JACC: CARDIOONCOLOGY VOL. 3, NO. 5, 2021

ORIGINAL RESEARCH

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

Alis Bonsignore, RKIN, PHD,[a] Thomas H. Marwick, MD, PHD, MPH,[b] Scott C. Adams, RKIN, PHD,[a,c] Babitha Thampinathan, BSC, RDSM,[c] Emily Somerset, MSC,[d] Eitan Amir, MB CHB, PHD,[e] Mike Walker, MSC,[f] Husam Abdel-Qadir, MD, PHD,[c,g] C. Anne Koch, MD, PHD,[h] Heather J. Ross, MD, MHSC,[c] Anna Woo, MD, SM,[f] Bernd J. Wintersperger, MD,[i] Mark J. Haykowsky, PHD,[j] Paaladinesh Thavendiranathan, MD, SM[c,i]

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_2peak) (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_2peak using a cycle ergometer. Regression models were used to examine the association between VO_2peak and clinical, imaging, and cardiac biomarkers individually and in combination.

RESULTS Among 147 patients (age 52.2 ± 9.3 years), the mean VO_2peak was 19.1 ± 5.0 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ (84.2% ± 18.7% of predicted); 44% had a VO_2peak below threshold for functional independence (<18 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$). In multivariable analysis, absolute global longitudinal strain (GLS) ($\beta = 0.58$; $P = 0.007$), age per 10 years (β: -1.61; $P = 0.001$), and E/e' (measure of diastolic filling pressures) ($\beta = -0.45$; $P = 0.038$) were associated with VO_2peak. GLS added incremental value in explaining the variability in VO_2peak. 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_2peak.

CONCLUSIONS Readily available clinical measures were associated with VO_2peak 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/).

From the [a]Faculty of Kinesiology and Physical Education, University of Toronto, Toronto, Ontario, Canada; [b]Baker Heart and Diabetes Institute, Melbourne, Victoria, and Menzies Research Institute, Hobart, Tasmania, Australia; [c]Ted Rogers Program in Cardiotoxicity Prevention, Division of Cardiology, Peter Munk Cardiac Centre, University Health Network, University of Toronto, Toronto, Ontario, Canada; [d]Rogers Computational Program, Ted Rogers Centre for Heart Research, Peter Munk Cardiac Centre,

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2021.08.010

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 noncancer (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_2peak] <18 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ [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_2peak) 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_2peak 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

BNP = B-type natriuretic peptide

CORE = cardio-oncology rehabilitation

CPET = cardiopulmonary exercise test

CRF = cardiorespiratory fitness

CTRCD = cancer therapy-related cardiac dysfunction

GLS = global longitudinal strain

hsTnI = high-sensitivity troponin I

LV = left ventricle/ventricular

LVEF = left ventricular ejection fraction

LVMi = left ventricular mass index

VO_2peak = peak oxygen consumption

University Health Network, University of Toronto, Toronto, Ontario, Canada; [e]Division of Medical Oncology, Princess Margaret Cancer Center, University of Toronto, Toronto, Ontario, Canada; [f]Ted Rogers Centre for Heart Research, Peter Munk Cardiac Centre, University Health Network, University of Toronto, Toronto, Ontario, Canada; [g]Women's College Hospital, University of Toronto, Toronto, Ontario, Canada; [h]Radiation Medicine Program, Princess Margaret Cancer Center, University of Toronto, Toronto, Ontario, Canada; [i]Joint Department of Medical Imaging, Toronto General Hospital, University Health Network, University of Toronto, Toronto, Ontario, Canada; and the [j]University of Alberta, Faculty of Nursing, College of Health Science, Edmonton, Alberta, Canada.

Anju Nohria, MD, served as Guest Editor-in-Chief for this paper.

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.

Manuscript received June 9, 2021; revised manuscript received August 16, 2021, accepted August 20, 2021.

CARDIOPULMONARY EXERCISE TESTING. VO_2peak 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_2peak 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_2 at ventilatory threshold was determined using the computerized V-slope method (15). The minute ventilation-carbon dioxide production relationship (VE/VCO_2 slope), carbon dioxide production (VCO_2), and oxygen pulse (VO_2/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_2peak 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^2 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_2peak <18 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$)

	Entire Group (N = 147)	VO_2peak ≥18 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ (n = 83)	VO_2peak <18 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ (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^2	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^2	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
Breast cancer diagnosis				
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
Breast cancer treatment				
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
CVD risk factors				
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
Cardiac medications				
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
Cardiac symptoms				
NYHA functional class I	130 (89)	76 (92)	54 (86)	0.20
NYHA functional class II	17 (11)	7(8)	10 (16)	0.20
Biomarkers				
BNP, pg/mL	14.6 (10.0-26.4)	14.1 (10.0-25.6)	17.0 (10.0-27.7)[a]	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. [a]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, CTRCD during treatment, radiation exposure, and epirubicin equivalent dose). VO_2peak 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_2peak <18 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$) (7).

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

JACC: CARDIOONCOLOGY, VOL. 3, NO. 5, 2021
DECEMBER 2021:678–691

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
CPET parameters				
Relative VO_2peak, mL $O_2 \cdot kg^{-1} \cdot min^{-1}$	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_2peak <18 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$	64 (44)	34 (33)	30 (68)	<0.001
Absolute VO_2peak, $L \cdot min^{-1}$	1.27 ± 0.33	1.33 ± 0.33	1.15 ± 0.31	0.004
Percent of VO_2peak predicted, %	84.2 ± 18.7	87.5± 18.3	76.4 ± 17.2	0.001
Ventilation threshold, %VO_2peak	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_2/VO_2	1.13 ± 0.1	1.13 ± 0.1	1.14 ± 0.1	0.64
VE/VCO_2	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
Echocardiography parameters				
LV ESV, mL/m^2	24.9 (21.2-29.4)	24.2 (21.0-28.2)	27.6 (23.7-31.9)	0.016
LV EDV, mL/m^2	58.1 (52.0-69.4)	58.1 (52.4-69.1)	58.1 (50.6-70.5)	0.97
3D-LVEF, %[a]	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'[b]	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[c]	2.2 ± 0.3	2.0 ± 0.3	<0.001
LAVi, mL/m^2	25.7 (21.7-32.6)	27.7 (22.3-33.1)	23.4 (21.1-29.0)	0.074
LVMi, g/m^2	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). [a]In 3 patients, 3D-LVEF was not available and 2D-LVEF was used. [b]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^2. None of the patients had abnormal hsTnI (>26 pg/mL) or BNP (>100 pg/mL). [c]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_2peak 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_2peak. 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_2peak for the cohort was 19.1 ± 5.0 mL O_2•kg^{-1}•min^{-1} (84.2% ± 18.7% of Wasserman-predicted VO_2peak for healthy individuals), and 64 (44%) participants had VO_2peak <18 mL O_2•kg^{-1}•min^{-1} (14.9 ± 2.3 mL O_2•kg^{-1}•min^{-1}; range 9.3-17.9 mL O_2•kg^{-1}•min^{-1}), 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_2peak

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_2peak (Table 3). Both BNP and hsTnI were not associated with VO_2peak. Abnormal GLS (<18%) was detected in 44 (30%) participants (16.5% ± 1.3%; range 12.7%-17.9%), and these individuals had a VO_2peak 23% lower than predicted for healthy individuals. Compared with participants with GLS ≥18%, individuals with GLS <18% had a 18% lower VO_2peak (16.6 ± 4.1 mL O_2•kg^{-1}•min^{-1} vs 20.2 ± 5.0 mL O_2•kg^{-1}•min^{-1}; $P < 0.001$) (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_2peak (Dependent Variable)

	Univariable Association With VO_2peak			Multivariable Association with VO_2peak		
	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^2)	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^2)	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 (%)[a]	0.72	0.17	<0.001	0.58	0.21	0.007

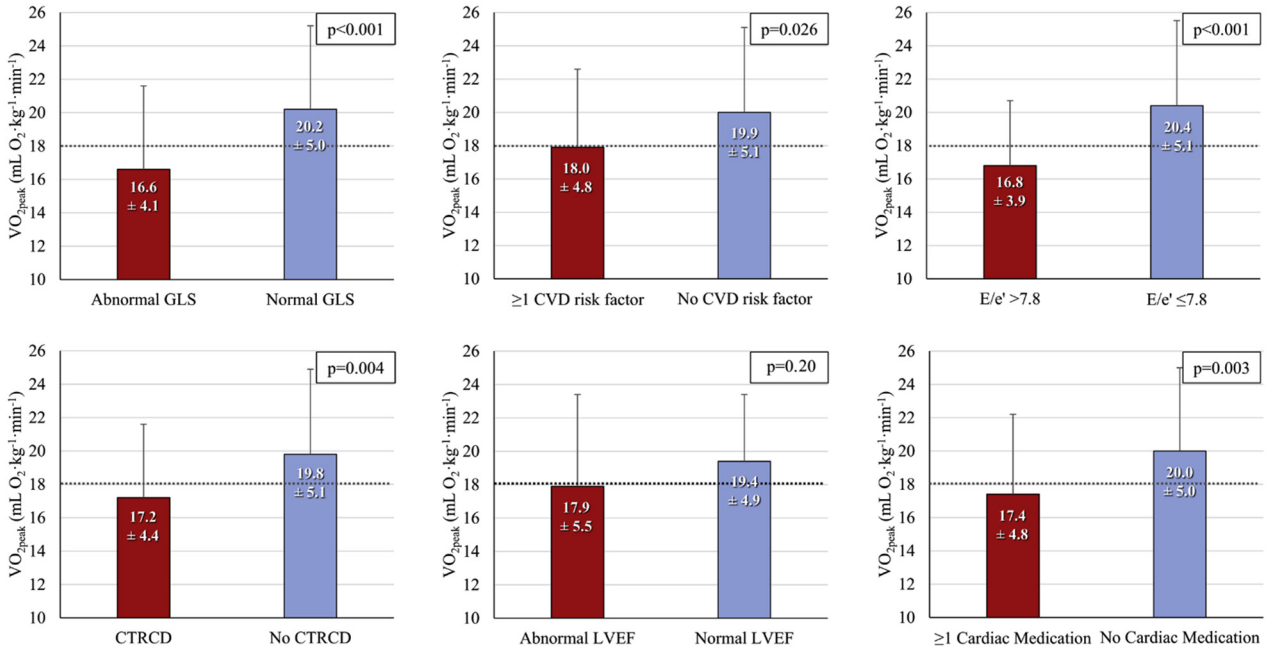
Multivariable association R = 0.545 for entire model. [a]GLS is entered into the model as an absolute value; all beta values represent the average change in VO_2peak for a unit change in continuous variables or presence of categorical variable except for age where the beta value is for every 10 years increase in age.

Abbreviations as in Tables 1 and 2.

VO_2peak 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_2peak 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_2peak. Abnormal GLS (ie, <18%) was also independently associated with VO_2peak (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_2peak. Compared with the clinical only model (CTRCD, cardiac medication use, ≥1 CVD risk factor, epirubicin equivalent dose, radiation dose, and age; $R^2 = 0.19$), the addition of cardiac biomarkers (BNP and hsTnI; $R^2 = 0.21$; $P = 0.344$) and echocardiography variables (3D-LVEF, LVMi, and E/e'; $R^2 = 0.26$; $P = 0.052$) improved the R^2 value that explains the variability in VO_2peak, but the incremental value was not statistically significant (Figure 2). The addition of GLS as a continuous ($R^2 = 0.30$; $P = 0.007$) or binary variable (GLS <18% vs ≥18%; $R^2 = 0.31$; $P = 0.003$) provided incremental value in explaining the

FIGURE 1 Comparison of VO_2peak for Various Clinical and Imaging Measures

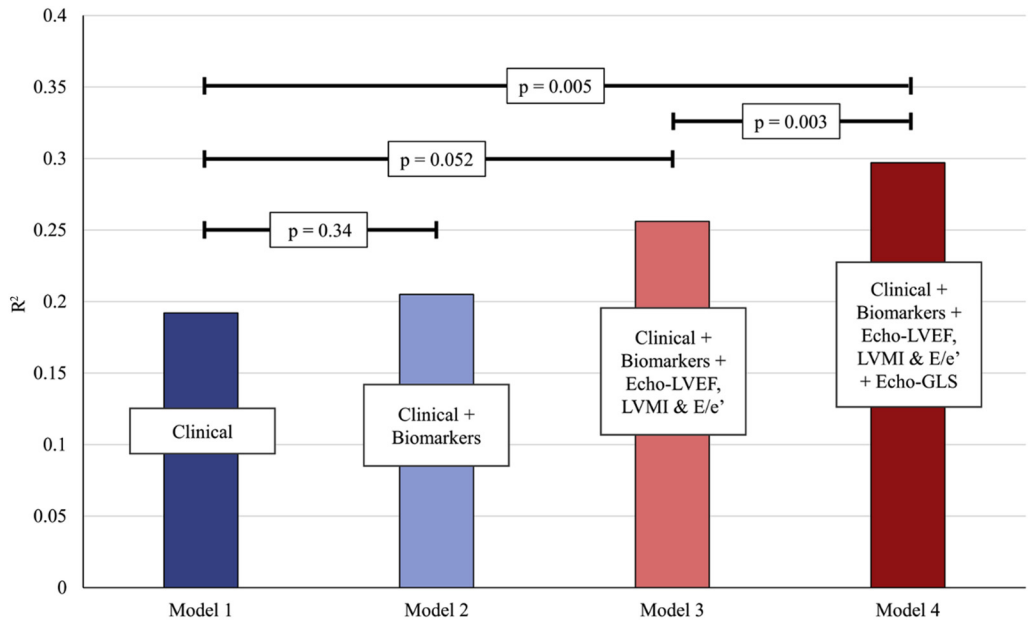


The bar graphs compare predicted VO_2 peak for patients with and without CTRCD during treatment and post-cancer treatment risk factors, cardiovascular medications, and echocardiography parameters. The *P* values represent between group differences in VO_2peak for univariable analyses. Abnormal LVEF <54%; abnormal GLS <18%. The **dashed line** indicates threshold for functional independence (VO_2peak = 18 mL O_2•kg^{-1}•min^{-1}). CVD = cardiovascular disease; GLS = global longitudinal strain; LVEF = left ventricular ejection fraction, E/e' = left ventricular filling pressures.

variability in VO_2peak 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_2peak 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%

FIGURE 2 **Incremental Value of Biomarker and Imaging Parameters to Predict VO_2peak**



GLS provided incremental value over clinical measures alone and over clinical/biomarker/and other echocardiography measures to predict VO_2peak. Clinical risk factors were age, cardiac medications, CVD risk factors, CTRCD during treatment, radiation exposure, and epirubicin equivalent dose; biomarkers included B-type natriuretic peptide and high-sensitivity troponin I. LVMI = left ventricular mass index; other abbreviations as in Figure 1.

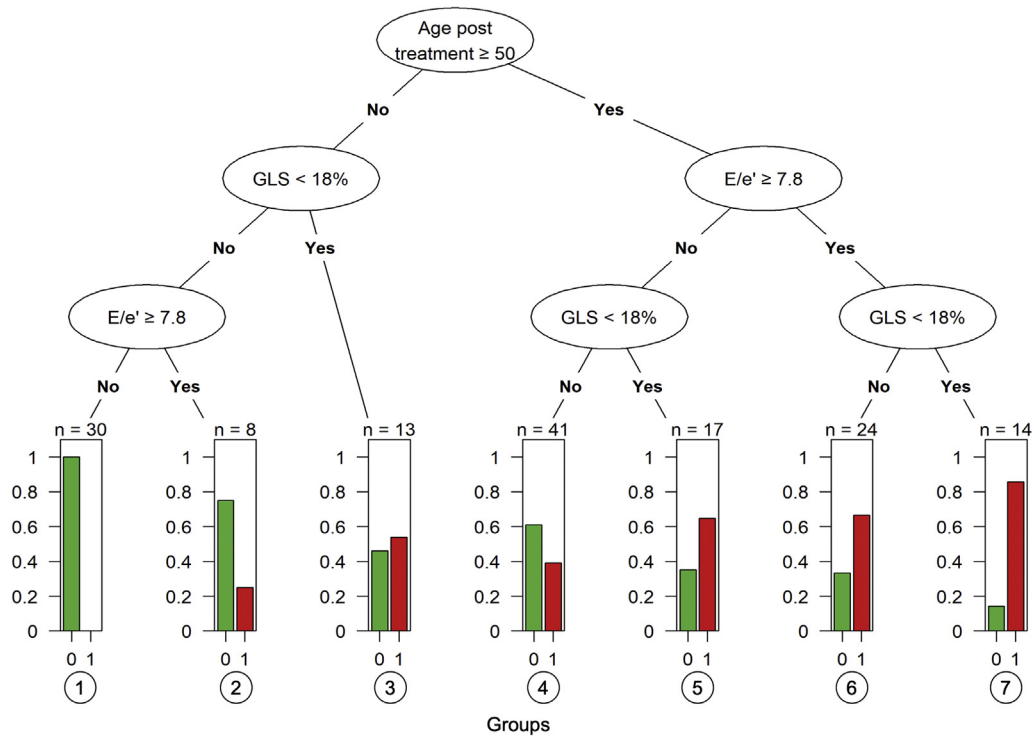
(95% CI: 73.4%-79.6%). A summary of proposed functional impairment risk-guided recommendations for surveillance and management, and prioritization for referral to specialized support services is provided in the **Central Illustration**.

DISCUSSION

This study examined associations between CRF as defined by VO_2peak 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_2peak. Using these parameters, we developed a diagnostic algorithm with good discriminatory value (AUC = 0.80) for identifying participants with compromised functional independence (ie, VO_2peak <18 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$) 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_2peak 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-

FIGURE 3 Tree Diagram for Detection of Compromised Functional Independence



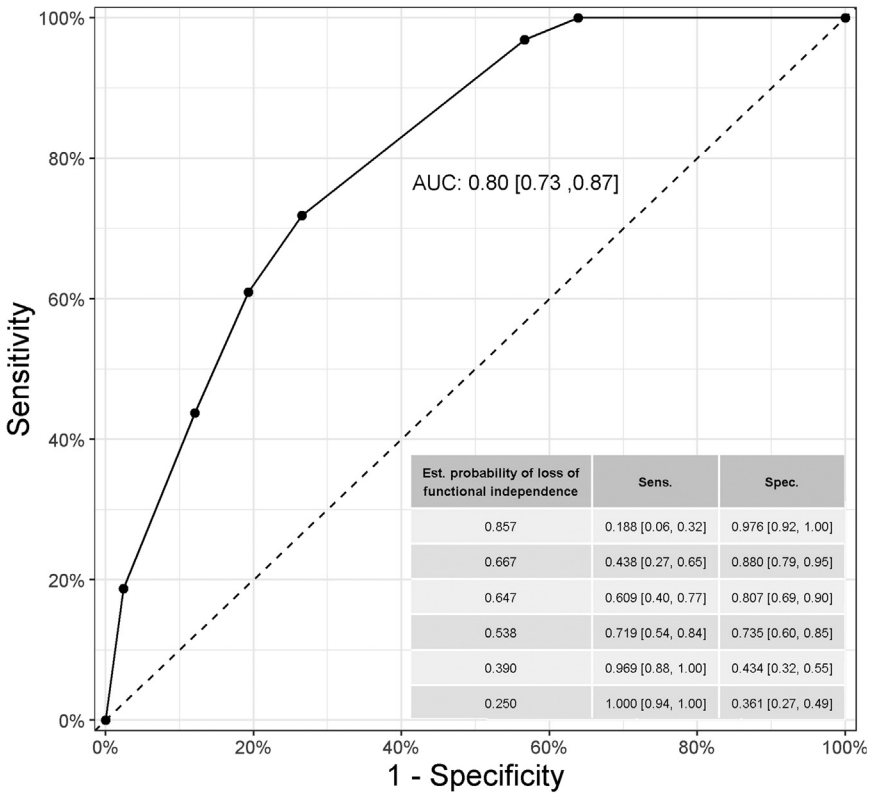
The 7 groups have different probabilities of loss of functional independence as shown in the box plots. Y-axis = probability. Probabilities are calculated based on the number of participants within each group that had VO_2peak impairment confirmed via CPET. **Red bars** = the probability of patients with VO_2peak <18 mL O_2•kg^{-1}•min^{-1}; **green bars** = probability of patients with VO_2peak ≥18 mL O_2•kg^{-1}•min^{-1}. The 7 groups are also shown in the **Central Illustration**. n indicates the number of participants meeting the criteria in that branch. GLS = global longitudinal strain.

cancer treatment, collective data in cancer (3) and noncancer (2) populations suggest that the reduced VO_2peak 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_2peak in the adjusted model. CTRCD was not independently associated with VO_2peak, 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_2peak. 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_2peak 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_2peak (22.9 ± 4.4 mL O_2•kg^{-1}•min^{-1}) compared with age-matched healthy control subjects (30.5 ± 3.4 mL O_2•kg^{-1}•min^{-1}). 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_2peak in our patients treated for HER2+

FIGURE 4 Receiver-Operating Characteristic Curves for the Optimal Tree Model

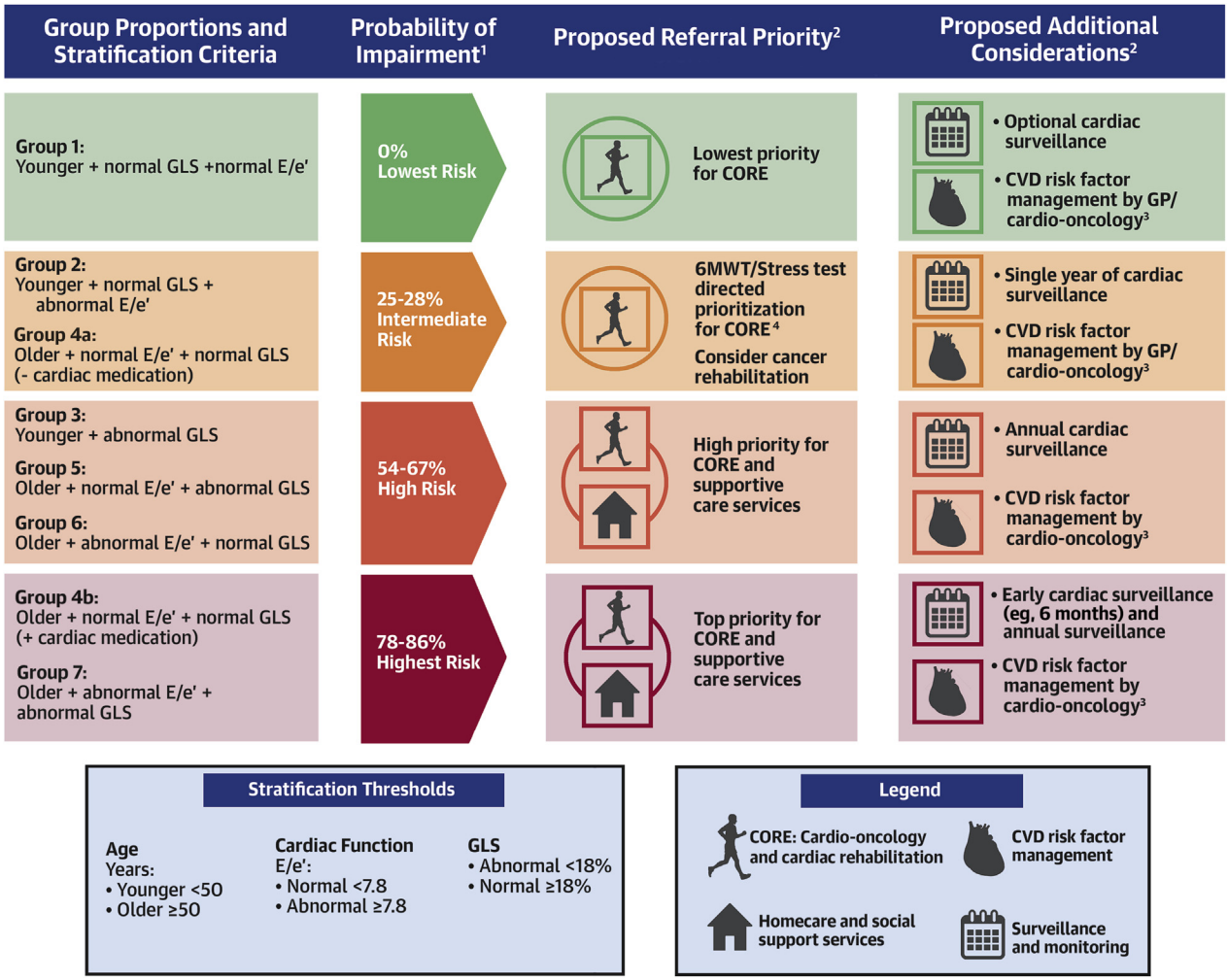


The table inserts provide the estimated probability of compromised functional independence at each node of the tree model shown in Figure 3. AUC = area under the curve.

breast cancer was significantly lower (24.6 mL O_2•kg^{-1}•min^{-1} vs 19.1 mL O_2•kg^{-1}•min^{-1}, respectfully), 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_2peak, 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_2peak 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)**



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%). [1]Probabilities calculated based on number of participants within each group that had VO_2peak impairment confirmed via cardiopulmonary exercise test. [2]These suggestions are based on author opinion and should be targets for future research studies. [3]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_2peak. Given that the final nested model had an R^2 of 0.31, these noncardiac variables may be important to explain the variability in VO_2peak 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_2peak remains relevant and likely translatable to other vendors. We used a VO_2peak threshold of 18 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ to define compromised functional independence across the age spectrum because no age-specific thresholds have been published (32). However, the mean VO_2peak values in our study were similar irrespective of the participants age category (**Table 2**), and the threshold of 18 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ was used in another recent study involving mixed cancer survivors of similar age (53 ± 13 years) (8). Furthermore, this VO_2peak threshold has not been directly associated with CVD risk; however, generally lower VO_2peak 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_2peak. Therefore, we were unable to determine if clinical and imaging parameters were associated with changes in VO_2peak 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_2peak (8). Finally, we did not have a control group of non-breast cancer survivors for comparing VO_2peak values; however, we contextualized our findings according to widely used predictive equation (ie, Wasserman et al [21]).

CONCLUSIONS

VO_2peak-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.

ACKNOWLEDGMENTS The authors thank the following Toronto General Hospital sonographers for echocardiography acquisition: Maala Soorikanthan, Jennifer Day, Jennifer Lam, Cathy Lau, Navdeep Boparai, and Andrew McClure. The authors also thank Maria Michalowska for supporting study start-up and procedures, and senior biostatistician Dr Steve Fan for analytic consultation.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This study was funded by an operating grant from the Canadian Institutes of Health Research (137132 and 142456); a Project Grant (1119955) from the National Health and Medical Research Council, Australia; an unrestricted grant from General Electric Healthcare; and personnel support from the Ontario Early Research Award. Dr Bonsignore is supported by the Canadian Institute of Health Research Fredrich Banting Doctoral Award. Dr Amir has received fees for expert testimony from Genentech/Roche. Dr Abdel-Qadir is supported by a National New Investigator Award from the Heart and Stroke Foundation of Canada; and has received honoraria from Amgen. Dr Wintersperger has received research support and speaker honorarium from Siemens Healthineers; and provides consultation to Bayer AG. Dr Haykowsky is funded by the Research Chair in Aging and Quality of life in the Faculty of Nursing at University of Alberta. Dr Thavendiranathan is supported by the Canadian Institutes of Health Research New Investigator Award (147814) and a Canada Research Chair in Cardio-oncology; and has received speaker honoraria from Amgen, Boehringer Ingelheim, and Takeda. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Paaladinesh Thavendiranathan, Ted Rogers Program in Cardiotoxicity Prevention, Peter Munk Cardiac Center, Toronto General Hospital, University of Toronto, 4N-490, 585 University Avenue, Toronto, Ontario M5G 2N2, Canada. E-mail: dinesh.thavendiranathan@uhn.ca. Twitter: @dineshpmcc1.

JACC: CARDIOONCOLOGY, VOL. 3, NO. 5, 2021
DECEMBER 2021:678–691

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_2 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.

REFERENCES

1. Abdel-Qadir H, Austin PC, Lee DS, et al. A population-based study of cardiovascular mortality following early-stage breast cancer. *JAMA Cardiol*. 2017;2(1):88. 10.1001/jamacardio.2016.3841

2. Fardman A, Banschick GD, Rabia R, et al. Cardiorespiratory fitness is an independent predictor of cardiovascular morbidity and mortality and improves accuracy of prediction models. *Can J Cardiol*. 2021;37(2):241–250. 10.1016/J.CJCA.2020.05.017

3. Groarke JD, Payne DL, Claggett B, et al. Association of post-diagnosis cardiorespiratory fitness with cause-specific mortality in cancer. *Eur Heart J Qual Care Clin Outcomes*. 2020;6(4):315–322. 10.1093/ehjqcco/qcaa015

4. Yu AF, Flynn JR, Moskowitz CS, et al. Long-term cardiopulmonary consequences of treatment-induced cardiotoxicity in survivors of ERBB2-positive breast cancer. *JAMA Cardiol*. 2020;5(3):309–317. 10.1001/jamacardio.2019.5586

5. Foulkes SJ, Howden EJ, Bigaran A, et al. Persistent impairment in cardiopulmonary fitness after breast cancer chemotherapy. *Med Sci Sport Exerc*. 2019;51(8):1573–1581. 10.1249/mss.0000000000001970

6. Brubaker P, Jensen A, Jordan J, et al. Exercise capacity is reduced in cancer survivors previously treated with anthracycline-based chemotherapy despite a preserved cardiac output response. *J Am Coll Cardiol. Img*. 2019;12(11P1):2267–2269. 10.1016/J.JCMG.2019.05.016

7. Forman DE, Arena R, Boxer R, et al. Prioritizing functional capacity as a principal end point for therapies oriented to older adults with cardiovascular disease: a scientific statement for health care professionals from the American Heart Association. *Circulation*. 2017;135(16):e894–e918. https://doi.org/10.1161/CIR.0000000000000483

8. Howden EJ, Foulkes S, Dillon HT, et al. Traditional markers of cardiac toxicity fail to detect marked reductions in cardiorespiratory fitness among cancer patients undergoing anti-cancer treatment. *Eur Heart J Cardiovasc Imaging*. 2021;22(4):451–458. https://doi.org/10.1093/ehjci/jeaa421

9. Herrero F, Balmer J, San Juan AF, et al. Is cardiorespiratory fitness related to quality of life in survivors of breast cancer? *J Strength Cond Res*. 2006;20(3):535–540. https://doi.org/10.1519/R-18215.1

10. Gilchrist SC, Barac A, Ades PA, et al. Cardio-oncology rehabilitation to manage cardiovascular outcomes in cancer patients and survivors: a scientific statement from the American Heart Association. *Circulation*. 2019;139(21):E997–E1012. https://doi.org/10.1161/CIR.0000000000000679

11. Thavendiranathan P, Abdel-Qadir H, Fischer HD, et al. Risk-imaging mismatch in cardiac imaging practices for women receiving systemic therapy for early-stage breast cancer: a population-based cohort study. *J Clin Oncol*. 2018;36(30):2980–2987. https://doi.org/10.1200/JCO.2018.77.9736

12. Thavendiranathan P, Negishi T, Somerset E, et al. Strain-guided management of potentially cardiotoxic cancer therapy. *J Am Coll Cardiol*. 2021;77(4):392–401. https://doi.org/10.1016/j.jacc.2020.11.020

13. Balady GJ, Arena R, Sietsema K, et al. Clinician's guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation*. 2010;122(2):191–225. https://doi.org/10.1161/CIR.0b013e3181e52e69

14. Bensimhon DR, Leifer ES, Ellis SJ, et al. Reproducibility of peak oxygen uptake and other cardiopulmonary exercise testing parameters in patients with heart failure (from the Heart Failure and A Controlled Trial Investigating Outcomes of exercise traiNing). *Am J Cardiol*. 2008;102(6):712–717. https://doi.org/10.1016/j.amjcard.2008.04.047

15. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol*. 2016;121(6):2020–2027. https://doi.org/10.1152/jappl.1986.60.6.2020

16. Guazzi M, Adams V, Conraads V, et al. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Circulation*. 2012;126(18):2261–2274. https://doi.org/10.1161/CIR.0b013e31826fb946

17. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr*. 2009;22(2):107–133. https://doi.org/10.1016/j.echo.2008.11.023

18. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2015;16(3):233–271. https://doi.org/10.1093/EHJCI/JEV014

19. Oikonomou EK, Kokkinidis DG, Kampaktsis PN, et al. Assessment of prognostic value of left ventricular global longitudinal strain for early prediction of chemotherapy-induced cardiotoxicity: a systematic review and meta-analysis. *JAMA Cardiol*. 2019;4(10):1007–1018. https://doi.org/10.1001/jamacardio.2019.2952

20. Seidman A, Hudis C, Pierri MK, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. *J Clin Oncol*. 2002;20(5):1215–1221. https://doi.org/10.1200/jco.2002.20.5.1215

21. Wasserman K, Hansen JE, Sue D, Whipp BJ, Casaburi R. *Principles of Exercise Testing and Interpretation. 4th edition*. Lippincott Williams and Wilkins; 2004.

22. Harrell FE. *Regression Modelling Strategies: With Applications to Linear Models, Logistic Regression and Survival Analysis. Springer*. 2015.

23. Youden WJ. Index for rating diagnostic tests. *Cancer*. 1950;3(1):32–35.10.1002/1097-0142(1950)3:1>32::aid-cncr2820030106<3.0.co;2-3.

24. Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology*. 2010:128–138. https://doi.org/10.1097/EDE.0b013e3181c30fb2

25. Foulkes S, Costello BT, Howden EJ, et al. Exercise cardiovascular magnetic resonance reveals reduced cardiac reserve in pediatric cancer survivors with impaired cardiopulmonary fitness. *J Cardiovasc Magn Reson*. 2020;22(1):1–10. https://doi.org/10.1186/S12968-020-00658-4

26. Peel AB, Thomas SM, Dittus K, Jones LW, Lakoski SG. Cardiorespiratory fitness in breast cancer patients: a call for normative values. *J Am Heart Assoc*. 2014;3(1):e000432. https://doi.org/10.1161/JAHA.113.000432

27. Kosmala W, Jellis CL, Marwick TH. Exercise limitation associated with asymptomatic left ventricular impairment. *J Am Coll Cardiol*. 2015;65(3):257–266. https://doi.org/10.1016/j.jacc.2014.10.044

28. Caballero L, Kou S, Dulgheru R, et al. Echocardiographic reference ranges for normal cardiac Doppler data: results from the NORRE Study. *Eur Heart J Cardiovasc Imaging*. 2015;16(9):1031–1041. https://doi.org/10.1093/ehjci/jev083

29. Boyd A, Stoodley P, Richards D, et al. Anthracyclines induce early changes in left ventricular systolic and diastolic function: a single centre study. *PLoS One*. 2017;12(4):e0175544.

30. Scott JM, Li N, Liu Q, et al. Association of exercise with mortality in adult survivors of childhood cancer. *JAMA Oncol*. 2018;4(10):1352–1358. https://doi.org/10.1001/jamaoncol.2018.2254

31. Schmidt K, Vogt L, Thiel C, Jäger E, Banzer W. Validity of the six-minute walk test in cancer patients. *Int J Sports Med*. 2013;34(7):631–636. https://doi.org/10.1055/S-0032-1323746

32. Morey MC, Pieper CF, Cornoni-Huntley J. Is there a threshold between peak oxygen uptake and self-reported physical functioning in older adults? *Med Sci Sports Exerc*. 1998;30(8):1223–1229. https://doi.org/10.1097/00005768-199808000-00007

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

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

Go to http://www.acc.org/jacc-journals-cme to take the CME/MOC/ECME quiz for this article.