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

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Abstract

ABSTRACT Background Identifying risk factors for cancer therapeutics-related cardiac dysfunction (CTRCD) is essential for early detection and prompt initiation of medical therapy for CTRCD. There has been no study investigating whether the sigmoid septum is a risk factor for anthracycline-induced CTRCD. Methods 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 LVEF $\leq$ 50% were excluded. CTRCD was defined as $\geq$ 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. Results CTRCD was observed in 36 patients (22%). The average LVEF and GLS were lower (61.6 vs. 65.0%, 18.7 vs. 20.3), LV mass index was higher (101.1 vs. 92.8 g/m²), and ASA was smaller (112.1 vs. 119.4 degree) in patients with CTRCD. In a multivariable Cox proportional hazard analysis, GLS (HR per 1% decrease 1.20, 95% CI 1.07-1.35, $P = 0.002$), ASA (HR per 1 degree increase 0.97, 95% CI 0.95-0.99, $P = 0.003$) and the history of ischemic heart disease (HR 5.13, 95% CI 1.94-13.56, $P = 0.001$) were identified as the independent determinants of CTRCD. C-statistics analysis and integrated discrimination improvement proved the significant incremental value of ASA for developing CTRCD. Conclusion Smaller ASA was the independent risk factor and had significant incremental value for CTRCD in patients with malignant lymphoma who received the CHOP-like regimen.

Original Investigations

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ABSTRACT

Background

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

Methods

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 LVEF [?] 50% were excluded. CTRCD was defined as [?] 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.

Results

CTRCD was observed in 36 patients (22%). The average LVEF and GLS were lower (61.6 vs. 65.0%, 18.7 vs. 20.3), LV mass index was higher (101.1 vs. 92.8 g/m²), and ASA was smaller (112.1 vs. 119.4 degree) in patients with CTRCD. In a multivariable Cox proportional hazard analysis, GLS (HR per 1% decrease 1.20, 95% CI 1.07-1.35, P = 0.002), ASA (HR per 1 degree increase 0.97, 95% CI 0.95-0.99, P = 0.003) and the history of ischemic heart disease (HR 5.13, 95% CI 1.94-13.56, P = 0.001) were identified as the independent determinants of CTRCD. C-statistics analysis and integrated discrimination improvement proved the significant incremental value of ASA for developing CTRCD.

Conclusion

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

Keywords:

Cancer therapeutics-related cardiac dysfunction, anthracycline-induced cardiotoxicity, sigmoid septum, aorto-septal angle

ABBREVIATIONS

ASA = the angle between the anterior-wall of the aorta and the ventricular septal surface (aorto-septal angle)

B-M ratio = the ratio of basal to mid interventricular septal diameter (basal-mid ratio)

CHOP = cyclophosphamide, doxorubicin, vincristine and prednisolone

CI = confidence interval

CTRCD = Cancer therapeutic-related cardiac dysfunction

DUST = discrete upper septal thickening

HR = hazard ratio

IDI = integrated discrimination improvement

LVEF = left ventricular ejection fraction

LVMi = left ventricular mass index

ML = malignant lymphoma

NRI = net reclassification index

R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone

INTRODUCTION

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 therapeutic-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 Identification of baseline risk factors for CTRCD is vital for early detection and prompt initiation of medical therapy, which are essential for improving left ventricular (LV) contraction after CTRCD develops.¹⁰⁻¹² Several baseline risk factors have been clarified in previous studies, including baseline LVEF, global longitudinal strain (GLS), age, general cardiovascular risk factors, a history of cardiovascular disease.^{4,11,13-15} Recently, LV hypertrophy was recognized as a risk factor for CTRCD in ML patients¹⁶, suggesting LV morphologic remodeling also represents an accumulated myocardial injury that may cause a vulnerable condition for CTRCD. On the other hand, the sigmoid septum, known as a synonym of discrete upper septal thickening, is considered one of LV morphologic remodeling. The previous investigation reported that the sigmoid septum was significantly related to LV diastolic dysfunction.¹⁷ However, no one clarified the association of the sigmoid septum with the incidence of CTRCD.

In the current 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 received the CHOP-like regimen.

MATERIALS AND METHODS

Study population

All ML patients who received the CHOP-like regimen (cyclophosphamide + doxorubicin + vincristine + prednisolone ± rituximab) from January 2008 to December 2017 at Nagoya City University Hospital were retrospectively reviewed. 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 at least one or more follow-up examinations were enrolled in the current study (Figure 1). Patients with LVEF < 50%

at baseline but no echocardiographic images of adequate quality were excluded. The current study was the sub-analysis of a previous study in which we described the clinical features of anthracycline-induced CTRCD¹⁸.

Study protocol

We retrospectively collected patients' clinical characteristics, including age, sex, body mass index, general cardiovascular risk factors, past history, laboratory data, chemotherapeutic regimen, performance status, and echocardiographic parameters from their medical records. The chemotherapeutic regimen, performance status, and dose of anthracycline were assessed by two hematologists. Patients with intravascular large B-cell lymphoma (IVL) and primary mediastinal large B cell lymphoma (PMLBCL) were enrolled as a subtype of diffuse large B-cell lymphoma (DLBCL) in the current study. Echocardiographic parameters and the incidences of symptomatic heart failure and cardiovascular death were obtained and assessed by two cardiologists in a blinded manner. In the current study, CTRCD was defined as a decline in LVEF of 10% or more from baseline and LVEF < 50% in the follow-up study.⁹

Cardiovascular risk factors were defined as hypertension, dyslipidemia, diabetes mellitus, and a history of smoking. Each cardiovascular risk factor was defined by the following criteria: hypertension, as a record of a history of hypertension or being on antihypertensive therapy; dyslipidemia, as a record of a history of dyslipidemia, serum low-density lipoprotein cholesterol level [?] 140 mg/dL, or being on cholesterol-lowering treatment; and diabetes mellitus, as a record of a history of diabetes mellitus, HbA1c [?] 6.5%, or being on blood glucose-lowering therapy. History of ischemic heart disease was defined as a history of myocardial infarction, angina pectoris, or coronary artery revascularization. The current study was approved by the ethics committee of our institution (No. 60-19-0125) and was carried out according to the principles of the Helsinki Declaration.

Echocardiography

Echocardiographic data were measured according to the recommendations of the American Society of Echocardiography¹⁹. 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 (TomTec Imaging System GmbH, Munich, Germany). To avoid a misdiagnosis of CTRCD, we re-measured LVEF, which was between 40% to 60% by the first measurer, by the second measurer (the other of the first measurer) to assess the accuracy of diagnosis. LV wall thickness was defined as the mean IVSd and PWd. LV mass was calculated using the following formula (10): $1.04 \times [(LVDd + IVS + PWd)^3 - LVDd^3] \times 0.8 + 0.6$. The grading of valvular diseases was assessed according to the guidelines of the Japanese Circulation Society.²⁰

As morphological parameters, we calculated the ratio of basal to mid interventricular septal diameter (basal-mid ratio, B-M ratio), and measured the angle between the anterior-wall of the aorta and the ventricular septal surface (aorto-septal angle, ASA) in the end diastolic phase to quantify discrete upper septal thickening (Figure 2).

Statistical analysis

Continuous variables were expressed as mean $\pm$ standard deviation. Continuous variables were compared using unpaired Student's t-test. Welch's test was used to compare continuous variables with heteroscedasticity. 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 BNP was assessed in Cox proportional hazard analyses.

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 all participants was the day of the first detection of CTRCD or final echocardiographic examination. Clinical variables recognized as risk factors for CTRCD were analyzed using univariate 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 univariate 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 univariate analyses as multivariable analysis 2. Multivariable Cox proportional hazard analyses were assessed by the forward stepwise method. Youden's index derived from receiver operating characteristics (ROC) curves were used to determine the cut-off value for risk factors for the primary endpoint. Event-free survival curves using the cut-off values were constructed by Kaplan-Meier analyses, and the log-rank test was used to assess the significance between curves.

To assess the incremental value of newly recognized risk factors for CTRCD, we defined two 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 current study, whereas model 2 had all independent risk factors identified in the current study, including newly recognized risk factors. First, we compared the c-statistics of each model, which was calculated as an area under the curve (AUC) to assess the utility of new risk factors. Second, we used the net reclassification index (NRI) and integrated discrimination improvement (IDI) to evaluate the incremental value of risk factors newly identified in this study²¹. In these analyses, patients with a probability ≥ 0.5 in logistic regression analyses in each model were considered to have CTRCD.

NRI was calculated according to the following formula:

$$\text{NRI} = [\text{P}(\text{up}|\text{D}=1) - \text{P}(\text{down}|\text{D}=1)] - [\text{P}(\text{up}|\text{D}=0) - \text{P}(\text{down}|\text{D}=0)]$$

where P is the proportion of patients, “up” is upward movement defined as a change into a higher probability of CTRCD based on model 1, “down” is downward movement defined as a change in the opposite direction, and D is the classification of whether CTRCD develops (developing CTRCD = 1, not developing CTRCD = 0).

IDI was calculated according to the following formula:

$$\text{IDI} = [(\text{P}_{\text{extended}}|\text{D}=1) - (\text{P}_{\text{basic}}|\text{D}=1)] - 1[(\text{P}_{\text{extended}}|\text{D}=0) - (\text{P}_{\text{basic}}|\text{D}=0)]$$

where $\text{P}_{\text{extended}}|\text{D}=1$ and $\text{P}_{\text{extended}}|\text{D}=0$ are the average values of the predicted probability of developing CTRCD in model 2 for the group that developed CTRCD and the group that did not, respectively; and $\text{P}_{\text{basic}}|\text{D}=1$ and $\text{P}_{\text{basic}}|\text{D}=0$ are the average values of the predicted probability of developing CTRCD in model 1 for the group that developed CTRCD and the group that did not, respectively.

Two-sided $P < 0.05$ was considered significant. All analyses were performed using SPSS ver. 26 (SPSS, Inc., Chicago, IL, USA).

RESULTS

Study population

Of 443 enrolled patients, 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 one patient without any echocardiographic images available for analysis were also excluded. In the comparison between the patients who underwent GLS measurements and those who were excluded because they could not have GLS measurements, no significant differences were observed in basic data and laboratory data (Table S1).

Finally, 167 patients were eligible for analysis in the current study (Figure 1). CTRCD was observed in 36 patients (22%) during the follow-up period, which was a median 305 days (IQR: 171-837). The mean and median number of follow-up echocardiographic examinations were 3.0 ± 2.6 and 2 (IQR, 1-4). Median interval duration of all echocardiographic follow-up study was 112 days (IQR, 50-238).

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, and the remaining received the CHOP regimen. Patients with DLBCL were 67% (n=111), including 4 and 2 patients with IVL and PMLBCL, respectively. The mean cumulative dose of doxorubicin was almost within the accurate range of 291.5 $\pm$ 95.3 mg/m² (Table 1).

Baseline echocardiographic parameters

Echocardiographic parameters at baseline for the entire cohort are presented in Table 2. Mean LVEF was 64.3 $\pm$ 6.2 % and 29 patients (18%) had valvular disease [?] moderate (n=5 aortic regurgitation, n=6 mitral regurgitation, n=23 tricuspid regurgitation, n=1 aortic stenosis). As a parameter of discrete upper septal thickening, the B-M ratio and ASA were 1.28 $\pm$ 0.24 and 117.8 $\pm$ 13.9 degree (Table 2).

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

Risk factors for CTRCD

In univariate Cox proportional hazard analyses, LVEF, GLS, LVMI, and ASA were significantly associated with the primary endpoint in baseline echocardiographic parameters. In regard to clinical baseline characteristics, age, performance status [?] 2, and history of ischemic heart disease were associated with the primary endpoint (Table 3). In the multivariable Cox proportional hazard analysis 1, GLS (HR per 1% decrease 1.19, 95% CI 1.06-1.33, P = 0.003) and ASA (HR per 1 degree increase 0.97, 95% CI 0.95-0.99, P = 0.004) were identified as independent risk factors. The multivariable analysis 2 clarified GLS (HR per 1% decrease 1.20, 95% CI 1.07-1.35, P = 0.002), ASA (HR per 1 degree increase 0.97, 95% CI 0.95-0.99, P = 0.003) and the history of ischemic heart disease (HR 5.13, 95% CI 1.94-13.56, P = 0.001) as the independent risk factors for the primary endpoint (Table 3).

ROC curves for GLS and ASA regarding the incidence of CTRCD are presented in Figure S1. Cut-off values were -19.4 % for GLS, and 117 degree for ASA. The AUC, sensitivity, and specificity at each cut-off value were 0.65, 0.61, and 0.63 for GLS; 0.67, 0.72, and 0.61 for ASA, respectively (Figure S1). 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 presented in Figure 4. The C-statistic (AUC) for model 2 was 0.72, which is superior to the 0.67 of model 1. The NRI and IDI were calculated between model 1 and model 2. The reclassification table for developing CTRCD is presented in Table 4, with a probability cut-off of 0.5. The NRI was (1 of 36 - 0 of 36) - (2 of 131 - 0 of 131) = 0.028 - 0.015 = 0.013 (95% CI -0.004-0.029; P = 0.95), and the IDI was (0.323 - 0.293) - (0.186 - 0.194) = 0.030 + 0.008 = 0.038 (95% CI 0.009-0.068; P = 0.017).

DISCUSSION

The current study demonstrated that ASA was the independent risk factor for CTRCD in patients with ML who received the CHOP-like regimen, and ASA had a significant incremental value to predict the development of CTRCD. Any other clinical characteristics at baseline and dose of anthracycline were not independent risk factors for CTRCD. Furthermore, when excluding patients with valvular diseases > moderate from the analyses, ASA was still an independent risk factor for developing CTRCD (Table S2).

The relationship of almost all of echocardiographic parameters, except LVEF and GLS, and CTRCD has not been examined previously. To the best of our knowledge, this investigation is the first study to detect the impact of morphological parameters in echocardiography on CTRCD. In our study, history of ischemic heart disease and lower GLS were risk factors for CTRCD, consistent with previous studies^{11,15,22,23}. We also found that smaller ASA was the new risk factor for CTRCD.

Smaller ASA / ventricular sigmoid septum

Several terms have been used to describe the sigmoid septum, including discrete upper septal thickening (DUST), subaortic ventricular septal bulge, and discrete upper septal knuckle. In general, the sigmoid septum is frequently observed in the elderly population²⁴⁻²⁶, although some investigators have reported this geometric change as part of the spectrum of hypertrophic cardiomyopathy, because of LV outlet obstruction²⁷⁻²⁹. Therefore, the sigmoid septum is considered to be the result of aging-related changes associated with aortic atherosclerosis or thickening and calcification of the aortic or mitral valve.^{30,31} In the current 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 (Table S3A). In the current study, in univariable Cox regression analysis, age was one of the significantly associated factors with CTRCD, consistent with previous reports. However, after multivariable analysis, ASA was proven as the independent risk factor for CTRCD, while age was not the independent determinant. That seemed to be why morphologic change as a result of aging was more specific and important for developing CTRCD than aging itself.

The clinical and prognostic significance of the sigmoid septum has not been clarified previously. A large prospective observational trial could not show the effects of the sigmoid septum on exercise capacity in a healthy population.³² In addition, a large retrospective study reported that the sigmoid septum was not independently associated with adverse clinical outcomes.³³ However, the criteria for the sigmoid septum in these previous studies were based on the B-M ratio, which is rather a representative parameter of DUST. One of the reasons why the sigmoid septum had a clinically significant meaning in our study was the use of ASA for the quantification of the sigmoid septum. In the previous study, ASA was found to be the independent predictor of LV diastolic dysfunction quantified by LV peak diastolic longitudinal strain rate in healthy older subjects, otherwise, age was not independently associated with LV diastolic dysfunction.¹⁷ We anticipate ASA could be an early predictor for LV dysfunction, resulting in being a risk factor for CTRCD.

GLS and a history of ischemic heart disease

Lower LVEF and smaller GLS in patients with normal LVEF were already recognized as risk factors for anthracycline-induced CTRCD.^{11,13,14,18} In the current 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.^{34,35} History of ischemic heart disease is also considered a risk factor for CTRCD.²³ Both decreased GLS and prior ischemic heart disease at baseline are generally considered to be associated with LV myocardial injury, even during LVEF is within normal limit. In the logistic regression analysis for lower GLS below the cut-off value in the current study, performance status [?] 2, higher total bilirubin and lower LVEF were the independent determinants (Table S3B). Considering a history of general risk factors of ischemic heart disease themselves including hypertension, hyperlipidemia, diabetes mellitus, and smoking were not identified as risk factors for CTRCD in this study, a history of ischemic heart disease might indicate the myocardial damage more directly.

Possible theory for developing CTRCD

Based on our main findings, echocardiography-proven lower LV longitudinal contraction and LV morphological changes were independent risk factors for CTRCD. These parameters are considered to progress according to cumulative exposure to myocardial tissue damage, which may be associated with several kinds of factors such as aging, obesity, performance status, and liver function (Table S3). Furthermore, although CTRCD defined by a decline in LVEF can recover to preserved LVEF by medical treatments for heart failure¹¹, anthracycline-induced cardiomyocyte toxicity is pathologically considered irreversible and cumulative.³⁶

Taken these mechanisms together, the frequency of anthracycline-induced CTRCD is defined upon the accumulated myocardial tissue damage that is the sum of the underlying myocardial damage before chemotherapy and additional myocardial tissue injury by anthracycline. We can guess the degree of myocardial tissue damage at baseline by lower GLS and the smaller ASA, as the most relevant risk factors for anthracycline-induced CTRCD.

Study limitations

The current 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. The differences between the group who underwent analyses and the group who excluded because of the absence of baseline or follow-up echocardiography are presented in Table S4. Baseline age was higher in the analyzed group, suggesting the attending physicians ordered echocardiographic examinations more frequently to potentially high-risk patients, possibly resulting in the high prevalence of CTRCD in the current study. Third, the timing of follow-up echocardiography also varied depending on the attending physician. The median interval duration between the follow-up examinations was 112 days, suggesting relatively well-quality follow-ups were performed. However, there was a possibility that the diagnosis of CTRCD was delayed or not be made. And fourth, the sensitivity and specificity of cut-off values evaluated in the same cohort used for derivation are biased due to over-optimism. Further study is needed to assess the prognostic value of ASA in a prospective cohort.

CONCLUSION

In addition to lower GLS, decreased ASA was found to be a new independent risk factor for anthracycline-induced CTRCD in patients with ML who received a CHOP-like regimen.

DECLARATIONS OF INTEREST

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

AUTHOR CONTRIBUTIONS

Takafumi Nakayama and Yoshihiro Seo designed and performed the research. Takafumi Nakayama wrote the paper, and Yoshihiro Seo oversaw the paper and the whole research. Takafumi Nakayama, Yoshiko Oshima and Junki Yamamoto collected the clinical data. Yasuhiro Shintani, Masashi Yokoi, Tsuyoshi Ito, Kazuaki Wakami, Shuichi Kitada, Toshihiko Goto, Shigeru Kusumoto, Tomonori Sugiura, Shinsuke Iida and Yoshihiro Seo revised the paper critically. All authors approved the submission of the paper of final version.

FIGURE LEGENDS

Figure 1.

Study flow diagram of patients' enrollment.

Figure 2.

Representative echocardiographic images when morphological parameters associated with the sigmoid septum were measured. Basal-mid ratio was defined as the ratio of basal to mid interventricular septal diameter (A), aorto-septal angle was defined as the angle between the anterior-wall of the aorta and the ventricular septal surface (B).

Figure 3.

Kaplan-Meier curves for CTRCD. CTRCD-free survival was calculated according to each cut-off value for GLS (A) and ASA (B) determined by receiver operating characteristic curves. Event-free survival rates were significantly lower in groups with lower GLS and smaller ASA.

Figure 4.

C-statistics for developing CTRCD. (A) Model 1 includes a history of ischemic heart disease and GLS as already known risk factors. (B) Model 2 includes a history of ischemic heart disease, GLS, and incremental variables of ASA. The AUC of models 1 and 2 were 0.67 and 0.72, respectively.

Figure S1.

Receiver operating characteristic curves to determine the cut-off values of GLS (A) and ASA (B) for Kaplan-Meier analyses. Areas under the curves (AUCs) were 0.65 for GLS and 0.67 for ASA. Sensitivities/specificities were 0.61/0.63 and 0.72/0.61 in GLS and ASA, respectively.

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Figure 1

Figure 2A

Figure 2A

Figure 3A

Figure 3B

Figure 4A

C statistics of history of ischemic heart disease and GLS (model 1)

Figure 4B

C statistics of history of ischemic heart disease, GLS and ASA for Cardiotoxicity (model 2)