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ORIGINAL RESEARCH

Validation and Refinement of Prediction Models to Estimate Exercise Capacity in Cancer Survivors Using the Steep Ramp Test

Martijn M. Stuiver, PhD,[a,b,c] Caroline S. Kampshoff, MSc,[d] Saskia Persoon, MSc,[e]
Wim Groen, PhD,[f] Willem van Mechelen, PhD,[d] Mai J.M. Chinapaw, PhD,[d]
Johannes Brug, PhD,[g] Frans Nollet, PhD,[e] Marie-José Kersten, PhD,[h] Goof Schep, PhD,[i]
Laurien M. Buffart, PhD[j,k,l]

From the [a]Department of Physical Therapy, Netherlands Cancer Institute, Amsterdam, The Netherlands; [b]Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; [c]ACHIEVE, Faculty of Health, Amsterdam University of Applied Sciences, Amsterdam, The Netherlands; [d]Department of Public & Occupational Health/EMGO+ Institute, VU University Medical Center, Amsterdam, The Netherlands; [e]Department of Rehabilitation, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; [f]Division of Psychosocial Research and Epidemiology, Netherlands Cancer Institute, Amsterdam, The Netherlands; [g]Faculty of Social and Behavioural Sciences, University of Amsterdam, Amsterdam, The Netherlands; [h]Department of Hematology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; [i]SportMáx, Maxima Medical Center, Eindhoven, The Netherlands; [j]Department of Epidemiology and Biostatistics/EMGO+ Institute and [k]Department of Medical Oncology, VU University Medical Center, Amsterdam, The Netherlands; and [l]Exercise Medicine Research Institute, Edith Cowan University, Joondalup, Australia.

Abstract

Objective: To further test the validity and clinical usefulness of the steep ramp test (SRT) in estimating exercise tolerance in cancer survivors by external validation and extension of previously published prediction models for peak oxygen consumption (Vo_{2peak}) and peak power output (W_{peak}).

Design: Cross-sectional study.

Setting: Multicenter.

Participants: Cancer survivors (N=283) in 2 randomized controlled exercise trials.

Interventions: Not applicable.

Main Outcome Measures: Prediction model accuracy was assessed by intraclass correlation coefficients (ICCs) and limits of agreement (LOA). Multiple linear regression was used for model extension. Clinical performance was judged by the percentage of accurate endurance exercise prescriptions.

Results: ICCs of SRT-predicted Vo_{2peak} and W_{peak} with these values as obtained by the cardiopulmonary exercise test were .61 and .73, respectively, using the previously published prediction models. 95% LOA were ±705mL/min with a bias of 190mL/min for Vo_{2peak} and ±59W with a bias of 5W for W_{peak}. Modest improvements were obtained by adding body weight and sex to the regression equation for the prediction of Vo_{2peak} (ICC, .73; 95% LOA, ±608mL/min) and by adding age, height, and sex for the prediction of W_{peak} (ICC, .81; 95% LOA, ±48W). Accuracy of endurance exercise prescription improved from 57% accurate prescriptions to 68% accurate prescriptions with the new prediction model for W_{peak}.

Conclusions: Predictions of Vo_{2peak} and W_{peak} based on the SRT are adequate at the group level, but insufficiently accurate in individual patients. The multivariable prediction model for W_{peak} can be used cautiously (eg, supplemented with a Borg score) to aid endurance exercise prescription.
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Many cancer survivors experience severe loss of exercise capacity.[1,2] This may interfere with performance of daily activities.[3] Also, poor exercise tolerance is a risk factor for overall mortality.[4-6] Exercise is recommended for cancer survivors, because it can improve physical fitness and health-related quality of life.[7]

For optimal exercise prescription for cancer survivors, cancer and cancer treatment−related side effects should be taken into account, as well as basic exercise principles such as specificity, progression, and overload.[8,9] To evaluate current exercise capacity and to ensure adequate training progression and overload during exercise programs, repeated exercise capacity testing is required.[9] One of the main indicators of individual exercise capacity is peak oxygen consumption (Vo_{2peak}).

The criterion standard of Vo_{2peak} assessment is a maximal incremental exercise test with breath gas analysis and electrocardiography, usually referred to as *cardiopulmonary exercise test* (CPET).[10] As the performance of CPET requires specific expertise and specialized equipment, the test is not readily available for exercise prescription in primary care or even in many hospital settings.[2] As a result, clinicians often turn to less resource-demanding (often submaximal) exercise tests, among which is the steep ramp test (SRT).

The SRT is a short maximal cycle ergometer test that was developed to support interval training prescription for patients with heart failure, without the need for breath gas analysis.[11] The test uses a fast increasing workload of 25W every 10 seconds. The maximum workload achieved is referred to as the *maximal short exercise capacity* (MSEC). The largely anaerobic nature of the SRT makes it suitable for dosing interval training and monitoring response.[11] In a sample of 37 cancer survivors, De Backer et al[12] showed that the SRT has excellent test-retest reliability and a small SEM. The MSEC also has a strong correlation with Vo_{2peak} and peak power output (W_{peak}) as assessed by a regular CPET,[12,13] and currently 2 linear regression equations to estimate Vo_{2peak} and W_{peak} from the MSEC in cancer survivors are available.[12] The SRT seems to be a promising measure to estimate aerobic exercise capacity and to tailor exercise prescriptions, not only for short bouts of interval training but also for longer endurance training bouts, to the capacity of individual cancer survivors. However, the prediction models as presented by De Backer et al[12] have not yet been externally validated in a different (and larger) sample of cancer survivors. Also, the predictions of Vo_{2peak} and W_{peak} by these equations lack precision, with 95% prediction margins of 616mL/min and 63W for Vo_{2peak} and W_{peak}, respectively.[12] This hampers the use of the SRT for valid estimation of Vo_{2peak} or W_{peak} and for tailoring other types of aerobic exercises (eg, endurance training with continuous load) in individual patients, because prescribed intensities are often too high or too low. Hence, further improvement of the prediction models is required before the SRT can be considered as a substitute for the CPET.

Better generalizability might be achieved by using a larger sample size to build the regression models. In addition, because age, sex, height, and weight are associated with maximal exercise capacity,[14] we hypothesized that the accuracy of the prediction of Vo_{2peak} and W_{peak} based on the MSEC could be improved by including these variables in the regression equation.

Thus, the objectives of this study were to externally validate the previously published prediction models for Vo_{2peak} and W_{peak}[12] in a larger sample of cancer survivors and to explore whether predictions of Vo_{2peak} and W_{peak} as well as exercise prescriptions could be improved by extending the regression model.

Methods

Patients and measurements

This study used data collected in 2 randomized controlled exercise trials—EXercise Intervention after Stem cell Transplantation study[15] and Resistance and Endurance exercise After Chemotherapy study[16,17]—in cancer survivors, which were part of the Alpe d'HuZes Cancer Rehabilitation program.[18] The EXercise Intervention after Stem cell Transplantation study was a multicenter randomized controlled trial in which 109 patients, who were recently treated with autologous stem cell transplantation for multiple myeloma or (non-)Hodgkin lymphoma, were recruited from 9 hospitals.[15] The Resistance and Endurance exercise After Chemotherapy study was a multicenter randomized controlled trial in which 277 patients diagnosed with breast, colon, ovarian, cervix, or testis cancer or lymphoma, who had recently completed primary cancer treatment (including chemotherapy), were recruited from 9 hospitals.[16,17] Approval for these studies was obtained from medical ethics committees of all participating centers, and all participants provided written informed consent.

Both trials included a CPET at baseline and follow-up assessments and used an SRT to support exercise prescription and adaptation. The present analysis uses the first SRT results of each patient, as obtained shortly after the baseline CPET. For the EXercise Intervention after Stem cell Transplantation study, this concerned patients in the intervention group only (n=54). Time between baseline CPET and SRT in all eligible patients ranged between 0 and 41 days. For the purposes of the present study, we only included available data from patients in whom the SRT and CPET were performed within 30 days and who had not yet started exercise training. Consequently, combined tests were available for 283 patients (85%) with a median interval of 8 days (interquartile range, 6−10d).

Exercise tests

Patients performed both tests on an electronically braked cycle ergometer using standardized protocols. Details of the testing procedures are described elsewhere.[15,16] In short, the CPET used a ramp protocol with gradually increasing workload that was adjusted to each patient with the aim to achieve the maximum performance within 8 to 12 minutes. Patients were instructed to cycle with a pedal frequency between 60 and 80rpm and were encouraged to continue cycling until exhaustion or inability to maintain the prescribed pedal frequency. During the test, heart rate was monitored continuously using a 12-lead electrocardiogram

List of abbreviations:

CI	confidence interval
CPET	cardiopulmonary exercise test
ICC	intraclass correlation coefficient
LOA	limits of agreement
MET	metabolic equivalent
MSEC	maximal short exercise capacity
SRT	steep ramp test
Vo_{2peak}	peak oxygen consumption
W_{peak}	peak power output

and expired gases were collected breath by breath using gas analysis for O_2, CO_2, and respiration volume. Vo_{2peak} (in milliliters per minute) was determined as the average oxygen uptake during the 15-second interval in which maximum oxygen uptake was attained. W_{peak} (in watts) was determined as the highest workload reached during the test.

The SRT started after a 4-minute warming-up process at 10W. During the test, the workload increased by 25W every 10 seconds, starting at 25W. The test ended when the cycling pedal frequency fell below 60rpm. The MSEC was calculated as the workload of the last completed stage plus 2.5W for each second in the current stage.[12]

Statistical analysis

Descriptive statistics for the sample were calculated using mean and SD, median and interquartile range, or frequency and percentage, as appropriate, on the basis of data type and distribution.

External validation and calibration-in-the-large

We first evaluated the external validity of the prediction models as derived by De Backer et al[12] by examining the accuracy of the predictions in the entire sample. Intraclass correlation coefficients (ICCs; 2-way random, absolute agreement, single measure) were calculated between the predicted values (denoted Vo_{2peak}^{pred} and W_{peak}^{pred}) and values measured during the CPET (denoted Vo_{2peak}^{cpet} and W_{peak}^{cpet}). Second, we updated the intercept of the regression equation to reflect the lower mean Vo_{2peak} and W_{peak} in our sample (referred to as *calibration-in-the-large*).[19] Third, we calculated and plotted limits of agreement (LOA) of Vo_{2peak}^{pred} and W_{peak}^{pred} with the corresponding values measured during the CPET by using the Bland-Altman method.[20] The error correlation (expressing the association between the mean of the values and their difference) was calculated and the corresponding regression line added to the Bland-Altman plot.

Model extension

To extend the 2 regression equations, we conducted multiple linear regression analysis using separate models for Vo_{2peak}^{cpet} and W_{peak}^{cpet} after visually confirming the linear relations between MSEC and Vo_{2peak}^{cpet} and W_{peak}^{cpet}. We started with a full model that included age, height, weight, and sex in addition to MSEC as predictors and used a stepwise backward selection procedure based on the minimization of Akaike's information criterion (an index of goodness of fit) to select sparse models that best predicted Vo_{2peak}^{cpet} and W_{peak}^{cpet}.[19,21] We repeated the LOA analyses as described above using Vo_{2peak}^{pred} and W_{peak}^{pred} estimates from the extended multivariable models.

Because estimation of model performance is usually over-optimistic when assessed in the sample in which a model is developed, and regression coefficients are typically too large, we performed internal validation by bootstrapping (100 boot-straps) on the full multivariable model (ie, before stepwise selection). Based on this, uniform shrinkage was applied to the regression coefficients of the reduced model.[19] The resulting regression equations for W_{peak}^{pred} and Vo_{2peak}^{pred} are presented as a nomogram.

Clinical performance

We evaluated the clinical performance of the original and the newly developed prediction model. For Vo_{2peak}, the percentage of participants whose Vo_{2peak} was misclassified by >1 metabolic equivalent (MET) value (taken as $3.5mL \cdot kg^{-1} \cdot min^{-1}$) was calculated. For W_{peak}, we evaluated clinical performance on the basis of exercise prescription. A typical exercise prescription at moderate to high intensity would be targeted at 60% of W_{peak}. Therefore, we calculated the number of participants for whom an exercise prescription of 60% W_{peak}^{pred} fell within ±10 percentage point range of the measured 60% W_{peak}^{cpet}.

Sensitivity analyses

We performed 2 sensitivity analyses: The first included only patients with a smaller than 7-day interval between the 2 tests to assess the effect of time between tests on the outcome. The second included patients with breast cancer only (the largest uniform subgroup in the sample) to assess the effect of heterogeneity of cancer diagnoses in our sample. All analyses were performed using the statistical software R version 3.2.1.[a]

Results

Sample characteristics

Of the 283 participants, 68 (24%) were men. The mean age was 53±11 years, and the majority (162, 57%) were breast cancer survivors (table 1).

External validation

Using the equation for Vo_{2peak}, as published by De Backer et al[12] (6.7*MSEC+356.7), the ICC of Vo_{2peak}^{pred} with Vo_{2peak}^{cpet} was .61 (95% confidence interval [CI], .41−.74). Vo_{2peak}^{pred} showed a bias of 190mL/min as compared with Vo_{2peak}^{cpet}, which likely reflected the lower mean Vo_{2peak} in our sample than in the derivation sample ($21.7mL \cdot kg^{-1} \cdot min^{-1}$ vs $29.4mL \cdot kg^{-1} \cdot min^{-1}$). After calibration-in-the-large, the 5% LOA were ±705mL/min. There was a negative error correlation: $r = -.22$ (fig 1A).

The ICC of W_{peak}^{pred} with W_{peak}^{cpet} was .73 (95% CI, .67−.78) using the equation for W_{peak} as published by De Backer et al (0.65*MSEC−3.88). The Bland-Altman analysis indicated a small bias of 5W, despite a larger difference in mean W_{peak} between our sample and the sample in which the equation was derived (141W vs 183W). After calibration-in-the-large, 95% LOA were ±59W, and there was a negative error correlation: $r = -.14$ (fig 1B).

Model extension

The final multivariable model for the prediction of Vo_{2peak} included weight and sex in addition to the MSEC (table 2). The explained variance (R^2) of this model was .58, and the ICC of Vo_{2peak}^{pred} with Vo_{2peak}^{cpet} was .73 (95% CI, .67−.78). Using this model for prediction, LOA improved to ±608mL/min, but the negative error correlation remained: $r = -.39$ (see fig 1A). After shrinkage, the equation was as follows: 676.8+3.92*MSEC+5.02*weight−327.6*female (using 1 for "female" and 0 for "male"). The equation is presented as a nomogram (fig 2A).

Table 1 Descriptive statistics of the sample (N=283)

Variable	Value
Sex: male	68 (24)
Age (y)	53±11
Height (cm)	170±9
Body weight (kg)	77.6±14.6
Cancer type	
Breast cancer	162 (57.2)
Colon cancer	49 (17.3)
Lymphomas	56 (19.8)
Ovarian cancer	8 (2.8)
Cervix cancer	4 (1.4)
Testis cancer	4 (1.4)
Treatment	
Chemotherapy	283 (100)
Radiotherapy	123 (43)
Surgery	227 (80)
Stem cell transplantation	32 (11)
Immunotherapy	51 (18)
Hormone therapy	114 (40)
Weeks since treatment	8±3.7
Vo_{2peak} (mL/min)	1713.7±476.0
Vo_{2peak} (mL·kg^{-1}·min^{-1})	21.7±5.7
W_{peak} (W)	141±43.1
MSEC (W)	231±60.4

NOTE. Values are mean ± SD or n (%).

For W_{peak}, the final model included height, sex, and age in addition to the MSEC (see table 2). The R^2 of this model was .67. The ICC of W_{peak}^{pred} with W_{peak}^{cpet} was .81 (95% CI, .76−.84). Compared to the original equation, LOA improved to ±48W, but the error correlation was larger: $r=-.33$ (see fig 1B). After shrinkage of the coefficients, the equation was 0.33*MSEC+124*height (m)−22.4*female−0.47*age−107. This equation is also presented as a nomogram (fig 2B).

Clinical performance

Using the original equation, 56% of the patients were misclassified by >1MET. An exercise prescription aimed at achieving 60% W_{peak}^{cpet} was inaccurate by >10 percentage points (eg, <50% or >70% of W_{peak}^{cpet}) in 43% of the sample. After calibration-in-the-large, this reduced to 44% and 39% of the patients, respectively. Using the reestimated, multivariable prediction models, the percentage further reduced to 36% and 32%, respectively.

Sensitivity analyses

No significant and meaningful differences in the LOA or clinical applicability were observed when restricting the sample to patients with a measurement interval <7 days (n=109) or breast cancer survivors only (n=139).

Discussion

This study examined the validity and clinical applicability of regression-based estimates of Vo_{2peak} and W_{peak} in cancer survivors by using the SRT. In particular, we evaluated the external validity of previously derived prediction models for this population and aimed to improve predictions by extending the regression models.

Our results confirm the linear relations of MSEC with Vo_2^{peak} and W_{peak} that were also described in previous studies of cancer survivors, patients with type 2 diabetes mellitus, and healthy children and adolescents.[12,13,22] As far as we know, no validation studies have been conducted to externally validate the prediction rules derived in these studies.

The bias observed in the LOA analysis shows that the accuracy of the predicted values Vo_{2peak}^{pred} and W_{peak}^{pred} is affected if the mean values of Vo_{2peak}^{cpet} and W_{peak}^{cpet} in the target population are different from those of the population in which the equation was derived (miscalibration in the large). Although predictions improved by extending the regression models, they are still suboptimal. The agreement between the values as predicted by the extended models and the actual values could be considered sufficiently high at the group level. However, higher agreement (ICCs, >0.9) is usually considered preferable for decision making at the individual level.[23] Also, the LOA, which have a stronger influence on clinical usability than the ICCs, are still wide. This is illustrated by the high percentage of patients that were misclassified by >1MET in the present study.
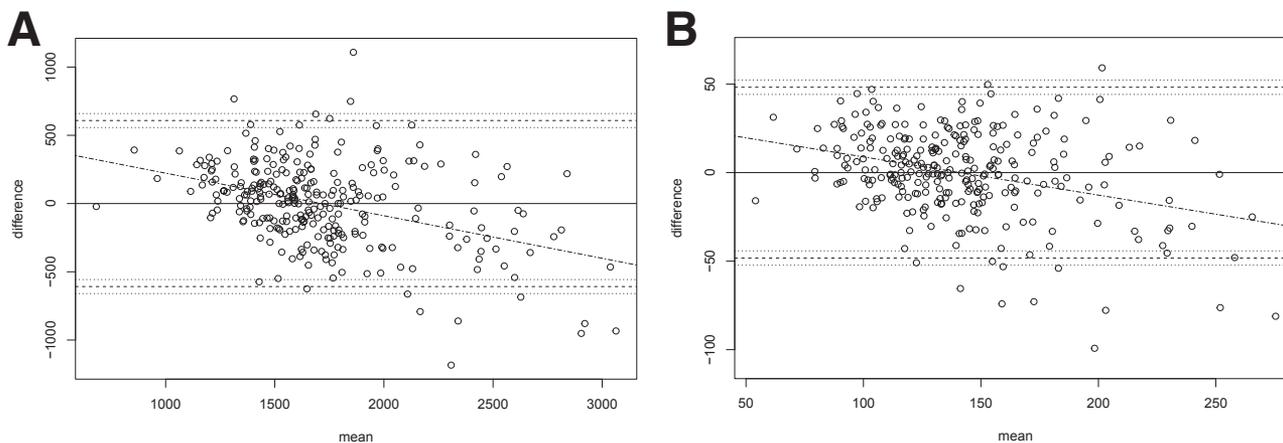

Fig 1 Bland-Altman plots for the estimation of Vo_{2peak} (A) and W_{peak} (B) after reestimation and extension of the prediction model. Dashed lines indicate 95% LOA; dotted lines indicate 95% confidence interval of the limits, and the diagonal line indicates linear regression fit of difference vs mean.

Table 2 Regression coefficients for multivariable linear regression model predicting $V_{O_{2}peak}$ and W_{peak} using the SRT

Variable	β	95% Confidence Interval for β	β After Shrinkage
$V_{O_{2}peak}$			
MSEC	3.97	3.29 to 4.65	3.92
Body weight	5.09	2.37 to 7.80	5.02
Sex: female	−332	−432 to −232	−328
W_{peak}			
MSEC	0.34	0.28 to 0.40	0.33
Age	−0.47	−0.75 to −0.19	−0.47
Height	126	82.1 to 169	124
Sex: female	−22.6	−31.9 to −13.3	−22.4

In addition to quantification of peak exercise capacity, identification of the limiting system (cardiovascular, pulmonary, musculoskeletal, psychological) and assessment of exercise-induced cardiovascular risks can be of relevance in the context of cancer rehabilitation. Such information cannot be obtained using the SRT. Also, without measuring gas exchange, it can be difficult to ascertain peak performance. Therefore, despite its advantage of being quick and easily applicable, the SRT should not be considered an alternative to a CPET when a valid measurement of $V_{O_{2}peak}$ is needed for an individual patient or when the exercise capacity limiting system needs to be identified for clinical decision making.

As expected, the clinical applicability of the original prediction model for the estimation of W_{peak} in cancer survivors was also insufficient for accurate aerobic exercise prescription (based on a constant percentage of estimated W_{peak}) in our sample. This could be improved considerably by calibration-in-the-large and even further after extending the equation with height, age, and sex. Nevertheless, clinicians should be aware of the possibility of over- or underestimation of exercise capacity when using W_{peak}^{pred} for individual exercise prescription. The observed negative error correlation implies an overestimation of $V_{O_{2}peak}$ and W_{peak} in cancer survivors with lower cardiorespiratory fitness and underestimation in those with high cardiorespiratory fitness. The

presented nomogram (see fig 2) is expected to have sufficient accuracy in about two thirds of cancer survivors.

One could argue on the basis of our results that CPET remains a preferred choice for exercise prescription. However, several studies have shown that even with available CPET data, accurate exercise prescription for cancer survivors, for example, based on the percentage of maximum heart rate, can be challenging because of changes in exercise response.[24-26] Also, repeated testing is required to ensure sufficient overload during the course of the exercise program, and repeated CPETs are difficult to implement in regular care. In a recent study, repeated SRTs was used in combination with Borg scores of perceived exertion to prescribe fixed load endurance exercise during chemotherapy. Patients after this program successfully maintained physical fitness throughout chemotherapy.[27] Clearly, more studies are needed to examine the accuracy of different ways to tailor exercise prescription, and the role of different exercise tests, in cancer survivors.

Study strengths

Strengths of this study include the relatively large sample that allowed for a robust analysis strategy, including sensitivity analyses by test interval and tumor type, and the use of a heterogeneous sample of cancer survivors. Although it is likely that the performance of the extended prediction models will be somewhat less when applied to other patients, our results are expected to translate reasonably to clinical practice because shrinkage was applied to the regression coefficients.[19,21]

Study limitations

This study also had some limitations that should be noted. We used data that were gathered in the context of randomized controlled trials evaluating the effects of exercise interventions in cancer survivors.[15,17] The timing of the tests relative to each other was not fixed, but depended on trial logistics. We tried to limit the potential effect of time between measurements by selecting only those cancer survivors who were tested on the CPET and SRT within a maximum range of 30 days. Because the sensitivity analysis in survivors with a maximum time interval between the tests of 7 days showed comparable results, we believe that the
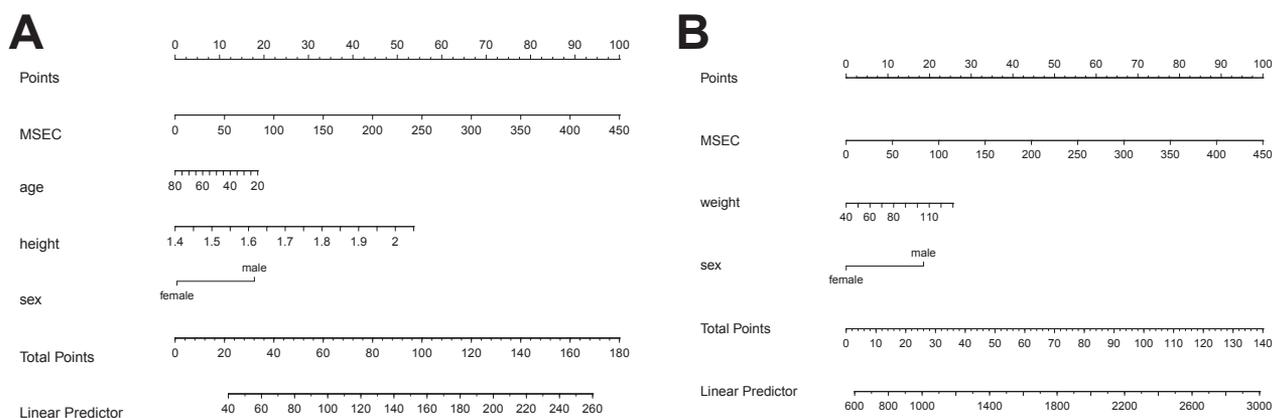
Fig 2 Nomograms for the prediction of W_{peak} (A) and $V_{O_{2}peak}$ (B). The value of each variable corresponds to a number of points on the top scale. Points are summed. The total points can then be used to read the linear predictor (estimated W_{peak} or $V_{O_{2}peak}$) from the bottom scale. For example, for a patient who achieves an MSEC of 250W (56 points), weighs 86kg (13 points), and is a female (0 points), the total points are 69, which corresponds to a linear predictor of ~1760mL/min.

timing had limited effect on our findings. Second, although the exercise tests were carried out according to standardized protocols, the SRT measurements were conducted by different physical therapists offering the exercise programs. This may have introduced random error in the measurements, reducing the observed validity of the SRT, but it does resemble the way the SRT will be used in clinical practice.

The sample was limited to cancer survivors who had recently completed treatment. It is unclear whether the results are generalizable to cancer survivors during active treatment. Factors such as fatigue, anxiety, nausea, or lack of motivation may be more prominent during active treatment, and may affect the workload achieved on the SRT more profoundly than that on the CPET, because of the short duration and steep increments used in the SRT. It is conceivable that this will influence the relation of the MSEC with Vo_{2peak} and W_{peak}. Future research should further explore these issues.

For cancer survivors who completed treatment, the presented nomogram provides added value to support personalized endurance exercise intensity prescription based on the SRT. However, the nomogram-predicted values should be considered a starting point and further adaptation (eg, using Borg scores) may still be necessary for individual patients.

Conclusions

The results of this study suggest that although predictions of Vo_{2peak} and W_{peak} based on the SRT could be considered acceptable at the group level, they do not provide sufficiently accurate estimations of endurance exercise capacity in individual cancer survivors. Nevertheless, the prediction of W_{peak} using the presented multivariable prediction rule or the associated nomogram can be used cautiously (eg, supplemented with a Borg score) to aid endurance exercise prescription in this population.

Supplier

a. R version 3.2.1; R Foundation for Statistical Computing.

Keywords

Exercise test; Exercise therapy; Neoplasms; Rehabilitation; Validation studies

Corresponding author

Martijn M. Stuiver, PhD, The Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Physiotherapy, Plesmanlaan 121, Amsterdam 1066CX, The Netherlands. *E-mail address:* m.stuiver@nki.nl.

Acknowledgments

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