Original Article

Cardiac exposure in left-sided breast cancer patients undergoing deep inspiratory breath hold radiation therapy

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Background: Left-sided breast cancer (BC) patients undergoing post-operative radiation therapy (PRT) may have higher risk of late cardiovascular toxicity, which may be reduced by hearth-sparing RT techniques. This study evaluated dosimetric parameters of the deep inspiration breath hold (DIBH) compared to free breathing (FB) RT. We analysed factors impacting on doses to the heart and cardiac substructures and sought anatomic factors allowing patient selection for DIBH.

Methods: The study group included 67 left-sided BC patients who underwent RT after breast-conserving surgery or mastectomy. Patients treated with DIBH were trained to hold their breath. Computed tomography (CT) scans were performed in both FB and DIBH patients. Plans were generated using 3-dimensional (3D) conformal RT. The dosimetric variables were obtained from dose-volume histograms, and the anatomical variables were derived from the CT scans. The variables in the two groups were compared by *t*-test, the U test, and the chi-squared test. Correlation analysis was performed using Pearson's correlation coefficient. Receiver operating characteristic curves were used to analyze the efficacy of the predictors.

Results: Compared to the FB, DIBH allowed for a mean dose reduction to the heart, left anterior descending coronary artery (LAD), left ventricle (LV), and right ventricle (RV) by 30.0%, 38.7%, 39.3%, and 34.7%, respectively. DIBH markedly increased the heart height (HH), heart chest wall distance (HCWD), the mean distance between the ipsilateral lung and breast (DBIB), and decreased the heart-chest wall length (HCWL) ($P<0.05$). The different value of HH, DBIB, HCWL, and HCWD between DIBH and FB were 1.31, 1.95, −0.67, and 0.22 cm, respectively (all $P<0.05$). ΔHH was an independent predictor of the mean dose to the heart, LAD, LV, and RV, with the area under the curve values of 0.818, 0.725, 0.821, and 0.820, respectively.

Conclusions: DIBH significantly reduced the dose to the entire heart and its substructures in left-sided BC patients undergoing post-operative RT. ΔHH predicts the mean dose to the heart and its substructures. These results may inform patient selection for DIBH.

Keywords: Breast cancer (BC); radiotherapy; deep inspiration breath hold (DIBH); heart protection

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Introduction

Post-operative radiation therapy (PRT) for breast cancer (BC) has been shown to considerably reduce the risk of locoregional recurrence and death (1-3). PRT includes the breast or chest wall, and in patients with high-risk features-additionally lymph node areas (4). Patients with operable BC carry a relatively good prognosis with 5-year overall survival (OS) in the range of 80–90% (5). Thus, late side effects from treatment may be highly relevant. One of the most common long-term health hazards of PRT is cardiovascular disease (CVD) (6). Notably, the dose administered to cardiac substructures is associated with cardiac events (6,7). In left-sided BC, a relevant dose can be received by the left ventricle (LV) and coronary arteries (8), given the close proximity of the heart to the target volume. Hence, left-sided BC patients are at higher risk of late-onset CVD (9). For example, in the study of Darby *et al.*, the risk of major coronary events increased linearly with the mean dose (Dmean) to the heart, at a rate of 7.4% per 1 Gy (10). Nilsson *et al.* demonstrated that the left anterior descending coronary artery (LAD) dose is strongly associated with the risk of high-grade coronary artery stenosis in left-sided BC patients (11). Alternatively, studies showed the mean heart dose and doses to cardiac substructures to be associated with elevated cardiac enzymes. Skyttä *et al.* found a positive correlation between Dmean to cardiac substructures and the cardiac troponin T serum level (12). The percentage volume of the LV receiving ≥2 Gy correlated significantly with NT-proBNP (13).

Techniques accounting for breathing movements, such as deep inspiration breath hold (DIBH) and inspiration breath hold (IBH), minimize unnecessary lung and heart RT doses (14,15). During DIBH and IBH, the lungs are inflated, the respiratory motion is minimized, and the heart position changes, leading to a lower exposure than with free breathing (FB) (16). However, breath-holding techniques are associated with additional time, costs, and a high workload. It is, therefore, essential to identify patients who may mostly benefit from them.

This study aimed to retrospectively examine the plausibility, feasibility, and potential benefits of DIBH, and to identify anatomical variables identifying patients likely to benefit most from this procedure. For this purpose, we compared RT doses to normal tissues in left-sided BC patients irradiated using DIBH and FB, and investigated the association between several anatomic features and dose exposure to the heart. We present this article in accordance with the STARD reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-23-160/rc)

Highlight box

Key findings
- DIBH enables a considerable reduction of radiation therapy doses to the heart.
- ΔHH is an independent predictor of DIBH benefit.

What is known and what is new?
- DIBH have showed the dosimetric benefits to the heart and cardiac substructures.
- We showed that anatomic characteristics correlate with cardiac doses and may inform patient selection for DIBH.

What is the implication, and what should change now?
- This study may contribute to optimizing of RT in breast cancer patients. Prospective clinical trials are warranted to confirm our findings.

Methods

Patients

We retrospectively analyzed the data including the parameters of CT planning scan images and Radiation plan for 67 left-sided BC consecutive patients from The Second Affiliated Hospital of Guangxi Medical University who received RT after breast-conserving surgery (BCS) or mastectomy. Due to the retrospective study design, informed consent was not required. The study was approved by The Second Affiliated Hospital of Guangxi Medical University Ethics Committee (approval No. 2023-KY0003). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Clinical staging and molecular subtype of all patients followed the Guidelines of the Chinese Society of Clinical Oncology (17). Three days before the CT simulation, patients in the DIBH group were trained by a physical therapist to hold their breath. The CT scans started after the chest had stabilized at the maximum height. A minimal breath-hold duration of at least 30 seconds was considered suitable (18). FB patients maintained smooth breathing during scanning. Real-time position management (RPM; Varian Medical Systems, Palo Alto, CA, USA) was used to measure the patients' respiration. An overview of the detailed procedure is shown in *Figure 1*.

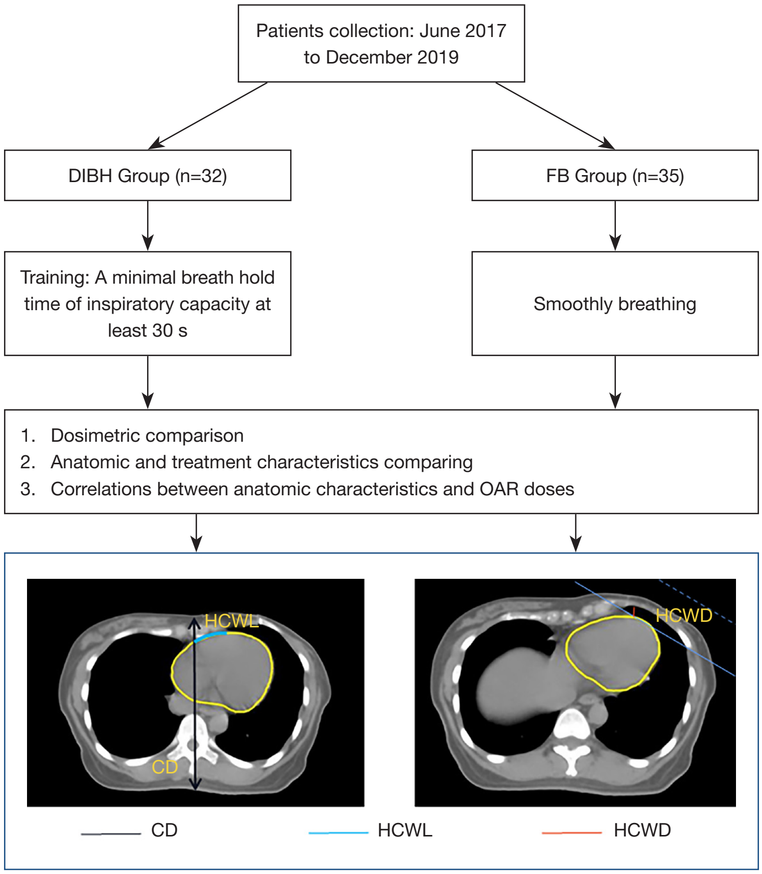

Figure 1 Flow chart for enrollment of left-sided breast cancer patients using DIBH and FB radiotherapy planning. DIBH, deep inspiration breath hold; FB, free breathing; OAR, organ at risk; CD, chest depth; HCWL, heart chest wall length; HCWD, heart chest wall distance.

Dosimetric assessment

The target regions and organs at risk (OARs), including heart, lungs, LAD, LV, and right ventricle (RV), were contoured according to the Radiation Therapy Oncology Group guidelines (19). In patients who underwent mastectomy, RT volumes included the chest wall, while, in patients after BCS, target volumes comprised the whole breast. Regional lymph nodes were irradiated in patients with high-risk features. All patients received 3-dimensional conformal RT. The Eclipse treatment planning system (TPS; Eclipse version 13.6, Varian Medical Systems) was used for contouring and planning. The prescribed dose was defined as 50 Gy in 25 fractions to the planning target volume. Additionally, patients after BCS received a 10 Gy sequential boost dose to the tumor bed. Before RT delivery, weekly cone-beam computed tomography was performed to verify position and examine the treatment reproducibility. The doses to the heart, LV, RV, and LAD were analyzed using the Dmean and maximum dose (Dmax). Additionally, a DVH was created to evaluate the dosimetric parameters of 5 and 20 Gy to the ipsilateral lung and 25 Gy to the heart.

Anatomic and treatment characteristics

According to previous studies, the study parameters anatomic variables were selected from the treatment scan fields (20,21). The chest depth (CD), heart chest wall length (HCWL), and heart chest wall distance (HCWD) were calculated (showed in *Figure 1*). And the distance between the ipsilateral lung and breast (DBIB) was defined as the distance between the mass centers of ipsilateral lung and the PTV breast (21). The heart height (HH), the heart and ipsilateral lung volumes were also analyzed in both groups. The difference between values and the average value of FB groups were denoted with "Δ", for example, ΔHH.

Statistical analysis

Statistical analyses were performed using R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria). For all analyses, a P value of <0.05 was considered statistically significant. The *t*-test, U-test, and chi-squared test were performed to compare the variables between the groups. Pearson's test was used for correlation analysis for differences between values in two groups and dose parameters (Dmean and Dmax). Relationships between anatomic variables and protective dose reduction (20%) were analyzed. Receiver operator characteristic (ROC) curve analyses were used for predicting parameter thresholds.

Results

Baseline characteristics

The study group included 67 patients (32 managed with DIHB and 35 with FB) treated between June 2017 and December 2019. The median age of the DIBH and FB groups was 48.5 years (range, 27–66 years) and 52 years (range, 35–73 years), respectively. The baseline characteristics, including age, clinical stage, histopathological grade, type of RT field, and systemic adjuvant treatment, were not different between the groups (*Table 1*).

Radiation dose distribution to OARs and cardiac substructures

The Dmean values in the DIBH group were lower than in the FB group for the heart (4.68 *vs.* 6.69 Gy, P<0.001), LAD (12.28 *vs.* 20.06, P=0.000), LV (4.71 *vs.* 7.76 Gy, P<0.001), and RV (5.66 *vs.* 8.67 Gy, P=0.000), corresponding to a decrease by 30.0%, 38.7%, 39.3%, and 34.7%, respectively. The Dmax values in the DIBH group were also lower than in the FB group for the heart (38.19 to 45.28 Gy, P<0.001), LAD (45.30 to 50.85 Gy, P=0.000), LV (31.37 to 44.03 Gy, P=0.000), and RV (35.96 to 49.96 Gy, P<0.001), corresponding to decrease by 15.6%, 10.9%, 28.8%, and 28.0%, respectively. Patients in the DIBH group also showed a significantly lower heart V25 than those in the FB group (2.60% and 6.23%, respectively, P=0.008). In contrast, the Dmean, V5, and V20 of the ipsilateral lung did not differ significantly between the groups (*Table 2*).

Anatomical characteristics

DIBH, compared with FB, resulted in higher ipsilateral lung volume (1,671 *vs.* 1,022 cc, P<0.001), HH (8.59 *vs.* 7.28 cm, P<0.001), DBIB (12.73 *vs.* 10.78 cm, P<0.001), CD (19.97 *vs.* 19.18 cm, P=0.052), and HCWD (1.57 *vs.* 1.35 cm, P=0.004) (*Table 3*). DIBH decreased the heart volume (505 *vs.* 558 cc, P=0.010) and HCWL (3.26 *vs.* 3.93 cm, P<0.001). The different value of HH, DBIB, CD, HCWL, and HCWD between DIBH and FB groups were 1.31, 1.95, 0.79, −0.67, and 0.22 cm, respectively.

Correlations between anatomic characteristics and organ at risk doses

ΔHH, ΔDBIB, and ΔHCWL between the FB and DIBH correlated with Heart, LAD, LV and RV Dmean and Dmax values (*Table 4*). A clear negative correlation was observed between these parameters and ΔHH, ΔDBIB, and ΔHCWL (P<0.05). In contrast, ΔHCWD correlated only with the heart Dmean (P<0.05) and not with other dose-volume parameters (P>0.05).

We further constructed the ROC curve to evaluate the predictive value of ΔHH, ΔDBIB, and ΔHCWL for >20% Dmean reduction. The highest efficiency was shown for ΔHH, with the area under the curve (AUC) values of 0.818, 0.725, 0.821, and 0.820 for heart, LAD, LV, and RV Dmean, respectively (all statistically significant; *Table 5* and *Figure 2*).

Discussion

Breast cancer patients have benefited from advanced radiation technologies through improved treatment outcomes and longer survival times. However, quality of life (QoL) problems caused by Side-effects should not be overlooked. Thus, DIBH application for reducing cardiac irradiation deserves further investigation.

In this study, DIBH allowed better separation of the heart and LAD to Radiation field, and reduced the irradiated heart volume. We showed that DIBH reduces the Dmean and Dmax to the heart, LAD, LV, and RV. We found that ΔHH has a strong correlation with cardiac mean dose reduction. These results may inform patient selection for DIBH.

Some studies have showed the benefit of DIBH for reducing the mean and maximum dose to the heart and to the LAD (22,23). However, previous studies demonstrated that patients do not benefit equally from DIBH (24). Owing to the complexity of this procedure, it is essential to select patients who will benefit most from it. The predictive value of anatomical and volume parameters for heart exposure

Table 1 Patient characteristics

Characteristics	Total (n=67)	DIBH group (n=32)	FB group (n=35)	P value
Age (years), median [range]	49.0 [27–73]	48.5 [27–66]	52 [35–73]	0.082
Clinical stage, n (%)				
I	6 (9.0)	2 (6.3)	4 (11.4)	
II	25 (37.3)	15 (46.9)	10 (28.6)	
III	30 (44.8)	12 (37.5)	18 (51.4)	0.403
IV	6 (9.0)	3 (9.4)	3 (8.6)	
Histopathological grade, n (%)				
1–2	32 (47.8)	15 (46.9)	17 (48.6)	
3	12 (17.9)	4 (12.5)	8 (22.9)	0.443
Unknown	23 (34.3)	13 (40.6)	10 (28.6)	
Vascular invasion, n (%)				
Yes	17 (25.4)	8 (25.0)	9 (25.7)	0.946
No	50 (74.6)	24 (75.0)	26 (74.3)	
Lymph node metastasis, n (%)				
Yes	49 (73.1)	24 (75.0)	25 (71.4)	0.742
No	18 (26.9)	8 (25.0)	10 (28.6)	
Neoadjuvant chemotherapy, n (%)				
Yes	16 (23.9)	6 (18.8)	10 (28.6)	0.346
No	51 (76.1)	26 (81.3)	25 (71.4)	
Adjuvant chemotherapy, n (%)				
Yes	61 (91.0)	31 (96.9)	30 (85.7)	0.242
No	6 (9.0)	1 (3.1)	5 (14.3)	
Targeted therapy, n (%)				
Yes	28 (41.8)	16 (50.0)	12 (34.3)	0.193
No	39 (58.2)	16 (50.0)	23 (65.7)	
Endocrine therapy, n (%)				
Yes	34 (50.7)	17 (53.1)	17 (48.6)	0.710
No	33 (49.3)	15 (46.9)	18 (51.4)	
RT, n (%)				
Breast/chest wall only	5 (7.5)	2 (6.3)	3 (8.6)	
Breast/chest wall and lymph nodes, except IMC	46 (68.7)	23 (71.8)	23 (65.7)	0.853
Breast/chest wall and lymph nodes, including IMC	16 (23.8)	7 (21.9)	9 (25.7)	
Boost, n (%)				
No	59 (88.1)	29 (90.6)	30 (85.7)	0.809
Yes	8 (11.9)	3 (9.4)	5 (14.3)	

DIBH, deep inspiratory breath hold; FB, free breathing; RT, radiation; IMC, internal mammary chain.

Table 2 Estimated cardiac doses for DIBH and FB

Parameter	DIBH group (median)	FB group (median)	Reduction	P value
Left lung mean dose (Gy)	14.13	13.76	+2.6%	0.461
Left lung V20 (%)	24.19	24.68	–2.0%	0.470
Left lung V5 (%)	58.90	56.92	+3.4%	0.247
Right lung mean dose (Gy)	1.33	1.20	+9.8%	0.224
Heart mean dose (Gy)	4.68	6.69	–30.0%	<0.001*
Heart max dose (Gy)	38.19	45.28	–15.6%	<0.001*
Heart V25 (%)	2.60	6.23	–58.2%	0.008*
LAD mean dose (Gy)	12.28	20.06	–38.7%	0.000*
LAD max dose (Gy)	45.30	50.85	–10.9%	0.000*
LV-mean (Gy)	4.71	7.76	–39.3%	<0.001*
LV-max (Gy)	31.37	44.03	–28.8%	0.000*
RV-mean (Gy)	5.66	8.67	–34.7%	0.000*
RV-max (Gy)	35.96	49.96	–28.0%	<0.001*

*, significant differences. DIBH, deep inspiratory breath hold; FB, free breathing; LAD, left anterior descending coronary artery; LV, left ventricle; RV, right ventricle.

Table 3 Median and standard deviation values of anatomic parameters

Parameter (CT-based)	DIBH group (median)	FB group (median)	Reduction	P value
HH (cm)	8.59	7.28	1.31 cm	<0.001*
DBIB (cm)	12.73	10.78	1.95 cm	<0.001*
CD (cm)	19.97	19.18	0.79 cm	0.052
HCWL (cm)	3.26	3.93	–0.67 cm	<0.001*
HCWD (cm)	1.57	1.35	0.22 cm	0.004*
Heart volume (cc)	505	558	–53 cc	0.010*
Ipsilateral lung volume (cc)	1,671	1,022	649 cc	<0.001*

*, significant differences. CT, computed tomography; HH, heart height; DBIB, the distance between ipsilateral lung and breast; CD, chest depth; HCWL, heart chest wall length; HCWD, heart chest wall distance; DIBH, deep inspiratory breath hold; FB, free breathing.

was also shown in some studies, including CD, maximum heart depth, tumor bed site, and heart volume in the radiation field (20,25). We demonstrated that out of various analyzed anatomical measures, ΔHH was the best and independent predictor of the Dmean to the heart, LAD, LV, and RV. Hence, this simple measure may identify patients necessitating effective heart protection.

A limitation of breath-holding techniques is their reproducibility, which may affect clinical outcomes (26). Current approaches to overcome this problem include surface-guided radiotherapy, RPM, and image-guided radiation therapy (27,28). DIBH also requires specific training and patient compliance, therefore, treatment efficacy with this technique may be variable. The predictive value of anatomical parameters for heart exposure dose has been highly regarded. This study offered information on potential utility of predictors for patients benefiting from DIBH. We studied some similar research (29,30). The investigation of comparing those parameters from FB and DIBH scans in some patients worthy of further study.

Table 4 Correlations between delta values of anatomic parameters and radiation doses

Variable	ΔHH	P value	ΔDBIB	P value	ΔHCWD	P value	ΔHCWL	P value
Heart								
Dmean	−0.72	<0.001*	−0.52	0.000*	−0.26	0.037*	−0.45	0.000*
Dmax	−0.61	<0.001*	−0.37	0.002*	−0.13	0.284	−0.45	0.000*
LAD								
Dmean	−0.52	0.000*	−0.40	0.000*	−0.19	0.118	−0.26	0.033*
Dmax	−0.58	<0.001*	−0.39	0.001*	−0.22	0.080	−0.31	0.012*
LV								
Dmean	−0.65	<0.001*	−0.65	<0.001*	−0.21	0.088	−0.40	0.001*
Dmax	−0.53	0.000*	−0.29	0.016*	−0.23	0.058	−0.39	0.001*
RV								
Dmean	−0.49	0.000*	−0.39	0.001*	−0.14	0.277	−0.32	0.008*
Dmax	−0.55	0.000*	−0.51	0.000*	−0.23	0.062	−0.31	0.012*

*, significant differences. Dmean, mean dose; Dmax, maximum dose; LAD, left anterior descending coronary artery; LV, left ventricle; RV, right ventricle; HH, heart height; DBIB, the distance between ipsilateral lung and breast; HCWD, heart chest wall distance; HCWL, heart chest wall length.

Table 5 Predictive values of particular anatomic parameters for cardiac doses

Parameter	ΔHH		ΔDBIB		ΔHCWL	
	AUC	95% CI	AUC	95% CI	AUC	95% CI
Heart Dmean	0.818	0.717, 0.919	0.729	0.597, 0.860	0.685	0.545, 0.824
LAD Dmean	0.725	0.602, 0.848	0.664	0.533, 0.796	0.585	0.446, 0.724
LV Dmean	0.821	0.720, 0.922	0.735	0.607, 0.862	0.715	0.587, 0.842
RV Dmean	0.820	0.717, 0.924	0.774	0.658, 0.890	0.705	0.580, 0.830

Dmean, mean dose; LAD, left anterior descending coronary artery; LV, left ventricle; RV, right ventricle; HH, heart height; DBIB, the distance between ipsilateral lung and breast; HCWL, heart chest wall length; AUC, the area under the curve; CI, confidence interval.

Our study has a few limitations. First, it was retrospective, conducted in a single center, and included patients who underwent both mastectomy and BCS. Additionally, some patients were administered nodal RT, including internal mammary lymph node RT, which increases cardiac exposure. Due to small patient samples, we could not perform stratified analyses considering these variables. Second, the doses to the OARs in each fraction were less strictly controlled than in prospective studies. Currently, advanced RT techniques, such as intensity-modulated RT and volumetric-modulated arc therapy, have been employed in DIBH planning. However, we have identified a reliable predictor for the DIBH benefit. It is imperative, however, that these observations are confirmed within prospective studies.

Conclusions

DIBH significantly reduces cardiac doses in left-sided BC patients undergoing RT. ΔHH may help select patients who will benefit most from DIBH. Future prospective studies are warranted to determine more robustly the dosimetric and clinical benefits of DIBH.

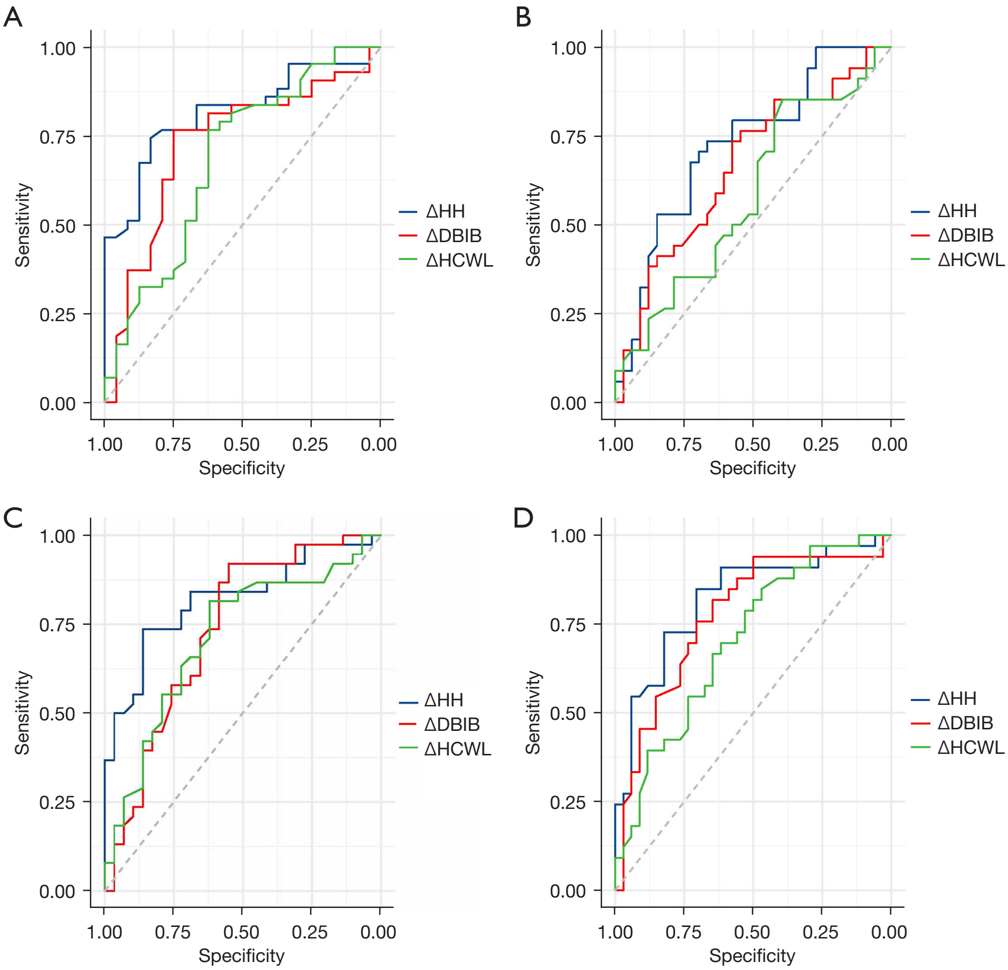

Figure 2 Receiver operating characteristic curves predicting for >20% reduction in mean heart dose (A), mean LAD dose (B), mean LV dose (C), and mean RV dose (D). HH, heart height; DBIB, the distance between ipsilateral lung and breast; HCWL, heart chest wall length; LAD, left anterior descending coronary artery; LV, left ventricle; RV, right ventricle.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-23-160/rc

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-23-160/dss

Peer Review File: Available at https://gs.amegroups.com/article/view/10.21037/gs-23-160/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-23-160/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by The Second Affiliated Hospital of Guangxi Medical University Ethics Committee (approval No. 2023-KY0003) and individual consent for this retrospective analysis was waived.

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