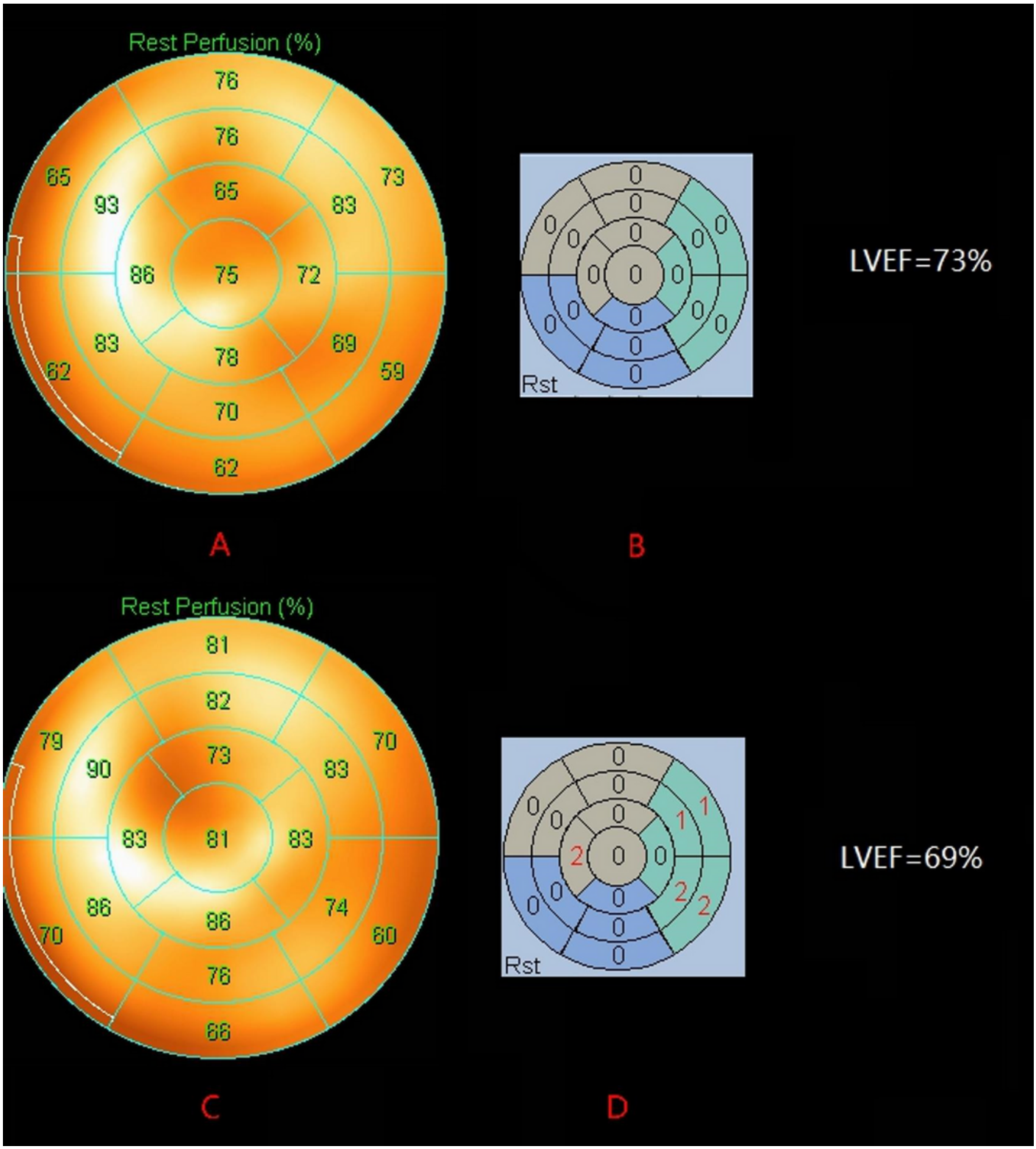

Figure 1

A typical case of significant change in G-MPI SRS of a DLBCL patient before and after R-CHOP chemotherapy. This was a typical case in which we observed a significant change in G-MPI SRS before and after R-CHOP chemotherapy. The left ventricular systolic function was normal before chemotherapy (LVEF: 73%)，and the MPI resting myocardial perfusion bull's eye chart showed even distribution of imaging agent in each wall of the left ventricle(1A) and SRS was 0 (1B)，which indicated that the left

ventricular myocardial perfusion before chemotherapy was good. The left ventricular systolic function was not significantly damaged after 6 courses of R-CHOP chemotherapy regimens (LVEF:69%□□while MPI resting myocardial perfusion bull's eye chart showed uneven distribution compared to that before chemotherapy (1C) and SRS was 8(1D), which revealed that after anthracycline chemotherapy in patients with DLBCL, although no obvious change in LVEF appeared, left ventricular myocardial perfusion had already shown to be abnormal.

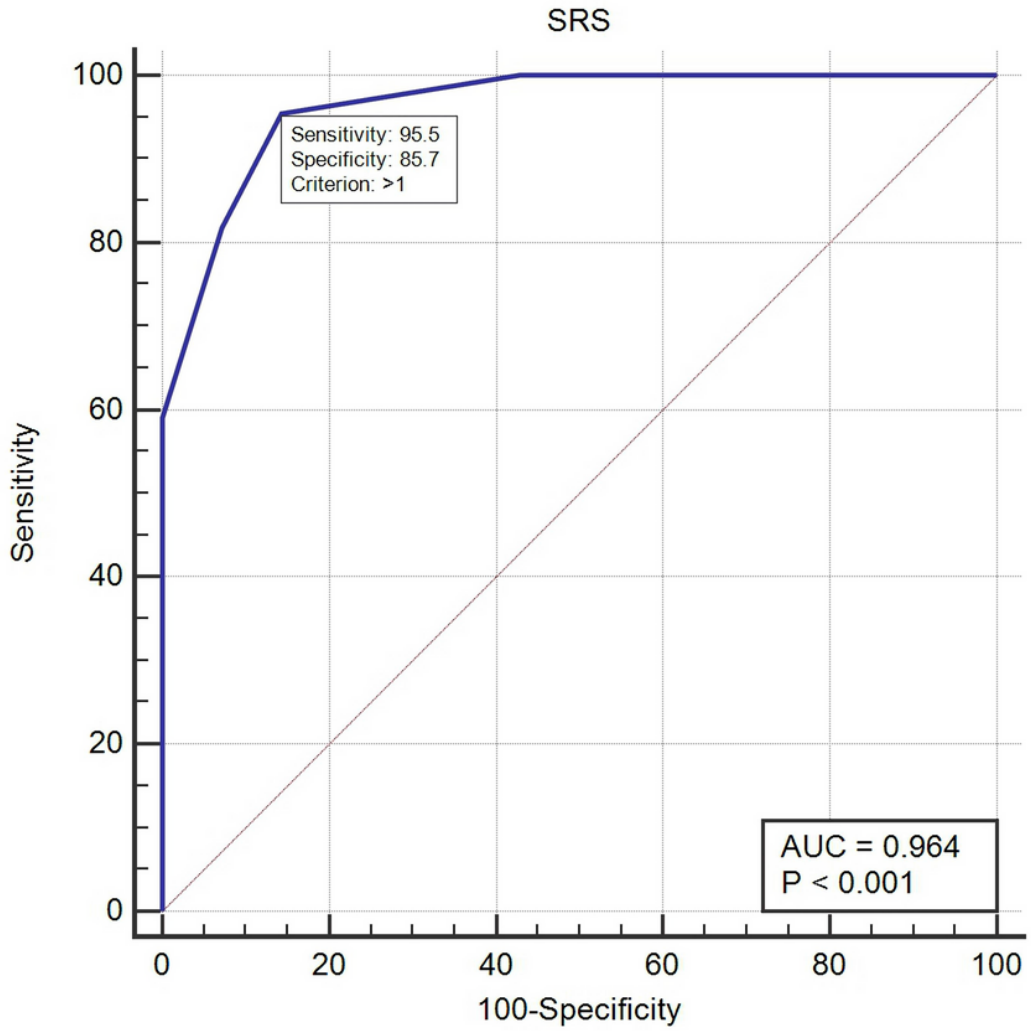

Figure 2

ROC curve analysis to identify the optimal SRS cutoff for predicting TRC. Receiver operating characteristic curve analysis identified an optimal SRS cutoff of >1 for predicting TRC after anthracycline chemotherapy, with a sensitivity of 95.5%, specificity of 85.7%, and area under the curve (AUC) of 0.964 (P< 0.001).