



Ventricular Sigmoid Septum as a Risk Factor for Anthracycline-Induced Cancer Therapeutics-Related Cardiac Dysfunction in Patients With Malignant Lymphoma

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Background: Identifying risk factors for cancer therapeutics-related cardiac dysfunction (CTRCD) is essential for the early detection and prompt initiation of medical therapy for CTRCD. No study has investigated whether the sigmoid septum is a risk factor for anthracycline-induced CTRCD.

Methods and Results: We enrolled 167 patients with malignant lymphoma who received a CHOP-like regimen from January 2008 to December 2017 and underwent both baseline and follow-up echocardiography. Patients with left ventricular ejection fraction (LVEF) $\leq 50\%$ were excluded. CTRCD was defined as a $\geq 10\%$ decline in LVEF and LVEF $< 50\%$ after chemotherapy. The angle between the anterior wall of the aorta and the ventricular septal surface (ASA) was measured to quantify the sigmoid septum. CTRCD was observed in 36 patients (22%). Mean LVEF and global longitudinal strain (GLS) were lower, left ventricular mass index was higher, and ASA was smaller in patients with CTRCD. In a multivariable Cox proportional hazard analysis, GLS (hazard ratio [HR] per 1% decrease 1.20; 95% confidence interval [CI] 1.07–1.35) and ASA (HR per 1° increase 0.97; 95% CI 0.95–0.99) were identified as independent determinants of CTRCD. An integrated discrimination improvement evaluation confirmed the significant incremental value of ASA for developing CTRCD.

Conclusions: Smaller ASA was an independent risk factor and had significant incremental value for CTRCD in patients with malignant lymphoma who received the CHOP-like regimen.

Key Words: Anthracycline-induced cardiotoxicity; Aorto-septal angle; Cancer therapeutics-related cardiac dysfunction; Sigmoid septum

Anthracycline is an effective chemotherapeutic agent for several kinds of malignant tumors, particularly in patients with malignant lymphoma (ML) and breast cancer.^{1–3} In contrast, anthracycline-induced cancer therapeutics-related cardiac dysfunction (CTRCD), defined by a decline in left ventricular ejection fraction (LVEF), often causes poor clinical outcomes and low quality of life in patients with cancer.^{4–9} Identifying baseline risk factors for CTRCD is vital for the early detection of CTRCD and prompt initiation of medical therapy, which are essential for improving left ventricular (LV) contraction after CTRCD develops.^{10–13} Several baseline risk factors have

been identified in previous studies, including baseline LVEF, global longitudinal strain (GLS), age, general cardiovascular risk factors, and a history of cardiovascular disease.^{4,11,14–16} Recently, LV hypertrophy was recognized as a risk factor for CTRCD in ML patients,¹⁷ suggesting LV morphologic remodeling also represents an accumulated myocardial injury that may result in vulnerability to CTRCD. Conversely, the sigmoid septum, known as a synonym of discrete upper septal thickening, is considered one type of LV morphologic remodeling. A previous study reported that the sigmoid septum was significantly related to LV diastolic dysfunction.¹⁸ However, no one has clari-

Received November 2, 2021; revised manuscript received February 26, 2022; accepted March 6, 2022; J-STAGE Advance Publication released online March 26, 2022 Time for primary review: 32 days

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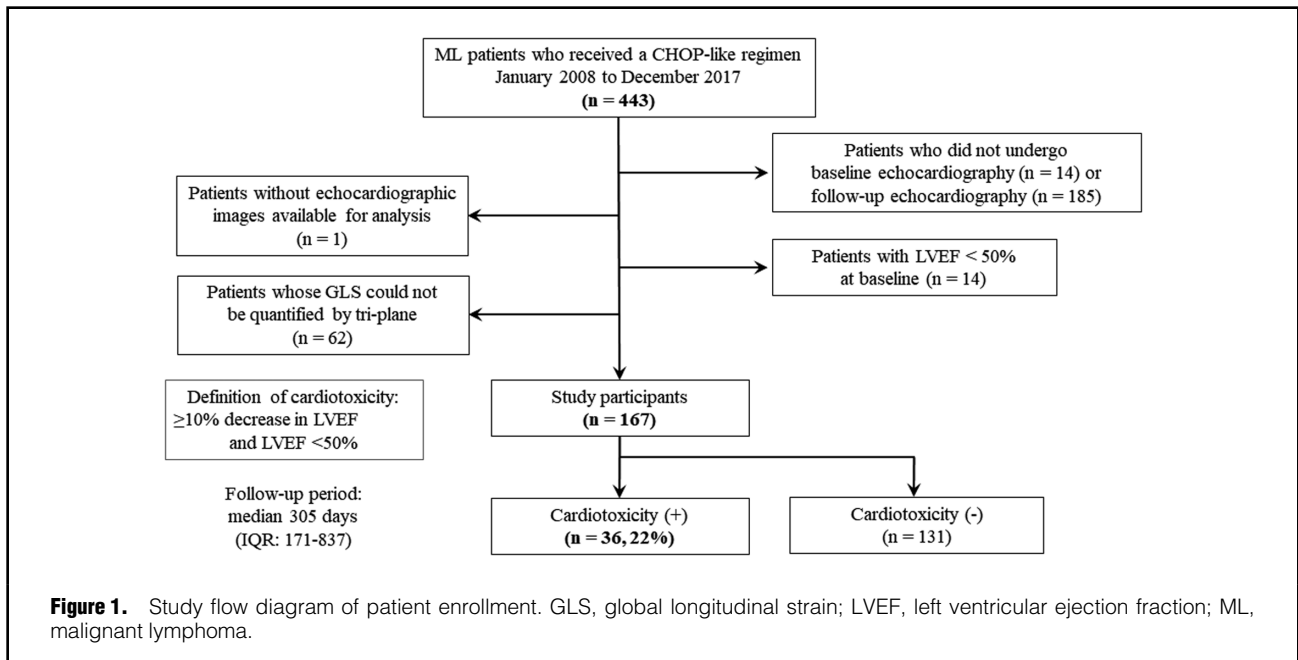
Y. Seo is a member of *Circulation Reports*' Editorial Team.

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ISSN-2434-0790





fied the association of the sigmoid septum with the incidence of CTRCD.

In the present study we focused on the presence of the sigmoid septum and aimed to reveal its impact on anthracycline-induced CTRCD in patients with ML who were treated with a CHOP-like (cyclophosphamide + doxorubicin + vincristine + prednisolone ± rituximab) regimen.

Methods

Study Population

Data for all ML patients who were treated with a CHOP-like regimen between January 2008 and December 2017 at Nagoya City University Hospital were reviewed retrospectively. The dosing and schedule for the CHOP-like regimen were standardized in this cohort. From this group, patients who underwent a baseline echocardiographic examination and ≥1 follow-up examination were enrolled in the study (Figure 1). Patients with an LVEF < 50% at baseline but no echocardiographic images of adequate quality were excluded. The present study is a subanalysis of a previous study in which we described the clinical features of anthracycline-induced CTRCD.¹⁹

Study Protocol

Patients' clinical characteristics, including age, sex, body mass index, general cardiovascular risk factors, past history, laboratory data, chemotherapeutic regimen, performance status, and echocardiographic parameters, were retrospectively collected from their medical records. The chemotherapeutic regimen, performance status, and dose of anthracycline were assessed by 2 hematologists. Patients with intravascular large B-cell lymphoma (IVL) and primary mediastinal large B cell lymphoma (PMLBCL) were enrolled in the present study as a subtype of diffuse large B-cell lymphoma (DLBCL). Echocardiographic parameters and the incidence of symptomatic heart failure and cardiovascular death were obtained and assessed by 2 cardiologists in a

blinded manner. In the present study, CTRCD was defined as a decline in LVEF of ≥10% from baseline and LVEF < 50% in the follow-up study.⁹

Cardiovascular risk factors were defined as hypertension, dyslipidemia, diabetes, and a history of smoking. Each cardiovascular risk factor was defined using the following criteria: hypertension was defined as a history of hypertension or being on antihypertensive therapy; dyslipidemia was defined as a history of dyslipidemia, serum low-density lipoprotein cholesterol ≥140 mg/dL, or being on cholesterol-lowering treatment; and diabetes was defined as a history of diabetes, HbA1c ≥6.5%, or being on blood glucose-lowering therapy. A history of ischemic heart disease was defined as a history of myocardial infarction, angina pectoris, or coronary artery revascularization.

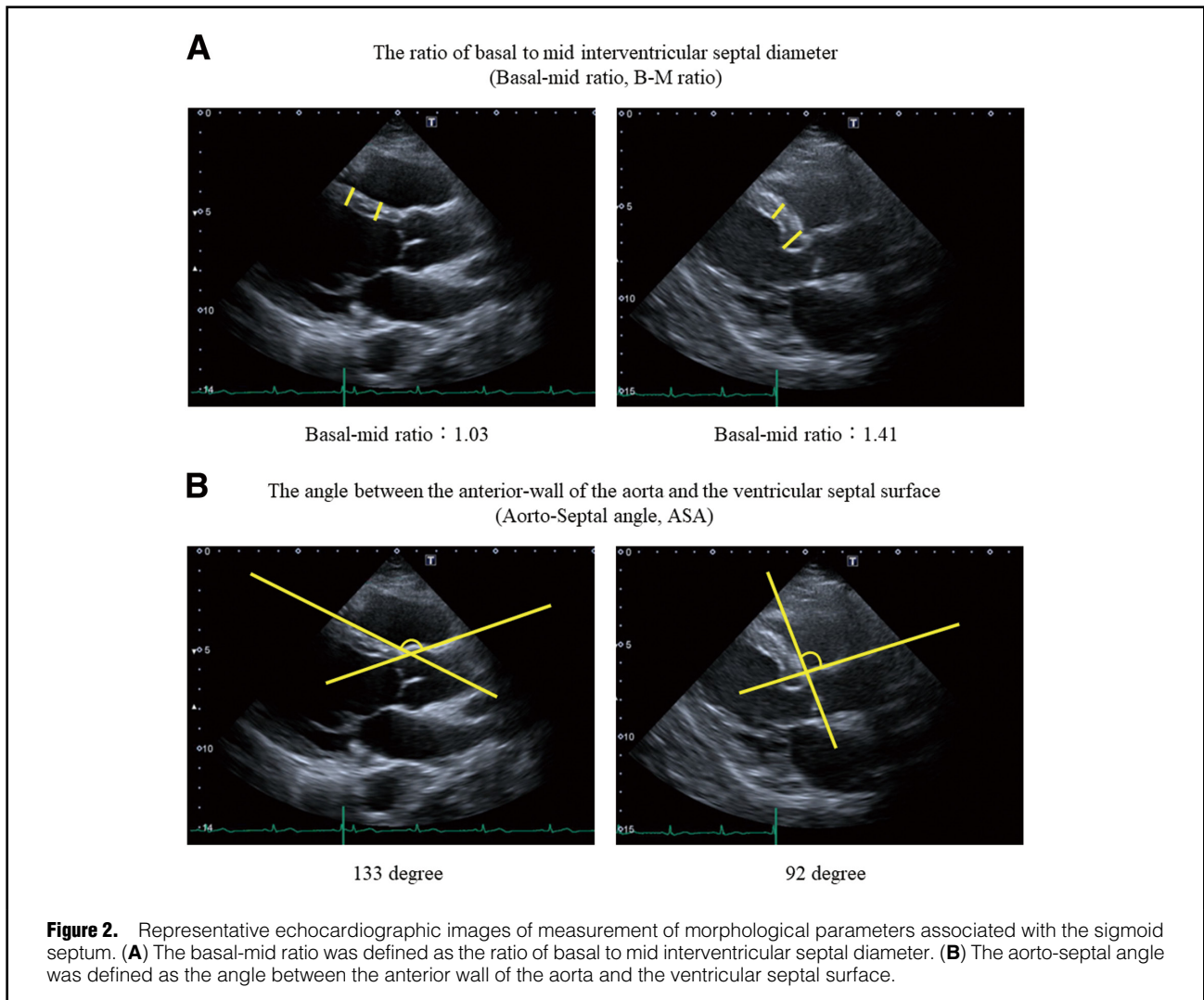
This study was approved by the Ethics Committee of Nagoya City University (No. 60-19-125) and was performed in accordance with the principles of the Declaration of Helsinki.

Echocardiography

Echocardiographic data were measured according to the recommendations of the American Society of Echocardiography.²⁰ However, avoiding the region of the sigmoid septum, the LV end-diastolic diameter (LVDd), interventricular septal wall thickness (IVSd), and posterior wall thickness (PWd) were measured at a mid-ventricular position. LVEF was calculated by the disk summation method using the TomTec Imaging System (Munich, Germany). To avoid a misdiagnosis of CTRCD, LVEF that had been measured as between 40% and 60% by one measurer was re-evaluated by a second measurer to assess the accuracy of diagnosis. LV wall thickness was defined as the mean IVSd and PWd. The LV mass index (LVMI) was calculated using the following formula:¹⁰

$$\text{LVMI} = 1.04 \times [(\text{LVDd} + \text{IVS} + \text{PWd})^3 - \text{LVDd}^3] \times 0.8 + 0.6$$

Valvular diseases were graded according to the guidelines



of the Japanese Circulation Society.²¹

As described in previous studies that investigated the sigmoid septum,^{18,22–26} we calculated the ratio of basal to mid-interventricular septal diameters (“B-M ratio”). We also measured the angle between the anterior wall of the aorta and the ventricular septal surface (i.e., aorto-septal angle [ASA]) during the end diastolic phase to quantify the sigmoid septum (**Figure 2**). To determine intra- and inter-rater reliability, the ASA was remeasured by the first rater (T.N.) and the second rater (J.Y.) in 30 patients who underwent baseline echocardiography between January 2016 and December 2017.

Statistical Analysis

Continuous variables are expressed as the mean \pm SD. For comparisons between groups of continuous variables, Welch’s test was used in the case of unequal variances and Student’s t-test was used in other cases. Categorical variables were analyzed using Pearson’s Chi-squared test. Cox proportional hazards analyses were performed to identify risk factors for the primary endpoint. The common logarithmic conversion was used when B-type natriuretic peptide was assessed in Cox proportional hazard analyses.

Intra- and inter-rater reliabilities were evaluated with intraclass correlation coefficients (ICC), with an ICC ≥ 0.80 considered the preferred level of reliability.²⁷

The primary endpoint was the incidence of CTRCD, and the initial time point for each survival analysis was the first day of the CHOP-like regimen. Follow-up censoring of participants with undetected CTRCD was the final echocardiographic examination. Clinical variables recognized as risk factors for CTRCD were analyzed using univariable Cox proportional hazards analyses. The GLS value was converted to an absolute value when assessed in Cox proportional hazard analyses, Kaplan-Meier analyses, and logistic regression analyses. In the first multivariable Cox proportional hazards analysis, echocardiographic parameters with $P < 0.05$ in the univariable analyses were analyzed to clarify the independent echocardiography-derived determinants of the event (Multivariable Analysis 1). Next, the independent echocardiographic parameters were adjusted by the clinical parameters with $P < 0.05$ in the univariable analyses as Multivariable Analysis 2. Multivariable Cox proportional hazard analyses were assessed by the forward stepwise method. The follow-up period varied among patients; therefore, we constructed time-dependent

Table 1. Baseline Characteristics				
Characteristic	Total (n=167)	CTRCD		P value
		Yes (n=36; 22%)	No (n=131; 78%)	
Basic data				
Age (years)	69.1±11.3	71.5±8.1	68.5±12.0	0.072
Male sex	91 (54)	21 (58)	70 (53)	0.60
BMI (kg/m ²)	20.9±2.3	21.2±1.9	20.8±2.4	0.19
R-CHOP	139 (83)	27 (75)	112 (85)	0.14
DLBCL	111 (67)	25 (69)	86 (66)	0.67
Performance status				0.88
0	33 (20)	7 (19)	26 (20)	
1	76 (46)	14 (39)	62 (47)	
2	37 (22)	10 (28)	27 (21)	
3	13 (8)	3 (8)	10 (8)	
4	8 (5)	2 (6)	6 (5)	
Doxorubicin dose (mg/m ²)	291.5±95.3	298.7±97.1	289.5±95.1	0.95
Cardiovascular risk factors				
Hypertension	58 (35)	13 (36)	45 (34)	0.84
Dyslipidemia	50 (30)	11 (31)	39 (30)	0.93
Diabetes	30 (18)	6 (17)	24 (18)	0.82
Smoking	68 (41)	19 (53)	49 (37)	0.10
History of cardiovascular disease				
Ischemic heart disease	7 (4)	5 (14)	2 (2)	0.001
Heart failure	5 (3)	1 (3)	4 (3)	0.93
Atrial fibrillation	9 (5)	2 (6)	7 (5)	0.96
Cerebral infarction	9 (5)	0 (0)	9 (7)	0.11
Laboratory measurements				
Hemoglobin (g/dL)	11.7±2.2	11.9±2.0	11.7±2.3	0.13
Albumin (g/dL)	3.5±0.8	3.5±0.7	3.5±0.8	0.21
Serum sodium (mEq/L)	139.2±3.9	139.2±3.4	139.2±4.1	0.42
eGFR (mL/min/1.73 m ²)	70.8±22.0	66.2±22.1	72.1±21.8	0.67
Total bilirubin (mg/dL)	0.7±0.7	0.7±0.4	0.7±0.7	0.53
BNP (pg/mL; n=147)	61.2±109.2	81.5±171.2	54.9±80.8	0.06
Echocardiography				
LVEF (%)	64.3±6.2	61.6±5.3	65.0±6.2	0.003
GLS (%)	-20.0±3.4	-18.7±2.9	-20.3±3.4	0.008
LV diastolic diameter (mm)	44.7±5.6	45.4±5.3	44.6±5.7	0.40
Valvular disease ≥ moderate	29 (18)	7 (19)	22 (17)	0.71
LV wall thickness (mm)	9.5±1.4	9.8±1.2	9.5±1.4	0.23
LV mass index (g/m ²)	94.6±22.4	101.1±18.5	92.8±23.1	0.047
Left atrial diameter (mm)	33.5±5.8	34.1±5.3	33.4±5.9	0.52
Valsalva sinus diameter (mm)	31.8±3.7	32.4±4.4	31.6±3.4	0.28
E wave (cm/s)	68.7±17.7	66.4±15.7	69.3±18.2	0.38
Deceleration time (ms)	230.1±61.9	232.1±67.1	229.6±60.6	0.83
B-M ratio	1.28±0.24	1.35±0.22	1.26±0.24	0.029
ASA (°)	117.8±13.9	112.1±14.2	119.4±13.4	0.005

Unless indicated otherwise, data are given as n (%) or the mean±SD. ASA, angle between the anterior-wall of the aorta and the ventricular septal surface; BMI, body mass index; B-M ratio, the ratio of basal to mid interventricular septal diameter; BNP, B-type natriuretic peptide; CTRCD, cancer therapeutics-related cardiac dysfunction; DLBCL, diffuse large B-cell lymphoma; eGFR, estimated glomerular filtration rate; GLS, global longitudinal strain; LV, left ventricular; LVEF, left ventricular ejection fraction; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone.

receiver operating characteristic (ROC) curves based on the incidence of the primary endpoint within 4 years from the initial time point, because <10% of patients were followed after 4 years. We used the inverse probability of censoring weighting technique to deal with censoring. SAS

analytical software was used to estimate the time-dependent ROC curves and corresponding C-statistics. Youden's index, derived from ROC curves, was used to determine the cut-off values for risk factors related to the primary endpoint. Event-free survival curves using the cut-off val-

Variable	Univariable analysis			Multivariable analysis 1			Multivariable analysis 2		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Echocardiography									
LVEF, per 10% decrease	1.88	1.08–3.28	0.026	–	–	–	–	–	–
IGLSI, per 1% decrease	1.17	1.05–1.30	0.005	1.19	1.06–1.33	0.003	1.20	1.07–1.35	0.002
LV diastolic diameter	1.01	0.94–1.07	0.88	–	–	–	–	–	–
Valvular disease ≥ moderate vs. ≤ mild	1.86	0.81–4.26	0.14	–	–	–	–	–	–
LV wall thickness	1.23	0.95–1.59	0.11	–	–	–	–	–	–
LV mass index, per 10-g/m ² increase	1.17	1.00–1.37	0.045	–	–	–	–	–	–
Left atrial diameter	1.02	0.96–1.09	0.45	–	–	–	–	–	–
Valsalva sinus diameter	1.02	0.93–1.13	0.65	–	–	–	–	–	–
E wave, per 10-cm/s increase	0.98	0.79–1.21	0.83	–	–	–	–	–	–
Deceleration time, per 10-ms increase	0.99	0.93–1.04	0.62	–	–	–	–	–	–
B-M ratio, per 0.1 increase	1.11	0.99–1.25	0.081	–	–	–	–	–	–
ASA, per 1° increase	0.97	0.95–0.99	0.007	0.97	0.95–0.99	0.004	0.97	0.95–0.99	0.003
Basic data									
Age, per 10-year increase	1.46	1.01–2.09	0.042	–	–	–	–	–	–
Male vs. female	1.14	0.59–2.22	0.70	–	–	–	–	–	–
BMI	1.06	0.93–1.22	0.39	–	–	–	–	–	–
R-CHOP vs. CHOP	0.48	0.23–1.03	0.059	–	–	–	–	–	–
DLBCL vs. non-DLBCL	1.29	0.63–2.62	0.49	–	–	–	–	–	–
Performance status ≥2 vs. ≤1	1.96	1.01–3.82	0.047	–	–	–	–	–	–
Doxorubicin dose, per 10-mg/m ² increase	0.99	0.95–1.02	0.40	–	–	–	–	–	–
Cardiovascular risk factors ≥2 vs. ≤1	1.54	0.79–3.01	0.21	–	–	–	–	–	–
History of ischemic heart disease, yes vs. no	4.59	1.75–12.00	0.002	–	–	–	5.13	1.94–13.56	0.001
Laboratory measurements									
Hemoglobin	0.98	0.85–1.14	0.81	–	–	–	–	–	–
Albumin	0.90	0.59–1.39	0.64	–	–	–	–	–	–
Serum sodium	0.94	0.85–1.05	0.28	–	–	–	–	–	–
eGFR, per 10-mL/min/1.73m ² increase	0.88	0.76–1.02	0.081	–	–	–	–	–	–
Total bilirubin	1.37	0.73–2.57	0.33	–	–	–	–	–	–
Log[BNP] (n=147)	1.69	0.80–3.56	0.17	–	–	–	–	–	–

CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisolone; CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

ues were constructed by Kaplan-Meier analyses, and the log-rank test was used to assess the significance of differences between curves.

To assess the incremental value of newly recognized risk factors for CTRCD, we defined 2 categorized models: Model 1 included the risk factors that were already considered risk factors in a previous study and were recognized independently for CTRCD in the present study, whereas Model 2 had all independent risk factors identified in the present study, including newly recognized risk factors. First, we compared the C-statistics of each model using SAS. We calculated the area under the curve (AUC) to assess the utility of new risk factors. Second, we used the continuous-net reclassification index (cNRI) and integrated discrimination improvement (IDI) to evaluate the incremental value of risk factors newly identified in the present study.^{28,29} In these analyses, patients with a probability ≥0.5 in logistic regression analyses in each model

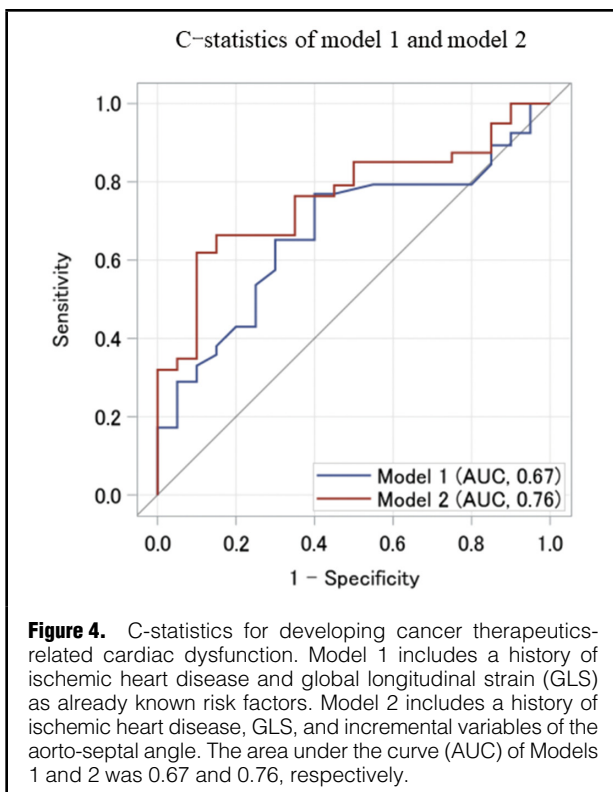
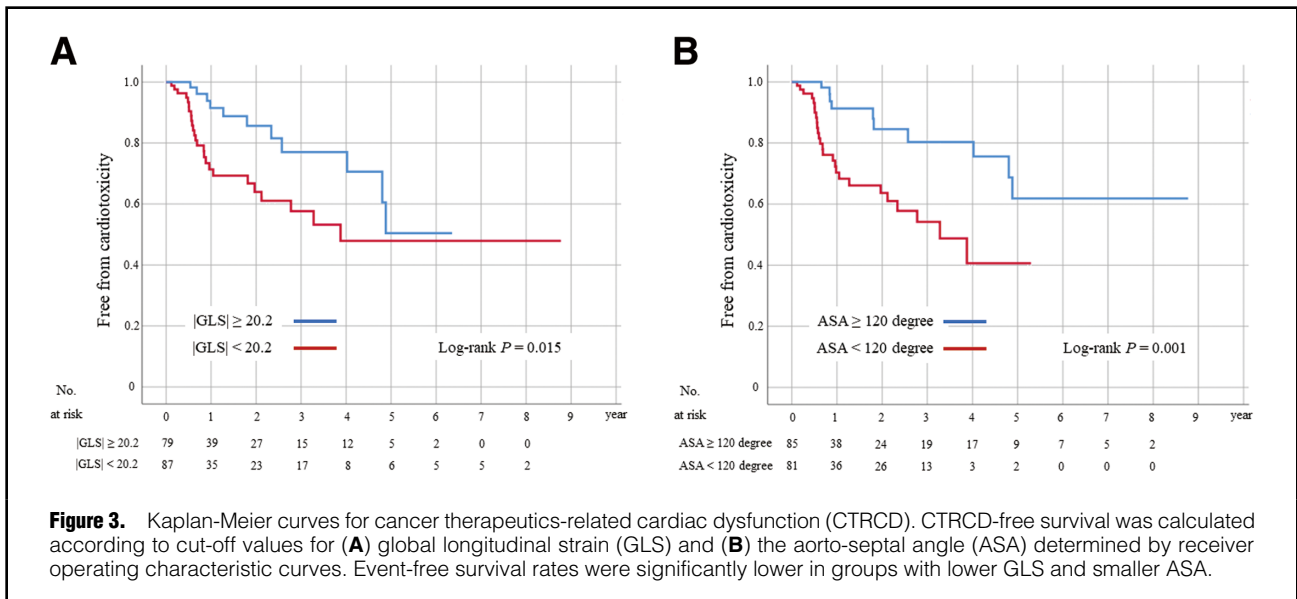
were considered to have CTRCD. The R package, *survIDINRI* was used to estimate the IDI and cNRI to compare the predictive models for the incidence of primary endpoint within 4 years.

Two-sided $P < 0.05$ was considered significant. Analyses were performed using SPSS ver. 26 (IBM Corp., Armonk, NY, USA), SAS ver. 9.4 (SAS Institute, Cary, NC, USA), and R ver. 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study Population

Of the 443 patients initially enrolled in this study, 14 patients without baseline echocardiography data and 185 patients without follow-up echocardiography data were excluded. Fourteen patients with LVEF <50%, 62 patients whose GLS could not be quantified by tri-plane, and 1 patient



without any echocardiographic images available for analysis were also excluded. In the comparison between patients who underwent GLS measurements and those who were excluded because they did not have GLS measurements, there were no significant differences in basic and laboratory data (Supplementary Table 1).

Finally, 167 patients were eligible for inclusion in the present study (Figure 1). CTRCD was observed in 36 patients (22%) during the follow-up period, which was a median of

305 days (interquartile range [IQR] 171–837 days). The mean and median number of follow-up echocardiographic examinations was 3.0 ± 2.6 and 2 (IQR 1–4), respectively. The median interval between the baseline and follow-up echocardiographic studies was 112 days (IQR 50–238 days).

Baseline Characteristics

The baseline characteristics of eligible patients are summarized in Table 1. No significant differences were found in baseline characteristics between patients with and without CTRCD, except for the prevalence of prior ischemic heart disease. Most patients (83%) received the R-CHOP regimen, with the remaining patients receiving the CHOP regimen. There were 111 patients with DLBCL (67%), including 4 and 2 patients with IVL and PMLBCL, respectively. The mean cumulative dose of doxorubicin was almost within the recommendation of a medical package insert of 291.5 ± 95.3 mg/m² (Table 1).

Baseline Echocardiographic Parameters

Echocardiographic parameters at baseline for the entire cohort are presented in Table 1. Mean LVEF was $64.3 \pm 6.2\%$ and 29 patients (18%) had moderate or greater valvular disease (aortic regurgitation, n=5; mitral regurgitation, n=6; tricuspid regurgitation, n=23; aortic stenosis, n=1). As a parameter of sigmoid septum, the B-M ratio and ASA were 1.28 ± 0.24 and $117.8 \pm 13.9^\circ$, respectively (Table 1). The ICCs for the intra- and inter-rater reliabilities were 0.97 and 0.94, respectively.

We found significant differences between patients with and without CTRCD in LVEF ($61.6 \pm 5.3\%$ vs. $65.0 \pm 6.2\%$, respectively; $P=0.003$), GLS ($18.7 \pm 2.9\%$ vs. $20.3 \pm 3.4\%$, respectively; $P=0.008$), LVMi (101.1 ± 18.5 vs. 92.8 ± 23.1 g/m², respectively; $P=0.047$), B-M ratio (1.35 ± 0.22 vs. 1.26 ± 0.24 , respectively; $P=0.029$), and ASA ($112.1 \pm 14.2^\circ$ vs. $119.4 \pm 13.4^\circ$, respectively; $P=0.005$).

Risk Factors for CTRCD

In the univariable Cox proportional hazard analyses, of the baseline echocardiographic parameters, LVEF, GLS,

LVMi, and ASA were significantly associated with the primary endpoint. With regard to clinical baseline characteristics, age, performance status ≥ 2 , and a history of ischemic heart disease were associated with the primary endpoint (Table 2). In Multivariable Analysis 1, GLS (hazard ratio [HR] per 1% decrease 1.19; 95% confidence interval [CI] 1.06–1.33; $P=0.003$) and ASA (HR per 1° increase 0.97; 95% CI 0.95–0.99; $P=0.004$) were identified as independent risk factors. Multivariable Analysis 2 identified GLS (HR per 1% decrease 1.20; 95% CI 1.07–1.35; $P=0.002$), ASA (HR per 1° increase 0.97; 95% CI 0.95–0.99; $P=0.003$), and a history of ischemic heart disease (HR 5.13; 95% CI 1.94–13.56, $P=0.001$) as independent risk factors for the primary endpoint (Table 2).

We constructed ROC curves to determine the abilities of GLS and ASA to predict the incidence of CTRCD and to determine the cut-off value for each. Based on ROC curves, the cut-off values for GLS and ASA were -20.2% and 120° , respectively. The AUC, sensitivity, and specificity were 0.63, 0.73, and 0.60, respectively, for the GLS cut-off value and 0.76, 0.77, and 0.85, respectively, for the ASA cut-off value. The Kaplan-Meier estimate curves for GLS and ASA are shown in Figure 3, with significant differences observed between each cut-off value.

Incremental Value of Newly Recognized Risk Factor

According to the independent risk factors for CTRCD in this study, we defined Model 1 as consistent with a history of ischemic heart disease and GLS, and Model 2 as consistent with a history of ischemic heart disease, GLS, and ASA. ROC curves for probability in Model 1 and Model 2 are shown in Figure 4. The C-statistic (AUC) for Model 2 was 0.76, which was superior to the C-statistic of 0.67 for Model 1 (Model 1–Model 2 = -0.089 ; 95% CI $-0.21, 0.028$). The reclassification tables for Model 1 and Model 2 are presented in Table 3. The cNRI and IDI were calculated to compare Model 1 and Model 2. The cNRI was 0.50 (95% CI $-0.046, 0.80$; $P=0.066$) and the IDI was 0.096 (95% CI $0.005-0.257$; $P=0.027$).

Discussion

The present study demonstrated that ASA was an independent risk factor for CTRCD in patients with ML who were treated with a CHOP-like regimen, and that ASA had a significant incremental value to predict the development of CTRCD. Any other clinical characteristics at baseline and the dose of anthracycline were not independent risk factors for CTRCD. Furthermore, when excluding patients with moderate or greater valvular diseases from the analyses, ASA was still an independent risk factor for developing CTRCD (HR per 1° increase 0.95; 95% CI 0.93–0.98; $P<0.001$).

The relationship between almost all echocardiographic parameters, except LVEF and GLS, and CTRCD has not been examined previously. To the best of our knowledge, this study is the first to detect the impact of morphologic echocardiography parameters on CTRCD. In the present study, a history of ischemic heart disease and lower GLS were risk factors for CTRCD, consistent with previous studies.^{11,16,30,31} We also found that smaller ASA was a new risk factor for CTRCD.

Smaller ASA/Ventricular Sigmoid Septum

Several terms have been used to describe the sigmoid sep-

Table 3. Estimated Reclassification Table From Model 1 and Model 2 at an Arbitrary Cut-off Value of 0.5

	Model 2		Total
	≥ 0.5	< 0.5	
CTRCD (n=36)			
Model 1			
≥ 0.5	31.6	3.3	34.9
< 0.5	9.3	20.0	29.3
Total	40.9	23.3	64.2
No CTRCD (n=131)			
Model 1			
≥ 0.5	16.4	11.7	28.1
< 0.5	10.7	64.0	74.7
Total	27.1	75.7	102.8

Patients with a model probability ≥ 0.5 are considered to have a high probability of developing cardiotoxicity. CTRCD, cancer therapeutics-related cardiac dysfunction.

tum, including discrete upper septal thickening, subaortic ventricular septal bulge, and discrete upper septal knuckle. The ASA has been used previously to quantify the sigmoid septum,^{18,24–26} as has the B-M ratio.^{22,23} In the present study, the ICCs for intra- and inter-rater reliabilities were satisfactory, which indicates that the ASA measurement can be considered reliable and reproducible.

In general, the sigmoid septum is frequently observed in the elderly population,^{32–34} although some investigators have reported this geometric change as part of the spectrum of hypertrophic cardiomyopathy, because of LV outlet obstruction.^{35–37} Therefore, the sigmoid septum is considered to be the result of aging-related changes associated with aortic atherosclerosis, hypertension, or thickening and calcification of the aortic or mitral valve.^{38–40} In the present study, higher age and higher body mass index were independently associated with the presence of sigmoid septum, as defined by the cut-off value of the ROC curve for CTRCD, in the logistic regression analysis (Supplementary Table 2). In the present study, in univariable Cox regression analysis, age was one of the factors significantly associated with CTRCD, consistent with previous reports.¹¹ However, after the multivariable analysis, ASA was proven as an independent risk factor for CTRCD, whereas age was not an independent determinant. This result may explain why a visible morphologic change due to aging was a more specific predictor for developing CTRCD than age alone.

Conversely, Cox regression analysis showed that the B-M ratio was not a significant predictor for developing CTRCD. However, Kaplan-Meier analysis with a cut-off value for the B-M ratio of 1.22, determined from a time-dependent ROC curve, demonstrated that patients with high B-M ratios had a significantly higher prevalence of CTRCD than patients with low B-M ratios (Supplementary Figure; log-rank $P=0.002$). Furthermore, when the B-M ratio was treated as a categorical variable (≥ 1.22), it was identified as an independent risk factor for developing CTRCD in both univariable analysis (HR 3.49; 95% CI 1.58–7.71; $P=0.002$) and multivariable analysis (HR 4.48; 95% CI 1.92–10.45; $P=0.001$). Nevertheless, a cut-off value of 1.22 for the B-M ratio could be arbitrary, because the source and adaptation groups were the same cohort. Therefore, we continued to use a continuous value for the B-M ratio in the main analyses of this study. However, the

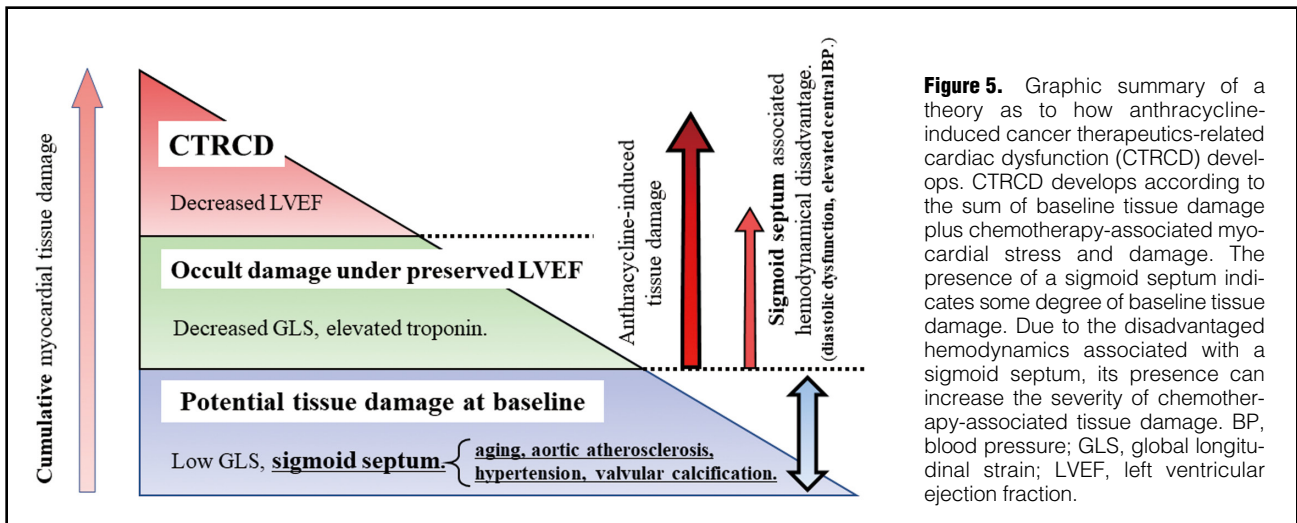


Figure 5. Graphic summary of a theory as to how anthracycline-induced cancer therapeutics-related cardiac dysfunction (CTRCD) develops. CTRCD develops according to the sum of baseline tissue damage plus chemotherapy-associated myocardial stress and damage. The presence of a sigmoid septum indicates some degree of baseline tissue damage. Due to the disadvantaged hemodynamics associated with a sigmoid septum, its presence can increase the severity of chemotherapy-associated tissue damage. BP, blood pressure; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction.

B-M ratio, treated as a continuous variable, was not significantly associated with CTRCD; this finding was probably due to the inadequate number of participants. Thus, a future study with a large number of participants or a prospective study with a B-M ratio cut-off of 1.22 are needed to confirm the utility of the B-M ratio.

Previous studies have not clarified the clinical or prognostic significance of the sigmoid septum. A large prospective observational trial could not show the effects of the sigmoid septum on exercise capacity in a healthy population.²³ In addition, a large retrospective study reported that the sigmoid septum was not independently associated with adverse clinical outcomes.²² However, in those studies, due to the strict parameters, only a small number of patients met the criteria for a sigmoid septum. These parameters included an upper septal thickness ≥ 14 mm and a B-M ratio ≥ 1.3 , with only 1.5% of patients meeting the criteria,²² or an upper septal thickness ≥ 13 mm in men or ≥ 12 mm in women and a B-M ratio ≥ 1.5 , with 7% meeting these criteria.²³ Applying these criteria to our cohort, only 14.3% and 12.6% of patients met the criteria, respectively. Furthermore, the Kaplan-Meier analyses revealed no significant differences in the prevalence of CTRCD between patients with and without a sigmoid septum based on these criteria (log-rank $P=0.17$ and $P=0.66$). In the previous studies, a mild-moderate sigmoid septum, with a B-M ratio ≥ 1.22 , may have been categorized as normal. We speculate that those criteria may explain why the results from the present study seem to differ to those from previous studies. Consequently, more investigations are warranted to determine an adequate cut-off value for the B-M ratio. In recent years, imaging technology and 3-dimensional echocardiography diagnostic capabilities have evolved;⁴¹ these advances may contribute to setting more appropriate criteria for classifying a sigmoid septum.

Anthracycline-induced cardiotoxicity is considered cumulative. Consequently, the sum of baseline cardiomyocyte tissue damage and any additional tissue damage due to chemotherapy contributes to the development of CTRCD. The sigmoid septum is one of several visible morphologic changes associated with aging, aortic atherosclerosis, hypertension, and valvular thickening and calcification. These associations suggest that the presence of a sigmoid

septum may indicate higher prior exposure to myocardial stress compared with the absence of a sigmoid septum. Furthermore, hemodynamically, the sigmoid septum was associated with LV diastolic dysfunction,¹⁸ increased central blood pressure, and increased aortic pressure wave reflection.²⁵ Greater wave reflection is also an independent predictor of adverse cardiovascular events.^{42,43} These hemodynamic disadvantages may have affected the higher frequency of CTRCD in patients with a sigmoid septum. We speculate that these mechanisms may be associated with developing CTRCD in patients with smaller ASAs who undergo anthracycline-containing chemotherapy (Figure 5). A previous study showed that the sigmoid septum was a risk factor of stroke relapse in patients with hypertension.⁴⁴ Future studies should investigate the impact of a sigmoid septum (defined adequately) on clinical outcomes in patients with heart diseases.

GLS and a History of Ischemic Heart Disease

Lower LVEF and smaller GLS in patients with normal LVEF are already recognized as risk factors for anthracycline-induced CTRCD.^{11,14,15,19} In the present study, LVEF was not an independent determinant for anthracycline-induced CTRCD in the multivariable analysis, probably because GLS can detect myocardial injury more sensitively than LVEF.^{45,46} A history of ischemic heart disease is also considered a risk factor for CTRCD.³¹ Both decreased GLS and prior ischemic heart disease at baseline are generally considered to be associated with LV myocardial injury, even when LVEF is within normal limits. In the logistic regression analysis in the present study for GLS below the cut-off value, performance status ≥ 2 , higher total bilirubin, and lower LVEF were independent determinants (Supplementary Table 3). Considering that a history of general risk factors of ischemic heart disease, including hypertension, hyperlipidemia, diabetes, and smoking, was not identified as a risk factor for CTRCD in the present study, a history of ischemic heart disease may indicate myocardial damage more directly.

Study Limitations

This study has some limitations. First, it was a single-center retrospective study, and enrollment volume was limited. Second, a relatively large number of patients who did not

undergo baseline or follow-up echocardiography were excluded. In the comparison between the group enrolled in the study and the group excluded because of the absence of baseline or follow-up echocardiography, the enrolled group was older (69.1 ± 11.3 vs. 64.9 ± 13.9 years; $P=0.002$), suggesting the attending physicians ordered echocardiographic examinations more frequently for potentially high-risk patients, possibly resulting in the high prevalence of CTRCD in the present study. Third, the timing of follow-up echocardiography also varied depending on the attending physician. The median interval between the follow-up examinations was 112 days, suggesting relatively good-quality follow-up was performed. However, there was a possibility that the diagnosis of CTRCD was delayed or not made. Fourth, the sensitivity and specificity of the cut-off values evaluated in the same cohort used for derivation are biased due to over-optimism. Further studies are needed to assess the prognostic value of ASA in a prospective cohort.

Conclusions

In addition to lower GLS and a history of ischemic heart disease, decreased ASA was found to be a new independent risk factor for anthracycline-induced CTRCD in patients with ML treated with a CHOP-like regimen.

Acknowledgments

The authors thank the patients who participated in this study and their families, as well as the operations staff. The authors also thank Hiroshi Inagaki and Ayako Masaki (Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan) for histologically diagnosing malignant lymphoma in this study.

Sources of Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosures

Y. Seo is a Fellow of the Japanese Circulation Society and a member of *Circulation Reports*' Editorial Team. The remaining authors declare no conflicts of interest associated with this study.

IRB Information

This study was approved by the Ethics Committee of Nagoya City University (No. 60-19-125).

Data Availability

The deidentified participant data will not be shared.

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Supplementary Files

Please find supplementary file(s);
<http://dx.doi.org/10.1253/circrep.CR-21-0145>