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Accuracy of mitral annular plane systolic excursion in diagnosing anthracycline-induced subclinical cardiotoxicity in patients with breast cancer - a retrospective cohort study

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Abstract

Background The mitral annular plane systolic excursion (MAPSE) is used to analyze the left ventricle longitudinal function. However, the accuracy of MAPSE in diagnosing oncological populations is unclear. In this study, we aimed to assess the accuracy of MAPSE in diagnosing subclinical cardiotoxicity in women with breast cancer undergoing anthracycline treatment.

Methods This retrospective cohort study included echocardiographic assessments of patients with breast cancer who underwent anthracycline treatment as part of their therapeutic regimen. Assessments were performed before treatment, after administering the first dose of anthracycline, after completing anthracycline treatment, and 6 and 12 months after treatment. Left ventricular ejection fraction was calculated using the modified biplane Simpson method. The performances of MAPSE and global longitudinal strain (GLS) were analyzed using receiver operating characteristic (ROC) curves. Their accuracies were measured using the area under the ROC curves.

Results Sixty-one patients were included in this study. Of them, 8.2% presented cardiotoxicity 6 months after treatment completion. Patients with cardiotoxicity had lower LVEF (47% vs. 63%; $p < 0.001$), MAPSE (10.23 mm vs. 12.25 mm; $p = 0.012$), and LV GLS (16.13% vs. 19.05%; $p = 0.005$) values than those without. A 12% reduction in the GLS exhibited sensitivity, specificity, and overall accuracy of 80%, 70%, and 78%, respectively. A relative reduction of 15% in MAPSE exhibited a sensitivity, specificity, and accuracy of 80%, 77%, and 81.2%, respectively. An absolute MAPSE reduction of 2 mm exhibited a sensitivity, specificity, and accuracy of 80%, 73.21%, and 81.2%, respectively. No differences were observed between the ROC curves.

Conclusion MAPSE showed similar accuracy to GLS in diagnosing subclinical cardiotoxicity in women with breast cancer undergoing anthracycline treatment.

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Introduction

Breast cancer is the most commonly diagnosed type of cancer worldwide [1], with 297,790 new cases and 43,170 deaths estimated to have occurred in the United States in 2023 [2]. The National Cancer Institute in Brazil reported that breast cancer affected 73,610 women and caused 18,139 deaths in 2023, accounting for the highest mortality rate among women in 2023 [3]. The main risk factors for breast cancer are female sex, older age, exposure to endogenous or exogenous estrogen, family history, alcohol intake, and gene mutations, such as breast cancer 1 and 2 genes [4].

Anthracyclines are drugs that damage deoxyribonucleic acid. However, they are an important therapeutic class for treating breast cancer [5–7], reducing the mortality rate by 20–30% [5]. Cardiotoxicity is the most common late complication caused by anthracyclines when used alone or in combination with other drugs, particularly trastuzumab [7–9]. The most accepted biochemical mechanism underlying the pathogenesis of cell damage is topoisomerase II-beta inhibition in cardiomyocytes [10]. This mechanism involves the formation of reactive oxygen species and intracellular complexes with iron molecules [10–13]. Anthracyclines are the primary cause of chemotherapy-related cardiotoxicity [10], with a dose-dependent incidence ranging from 5% (accumulated doxorubicin dose of 400 mg/m^2) to 26% (accumulated doxorubicin dose of 550 mg/m^2) [11].

In addition to the cumulative dose, the presence of additional risk factors may increase the risk of anthracycline-induced cardiotoxicity. Systemic arterial hypertension (SAH) increases the risk of congestive heart failure in cancer survivors exposed to anthracyclines by 12.4-fold [14]. The use of trastuzumab, cyclophosphamide, or radiotherapy also increases the risk of anthracycline-induced cardiotoxicity [15, 16].

Chemotherapy-related cardiotoxicity is defined as a percentage reduction in left ventricular (LV) ejection fraction (LVEF) below a specific cutoff point on echocardiography [13, 17–20]. The most recent consensus of the British Cardio-Oncology Society and Brazilian Society of Cardiology stipulates the specific cutoff point as an LVEF reduction of 50% [21, 22]. LVEF reduction is a late event that is seldom reversible; therefore, detecting subclinical cardiotoxicity phases accelerates the implementation of therapeutic and preventive measures [13, 17, 18, 20, 21].

LV global longitudinal strain (GLS) measurements have shown good accuracy in diagnosing subclinical cardiotoxicity [22], with a relative decrease in serial measurements resulting in greater sensitivity and specificity than isolated measurements [18–21]. The cutoff points range from 12% [22] to 15% [18, 19, 21, 23] of this relative decrease in relation to the baseline value.

Systolic LV shortening along the longitudinal axis can be measured using the mitral annular plane systolic excursion (MAPSE) on M-mode echocardiography. MAPSE is positively correlated with LV GLS, with a slightly higher value observed in women, and tends to decrease with age [24, 25]. MAPSE values < 8 mm can diagnose an LVEF reduction < 50% with a sensitivity and specificity of 90% and 82%, respectively, whereas MAPSE values > 10 mm diagnosed a > 55% LVEF with sensitivity and specificity of 92% and 87%, respectively [26].

The benefits of MAPSE include being easy to perform, less dependence on a good acoustic window or image quality, more accessibility, and being a universal measurement parameter [25, 26]. Nevertheless, the accuracy of MAPSE in diagnosing anthracycline-induced cardiotoxicity is unclear, with only a few studies analyzing patients with cancer. While reduced MAPSE after anthracycline treatment has been reported, the clinical implications of this finding are uncertain [27].

To date, studies comparing the accuracy of LV MAPSE and GLS in diagnosing subclinical cardiotoxicity in patients with breast cancer undergoing anthracycline treatment are lacking. In the present study, we aimed to assess the accuracy of MAPSE in diagnosing subclinical cardiotoxicity in women with breast cancer undergoing anthracycline treatment.

Materials and methods

Study design

In this retrospective cohort study, the echocardiographic data and clinical outcomes of patients with breast cancer were analyzed. The patients underwent chemotherapy with anthracyclines at a single medical center in Feira de Santana, BA, Brazil, between June 2014 and July 2015. This study was approved by the Research Ethics Committee of the State University of Feira de Santana (approval number: 69195). The patients underwent echocardiography before doxorubicin treatment, after the first dose of doxorubicin, after treatment completion, and 6 and 12 months after treatment. The research reported in this paper adhered to Standing for Reporting of Diagnostic Accuracy Studies (STARD) 2015 guidelines.

Population and sampling

The study population included women with a primary diagnosis of breast cancer who received at least one dose of doxorubicin. Inclusion criteria were age > 18 years, signing an informed consent form, and presence of a good echocardiographic window. Exclusion criteria were

the presence of uncontrolled SAH, moderate or severe heart valve disease, LVEF < 55% before treatment, positive findings for Chagas disease, a previous diagnosis of heart failure or coronary artery disease, a wide QRS complex on baseline electrocardiography, rhythm other than the sinus on baseline electrocardiography, or use of an echocardiogram with poor technical quality. The epidemiological data used in this study was retrieved from medical records.

Echocardiography

An ultrasound machine (Vivid E9; GE Healthcare, Milwaukee, WI, USA) with multifrequency electronic sector transducer (2.5–3.5 MHz), pulsed-wave Doppler, continuous-wave Doppler, tissue Doppler, speckle tracking, color flow mapping, and electrocardiogram monitoring were used for transthoracic echocardiography. Echocardiography was performed by the same echocardiographer following the recommendations of the American Society of Echocardiography [28]. The digital records of the tests were stored for subsequent analyses. All echocardiographic variables were reanalyzed offline by a second experienced echocardiographer. EchoPAC Software (version 202; GE Healthcare) was used for all analyses.

Images were acquired in the left lateral decubitus or supine position. Echocardiographic sections were acquired in the parasternal long- and short-axis positions; apical four-, five-, and three-chamber views; and suprasternal and subcostal views using M-mode, two-dimensional, pulsed-wave, continuous-wave, color, and tissue Doppler imaging. The following structures were assessed on images acquired in two-dimensional mode in parasternal long-axis sections: end-diastole ascending aorta and end-systole left atrium dimensions, LV diastolic and systolic diameters, and interventricular septum and posterior LV wall diastolic thicknesses [28, 29]. M-mode images were used to calculate the tricuspid annular plane systolic excursion for analyzing the right ventricular systolic function and the MAPSE for analyzing the LV longitudinal systolic function (Fig. 1). Both parameters were measured in apical four- and two-chamber views from the distance of the systolic excursion of the annular segment along the longitudinal plane [28, 30]. MAPSE is expressed as the mean septal and lateral wall values.

The mitral transvalvular flow was analyzed in the apical four-chamber view using pulsed-wave Doppler imaging, with the sample volume placed at the tips of the mitral leaflets during diastole. The E wave corresponded to the early LV diastolic filling velocity, whereas the A wave corresponded to the late LV filling velocity during atrial contraction; therefore, the E/A ratio was calculated. The E-wave deceleration time was calculated in milliseconds [28]. The myocardial performance index was calculated using pulsed-wave Doppler echocardiography according to the following formula: mitral annulus opening and closing time − ejection time/ejection time [28]. Tissue

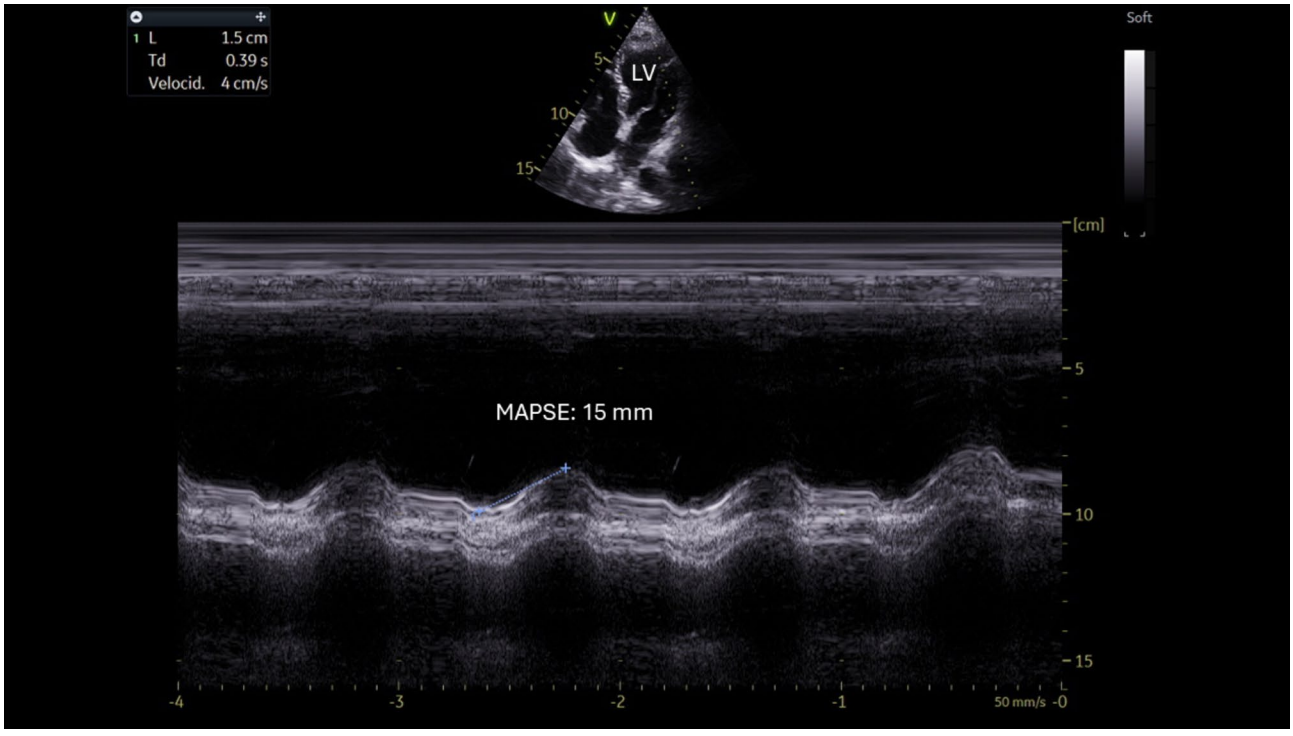

Fig. 1 Echocardiographic assessment using M-mode from a 65-year-old female patient post-chemotherapy. The figure illustrates a normal value for mitral annular plane systolic excursion (MAPSE). LV: left ventricle

Doppler imaging of the septal, lateral, anterior, and inferior mitral annuli and the lateral region of the tricuspid annulus was used to calculate the systolic (S') and early diastolic (e') velocities [28].

LVEF was calculated using the modified biplane Simpson method in LV apical four- and two-chamber views. Echocardiographic two-dimensional grayscale images were obtained in apical four-, three-, and two-chamber views to measure the LV GLS. The aortic valve closure time was calculated using pulsed-wave Doppler echocardiography flow tracing in the aortic valve. All professionals involved in GLS image acquisition were trained to perform the procedure. The point tracking quality was checked and manually adjusted if necessary. LV GLS was calculated using the mean longitudinal strain values in the basal, middle, and apical segments obtained in the LV apical four-, three-, and two-chamber views [28]. In the present study, clinical cardiotoxicity was defined based on the criterion of an absolute LVEF reduction > 10% reaching values < 50% [21, 22].

Table 1 Patients' baseline clinical and demographic characteristics

Variable	Total sample (*N* = 61)
Age (years)	50 (22–79)
Height (cm)	157 (137–170)
Weight (kg)	64.5 (40–103)
Body surface (m^2)	1.64 (1.26–2.02)
Body mass index (kg/m2)	26.48 (17.9–44)
Waist circumference (cm)	88 (64–116)
SBP (mmHg)	130 (100–260)
DBP (mmHg)	80 (60–140)
Heart rate (bpm)	78.5 (63–120)
SAH	26 (42.6%)
Type 2 diabetes mellitus	4 (6.6%)
CAD	0 (0%)
Smoking	3 (4.9%)
Dyslipidemia	5 (8.2%)
Alcohol use disorder	9 (14.8%)
Obesity	4 (6.6%)
Sedentary lifestyle	45 (73.8%)
ACEI use	8 (13%)
Beta-blocker use	1 (1.6%)
ARB use	8 (13%)
Radiotherapy	47 (77%)
Trastuzumab	14 (22.9%)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CAD, coronary artery disease; DBP, diastolic blood pressure; SAH, systemic arterial hypertension; SBP, systolic blood pressure

Numerical variables are expressed as medians and ranges

The Dubois formula was used to calculate the body surface area: body surface area = $0.007184 \times \text{height}^{0.725} \times \text{weight}^{0.425}$

Body mass index was calculated using the following formula: weight/height^2. Weight was measured in kilograms and height in meters

No patient presented with cardiotoxicity after the first dose of doxorubicin or after treatment completion. Five (8.2%) patients presented with cardiotoxicity 6 months after treatment completion, whereas no new cardiotoxicity cases were observed 12 months after treatment completion.

Statistical analysis

Numerical variables are presented as medians and ranges, whereas categorical variables are presented as relative and absolute frequencies. The Mann–Whitney U test was used to analyze differences in numerical variables between groups, whereas Fisher's exact test was used to analyze differences in categorical variables. Pearson's correlation coefficient was calculated to assess the correlation between the MAPSE and GLS. The interclass correlation coefficient (ICC) was calculated to assess inter-observer variations in LVEF, MAPSE, and GLS.

The relative changes in MAPSE (MAPSE*rel*) between the echocardiographic findings in the exam taken before the time of diagnosis of cardiotoxicity and the baseline values were used to assess the sensitivity, specificity, and accuracy of MAPSE. Receiver operating characteristic (ROC) curves were constructed to determine the best cutoff points. Following the same procedure, absolute MAPSE reduction (ΔMAPSE) and relative changes in GLS (GLS*rel*) were also assessed. DeLong's test was used to compare the correlation between the two ROC curves.

Upon defining the cutoff points, the sensitivity, specificity, and accuracy of MAPSE*rel*, ΔMAPSE, and GLS*rel* were calculated by qualitatively analyzing each parameter alone or in combination. Statistical significance was set at $p < 0.05$ (two-tailed), and 95% confidence intervals (CIs) were calculated. Statistical analyses were performed using R software (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

Clinical and demographic data

In total, 61 patients were included in the analysis. The median age of the participants was 50 (range, 22–79) years, and their median body mass index was 26.48 (range, 17.9–44) kg/m^2. Twenty-six (42.6%) patients had SAH, four (6.6%) had type 2 diabetes, three (4.9%) were smokers, and forty-five (73.8%) were not practicing any form of physical exercise. No patient had coronary artery disease. Furthermore, 47 (77%) patients underwent radiotherapy, 14 (22.9%) received concomitant trastuzumab, and 17 (27%) used medication to control SAH. Patients' clinical and demographic characteristics are presented in Table 1.

Patients with cardiotoxicity 6 months after treatment completion had a higher median age (59 vs. 49.5; $p = 0.854$) and relative prevalence of SAH (80% vs. 39.3%; $p = 0.156$), diabetes mellitus (20% vs. 5.4%; $p = 0.310$), angiotensin-receptor blocker use (60% vs. 8.9%; $p = 0.014$), and concomitant trastuzumab use (40% vs. 21.4%; $p = 0.293$) than those without cardiotoxicity.

None of the patients treated with angiotensin-converting enzyme inhibitors experienced cardiotoxicity. No significant differences in the median cumulative doxorubicin dose were observed between the groups (238.7 mg/m^2 vs. 239.5 mg/m^2; $p=0.683$).

Echocardiographic data

All patients underwent echocardiography before the first dose of doxorubicin. The median LVEF, LV GLS, and MAPSE were 66% (range: 56–75), 19.77% (range: 15.10–26.73), and 13.5 mm (range: 8.75–16.25), respectively. No differences were observed in baseline LVEF, MAPSE, or GLS between patients with cardiotoxicity and those without. Table 2 presents the baseline echocardiographic parameters in each group. The ICCs for LVEF, GLS, and MAPSE were 0.93 (95% CI: 0.87–0.96), 0.82 (95% CI: 0.71–0.89), and 0.88 (95% CI: 0.73–0.94), respectively. These values were considered appropriate.

Table 2 Echocardiographic measurements before the first dose of doxorubicin in the groups with and without cardiotoxicity

Variable	Without cardiotoxicity ($n=56$)	With cardiotoxicity ($n=5$)	*p*-value
LVDD (mm)	45.00 (34.00–50.00)	49.00 (41.00–50.00)	0.046
LVSD (mm)	28.50 (20.00–34.00)	31.00 (27.00–35.00)	0.044
Septum (mm)	8.00 (6.00–14.00)	10.00 (6.00–12.00)	0.269
LVPW (mm)	8.00 (6.00–12.00)	10.00 (6.00–10.00)	0.133
LVEF (%)	66.00 (58.00–75.00)	64.00 (56.00–66.00)	0.121
Ascending aorta (mm)	29.00 (24.00–37.00)	30.00 (26.00–32.00)	0.432
LA (mm)	33.00 (26.00–41.00)	33.00 (27.00–36.00)	0.466
LA volume (mL)	40.00 (19.00–74.00)	48.00 (23.00–55.00)	0.643
LA volume index (mL/m^2)	22.52 (12.20–41.61)	23.76 (19.87–27.07)	0.925
MAPSE (mm)	13.50 (8.75–16.25)	13.25 (12.00–13.75)	0.608
GLS (%)	19.94 (15.10–26.73)	17.80 (16.40–20.90)	0.211
E wave (cm/s)	69.00 (39.00–100.00)	59.00 (55.00–77.00)	0.437
A wave (cm/s)	67.00 (34.00–97.00)	88.00 (46.00–118.00)	0.187
E/A ratio	1.06 (0.41–1.97)	0.79 (0.65–1.20)	0.091
Deceleration time (ms)	187.50 (75.00–306.00)	219.00 (179.00–264.00)	0.127
Septal e' wave (cm/s)	8.00 (4.00–12.00)	6.00 (5.00–9.00)	0.131
Lateral e' wave (cm/s)	11.00 (5.00–18.00)	9.00 (7.00–11.00)	0.139
Mean septal, lateral, anterior, and inferior e' (cm/s)	9.75 (4.50–14.75)	6.25 (6.00–10.00)	0.057
Mean septal, lateral, anterior, and inferior s' (cm/s)	6.88 (5.00–10.25)	6.50 (5.50–8.25)	0.653
E/e' ratio	7.11 (4.27–19.11)	9.83 (5.50–12.32)	0.127
MPI	0.46 (0.27–0.66)	0.54 (0.00–0.61)	0.346
TAPSE (mm)	21.00 (15.00–29.00)	19.00 (17.00–23.00)	0.317

GLS, left ventricular global longitudinal strain; LA, left atrium; LVDD, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction (calculated using the modified biplane Simpson method); LVPW, left ventricular posterior wall; LVSD, left ventricular systolic diameter; MAPSE, mitral annular plane systolic excursion; MPI, myocardial performance index; TAPSE, tricuspid annular plane systolic excursion

Numerical variables are expressed as medians and ranges

The Mann–Whitney test was used to analyze numerical variables

Patients with cardiotoxicity 6 months after treatment completion had lower LVEF (47% vs. 63%; $p<0.001$), MAPSE (10.23 mm vs. 12.25 mm; $p=0.012$), and LV GLS (16.13% vs. 19.05%; $p=0.005$) values than those without. The changes in MAPSE were more significant in patients with cardiotoxicity than in those without. Furthermore, a greater relative reduction in MAPSE*rel* (−18.18% vs. −5.79; $p=0.004$) and a greater reduction in ΔMAPSE (−2.5 mm vs. −0.75 mm; $p=0.007$) were observed in patients with cardiotoxicity than in those without. Similar findings were observed for LV GLS*rel*, which showed a greater reduction in patients with cardiotoxicity (−9.62% vs. −4.91%; $p=0.0115$). Table 3 presents the echocardiographic parameters in the groups.

MAPSE AND GLS CHARACTERISTICS DURING FOLLOW-UP

The MAPSE and GLS values showed a moderate positive linear correlation at all time points. The correlation coefficient (r) was 0.545 (95% CI: 0.34–0.70, $p<0.01$) before treatment (Figs. 2) and 0.648 (95% CI: 0.474–0.774, $p<0.01$) 6 months after treatment completion (Fig. 3).

MAPSE and GLS performance in diagnosing subclinical cardiotoxicity

The MAPSE*rel* ROC curve showed an area under the curve (AUC) of 81.2% (95% CI: 63.2–99.3%), similar to that of the ΔMAPSE ROC curve (AUC=81.2% [95% CI: 60.9–100%]). The AUC of the GLS*rel* ROC curve was 77.5% (95% CI: 58.8–96.2%). The GLS*rel*, MAPSE*rel* (Fig. 4), and ΔMAPSE (Fig. 5) ROC curves were similar with no statistically significant differences.

The qualitative sensitivity and specificity were assessed using the best performance cutoff points for each measurement. A MAPSE*rel*≥15% exhibited a sensitivity, specificity, and accuracy of 60% (95% CI: 14.7–94.7%), 85.7% (95% CI: 73.8–91.8%), and 83.6% (95% CI: 71.9–91.8%), respectively. A ΔMAPSE of ≥2.5 mm exhibited an accuracy of 86.9% (95% CI 75.8–94.2%) with a low sensitivity of 20% (95% CI: 0.5–71.6%), whereas a ΔMAPSE of ≥2 mm exhibited a sensitivity and specificity of 80% (95% CI: 28.4–99.5%) and 80.4% (95% CI: 88.2–89.4%), respectively, which were considered good values. A GLS*rel* of ≥12% exhibited a sensitivity, specificity, and accuracy of 80% (95% CI: 28.4–99.5%), 69% (95% CI: 55.9–81.2%), and 70.5% (95% CI: 57.4–81.5%), respectively. A parallel combination of GLS*rel*≥12% and ΔMAPSE≥2 mm exhibited a sensitivity, specificity, and accuracy of 96% (95% CI: 68.1–99.2%), 55.48% (95% CI: 32.6–74%), and

Table 3 Echocardiographic measurements 6 months after treatment completion in the groups with and without cardiotoxicity

Variable	Without cardiotoxicity (*n* = 56)	With cardiotoxicity (*n* = 5)	*p*-value
LVDD (mm)	45 (35–56)	47 (39–55)	0.468
LVSD (mm)	29.5 (22–40)	36 (30–47)	0.006
Septum (mm)	8 (6–13)	10 (6–11)	0.088
LVPW (mm)	8 (6–12)	9 (8–10)	0.011
LVEF (%)	63 (51–72)	47 (31–49)	< 0.001
Ascending aorta (mm)	29.5 (24–39)	30 (29–34)	< 0.243
LA (mm)	33 (28–41)	34 (30–42)	0.641
LA volume (mL)	39.5 (18.5–69.5)	36.5 (34–72)	0.659
LA volume index (mL/m^2)	23.92 (13.41–41.08)	24.01 (19.61–39.78)	0.925
MAPSE (mm)	12.25 (8–16.25)	10.25 (5.25–12)	0.012
MAPSE*rel* (%)	5.79 (25.42–20.51)	−18.18 (−59.62–−11.11)	0.004
ΔMAPSE (mm)	−0.75 (−3.75–2.00)	−2.50 (−7.75–−1.50)	0.007
GLS (%)	19.05 (10.2–23.9)	16.13 (8.17–17.27)	0.005
GLS*rel* (%)	−4.91 (−43.65–17.24)	−9.62 (−54.1–−4.27)	0.115
E wave (cm/s)	67 (40–104)	52 (35–116)	0.111
A wave (cm/s)	62 (38–99)	79 (40–102)	0.738
E/A ratio	1.09 (0.53–2.00)	0.65 (0.51–2.76)	0.097
Deceleration time (ms)	183 (106–266)	227 (139–335)	0.446
Septal e' wave (cm/s)	7.0 (4.0–11.0)	4.0 (3.0–5.0)	0.002
Lateral e' wave (cm/s)	9.0 (2.0–15)	7.0 (3.0–8.0)	0.046
Mean septal, lateral, anterior, and inferior e' (cm/s)	7.75 (3.0–13.0)	5.5 (4.0–6.25)	0.009
Mean septal, lateral, anterior, and inferior s' (cm/s)	6.25 (4.50–9.50)	7.25 (3.83–29.00)	0.851
E/e' ratio	8.53 (5.07–17.65)	8.32 (5.07–17.65)	0.862
MPI	0.5 (0.0–0.76)	0.18 (0.0–0.9)	0.239
TAPSE (mm)	20 (12–28)	16.5 (14–17)	0.007

GLS, left ventricular global longitudinal strain; LA, left atrium; LVDD, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction (calculated using the modified biplane Simpson method); LVPW, left ventricular posterior wall; LVSD, left ventricular systolic diameter; MAPSE, mitral annular plane systolic excursion; MPI, myocardial performance index; TAPSE, tricuspid annular plane systolic excursion

Numerical variables are expressed as medians and ranges

The Mann–Whitney test was used to analyze numerical variables

91% (95% CI: 77.8–94.7%). These data are presented in Table 4.

Discussion

In this retrospective cohort study involving 61 women with breast cancer treated with doxorubicin, the incidence of cardiotoxicity, indicated by an LVEF reduction below 50%, was 8.2% approximately 6 months after the administration of the last doxorubicin dose, and was higher than expected for the administration of a median doxorubicin dose of 238.7 mg/m^2 [8, 10]. The cohort of the present study included relatively young patients; however, the median age was 50 years. A sedentary lifestyle (73.8%), SAH (42.6%), and combined treatment with radiotherapy (77%) increased the risk of cardiotoxicity in this study population [12, 17]. The incidence of cardiotoxicity induced by a cumulative doxorubicin dose of approximately 400 mg/m^2 is approximately 5% [8, 10, 15, 17], which increases with one or more additional risk factors [17]. In the present study, patients with cardiotoxicity were approximately 10 years older, had a higher prevalence of SAH (80% vs. 39.3%), diabetes mellitus (20% vs. 5.4%), and obesity (20% vs. 5.4%), and had a higher frequency of using trastuzumab combined with doxorubicin (40% vs. 21.4%) than those without cardiotoxicity. These are well-known risk factors for cardiotoxicity [12, 15, 17]. The use of angiotensin receptor blockers was more prevalent among patients with cardiotoxicity (60% vs. 8.9%) than among those without cardiotoxicity, possibly because of the higher incidence of SAH in patients with cardiotoxicity. However, no direct associations were observed.

Before the administration of the first dose of doxorubicin, echocardiographic data were within the normal range for the Brazilian population [31]. The LV diastolic diameter (49 mm vs. 45 mm) and systolic diameter (31.0 mm vs. 28.5 mm) were higher in patients with cardiotoxicity than in those without cardiotoxicity owing to the higher incidence of SAH in patients with cardiotoxicity. The LVEF, MAPSE, GLS, and tricuspid annular plane systolic excursion values were similar between patients with and without cardiotoxicity. Echocardiography performed 6 months after treatment completion showed a lower LVEF (47% vs. 63%), MAPSE (10.25 mm vs. 12.25 mm), GLS (16.13% vs. 19.05%), and tricuspid annular plane systolic excursion (20 mm vs. 16.5 mm) in patients with cardiotoxicity than in those without. This finding indicates systolic disorder in both ventricles, which is compatible with anthracycline-induced myocardial injury [13–16]. Patients with cardiotoxicity showed a greater reduction in GLS*rel* (−9.62% vs. −4.91%), MAPSE*rel* (−18.18% vs. −5.79), and ΔMAPSE (−2.5 mm vs. −0.75 mm) compared with the baseline values. Both MAPSE and GLS can be used to estimate LV systolic function; however, MAPSE characteristics in patients with cardiotoxicity have not been sufficiently described and studied. Diastolic function assessment showed low septal (4.0 vs. 7.0 m/s) and lateral (7.0 vs. 9.0 cm/s) values in patients with cardiotoxicity, with no differences in other diastolic function measurements. Early diastolic changes have been described in patients using anthracyclines; however, their usefulness in predicting LVEF reduction remains unclear [8, 32].

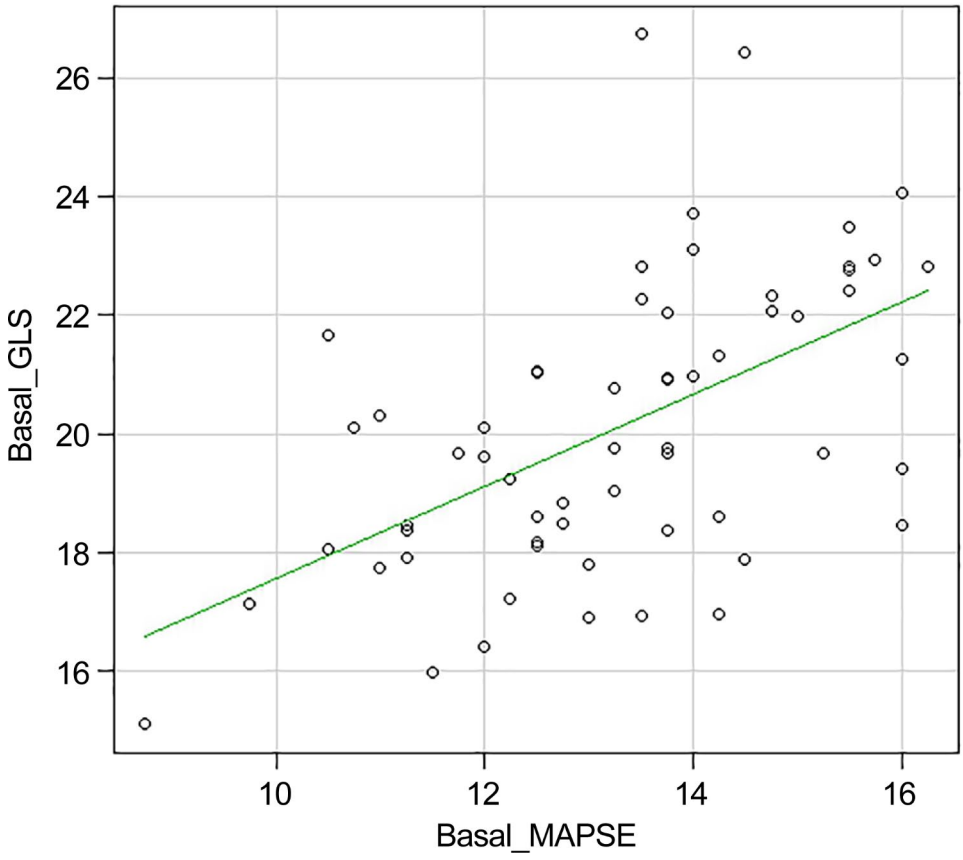

Fig. 2 Scatter plot of mitral annular plane systolic excursion and global longitudinal strain measurements before doxorubicin treatment
Basal_MAPSE, MAPSE measurement before doxorubicin treatment; Basal_GLS, GLS measurement before doxorubicin treatment
MAPSE is measured in mm; GLS is measured in percentage
$r = 0.545$; 95% CI (0.34–0.70); $p < 0.01$
GLS, global longitudinal strain; MAPSE, mitral annular plane systolic excursion

In the cohort of the present study, the correlation coefficient (r) between the MAPSE and GLS before treatment was 0.545 (95% CI: 0.34–0.70), which increased shortly after treatment completion to 0.648 (95% CI: 0.474–0.774). These findings are consistent with those of previous studies that reported higher correlation coefficients between the MAPSE and GLS in patients with heart disease than those of healthy people [33]. Few prospective studies have investigated the relationship between MAPSE and GLS in patients treated with anthracyclines.

In the present study, MAPSE*rel* showed satisfactory performance in diagnosing subclinical cardiotoxicity, with an accuracy similar to that of GLS*rel* (81.2% vs. 77.5%). The ΔMAPSE and GLS*rel* showed similar performance in predicting LVEF reduction (81.2% vs. 77.5%). MAPSE*rel* ≥ 15% exhibited a sensitivity and specificity of 60% and 85.7%, respectively, and ΔMAPSE ≥ 2 mm exhibited a sensitivity and specificity of 80% and 80.4%, respectively. The role of MAPSE as an indirect marker of LVEF is unknown [26, 34], and its potential to predict LVEF reduction in patients with cardiotoxicity has been poorly described. To the best of our knowledge, only one study has analyzed the accuracy of MAPSE in diagnosing anthracycline-induced subclinical cardiotoxicity, reporting a sensitivity and specificity of 74.5% and 54.9%, respectively, with a reduction in ΔMAPSE ≥ 2 mm [35]. Conversely, a ≥ 12% reduction in GLS*rel* exhibited a sensitivity and specificity of 80% and 69%, respectively, whereas a ≥ 15% reduction in GLS*rel* exhibited a sensitivity and specificity of 40% and 78%, respectively. The GLS*rel* of ≥ 15% in the present study was lower than that of previous studies, whereas the GLS*rel* of ≥ 12% in the present study was consistent with that of previous studies [19–22]. Combining a ΔMAPSE reduction of ≥ 2 and a GLS*rel* reduction of ≥ 12% increased the sensitivity to 96% and reduced the specificity to 55.48%. This combination exhibited a high negative predictive value.

The present study is one of few to assess the accuracy of MAPSE in diagnosing anthracycline-induced cardiotoxicity and included the largest Brazilian cohort ever used to study the research topic. However, this study had some limitations that must be highlighted as potential sources of bias, including the small sample size, the single-center origin of the patients, the retrospective nature of the

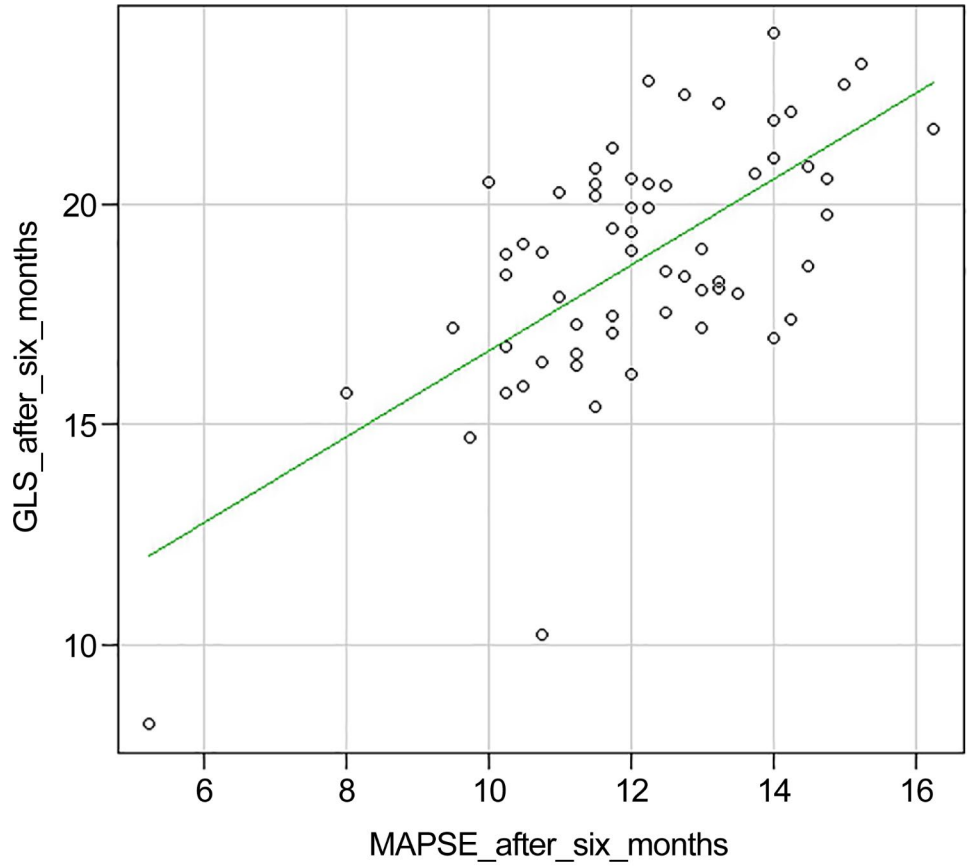

Fig. 3 Scatter plot of mitral annular plane systolic excursion and global longitudinal strain measurements 6 months after treatment completion
MAPSE-after_six_months: MAPSE measurement 6 months after treatment completion; GLS_after_six_months: GLS measurement 6 months after treatment completion
MAPSE is measured in mm; GLS is measured in percentage
$r = 0.648$; 95% CI (0.474–0.774); $p < 0.01$
GLS, global longitudinal strain; MAPSE, mitral annular plane systolic excursion

study design, and the fact that the echocardiographer was not blinded to the elapsed treatment time.

The findings of this study have the potential to influence the follow-up of patients with cancer receiving anthracycline. MAPSE has some advantages over GLS, as it is less dependent on good acoustic windows, easier to acquire, and widely available in all echocardiographic devices. MAPSE is a particularly valuable instrument for assessing LV systolic function in women with breast cancer undergoing mastectomy on the left side, which can considerably interfere with the echocardiogram's quality and accurate GLS assessment; therefore, MAPSE is more frequently used worldwide. In developing countries such as Brazil, where approximately 70% of the population uses the Unified Health System, GLS assessment hinders serial GLS measurements. Therefore, serial MAPSE measurements may be a suitable solution to this problem. MAPSE is easy to measure, thus enabling trained non-cardiologists to use M-mode, increasing its availability [33].

Conclusions

In this study, MAPSE and GLS showed similar accuracies in diagnosing cardiotoxicity in women with breast cancer undergoing anthracycline treatment. MAPSE may have a role in the diagnosis and follow-up of patients with subclinical cardiotoxicity. New studies with larger samples are needed to better understand the role of MAPSE in diagnosing subclinical cardiotoxicity.

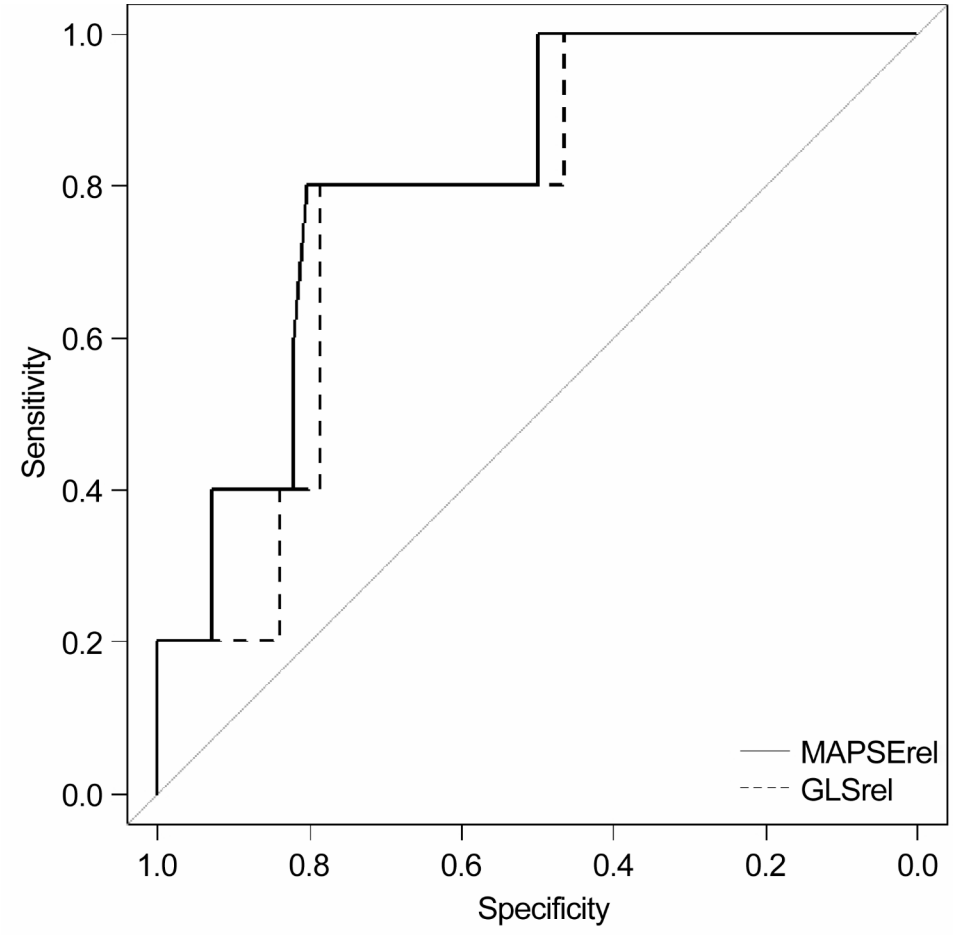

Fig. 4 Comparison of the receiver operating characteristic curves for GLS*rel* and MAPSE*rel* in diagnosing subclinical cardiotoxicity
GLS, global longitudinal strain; GLS*rel*, relative change in left ventricular GLS; MAPSE, mitral annular plane systolic excursion; MAPSE*rel*, relative change in MAPSE
DeLong test; $p = 0.526$

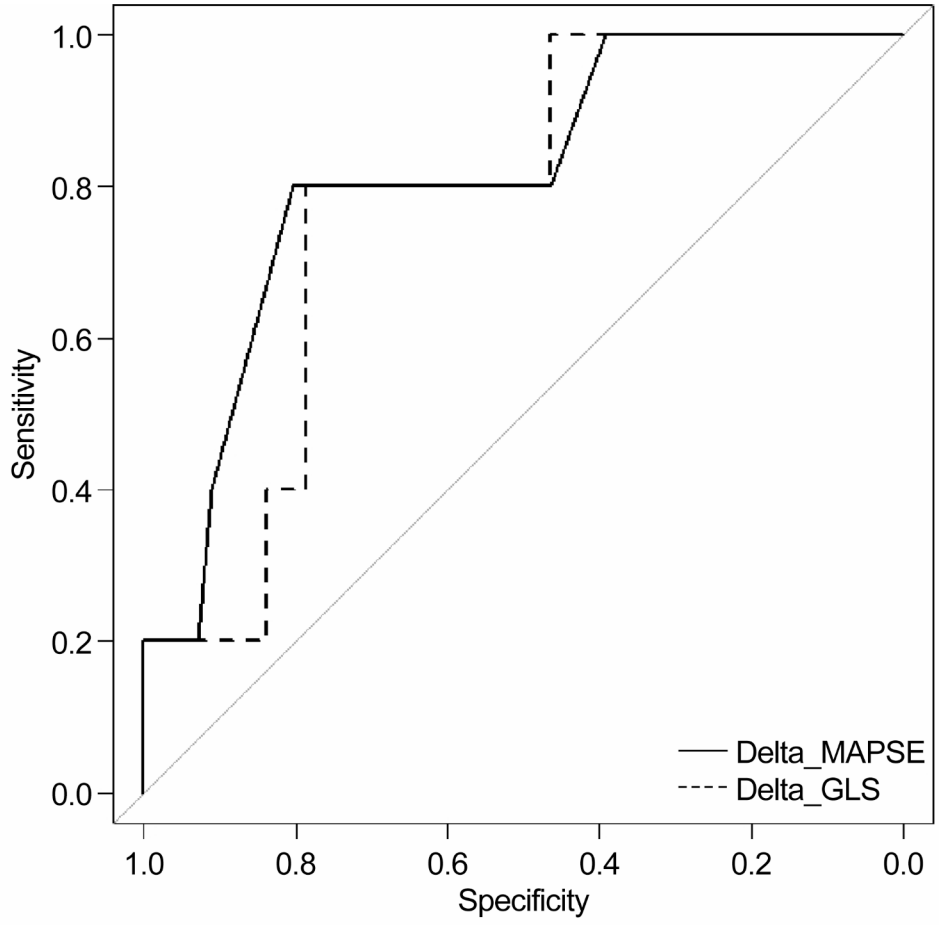

Fig. 5 Comparison of the receiver operating characteristic curves for GLS*rel* and ΔMAPSE in diagnosing subclinical cardiotoxicity
GLS, global longitudinal strain; GLS*rel*, relative changes in left ventricular GLS; MAPSE, mitral annular plane

Table 4 Sensitivity and specificity of the mitral annular plane systolic excursion and global longitudinal strain considering the qualitative assessment of the cutoff points

Change	Sensitivity (%) with 95% CI	Specificity (%) with 95% CI	Accuracy (%) with 95% CI
MAPSE*rel* reduction ≥ 15%	60 (14.7–94.7)	85.7 (73.8–93.6)	83.6 (71.9–91.8)
ΔMAPSE reduction ≥ 2 mm	80 (28.4–99.5)	80.4 (67.6–89.8)	80.3 (68.2–89.4)
ΔMAPSE reduction ≥ 2.5 mm	20 (0.5–71.6)	92.9 (82.7–98)	86.9 (75.8–94.2)
GLS*rel* reduction ≥ 12%	80 (28.4–99.5)	69% (55.9–81.2)	70.5 (57.4–81.5)
Combined GLS*rel* ≥ 12% and MAPSE*rel* ≥ 15%	92 (61.3–97.8)	59.13 (41.8–82.3)	88.8 (81.9–97.3)
Combined GLS*rel* reduction ≥ 12% and ΔMAPSE reduction ≥ 2 mm	96 (68.1–99.2)	55.48 (32.6–74)	91 (77.8–94.7)

CI, confidence interval; GLS, global longitudinal strain; GLS*rel*, relative change in left ventricular GLS; MAPSE, mitral annular plane systolic excursion; ΔMAPSE, absolute difference in MAPSE measurement; MAPSE*rel*, relative change in MAPSE measurement

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Author contributions
LFBB, MDTM, VMCS conceived and designed this study.LFBB and ALCA were responsible for the investigation, formal analysis, and data curation. LFBB was the major contributor for writing the manuscript.VMCS reviewed and edited the manuscript.All authors read and approved the final manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Consent for publication
not applicable.

Competing interests
The authors declare no competing interests.

Human Ethics and Consent to Participate

This study was approved by the Research Ethics Committee of the State University of Feira de Santana (approval number: 69195). All the study participants signed an informed consent form.

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