**SUPPLEMENTARY DIGITAL CONTENT**

**Table of Contents**

|  |  |
| --- | --- |
| **eMethods** | 2 |
| **Supplemental Table 1.** Variables considered for exercise oncology VO2peak prediction model. | 4 |
| **Supplemental Table 2.** Variables retained for exercise oncology VO2peak prediction model by stepwise selection. | 5 |
| **Supplemental Table 3.** Results using a stepwise selection threshold of 80% | 6 |
| **Supplemental Table 4.** Sensitivity analyses of the concordance correlation coefficient and Bland-Altman limits of agreement among baseline CPET measurements. | 7 |
| **eReferences** | 8 |

**eMethods**

Full details regarding the study sample, recruitment and procedures have been reported previously.1 Eligible patients were ≥ 1 year to <5 years after completion of primary adjuvant therapy, had a VO2peak below age-sex-matched active levels,2 and cardiology ECG clearance as per established practice guidelines.3 Patients were randomly assigned in a 1:1:1 ratio to receive either one of two exercise dosing regimens (linear or non-linear) or attention control. All study procedures were reviewed and approved by Duke University Medical Center and Memorial Sloan Kettering Cancer Center institutional review boards. All patients provided written informed consent.

**Cardiopulmonary Exercise Testing**

VO2peak (ml O2.kg-1.min-1) was assessed by an incremental CPET on an electronic motorized treadmill test with 12-lead ECG monitoring (Mac® 5000, GE Healthcare) according to standard procedures.3,4 Breath-by-breath (averaged every 30 secs) expired gases were collected via a mouthpiece and analyzed continuously by a calibrated metabolic measurement system (Parvo Medics, TrueOne 2400). The treadmill protocol was selected with the goal of patients achieving a maximal effort within 8 to 12 mins. Prior to starting the test, a warmup was completed to familiarize the patient with the treadmill and identify a comfortable walking speed between 1.5 – 4.0mph. During warm up, heart rate response (~20 bpm above resting, varied with age), gait, and perceived level of exertion (RPE ~8-10) were assessed to determine starting walking speed. Following three mins of rest, the test began at the individually identified warmup speed and 0% grade for two minutes. During the first stage, metabolic metrics (VE, RER, FEO2) and heart rate response, as compared to rest, were assessed to select the increment of grade (2 or 3%) increase for subsequent stages. A 3% increase per stage was standard; however, if a patient demonstrated a large increase in VE / RR and/or RER stayed elevated, a 2% increase in grade was selected. Grade was subsequently increased every two minutes until a clear decrease in FECO2 from its highest value occurred; after this stage grade remained constant and speed was increased every minute until exhaustion. Speed increases were 0.2 or 0.3 depending on patient’s gait and the perceived amount of effort left prior to self-terminating the test. Acceptable CPET criteria for this analysis included any two of the following: (1) a plateau in VO2, concurrent with an increase in treadmill grade or speed, (2) respiratory exchange ratio ≥ 1.10, (3) attainment (± 10 bpm) of age-predicted heart rate, and (4) volitional exhaustion as measured by a rating of perceived exertion ≥ 18 on the Borg scale.

Submaximal VO2 was assessed upon CPET completion and data were used for Ex-Oncsub. A trained exercise physiologist identified ventilatory threshold defined by the following criteria: (1) drop in FECO2 after a peak or plateau, (2) nonlinear increase in VE, (3) RER between 0.98 - 1.02. Age-predicted peak heart rate was calculated using: 220 - age; age-predicted heart rate at 80% of peak (i.e., submaximal) was calculated using: [((220 - age) – rest heart rate) \* 0.8) + rest heart rate].

**Estimated VO2peak**

Treadmill speed and grade derived from the CPET were used to estimate VO2peak using the American College of Sports Medicine (ACSM)5: VO2peak = [(speed (m/min) x 0.1) + (speed (m/min) x fractional grade x 1.8)] + 3.5] and The Fitness Registry and the Importance of Exercise National Database (FRIEND)6: VO2peak = [speed (m/min) x (0.17 + fractional grade x 0.79) + 3.5] equations.

**Statistical Analysis**

Data from all arms of the trial were combined for these analyses. VO2peak as measured by CPET and as estimated by ACSM and FRIEND models were summarized using descriptive statistics at each evaluation timepoint (baseline, midpoint and follow-up) and overall. Bland-Altman plots were used to display the difference between measured and estimated VO2peak measures along the Y-axis and the average of measured and estimated observations along the X-axis, along with the average bias and 95% limits of agreement.7 The data were visually inspected and log transformed prior to computing the limits of agreement in order to meet the assumptions of the method; VO2peak values were transformed back to the original scale for interpretation of results. Estimates of the standard deviation of the difference in VO2peak between methods reflect the within- and between-participant variation to account for repeated VO2peak measurements.7,8 The concordance in ACSM- and FRIEND-estimated and measured VO2peak was evaluated by Lin's concordance correlation coefficient (CCC),9 also with standard deviation that accounts for the longitudinal experimental design.7 A CCC value of 1 indicates perfect agreement; values <0.6 were considered to be poor agreement.10 Based on previous work that a 3.5 ml O2.kg-1.min-1 (i.e., 1 metabolic equivalent [MET]) higher VO2peak is associated with a ~20% reduced risk of all-cause mortality,11 we used this value to serve as an acceptable difference threshold for estimated VO2peak values (i.e., difference between estimated and CPET VO2peak of <3.5 ml O2.kg-1.min-1 considered an acceptable value).

Five-fold cross validation was used to develop the Ex-Onc estimated VO2peak equations. Variables, selected on the basis of previous literature and potential to impact VO2peak6, were considered for inclusion (**Supplemental Table 1).** Two variables introduced collinearity issues: measured vs estimated heart rate and heart reserve. These variables were removed prior to fitting stepwise selection model. The cross validation was based on a linear model with an outcome of CPET VO2peak and a random intercept to account for repeated CPET measurements to the same patient at up to three timepoints. Variables retained by stepwise selection (p-value ≤ 0.20) in at least in at least 50% of the models were included in the final models. As a sensitivity analysis, we also examined how results would differ if variables selected in at least 80% of the models were retained. The average root mean squared error (RMSE) across the cross validation models is presented to indicate model accuracy based on the difference between estimated VO2peak and CPET VO2peak values.12 The average fixed effects from the random intercept model were used to generate estimated values for the Onc equations. The CCC between Ex-Oncpeak and Ex-Oncsub VO2peak and CPET VO2peak was calculated. To address whether there is a difference in validity between ACSM, FRIEND and ExOnc estimated VO2peak, bootstrapping was used to obtain the difference in the RMSE between the Ex-Onc estimates and the ACSM/FRIEND estimates. Analyses were performed in R version 4.0.0.13

**Supplemental Table 1.** Variables considered for exercise oncology VO2peak prediction models.

|  |  |
| --- | --- |
| **Ex-Oncpeak** | **Ex-Oncsub** |
| Peak Treadmill Speed (mph) | Submaximal Treadmill Speed (mph) |
| Peak Treadmill Grade (decimal) | Submaximal Treadmill Grade (decimal) |
| Interaction between peak speed and grade | Interaction between submaximal speed and grade |
| Resting HR (bpm) | Resting HR (bpm) |
| Resting SBP (mmHg) | Resting SBP (mmHg) |
| Body mass index (kg/m2) | Body mass index (kg/m2) |
| Weight (kg) | Weight (kg) |
| Height (cm) | Height (cm) |
| Age (years) | Age (years) |
| Measured Peak HR (bpm) | Measured Submaximal HR (bpm) |
| Difference between measured and age-predicted peak HR (bpm) | Difference between measured and age-predicted submaximal HR (bpm) |
| Peak HR reserve (Peak - resting HR, bpm) | Submaximal HR reserve (Submaximal - resting HR, bpm) |
| Hb (g/dL) | Hb (g/dL) |
| History of radiation therapy (Y/N) | History of radiation therapy (Y/N) |
| History of chemotherapy (Y/N) | History of chemotherapy (Y/N) |
| Current endocrine therapy (Y/N) | Current endocrine therapy (Y/N) |
| Smoking history (Y/N) | Smoking history (Y/N) |

**Abbreviations:** HR, heart rate; bpm, beats per minute; SBP, systolic blood pressure; Hb, hemoglobin.

**Supplemental Table 2.** Variables retained by stepwise selection (p-value ≤ 0.20)

|  |  |  |
| --- | --- | --- |
| Ex-Oncpeak |  | Ex-Oncsub |
| Variable | **Percentage Kept** |  | **Variable** | **Percentage Kept** |
| Body mass index (kg/m2) | 100 |  | Body mass index (kg/m2) | 100 |
| Peak treadmill grade (decimal) | 100 |  | History of radiation therapy (Y/N) | 100 |
| Peak treadmill speed (mph) | 100 |  | Age (years) | 80 |
| History of chemotherapy (Y/N) | 80 |  | Submaximal treadmill speed (mph) | 60 |
| Age (years) | 60 |  | Hb (g/dL) | 40 |
| Measured peak HR (bpm) | 60 |  | Resting SBP (mmHg) | 40 |
| Hb (g/dL) | 40 |  | Current endocrine therapy (Y/N) | 40 |
| Current endocrine therapy (Y/N) | 40 |  | History of chemotherapy (Y/N) | 40 |
| History of radiation therapy (Y/N) | 40 |  | Submaximal treadmill grade (decimal) | 40 |
| Resting HR (bpm) | 40 |  | Interaction between submaximal speed and grade | 40 |
| Smoking history | 40 |  | Measured submaximal HR (bpm) | 20 |
| Resting SBP (mmHg) | 40 |  | Smoking history | 0 |
| Interaction between peak speed and grade | 20 |  |  |  |

**Abbreviations:** HR, heart rate; bpm, beats per minute; SBP, systolic blood pressure; Hb, hemoglobin

**Supplemental Table 3. Results using a stepwise selection threshold of 80%**

|  |  |  |
| --- | --- | --- |
|  | Oncpeak | Oncsub |
| Model Equation | [(-0.22 x BMI) + 27.1 x peak fractional grade) + (3.62 x peak treadmill speed (mph)) + (0.27 if previous chemotherapy) + 13.5] | [(-0.19 \* age in years) + (-0.38 \* BMI) + (0.24 if previous radiation therapy) + 44.46] |
| VO2peak, ml O2.kg-1.min-1 | 22.3(20.2-24.1) | 22.5(20.4-24.3) |
| Median difference between measured and estimated VO2peak, ml O2.kg-1.min-1 (Q1, Q3) | 0.0(-1.8-1.8) | -0.3(-2.4-1.7) |
| Values within 3.5 ml O2.kg-1.min-1 | 305 (80%) | 262 (71%) |
| Median Root Mean Square Error (minimum, maximum) | 2.74 (2.64, 3.02) | 3.28 (2.94, 3.8) |

**Abbreviations:** BMI, body mass index; VO2peak, peak oxygen consumption.

**Supplemental Table 4.** Sensitivity analyses of the concordance correlation coefficient and Bland-Altman limits of agreement among baseline CPET measurements.

|  |  |  |
| --- | --- | --- |
|  | Primary Results (with repeated measures) | Sensitivity Analyses (baseline measurement only) |
| Concordance Correlation Coefficient (95% Confidence Interval) |  |  |
|  | ACSM | 0.31 (0.27, 0.36) | 0.36 (0.29, 0.43) |
|  | FRIEND | 0.53 (0.48, 0.58) | 0.58 (0.50, 0.65) |
|  | HF FRIEND | 0.75 (0.71, 0.79) | 0.75 (0.69, 0.81) |
|  | Oncpeak | 0.81 (0.77, 0.84) | 0.82 (0.77, 0.86) |
|  | Oncsub | 0.68 (0.63, 0.72) | 0.71 (0.63, 0.77) |
| Bias (Bland-Altman Limits of Agreement) |  |  |
|  | ACSM | 1.34 (0.98, 1.84) | 1.29 (0.98, 1.71) |
|  | FRIEND | 1.19 (0.94, 1.51) | 1.17 (0.93, 1.45) |
|  | HF FRIEND | 0.99 (0.78, 1.25) | 0.97 (0.78, 1.22) |
|  | Oncpeak | 1.0 (0.81, 1.24) | 1.01 (0.82, 1.23) |
|  | Oncsub | 1.0 (0.77, 1.30) | 1.01 (0.79, 1.30) |

**Abbreviations:** ACSM, American College of Sports Medicine; FRIEND, Fitness Registry and the Importance of Exercise National Database; HF, heart failure; Oncpeak, Oncology peak; Oncsub, Oncology submaximal.

**eReferences**

1. Scott JM, Thomas SM, Peppercorn JM, et al. Effects of Exercise Therapy Dosing Schedule on Impaired Cardiorespiratory Fitness in Patients With Primary Breast Cancer: A Randomized Controlled Trial. Circulation 2020;141:560-70.

2. Fitzgerald MD, Tanaka H, Tran ZV, Seals DR. Age-related declines in maximal aerobic capacity in regularly exercising vs. sedentary women: a meta-analysis. J Appl Physiol (1985) 1997;83:160-5.

3. ATS/ACCP. ATS/ACCP Statement on cardiopulmonary exercise testing. American journal of respiratory and critical care medicine 2003;167:211-77.

4. 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;122:191-225.

5. American College of Sports Medicine. ACSM's Guidelines for Graded Exercise Testing and Prescription. 10th Edition. Philadelphia: Wolters Kluwer (Lippincott Williams & Wilkins), 2018, pp. 226-267.2018.

6. Kokkinos P, Kaminsky LA, Arena R, Zhang J, Myers J. New Generalized Equation for Predicting Maximal Oxygen Uptake (from the Fitness Registry and the Importance of Exercise National Database). Am J Cardiol 2017;120:688-92.

7. Bland JM, Altman DG. Agreement between methods of measurement with multiple observations per individual. J Biopharm Stat 2007;17:571-82.

8. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307-10.

9. Carrasco JL, Jover L. Estimating the generalized concordance correlation coefficient through variance components. Biometrics 2003;59:849-58.

10. Lin LI. A concordance correlation coefficient to evaluate reproducibility. Biometrics 1989;45:255-68.

11. Kodama S, Saito K, Tanaka S, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: A meta-analysis. JAMA 2009;301:2024-35.

12. Witten D, Tibshirani R, Hastie T, James G. An Introduction to Statistical Learning: With Applications in R. Germany: Springer New York; 2013.

13. R: A language and environment for statistical computing. R Foundation for Statistical Computing. 2020. 2020, at https://www.R-project.org/.)