

## ORIGINAL RESEARCH

# Clinical, Echocardiographic, and Biomarker Associations With Impaired Cardiorespiratory Fitness Early After HER2-Targeted Breast Cancer Therapy



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## ABSTRACT

**BACKGROUND** Cardiorespiratory fitness (CRF) is reduced in cancer survivors and predicts cardiovascular disease (CVD)-related and all-cause mortality. However, routine measurement of CRF is not always feasible.

**OBJECTIVES** The purpose of this study was to identify clinical, cardiac biomarker, and imaging measures associated with reduced peak oxygen consumption (VO<sub>2</sub>peak) (measure of CRF) early post-breast cancer therapy to help inform CVD risk.

**METHODS** Consecutive women with early-stage HER2+ breast cancer receiving anthracyclines and trastuzumab were recruited prospectively. Within 6 ± 2 weeks of trastuzumab completion, we collected clinical information, systolic/diastolic echocardiographic measures, high-sensitivity troponin I, B-type natriuretic peptide, and VO<sub>2</sub>peak using a cycle ergometer. Regression models were used to examine the association between VO<sub>2</sub>peak and clinical, imaging, and cardiac biomarkers individually and in combination.

**RESULTS** Among 147 patients (age 52.2 ± 9.3 years), the mean VO<sub>2</sub>peak was 19.1 ± 5.0 mL O<sub>2</sub> · kg<sup>-1</sup> · min<sup>-1</sup> (84.2% ± 18.7% of predicted); 44% had a VO<sub>2</sub>peak below threshold for functional independence (<18 mL O<sub>2</sub> · kg<sup>-1</sup> · min<sup>-1</sup>). In multivariable analysis, absolute global longitudinal strain (GLS) (β = 0.58; P = 0.007), age per 10 years (β: -1.61; P = 0.001), and E/e' (measure of diastolic filling pressures) (β = -0.45; P = 0.038) were associated with VO<sub>2</sub>peak. GLS added incremental value in explaining the variability in VO<sub>2</sub>peak. The combination of age ≥50 years, E/e' ≥7.8, and GLS <18% identified a high probability (85.7%) of compromised functional independence, whereas age <50 years, E/e' <7.8, and GLS ≥18% identified a low probability (0%). High-sensitivity troponin I and B-type natriuretic peptide were not associated with VO<sub>2</sub>peak.

**CONCLUSIONS** Readily available clinical measures were associated with VO<sub>2</sub>peak early post-breast cancer therapy. A combination of these parameters had good discrimination to identify patients with compromised functional independence and potentially increased future CVD risk. (J Am Coll Cardiol CardioOnc 2021;3:678-691) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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Many breast cancer survivors have elevated risk for cardiovascular disease (CVD) and CVD-related mortality (1). CVD risk stratification following cancer therapy remains a challenge; however, cardiorespiratory fitness (CRF) is emerging as a robust CVD prognosticator in non-cancer (2) and cancer populations (3). Breast cancer survivors have reduced CRF measured 12 months after cancer treatment and years into survivorship (4-6). Furthermore, irrespective of age, up to 26% of breast cancer survivors have CRF below the threshold for functional independence (defined as peak oxygen consumption [VO<sub>2</sub>peak] <18 mL O<sub>2</sub>·kg<sup>-1</sup>·min<sup>-1</sup> [7]; hereafter described as “*compromised functional independence*”) within 6 months of treatment completion (8). Reduced CRF is associated with lower health-related quality of life and is a strong independent predictor of cause-specific (ie, cancer and cardiac) and overall mortality in cancer survivors (3,9).

Cardiopulmonary exercise testing (CPET) is the gold standard to quantify CRF. However, cancer survivors are not routinely referred for CPET in clinical practice, and many oncology and cardio-oncology programs are not able to conduct CPETs routinely because of a lack of availability and cost. Therefore, identifying clinically utilized markers associated with impaired CRF following cancer therapy may help identify patients at future CVD risk as well as patients who may benefit from CVD risk screening and management, longer-term cardiovascular follow-up, and interventions to mitigate CVD risk and improve CRF (eg, via cardio-oncology rehabilitation [CORE]) (10).

In women with HER2+ breast cancer receiving anthracycline and trastuzumab therapy, we evaluated if commonly available clinical parameters, cardiac biomarkers, or echocardiographic measures at the end of cancer therapy, individually or together in a diagnostic algorithm, were associated with CRF (measured as VO<sub>2</sub>peak) and could identify individuals with compromised functional independence. In this potentially high CVD-risk group (11), we

hypothesized that age, cancer therapy-related cardiac dysfunction (CTRCD) history, diastolic function, and global longitudinal strain (GLS) would be associated with VO<sub>2</sub>peak and, when considered in combination, these parameters could identify individuals with compromised functional independence who may have a related increased risk for future CVD.

## METHODS

**PARTICIPANTS.** Women with early-stage (stage I-III) HER2+ breast cancer were recruited prospectively from Princess Margaret Cancer Center and other University of Toronto-affiliated hospitals. All participants were enrolled in the EMBRACE-MRI (Evaluation of Myocardial Changes During BReast Adenocarcinoma Therapy to Detect Cardiotoxicity Earlier With MRI; NCT02306538) study or the Toronto arm of the SUCCOUR (Strain Surveillance of Chemotherapy for Improving Cardiovascular Outcomes) study (12) and were asked to complete a CPET at the end of cancer therapy as part of a substudy. Inclusion criteria were as follows: 1) ≥18 years of age; 2) treatment with anthracyclines followed by trastuzumab with or without radiotherapy; and 3) plans to complete end of treatment cardiac and clinical assessments. Exclusion criteria were history of myocardial infarction or previous heart failure, current unstable angina, persistent arrhythmia, or a history of more than moderate valvular heart disease.

Complete clinical assessment (history, physical examination, imaging, cardiac biomarkers) along with CPET occurred within 6 ± 2 weeks of trastuzumab completion. The study was approved by the Research Ethics Board at the University Health Network. Written informed consent was obtained from all participants.

## ABBREVIATIONS AND ACRONYMS

<b>BNP</b>	= B-type natriuretic peptide
<b>CORE</b>	= cardio-oncology rehabilitation
<b>CPET</b>	= cardiopulmonary exercise test
<b>CRF</b>	= cardiorespiratory fitness
<b>CTRCD</b>	= cancer therapy-related cardiac dysfunction
<b>GLS</b>	= global longitudinal strain
<b>hsTnI</b>	= high-sensitivity troponin I
<b>LV</b>	= left ventricle/ventricular
<b>LVEF</b>	= left ventricular ejection fraction
<b>LVMi</b>	= left ventricular mass index
<b>VO<sub>2</sub>peak</b>	= peak oxygen consumption

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

**CARDIOPULMONARY EXERCISE TESTING.** VO<sub>2</sub>peak was assessed via CPET performed on an upright electronically braked cycle ergometer (Lode Corival) with 12-lead ECG monitoring. After 2 minutes of rest, subjects completed a 10 watt/min ramp protocol (13). Breath-by-breath respiratory gas analyses were acquired by a commercially available metabolic measurement system (Medgraphics, Ultima Series). VO<sub>2</sub>peak was defined as the highest rate of oxygen consumption over a 15- to 20-second interval within the last 90 seconds of exercise (14). VO<sub>2</sub> at ventilatory threshold was determined using the computerized V-slope method (15). The minute ventilation-carbon dioxide production relationship (VE/VCO<sub>2</sub> slope), carbon dioxide production (VCO<sub>2</sub>), and oxygen pulse (VO<sub>2</sub>/heart rate) were calculated as previously described (16). Test termination was triggered by exhaustion, symptoms, or standard reasons for test discontinuation (13). Heart rate recovery was calculated as the difference in heart rate at peak exercise and 1 minute following exercise cessation (13). CPETs were conducted by experienced exercise physiologists blinded to participants' involvement in research.

**ECHOCARDIOGRAPHY.** Transthoracic echocardiograms were performed using a GE ultrasound system (E9, GE Healthcare) by experienced sonographers as per established guidelines (17,18). For measurement of GLS, 4-, 3-, and 2-chamber apical images of the left ventricle (LV) for 3 cardiac cycles were obtained at high frame rates (40-80 frames/s). GLS was measured using automated myocardial contours generated by placing 3 seed points on each of the 3 long-axis views using EchoPAC V202 (AFI, GE Healthcare). Contour adjustment was performed as necessary. After 3 attempts, poorly tracked segments were excluded and GLS was recorded as the average of the remaining segments.

A 3-dimensional (3D) full volume (>20 volumes/s) data set of the LV was used to measure 3D left ventricular ejection fraction (LVEF) using EchoPAC version 202 (4D AutoLVQ, GE Healthcare). Diastolic parameters including early (E) and late diastolic (A) mitral inflow velocities, deceleration time, tissue Doppler imaging-based early diastolic mitral septal and lateral annular velocities (e'), left atrial volume, and tricuspid regurgitation velocity were measured (17). For assessment of left-sided filling pressures, the E/e' ratio was calculated using the average of the tissue Doppler imaging septal and lateral annular velocities (e'). LV mass was calculated using the Devereux formula and normalized by body surface area (LVMI). All cardiac measures were quantified using deidentified images by an experienced sonographer (B.T.) blinded to clinical data.

GLS values were reported as absolute numbers. LV systolic dysfunction was defined by 3D-LVEF <54% or abnormal GLS as <18% (18). This value for abnormal GLS was based on the lower limit of normal threshold provided in the ASE guidelines for the GE vendor (18) and the median value identified to be prognostic in a recent meta-analysis of patients predominantly with breast cancer (19). CTRCD during cancer treatment was defined as: 3D-LVEF reduction of ≥10% to <55% without heart failure symptoms or ≥5% with symptoms (20) or a ≥10% reduction in LVEF in those with baseline LVEF <55%.

**BIOMARKER MEASUREMENTS.** Blood samples for B-type natriuretic peptide (BNP), high-sensitivity troponin I (hsTnI), and a complete blood count were obtained at the time of echocardiography. hsTnI and BNP assays were performed on the ARCHITECT i2000 immunoassay analyzer (Abbott Diagnostics) using the manufacturer's reagents.

**STATISTICAL ANALYSIS.** Continuous variables are presented as mean ± SD or median (25th and 75th percentiles [Q1-Q3]) and categorical data are presented as frequencies and percentages. Patient characteristics, clinical information, imaging data, and CPET data were compared between groups using an Student's *t*-test or Fisher exact test as appropriate. Mann-Whitney *U* test was used to compare differences between groups for non-normally distributed data. Univariable and multivariable linear regression analyses were performed to estimate associations among VO<sub>2</sub>peak and clinical, cardiac imaging, and biomarker parameters. We included both categorical parameters (ie, history of CTRCD during treatment; use of statins, beta-blockers, angiotensin II receptor blockers, or angiotensin-converting enzyme inhibitors; presence of CVD risk factors [hypertension, diabetes, dyslipidemia, and current or previous smoking]; and radiation exposure) and continuous parameters (age; post-treatment 3D-LVEF, GLS, LVMI, average [septal, lateral] E/e'; BNP; hsTnI; epirubicin equivalent dose). BNP was log transformed for the regression analysis. To facilitate interpretation and clinical application, we conducted sensitivity analyses by dichotomizing participants into normal and abnormal GLS (ie, ≥18% vs <18%) (18). The tolerance and variance inflation factor collinearity statistics were used to assess multicollinearity within models. Linearity assumption of continuous variables was tested by including the square of the variable in the model. The incremental value of BNP, hsTnI, 3D-LVEF, LVMI, E/e', and GLS were assessed via nested models using the F-statistic and the R<sup>2</sup> value. The reduced model contained clinical risk factors chosen

**TABLE 1 Patient Characteristics Following Therapy for the Entire Group and Dichotomized By Compromised Functional Independence (VO<sub>2</sub>peak <18 mL O<sub>2</sub> · kg<sup>-1</sup> · min<sup>-1</sup>)**

	Entire Group (N = 147)	VO <sub>2</sub> peak ≥18 mL O <sub>2</sub> · kg <sup>-1</sup> · min <sup>-1</sup> (n = 83)	VO <sub>2</sub> peak <18 mL O <sub>2</sub> · kg <sup>-1</sup> · min <sup>-1</sup> (n = 64)	P Value
Age, y	52.2 ± 9.3	49.4 ± 9.5	55.8 ± 7.7	<0.001
Cardiotoxicity	34 (23)	17 (20)	17 (27)	0.43
Body mass index, kg/m <sup>2</sup>	26.4 ± 5.2	24.6 ± 3.9	28.8 ± 5.7	0.004
Heart rate, beats/min	77.9 ± 11.5	76.8 ± 11.3	79.4 ± 11.6	0.79
Systolic BP, mm Hg	120.2 ± 14.8	115.6 ± 14.3	126.2 ± 13.4	0.54
Diastolic BP, mm Hg	76.5 ± 9.7	74.8 ± 10.1	78.8 ± 8.7	0.27
Epirubicin equivalent dose, mg/m <sup>2</sup>	304.3 (296.8-312.5)	302.5 (299.6-305.9)	301.4 (297.3-305.0)	0.14
Days post-trastuzumab	40 (29-55)	41 (29-56)	39 (30-62)	0.74
Mean heart radiation dose, cGy	174.0 ± 81.3	191.2 ± 85.1	152.7 ± 66.1	0.008
Postmenopause	72 (49)	29 (35)	43 (67)	<0.001
<b>Breast cancer diagnosis</b>				
Stage 1	92 (63)	55 (66)	37 (58)	0.31
Stage 2	18 (12)	8 (10)	10 (16)	0.32
Stage 3	36 (24)	19 (23)	17 (26)	0.70
ER+	97 (66)	59 (71)	38 (59)	0.16
PR+	65 (44)	41 (53)	24 (38)	0.18
Left side	90 (61)	55 (66)	35 (55)	0.17
Right side	57 (41)	28 (34)	29 (45)	0.17
<b>Breast cancer treatment</b>				
Endocrine therapy	97 (66)	59 (71)	38 (59)	0.14
Radiation	137 (86)	78 (94)	59 (92)	0.75
Lumpectomy	79 (53)	43 (52)	36 (56)	0.62
Mastectomy	48 (37)	29 (35)	19 (30)	0.60
Double mastectomy	19 (13)	11 (13)	8 (13)	0.55
<b>CVD risk factors</b>				
Hypertension	22 (20)	6 (7)	16 (25)	0.004
Diabetes	7 (5)	1 (2)	6 (9)	0.043
Current smoker	7 (6)	4 (5)	3 (5)	1.00
Previous smoker	30 (20)	19 (23)	11 (17)	0.42
Dyslipidemia	15 (7)	6 (7)	9 (14)	0.27
1+ CVD risk factor	60 (41)	31 (37)	29 (45)	0.40
<b>Cardiac medications</b>				
Beta-blockers	26 (19)	13 (16)	13 (20)	0.52
Angiotensin II receptor blockers	14 (10)	4 (5)	10 (16)	0.044
ACE inhibitors	26 (18)	13 (16)	13 (20)	0.52
Statins	14 (10)	6 (7)	8 (13)	0.40
<b>Cardiac symptoms</b>				
NYHA functional class I	130 (89)	76 (92)	54 (86)	0.20
NYHA functional class II	17 (11)	7(8)	10 (16)	0.20
<b>Biomarkers</b>				
BNP, pg/mL	14.6 (10.0-26.4)	14.1 (10.0-25.6)	17.0 (10.0-27.7) <sup>a</sup>	0.72
High-sensitivity troponin I, pg/mL	3.0 ± 2.6	3.0 ± 2.7	3.0 ± 3.2	0.51
Hemoglobin, g/L	127.1 ± 11.2	126.2 ± 12.0	128.2 ± 9.9	0.27

Values are mean ± SD, n (%), or median (Q1-Q3). Mean radiation dose available in 88 participants. <sup>a</sup>The fact that the median and the Q1 are the same reflect the fact that the lower reported level of BNP is 10 pg/mL and majority of the patient in this group had a BNP value of 10 pg/mL.  
 ACE= angiotensin converting enzyme; BNP = brain natriuretic peptide; BP = blood pressure; CVD = cardiovascular disease; Q1-Q3 = interquartile range; NYHA = New York Heart Association.

based on their known association with CVD risk (ie, age, cardiac medications, CVD risk factors, CTCRD during treatment, radiation exposure, and epirubicin equivalent dose). VO<sub>2</sub>peak data was characterized as percent predicted based on age and sex for healthy individuals (via Wasserman equations [21]) and then

stratified by age group (ie, <40, 40-49, 50-59, and ≥60 years); and using the threshold for functional independence (defined as VO<sub>2</sub>peak <18 mL O<sub>2</sub>·kg<sup>-1</sup>·min<sup>-1</sup>) (7).

We developed a decision support tool to identify individuals with compromised functional

**TABLE 2 CPET Outcomes and Cardiac Imaging Parameters for the Entire Group and by GLS Groups**

	Entire Group (N = 147)	GLS ≥18% (N = 103)	GLS <18% (n = 44)	P Value
<b>CPET parameters</b>				
Relative VO <sub>2</sub> peak, mL O <sub>2</sub> ·kg <sup>-1</sup> ·min <sup>-1</sup>	19.1 ± 5.0	20.2 ± 5.0	16.6 ± 4.1	<0.001
Age, y				
<40	19.6 ± 4.0	20.9 ± 4.2	16.8 ± 1.3	0.037
40-49	20.2 ± 5.5	21.0 ± 5.6	18.3 ± 4.8	0.21
50-59	18.6 ± 5.1	19.8 ± 5.0	16.1 ± 4.4	0.004
≥60	19.0 ± 5.1	19.9 ± 5.2	15.5 ± 2.9	0.017
VO <sub>2</sub> peak <18 mL O <sub>2</sub> ·kg <sup>-1</sup> ·min <sup>-1</sup>	64 (44)	34 (33)	30 (68)	<0.001
Absolute VO <sub>2</sub> peak, L·min <sup>-1</sup>	1.27 ± 0.33	1.33 ± 0.33	1.15 ± 0.31	0.004
Percent of VO <sub>2</sub> peak predicted, %	84.2 ± 18.7	87.5 ± 18.3	76.4 ± 17.2	0.001
Ventilation threshold, %VO <sub>2</sub> peak	64.4 ± 8.1	63.9 ± 8.4	65.7 ± 7.2	0.23
Maximal power output, W	93.5 ± 32.3	96.1 ± 27.2	87.6 ± 41.5	0.15
Peak RER, VCO <sub>2</sub> /VO <sub>2</sub>	1.13 ± 0.1	1.13 ± 0.1	1.14 ± 0.1	0.64
VE/VCO <sub>2</sub>	30.3 ± 3.8	30.2 ± 3.5	30.6 ± 4.3	0.54
Peak heart rate, beats/min	141.1 ± 19.7	142.3 ± 19.5	138.3 ± 20.3	0.53
Peak heart rate predicted, %	84.0 ± 11.0	84.5 ± 10.8	82.8 ± 11.2	0.38
Peak systolic BP, mm Hg	162.7 ± 23.2	161.9 ± 21.4	164.6 ± 27.0	0.52
Peak diastolic BP, mm Hg	79.7 ± 11.4	79.7 ± 10.9	79.8 ± 12.8	0.94
FEV1, %	88.0 ± 14.0	88.7 ± 14.0	86.3 ± 14.1	0.34
Heart rate recovery, beats/min	21.0 ± 12.0	21.6 ± 12.6	19.6 ± 10.0	0.34
Oxygen pulse, ml/beat	13.5 ± 3.0	14.2 ± 3.1	12.0 ± 2.3	<0.001
<b>Echocardiography parameters</b>				
LV ESV, mL/m <sup>2</sup>	24.9 (21.2-29.4)	24.2 (21.0-28.2)	27.6 (23.7-31.9)	0.016
LV EDV, mL/m <sup>2</sup>	58.1 (52.0-69.4)	58.1 (52.4-69.1)	58.1 (50.6-70.5)	0.97
3D-LVEF, % <sup>a</sup>	57.4 ± 4.1	59.1 ± 3.6	54.1 ± 3.5	<0.001
3D-LVEF <54%	24 (16)	6 (6)	18 (40)	<0.001
E/e' <sup>b</sup>	7.3 ± 2.0	7.1 ± 2.0	7.6 ± 1.7	0.23
e' lateral, cm/s	11.1 ± 3.2	11.7 ± 3.1	9.5 ± 3.0	<0.001
e' septal, cm/s	8.1 ± 2.3	8.6 ± 2.3	7.0 ± 1.6	<0.001
E velocity, cm/s	65.2 ± 15.4	67.8 ± 15.9	58.9 ± 12.2	0.001
A velocity, cm/s	58.1 ± 17.1	56.3 ± 16.5	62.8 ± 17.6	0.034
E/A ratio	1.2 ± 0.45	1.3 ± 0.5	1.0 ± 0.35	<0.001
DT, ms	190.5 (169.5-232.4)	192.0 (169.7-231.0)	192.0 (167.8-240.9)	0.59
TR velocity, m/s	2.1 ± 0.3 <sup>c</sup>	2.2 ± 0.3	2.0 ± 0.3	<0.001
LAVi, mL/m <sup>2</sup>	25.7 (21.7-32.6)	27.7 (22.3-33.1)	23.4 (21.1-29.0)	0.074
LVMi, g/m <sup>2</sup>	62.1 ± 14.4	63.4 ± 17.1	61.6 ± 13.0	0.48
GLS, %	19.2 ± 2.3	20.4 ± 1.6	16.6 ± 1.3	<0.001

Values are mean ± SD, n (%), or median (Q1-Q3). <sup>a</sup>In 3 patients, 3D-LVEF was not available and 2D-LVEF was used. <sup>b</sup>E/e' measurements were not possible in 2 patients. Only 1 (1%) patient in the normal strain group had an E/e' >14, whereas 3 (2%) patients in the abnormal strain group and 1 (1%) patient in the normal strain group had an abnormal LVMi of >95 g/m<sup>2</sup>. None of the patients had abnormal hsTnI (>26 pg/mL) or BNP (>100 pg/mL). <sup>c</sup>TR velocity was only available in 79 patients because of either absence of tricuspid regurgitation or incomplete Doppler wave form.

CPET = cardiopulmonary exercise test; DT = deceleration time; ESV = end-systolic volume; EDV = end-diastolic volume; GLS = global longitudinal strain; LV = left ventricular; LAVi = left atrial volume index; LVMi = left ventricular mass index; LVEF = left ventricular ejection fraction; other abbreviations as in [Table 1](#).

independence using clinical and imaging measures with an integrated approach. We trained a conditional inference tree model (22) using variables independently associated with VO<sub>2</sub>peak in our multivariable linear regression analysis as inputs. Relevant continuous independent variables were dichotomized based on thresholds determined by Youden's J statistic (23). Using repeated 5-fold cross validation, the tree model's hyperparameters were tuned by maximizing the scaled Brier scores (24). Details are provided in the [Supplemental Appendix](#). A receiver-operating characteristics (ROC) curve was

used to demonstrate the final tree model's power to evaluate the risk of compromised functional independence and to determine the optimal predicted threshold for classification. We internally validated the model by calculating the over-optimism bias using bootstrap resampling method, and we provided both apparent and bias-adjusted areas under the curve (AUCs) (22). Statistical analysis was conducted using SPSS version 27.0 (IBM) and R version 3.5.3 with tidyverse, party, mlr, ROCR, pROC, and FactoMineR packages. Statistical significance was defined as  $P < 0.05$ .

## RESULTS

**PARTICIPANTS.** We recruited 177 eligible women between November 2013 and January 2019. A total of 30 participants declined CPET, leaving 147 for inclusion. There were no differences in post-therapy GLS (19.2% ± 2.3% vs 19.5% ± 1.8%; *P* = 0.626), LVEF (57.5% ± 4.2% vs 57.3% ± 3.0%; *P* = 0.850), or age (52.2 ± 9.3 years vs 54.6 ± 9.1 years; *P* = 0.184) between participants who did and did not complete CPET. Participant demographic and clinical characteristics are provided in [Table 1](#). In total, 60 (41%) participants had ≥1 CVD risk factor and 34 (23%) developed CTRCD during treatment.

**CPET-DERIVED VO<sub>2</sub>peak.** The median (Q1-Q3) time from final trastuzumab treatment to CPET was 40 days (29-55 days). CPET results are summarized in [Table 2](#). Mean VO<sub>2</sub>peak for the cohort was 19.1 ± 5.0 mL O<sub>2</sub>·kg<sup>-1</sup>·min<sup>-1</sup> (84.2% ± 18.7% of Wasserman-predicted VO<sub>2</sub>peak for healthy individuals), and 64 (44%) participants had VO<sub>2</sub>peak <18 mL O<sub>2</sub>·kg<sup>-1</sup>·min<sup>-1</sup> (14.9 ± 2.3 mL O<sub>2</sub>·kg<sup>-1</sup>·min<sup>-1</sup>; range 9.3-17.9 mL O<sub>2</sub>·kg<sup>-1</sup>·min<sup>-1</sup>), suggesting compromised functional independence. Comparison of clinical characteristics between patients with and without compromised functional independence is provided in [Table 1](#).

### ASSOCIATION BETWEEN CLINICAL, IMAGING AND BLOOD BIOMARKERS AND VO<sub>2</sub>peak

In univariable analysis, absolute GLS (β coefficient: 0.72; *P* < 0.001), E/e' (β: -0.76; *P* < 0.001), cardiac medication use (β: -2.59; *P* = 0.003), presence of ≥1 CVD risk factor (β: -1.87; *P* = 0.026), age per 10 years (β: -2.08 per 10 years; *P* < 0.001), and history of CTRCD (β: -2.60; *P* = 0.008) were associated with VO<sub>2</sub>peak ([Table 3](#)). Both BNP and hsTnI were not associated with VO<sub>2</sub>peak. Abnormal GLS (<18%) was detected in 44 (30%) participants (16.5% ± 1.3%; range 12.7%-17.9%), and these individuals had a VO<sub>2</sub>peak 23% lower than predicted for healthy individuals. Compared with participants with GLS ≥18%, individuals with GLS <18% had a 18% lower VO<sub>2</sub>peak (16.6 ± 4.1 mL O<sub>2</sub>·kg<sup>-1</sup>·min<sup>-1</sup> vs 20.2 ± 5.0 mL O<sub>2</sub>·kg<sup>-1</sup>·min<sup>-1</sup>; *P* < 0.001) ([Figure 1](#)) and lower peak oxygen pulse (12.0 ± 2.3 mL/beat vs 14.2 ± 3.1 mL/beat; *P* < 0.001) ([Table 2](#)). A greater proportion of patients with abnormal GLS had compromised functional independence (68%) vs those with normal GLS (33%; *P* < 0.001). Comparison of clinical and exercise measures between patients with GLS above and below 18% are provided in [Supplemental Tables 1 and 2](#), respectively.

**TABLE 3 Univariable and Multivariable Association Between Clinical and Imaging Parameters and Biomarkers and VO<sub>2</sub>peak (Dependent Variable)**

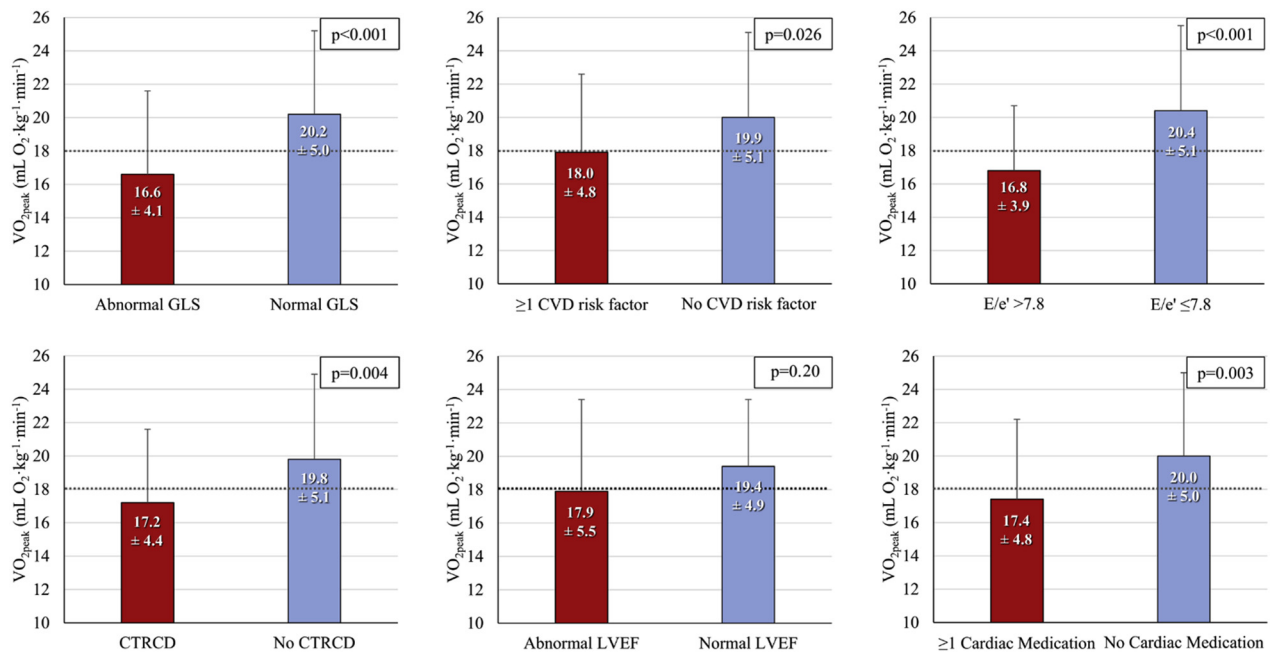
	Univariable Association With VO <sub>2</sub> peak			Multivariable Association with VO <sub>2</sub> peak		
	Beta	SE	P Value	Beta	SE	P Value
Cardiotoxicity diagnosis (Y/N)	-2.60	0.96	0.008	-1.25	1.10	0.24
Cardiac medication use (Y/N)	-2.59	0.86	0.003	-0.54	0.95	0.57
≥1 CVD risk factor (Y/N)	-1.87	0.83	0.026	-0.59	0.82	0.48
Total epirubicin equivalent dose (mg/m <sup>2</sup> )	0.012	0.02	0.472	-0.001	0.02	0.93
Radiation exposure (Y/N)	-1.03	1.16	0.38	-0.70	1.10	0.51
Age (per 10 y)	-2.08	0.41	<0.001	-1.61	0.46	0.001
3D-LVEF (%)	0.14	0.10	0.15	-0.07	0.11	0.50
LVMi (g/m <sup>2</sup> )	0.005	0.03	0.87	0.05	0.03	0.07
E/e'	-0.76	0.21	<0.001	-0.45	0.22	0.038
BNP (pg/mL)	-0.10	1.59	0.95	1.86	1.59	0.25
High-sensitivity troponin I (pg/mL)	0.030	0.14	0.84	-0.005	0.14	0.97
GLS (%) <sup>a</sup>	0.72	0.17	<0.001	0.58	0.21	0.007

Multivariable association R = 0.545 for entire model. <sup>a</sup>GLS is entered into the model as an absolute value; all beta values represent the average change in VO<sub>2</sub>peak for a unit change in continuous variables or presence of categorical variable except for age where the beta value is for every 10 years increase in age.  
Abbreviations as in [Tables 1 and 2](#).

VO<sub>2</sub>peak was also significantly lower in patients with CTRCD history, who were on ≥1 cardiovascular medication, or who had ≥1 CVD risk factor compared with those without ([Figure 1](#)). VO<sub>2</sub>peak did not differ significantly between those with reduced (mean LVEF for subgroup 51.2% ± 2.2%; range 45.0%-53.0%) and preserved 3D-LVEF (mean LVEF for subgroup 58.9% ± 3.3%; range 54.0%-69.0%) ([Figure 1](#)). In multivariable analysis, absolute GLS (β: 0.58; *P* = 0.007), age per 10 years (β: -1.61 per 10 years; *P* = 0.001), and E/e' (β: -0.45; *P* = 0.038) remained associated with VO<sub>2</sub>peak. Abnormal GLS (ie, <18%) was also independently associated with VO<sub>2</sub>peak ([Supplemental Table 2](#)). There was no evidence for collinearity between included variables, and the linear assumption was not violated for continuous parameters.

### INCREMENTAL VALUE OF CLINICAL, IMAGING, AND BLOOD BIOMARKERS TO EXPLAIN VARIABILITY IN VO<sub>2</sub>peak

Compared with the clinical only model (CTRCD, cardiac medication use, ≥1 CVD risk factor, epirubicin equivalent dose, radiation dose, and age; R<sup>2</sup> = 0.19), the addition of cardiac biomarkers (BNP and hsTnI; R<sup>2</sup> = 0.21; *P* = 0.344) and echocardiography variables (3D-LVEF, LVMi, and E/e'; R<sup>2</sup> = 0.26; *P* = 0.052) improved the R<sup>2</sup> value that explains the variability in VO<sub>2</sub>peak, but the incremental value was not statistically significant ([Figure 2](#)). The addition of GLS as a continuous (R<sup>2</sup> = 0.30; *P* = 0.007) or binary variable (GLS <18% vs ≥18%; R<sup>2</sup> = 0.31; *P* = 0.003) provided incremental value in explaining the

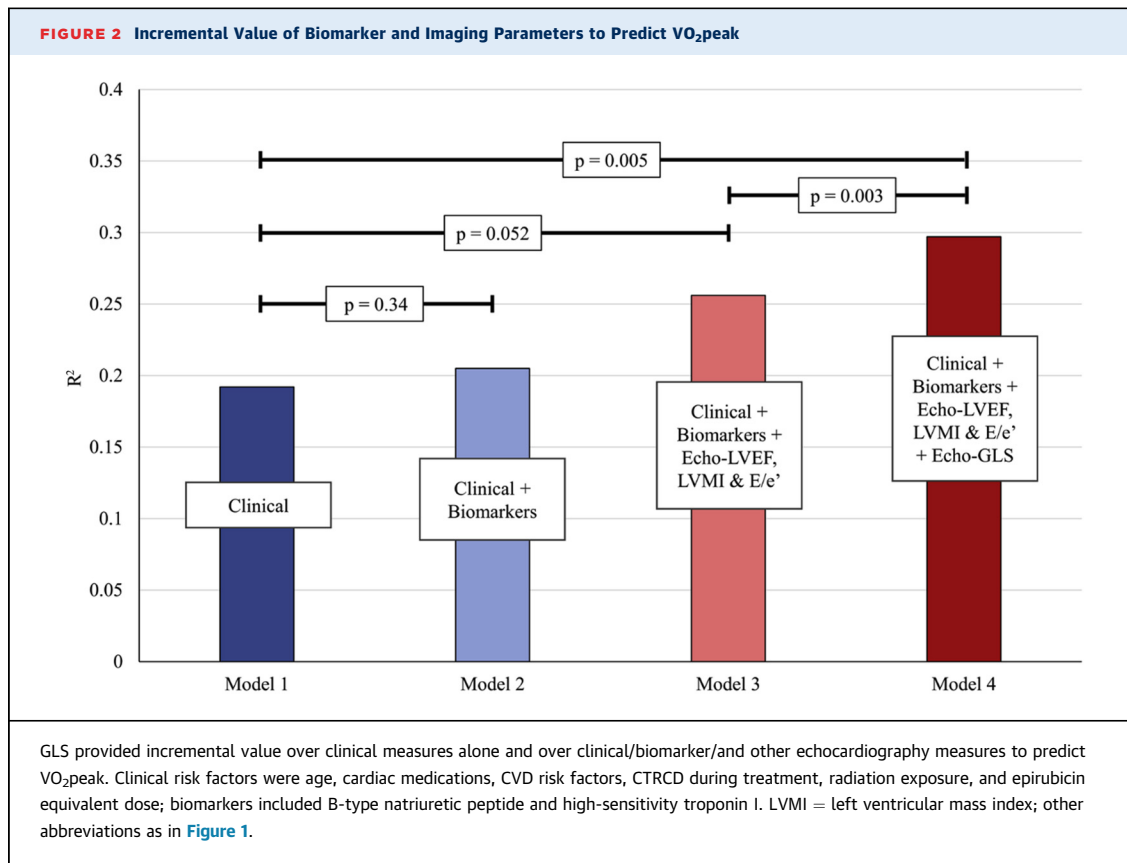
**FIGURE 1** Comparison of VO<sub>2</sub>peak for Various Clinical and Imaging Measures

The bar graphs compare predicted VO<sub>2</sub> peak for patients with and without CTRCD during treatment and post-cancer treatment risk factors, cardiovascular medications, and echocardiography parameters. The *P* values represent between group differences in VO<sub>2</sub>peak for univariable analyses. Abnormal LVEF <54%; abnormal GLS <18%. The **dashed line** indicates threshold for functional independence (VO<sub>2</sub>peak = 18 mL O<sub>2</sub>·kg<sup>-1</sup>·min<sup>-1</sup>). CVD = cardiovascular disease; GLS = global longitudinal strain; LVEF = left ventricular ejection fraction, E/e' = left ventricular filling pressures.

variability in VO<sub>2</sub>peak over the clinical model and all other variables.

**AN INTEGRATED APPROACH TO THE DETECTION OF COMPROMISED FUNCTIONAL INDEPENDENCE.** The E/e' threshold of ≥7.8 (mean for subgroup 9.5 ± 1.8; range 7.8-18.3) best identified individuals with compromised functional independence and was included in the analysis (Figure 1, Supplemental Table 2). The final tree model (Figure 3) selected age (≥50 years), GLS (<18%), and E/e' (≥7.8) as the most important variables for detecting individuals with compromised functional independence (AUC = 0.80; 95% CI: 0.74-0.86) (Figure 4). The optimism corrected AUC was 0.75. Younger participants (age <50 years) had low probability of compromised functional independence (Groups 1 and 2) unless the GLS was <18% (Group 3) (Figure 3, Central Illustration). Older participants (age ≥50 years) generally had high probability of compromised functional independence (Groups 5-7) unless E/e' was <7.8 and GLS was ≥18% (Group 4). Within Group 4 only, being on cardiac medications helped further stratify the participants into a higher (78%, Group 4b) (Central Illustration) and

lower (28%, Group 4a) probability of having compromised functional independence and improved the overall AUC of the model (Supplemental Figure 1). Participants who met all 3 criteria had the highest probability of compromised functional independence (85.7%; Group 7), whereas those who met none of the criteria had the lowest probability (0%; Group 1). The relative VO<sub>2</sub>peak values as a continuous measure for groups 1-7 is provided in Supplemental Figure 2. The ROC analysis suggested that an optimal decision rule to detect compromised functional independence was to meet either the GLS or E/e' criteria in older participants (ie, age ≥50 years and E/e' ≥7.8 or GLS <18%; Groups 5-7), or the GLS criteria in younger participants (ie, age <50 years and GLS <18%; Group 3). This rule corresponded to the predicted risk threshold of 53.8% corresponding to the point on the ROC closest to the perfect model. This classifier for detecting individuals with compromised functional independence had sensitivity of 71.9% (95% CI: 54.6%-83.6%), specificity of 73.5% (95% CI: 59.9%-84.6%), positive predictive value 67.6% (95% CI: 58.0%-78.0%), and negative predictive value of 77.2%



(95% CI: 73.4%-79.6%). A summary of proposed functional impairment risk-guided recommendations for surveillance and management, and prioritization for referral to specialized support services is provided in the **Central Illustration**.

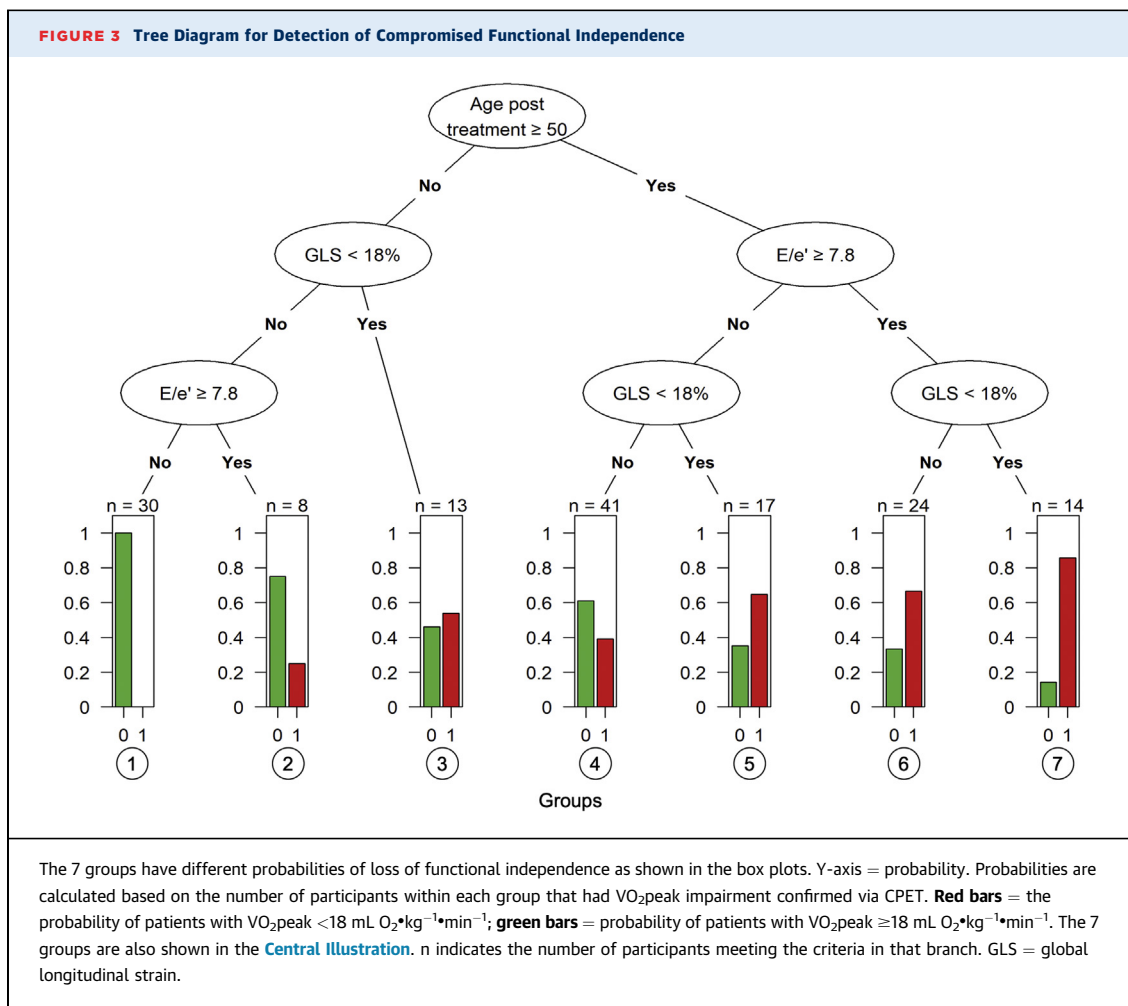
## DISCUSSION

This study examined associations between CRF as defined by VO<sub>2</sub>peak and clinical, cardiac biomarker, and cardiac imaging parameters in women early following treatment for HER2+ breast cancer. Age, GLS, and E/e' were associated independently with VO<sub>2</sub>peak. Using these parameters, we developed a diagnostic algorithm with good discriminatory value (AUC = 0.80) for identifying participants with compromised functional independence (ie, VO<sub>2</sub>peak <18 mL O<sub>2</sub>•kg<sup>-1</sup>•min<sup>-1</sup>) and, by association, likely higher risk of future CVD. Our work suggests that along with age, subclinical abnormalities in echocardiography parameters (GLS, E/e') at the end of cancer treatment are clinically important given their association with CRF and the ability to detect functional impairment. Once validated, this algorithm can be used to help stratify patients according to their

relative need for continued cardiovascular follow-up, CVD risk factor screening and management, and targeted interventions (eg, CORE [10]) to reduce CVD risk as well as mobilize supportive care services to manage functional impairments.

**CRF IMPAIRMENT IN CANCER SURVIVORS.** Our work in a uniform cohort of women with breast cancer receiving cancer therapy with high CVD potential demonstrates that VO<sub>2</sub>peak was 16% below the Wasserman-predicted age- and sex-based values for healthy individuals early after completion of therapy (21), and 44% of participants had compromised functional independence (7). Supporting the clinical significance of our findings, Groarke et al (3) recently described the association between CRF assessed at a median of 7 years postdiagnosis (measured as METS of task) and mortality in 1,632 participants with mixed adult-onset cancers. The 10-year cumulative mortality risk (ie, cardiac, cancer, and all-cause) was 13%, 20%, and 42% for high, intermediate, and low CRF groups, respectively (3). Each 1-metabolic equivalent of task decrease in CRF was associated with a 14% increase in cardiovascular mortality. Although our study focuses on CRF measurements early post-





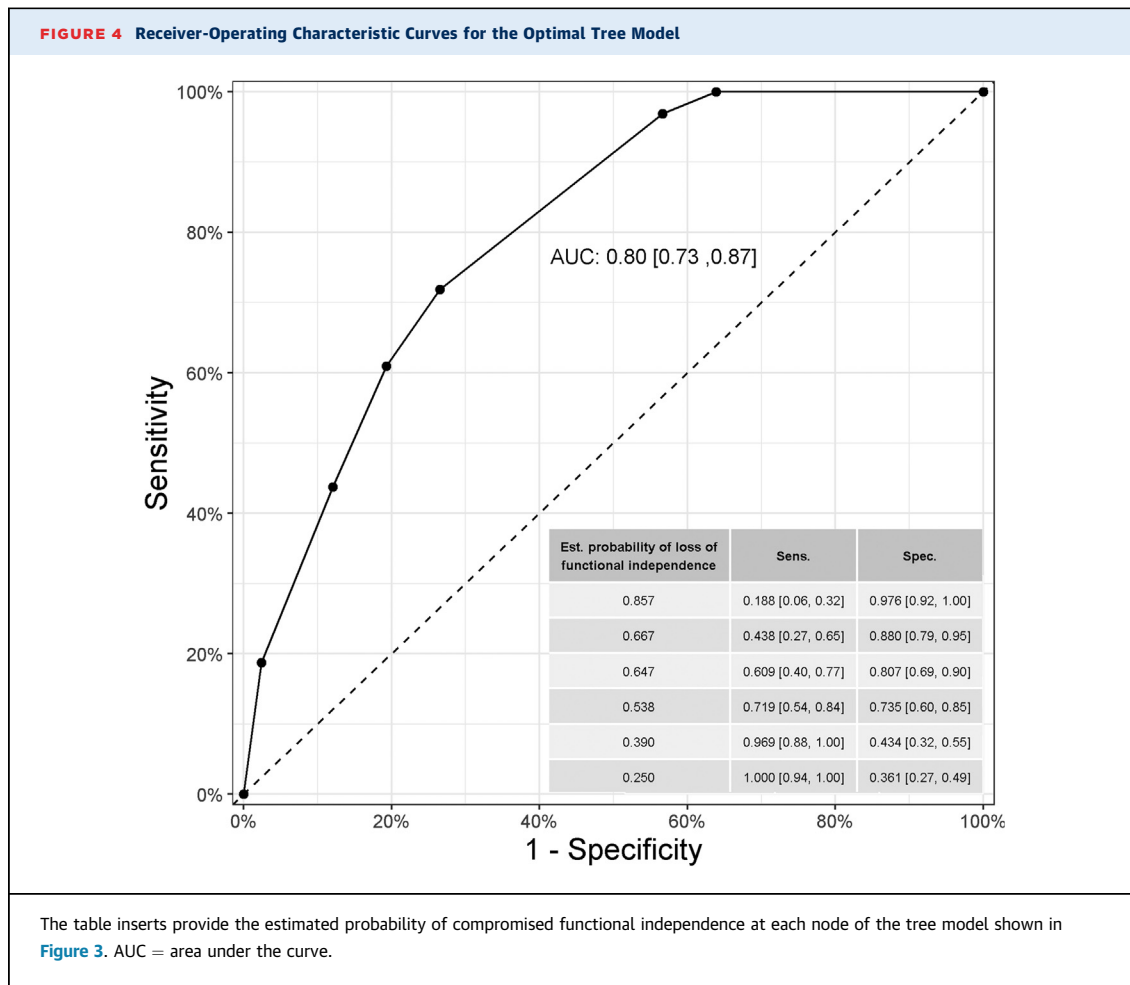
cancer treatment, collective data in cancer (3) and noncancer (2) populations suggest that the reduced VO<sub>2</sub>peak identified in our patients is likely prognostically important and is a potential method to inform clinical care.

#### FACTORS ASSOCIATED WITH CRF IN CANCER SURVIVORS.

Formal assessment of CRF should be considered post-cancer treatment (10) in centers with access to CPET; however, it is either not available for this purpose or remains a limited resource in most centers. Thus, we identified commonly available factors that were associated with CRF. Our finding that older age, CVD risk factors, and cardiac medications prescription were associated with reduced CRF is clinically relevant given prior work demonstrating a doubling in the risk of heart failure in older breast cancer survivors and those with CVD risk factors (11). However, only age was independently associated with lower VO<sub>2</sub>peak in the adjusted model. CTRCD was not independently associated with VO<sub>2</sub>peak, likely because of its association with other

echocardiographic variables (eg, GLS, E/e'). Interestingly, elevations in hsTnI and BNP were also not associated with VO<sub>2</sub>peak. These cardiac biomarkers, although useful in identifying cardiac injury during treatment, may not reflect the status of participants' CRF early post-cancer therapy.

Our findings confirm the relationship between GLS and VO<sub>2</sub>peak previously reported in survivors of pediatric cancers at long-term follow-up (25) and in women with HER2+ breast cancer, a median of 7 years after trastuzumab treatment (4). In the latter study, 22 women with a prior history of CTRCD had persistently reduced LVEF and GLS and a 25% lower VO<sub>2</sub>peak (22.9 ± 4.4 mL O<sub>2</sub>•kg<sup>-1</sup>•min<sup>-1</sup>) compared with age-matched healthy control subjects (30.5 ± 3.4 mL O<sub>2</sub>•kg<sup>-1</sup>•min<sup>-1</sup>). Our study extends these findings by demonstrating that impairment may already be present early following treatment. Furthermore, compared with breast cancer survivors with a similar age before receiving cancer therapy (26), the VO<sub>2</sub>peak in our patients treated for HER2+















breast cancer was significantly lower (24.6 mL O<sub>2</sub>·kg<sup>-1</sup>·min<sup>-1</sup> vs 19.1 mL O<sub>2</sub>·kg<sup>-1</sup>·min<sup>-1</sup>, respectively), highlighting the potential important impact of anthracycline and trastuzumab therapies on CRF. We also identified an association between E/e' (a measure of left sided filling pressures) and VO<sub>2</sub>peak, similar to that described recently in participants with non-ischemic heart disease (27). Interestingly, the E/e' threshold of ≥7.8 associated with worse VO<sub>2</sub>peak in our study was slightly above the recently reported mean normal E/e' value in healthy women (7.2 ± 2.0) with age similar to our cohort (28). Previous data have demonstrated that diastolic dysfunction often precedes or concurrently changes with GLS (29). It is possible that both systolic and diastolic changes in our participants contributed to reduced CRF. The lack of association between 3D-LVEF and CRF in our study is similar to that described in pediatric cancer survivors (30), suggesting that LVEF alone may miss clinically important reductions in CRF. A recent study of participants with mixed cancers and treatments did not identify a relationship between changes in resting





LV function parameters and CRF (8). However, this may be because most participants in that study received lower CVD risk cancer therapy (only 56% received anthracyclines), received short cancer regimens (~4 months vs 14-15 months in our study), and did not focus on identifying a relationship between end-of treatment clinical/imaging measures and CRF.

**CLINICAL IMPLICATIONS.** Women with HER2+ breast cancer treated with anthracyclines and trastuzumab are at high risk of reduced CRF at end of treatment and potential related increases in future CVD risk (11). Currently, there are no decision-making frameworks to help clinicians determine which participants are at high CVD risk at the end of cancer therapy. Our study demonstrates an integrated approach (Central Illustration) using age and echocardiography measured GLS and E/e' as one method to screen for patients with CRF impairment and, by association, potentially higher future CVD risk. However, further work is needed to validate our approach and link it directly to CVD risk. If validated,

**CENTRAL ILLUSTRATION** A Proposed Decision Support Algorithm for Cardio-Oncology and Cardiac Rehabilitation (CORE)

Group Proportions and Stratification Criteria	Probability of Impairment <sup>1</sup>	Proposed Referral Priority <sup>2</sup>	Proposed Additional Considerations <sup>2</sup>
<b>Group 1:</b> Younger + normal GLS + normal E/e' 	0% Lowest Risk	 Lowest priority for CORE	 • Optional cardiac surveillance  • CVD risk factor management by GP/ cardio-oncology <sup>3</sup>
<b>Group 2:</b> Younger + normal GLS + abnormal E/e' <b>Group 4a:</b> Older + normal E/e' + normal GLS (- cardiac medication)	25-28% Intermediate Risk	 6MWT/Stress test directed prioritization for CORE <sup>4</sup> Consider cancer rehabilitation	 • Single year of cardiac surveillance  • CVD risk factor management by GP/ cardio-oncology <sup>3</sup>
<b>Group 3:</b> Younger + abnormal GLS <b>Group 5:</b> Older + normal E/e' + abnormal GLS <b>Group 6:</b> Older + abnormal E/e' + normal GLS	54-67% High Risk	 High priority for CORE and supportive care services	 • Annual cardiac surveillance  • CVD risk factor management by cardio-oncology <sup>3</sup>
<b>Group 4b:</b> Older + normal E/e' + normal GLS (+ cardiac medication) <b>Group 7:</b> Older + abnormal E/e' + abnormal GLS	78-86% Highest Risk	 Top priority for CORE and supportive care services	 • Early cardiac surveillance (eg, 6 months) and annual surveillance  • CVD risk factor management by cardio-oncology <sup>3</sup>

Stratification Thresholds		
<b>Age</b> Years: • Younger <50 • Older ≥50	<b>Cardiac Function</b> E/e': • Normal <7.8 • Abnormal ≥7.8	<b>GLS</b> • Abnormal <18% • Normal ≥18%

Legend	
	CORE: Cardio-oncology and cardiac rehabilitation
	CVD risk factor management
	Homecare and social support services
	Surveillance and monitoring

Bonsignore, A. et al. J Am Coll Cardiol CardioOnc. 2021;3(5):678-691.

Using study results, the algorithm provides a potential approach (to be validated in future studies) to investigations, referrals, follow-up, and interventions in women with HER2+ breast cancer post-treatment based on probability of compromised functional independence. Group numbers refer to Figure 3. Proportion of patients in each group: group 1 (20%), group 2 (5%), group 3 (9%), group 4a (22%), group 4b (6%), group 5 (12%), group 6 (16%), group 7 (10%). <sup>1</sup>Probabilities calculated based on number of participants within each group that had VO<sub>2</sub>peak impairment confirmed via cardiopulmonary exercise test. <sup>2</sup>These suggestions are based on author opinion and should be targets for future research studies. <sup>3</sup>CVD risk factor management includes pharmaceutical and behavioral (eg, physical activity promotion, nutrition support, smoking cessation) interventions. Duration of CVD risk factor management and follow-up by cardio-oncology programs will depend on findings during surveillance. Longer term follow-up may be needed in the highest risk groups.

this algorithm could inform the need for more intensive surveillance and management in settings lacking resources for CPET. Described in the **Central Illustration**, patients with the highest risk of CRF impairment may benefit from early (eg, within 6 months) and annual cardiac surveillance, aggressive cardiovascular risk factor management, and longer-term cardiovascular follow-up in a cardio-oncology

program, and are top priority for referral to CORE or to individual programs (eg, exercise, nutritional counselling, psychosocial support) as available. High-risk patients could be considered for annual cardiac surveillance, shorter-term follow-up in a cardio-oncology program, and as the next highest priority for referral to CORE and supportive services. The intermediate-risk group could be further risk

stratified using a 6-minute walk test (31) or non-gas stress testing as available to estimate CRF, have cardiac surveillance at least once post-treatment time point (eg, at 1 year), and have ongoing risk factor management by their general practitioner. The lowest-risk group may be considered for optional cardiac surveillance and ongoing cardiac risk factor management by their general practitioner. The latter 2 groups can also be considered for cancer rehabilitation programs when available.

**STUDY LIMITATIONS.** We did not assess whether noncardiac (eg, vascular, skeletal muscle) factors were associated with VO<sub>2</sub>peak. Given that the final nested model had an R<sup>2</sup> of 0.31, these noncardiac variables may be important to explain the variability in VO<sub>2</sub>peak and would need to be considered when validating our work. However, oxygen pulse (an indirect composite measure of stroke volume and oxygen extraction) was reduced in those with GLS <18%, suggesting that central abnormalities likely contribute to reduced CRF in our sample. The GLS threshold of 18% used in this study was based on a single echocardiography vendor. However, the independent association of GLS as a continuous measure with VO<sub>2</sub>peak remains relevant and likely translatable to other vendors. We used a VO<sub>2</sub>peak threshold of 18 mL O<sub>2</sub>·kg<sup>-1</sup>·min<sup>-1</sup> to define compromised functional independence across the age spectrum because no age-specific thresholds have been published (32). However, the mean VO<sub>2</sub>peak values in our study were similar irrespective of the participants age category (Table 2), and the threshold of 18 mL O<sub>2</sub>·kg<sup>-1</sup>·min<sup>-1</sup> was used in another recent study involving mixed cancer survivors of similar age (53 ± 13 years) (8). Furthermore, this VO<sub>2</sub>peak threshold has not been directly associated with CVD risk; however, generally lower VO<sub>2</sub>peak is associated with higher risk of CVD, and the loss of functional independence likely limits health protective behaviors. We did not have pretreatment measurements of VO<sub>2</sub>peak. Therefore, we were unable to determine if clinical and imaging parameters were associated with changes in VO<sub>2</sub>peak during cancer treatment. However, a recent study in a diverse group of cancer participants demonstrated a lack of association between changes in imaging parameters and change in VO<sub>2</sub>peak (8). Finally, we did not have a control group of non-breast cancer survivors for comparing VO<sub>2</sub>peak values; however, we contextualized our findings according to widely used predictive equation (ie, Wasserman et al [21]).

## CONCLUSIONS

VO<sub>2</sub>peak-defined CRF is significantly reduced in a large portion of HER2+ breast cancer survivors treated with anthracyclines and trastuzumab (± radiotherapy). We propose an algorithm, based on age, echocardiography-measured GLS, and E/e', to stratify participants according to probability of experiencing CRF-defined compromised functional independence. Once validated, this approach could be utilized to identify higher CVD risk participants who would benefit from enhanced cardiovascular follow-up, cardioprotective strategies, and referral to key rehabilitation and support services with the goal of improving CRF and, ultimately, reducing CVD burden in cancer survivors.

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## PERSPECTIVES

**COMPETENCY IN PATIENT CARE:** Identifying women with HER2+ breast cancer at high risk of future CVD at end of cancer treatment remains challenging. Recognizing patients with poor CRF may be a method to risk stratify patients given its known prognostic value for future CVD. However, routine measurement of CRF using cardiopulmonary exercise stress testing is not widely feasible in cancer survivors. We identified routinely available clinical and echocardiography measures (GLS and E/e') that were associated with CRF as measured by peak VO<sub>2</sub> at the end of cancer therapy. We demonstrate that an integrative approach using age and echocardiography-measured GLS

and E/e' can be used to identify patients who have poor CRF (AUC = 0.80) and, by association, are at potentially higher risk of future CVD.

**TRANSLATIONAL OUTLOOK:** Once validated, routinely available clinical measures can help identify women with HER2+ breast cancer treated with anthracyclines and trastuzumab with poor CRF to inform long-term cardiac care and referral to specialized assessment, rehabilitation, and social support services. The prognostic implication of the proposed diagnostic algorithm for targeted referral and interventions needs to be determined.

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**KEY WORDS** anthracyclines, cardiopulmonary exercise testing, echocardiography, exercise training, global longitudinal strain, trastuzumab

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**APPENDIX** For an expanded Methods section as well as supplemental tables and figures, please see the online version of this paper.

