“Development of a reference chart for monitoring aerobic capacity during multidisciplinary medical specialist oncology rehabilitation”

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ABSTRACT

Background

Cancer survivors may experience reduced aerobic capacity. The University Medical Center Utrecht (UMCU) offers multidisciplinary medically specialized oncology rehabilitation programs (MSOR) which entails, among other interventions, an exercise program called OncoFit. Gaining insight in the aerobic capacity over the course of the MSOR could lead to more motivation and the ability to tailor the program to the individual. However, no tools exist yet to provide this insight.

Aim

To develop a reference chart to monitor aerobic capacity of patients who have been treated for cancer, during multidisciplinary medical specialist oncology rehabilitation.

Methods

Data is retrospectively collected from participants of the MSOR program at the UMCU, following a medical specialistic oncology treatment. The aerobic capacity was measured using a Steep Ramp Test (SRT). The models were created using Generalized Additive Models for Location, Scale, and Shape. The reference chart was created from the models to display the aerobic capacity of population centiles over the course of the MSOR.

Results

76 patient records with 169 SRTs (2-5 measurements per participant) were analyzed. The reference chart showed an increase in aerobic capacity, with patients with higher baseline SRT improving more than those with lower baseline SRT. Three patient cases were plotted on the chart to demonstrate its clinical potential.

Conclusion and key findings

The developed reference chart may be a valuable tool for monitoring the aerobic capacity of patients who received treatment for cancer during the MSOR. It assists clinicians in tailoring the program to individual patients and aids patients in goal setting and tracking progress, potentially enhancing motivation. Future studies could focus on developing reference charts that consider different patient characteristics, including cancer type and treatment, as well as different exercise modalities.

Keywords: Reference chart; multidisciplinary medically specialized oncology rehabilitation program; aerobic capacity; monitoring; Generalized additive models for location scale and shape

INTRODUCTION

In the Netherlands the incidence of all types of cancer was 123,672, with a prevalence rate of 379,454 in 2021[1]. These cancer rates are growing, in 2040 it is anticipated to reach 28.4 million new cases of cancer worldwide, a rise of 47 percent from 2020[2]. However, due to improved diagnosis and treatment modalities, cancer survival rates are also growing, which results in an increase in the number of cancer survivors[3,4]. These survivors, unfortunately, may endure long-term side effects and repercussions from the cancer treatment. Depression, anxiety, cancer-related fatigue (CRF), and reduced physical functioning are long-term and late effects of cancer treatment that should be considered[5–10].

An important determinant of the level of physical functioning is aerobic capacity. Aerobic capacity is defined as the maximum amount of oxygen that can be taken in, transported and used by the muscles during prolonged exercise[11]. It has been shown that the aerobic capacity, as measured by the maximal oxygen consumption (VO_{2max}), can drastically be impaired in patients who received cancer treatment[12]. This is concerning, given the evidence indicating that a poor VO_{2max} is related to a poorer quality of life, treatment induced cardiotoxicity, and an increased risk of cancer-related mortality[13–17].

The University Medical Center Utrecht (UMCU) offers multidisciplinary medically specialized oncology rehabilitation programs (MSOR) under the supervision of a rehabilitation physician[18]. Along with interventions from occupational therapists, psychologists, dieticians, and social workers, MSOR also entails a tailored physical exercise program called OncoFit. The OncoFit focuses on enhancing physical strength and aerobic capacity under the supervision of a physical therapist. Evidence shows that aerobic training, strength training, or a combination of both can positively influence physical functioning and mental health in patients after cancer treatment[6,19].

Despite the scientific advice for physical activity, less than 30% of cancer survivors manage to meet the current physical activity guidelines[20]. Depression, fears, lack of knowledge and awareness of exercise programs, and no motivation were identified as psychological barriers for physical activity for cancer survivors[21]. According to the health belief model (HBM), patients are thought to be willing to adopt healthy behavior changes if they improve motivation[22]. Facilitators for improving motivation for a physical exercise program for cancer survivors were if it involved personal goal setting, if it was tailored to the individual, and if it included feedback[23]. Being able to monitor the aerobic capacity over the course of their rehabilitation program could be a solution to provide in these facilitators.

However, no tools exist yet to do so. A reference chart is one tool that might be used to monitor this. Based on the aerobic capacity of previous participants, this tool would display the estimated course of aerobic capacity of a patient taking part in the MSOR. Therefore, using the reference chart would allow health care professionals delivering the exercise intervention to tailor the MSOR for the patient. Furthermore, the tool could be used in the personal goal setting of patients and to get feedback on their progress[24,25]. Hence, patients' motivation could be increased by a reference chart[30,31]. A similar reference chart has been developed to monitor cancer-related fatigue of individuals living with and beyond cancer, participating in a 3-months cancer specific exercise program[26]. The aim of this study is to develop a reference chart to monitor aerobic capacity of patients who have been treated for cancer, during multidisciplinary medical specialist oncology rehabilitation.

METHODS

Study design and participants

The study was a quantitative retrospective dossier study. The electronic patient database (EPD) was retrospectively accessed to obtain the source data by a researcher not involved in patient care. Data is collected from individuals participating in the MSOR program at the UMCU, following a medical specialistic oncology treatment. To be included in the MSOR at least one physical and one psychological complaint needed to be present. There were no cancer-type restrictions. Data were only extracted from the EPD if participants took part in the MSOR and if at least two measurements of the Steep Ramp Test (SRT) were available. Furthermore, in accordance with the duration of the MSOR lasting for twelve weeks, data beyond 84 days from the start of an individual's MSOR was excluded in the analysis. Data was also not extracted from participants who objected to the use of their medical data for research purposes.

Program Description

The MSOR lasts for twelve weeks. As stated earlier, along with interventions from occupational therapists, psychologists, dieticians, and social workers, the MSOR also entails a tailored physical exercise program called OncoFit. This program focuses on enhancing physical strength and aerobic capacity under the supervision of a physical therapist. The Oncofit is performed at least once per week, but usually twice. As part of usual medical care, various health care professionals made multiple measures throughout the MSOR on various occasions.

Aerobic Capacity-measurement and Data Collection

The main parameter/endpoint being analyzed is the aerobic capacity measured over the course of the MSOR. Whereas the Cardiopulmonary Exercise Testing (CPET) is been considered the golden standard to measure aerobic capacity, the SRT seems to be a valid tool to estimate aerobic capacity in survivors of cancer[27]. The SRT has a Minimal Important Change (MIC) of 0.26 W/kg for patients who were treated for cancer[27]. The SRT was performed according to the protocol described by Meyer et al. (1996)[28]. First, participants were instructed on the test. Next, they performed a three-minute warming up with a work rate of 0 Watt. After the warming-up, the test started with a work rate of 25 Watts. The work rate was then continuously increased by 25 Watts every ten seconds. Participants were instructed to keep cycling until exhaustion, with a pedaling frequency of at least 60 rotates per minute (RPM). The test stopped if the RPM dropped below 60. The aerobic capacity was determined using the maximum achieved Watts (SRT-WRpeak)[27]. According to daily care procedures, the aerobic capacity was measured at baseline (T0), after six weeks (T1), and after twelve weeks when the MSOR ends (T2). Demographic and diagnosis information were collected at T0 and consists of: age, sex, length (cm), weight (kg), and type of cancer.

Statistical analysis

Statistical analyses was performed using IBM SPSS Statistics 27 (Version)[29] and R Statistical Software (v4.4.1; R Core Team 2021)[30].

To investigate the distribution of each of the demographic and diagnosis information, exploratory data analysis was performed. When the continuous data followed a normal distribution, it was presented as means with standard deviations (SD). When it did not, it was presented as medians with interquartile ranges. To determine whether continuous variables followed a normal distribution, histograms, P-P plots, and the Shapiro-Wilk test were used. Frequencies and percentages were computed for the categorical variables. In case a participant missed demographic and/or diagnosis information, this was considered as missing at random (MAR). For the missing values multiple imputation (MI) was performed, as MI produces more valid parameter estimates than ad hoc techniques[31].

The statistical models to create the reference chart described the variation of aerobic capacity of patients who received treatment for cancer, over the course of the MSOR. Briefly, a Box-Cox Cole and Green distribution was used to model changes in the median, variance, and skewness for the outcome (aerobic capacity) over time, via Generalized Additive Models for Location Scale and Shape (GAMLSS)[32]. The parameter aerobic capacity was flexibly modeled with cubic splines. The optimal degrees of freedom (knots) for the aerobic capacity was determined using the "find.hyper" function in GAMLSS. We used the ggplot2 package to visualize the 5th, 10th, 25th, 50th, 75th, 90th, and 95th centiles of the model[33].

We examined each model's goodness of fit by calculating the percentage of actual observations which fell below each specified centile in the model. We then performed a Chi-Square goodness-of-fit test on the outcomes of these calculations to conclude whether there is a significant difference between the observed and expected values. If the p-value is greater than 0.05 (not statistically significant), it suggests that there is no significant difference between the observed and expected values. This will indicate a good model's fit. We then carried out sensitivity analyses by modeling aerobic capacity using a limited dataset which contained only one randomly selected observation per individual to examine the potential influence of serially correlated data. We calculated the absolute differences at each time point between the 5th, 10th, 25th, 50th, 75th, 90th, and 95th centile curves generated using the full and limited datasets; a difference of less than 10% was considered acceptable[34]. This analysis has been selected since it is a widely employed method in similar studies[26,34–36].

RESULTS

A total of 289 patient records with SRT measurements conducted between November 2016 and February 2023 were assessed for inclusion. A total of 133 records were excluded from the study due to containing only one SRT measurement. Additionally, 80 records were excluded due to having SRT measurements with a gap of more than 84 days between the baseline and follow-up measurements. This resulted in 76 eligible patient records, with a total of 169 conducted SRTs. The average was 2.2 (range 2-5) measurements per participant. Table 1 presents demographic and diagnosis information.

Table 1: Demographic and diagnosis information. SD = Standard deviation, n = number of individuals, BMI = Body Mass Index

	Total
Age (years, mean ± SD)	47.29 ± 13.107
Sex distribution (n female, %)	49 (64.5)
Body Mass Index (BMI)	25.65
Cancer type (n %)	
- ***Hematologic***	20 (26.3)
- ***Cervical cancer***	14 (18.4)
- ***Breast cancer***	13 (17.1)
- ***Gastrointestinal***	8 (10.5)
- ***Other***	21 (27.6)

Figure 1 depicts the reference chart, which was developed using the method described earlier. The centile curves demonstrated an increase in SRT-WRpeak scores throughout the 84-day duration of the MSOR, signifying an enhancement in aerobic capacity. The median prediction for aerobic capacity improved from approximately 150 SRT-WRpeak at baseline to 200 SRT-WRpeak at 84 days. Additionally, a higher baseline SRT-WRpeak score suggests a greater improvement in aerobic capacity compared to a lower baseline score. The improvement from baseline to 84 days was 31 points for the 10^{th} centile and 66 points for the 90^{th} centile. The lowest centile improved with 0.31 W/kg, surpassing the MIC threshold of the SRT of 0.26 W/kg.

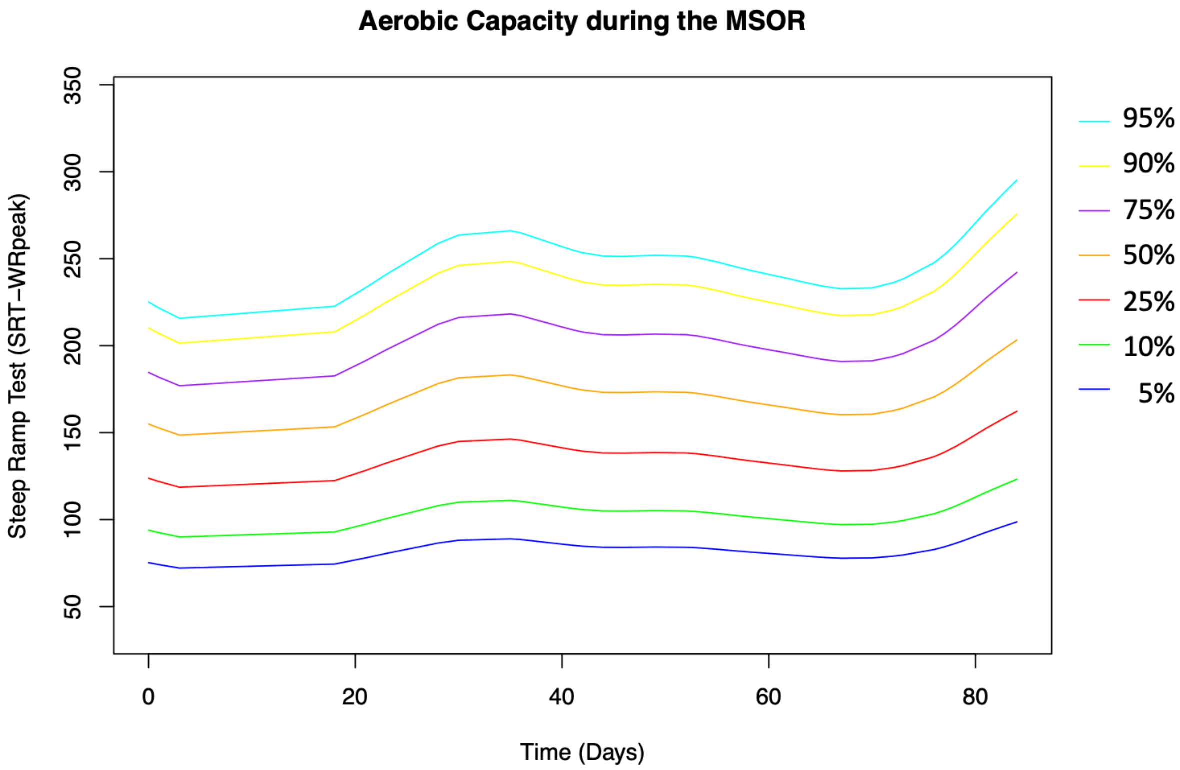

Figure 1: The aerobic capacity reference chart. The 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles are shown. The orange line represents the 50th centile. An increase in SRT-WRpeak implicates an improvement in aerobic capacity. SRT-WRpeak = Steep Ramp Test maximum achieved Watts.

When examining each model's goodness of fit, we calculated the percentage of actual observations which fell below each specified centile in the model. These percentages are depicted in Table 2. The Chi-Square goodness-of-fit test resulted in a p-value of 0.227, meaning there is no significant difference between the observed and expected value. This implicates a good model's fit. During the sensitivity analysis of the reference chart, the centile curves demonstrated validity and robustness. When limiting the dataset to only one observation per patient, the maximum difference between the centiles was 4.23%, which was below the *a priori* 10% threshold for acceptability.

Table 1: Examining model's fit. Values are displayed for the percentage of observations which fell below each model centile. Ideally, 50% of cases would fall below the 50th centile, 75% of cases would fall below the 75th centile, etc. The p-value is calculated using a Chi-Square goodness-of-fit test.

Model centile	% of observations below
5th	6.86
10th	10.86
25th	22.26
50th	50.26
75th	76
90th	89.14
95th	95.43
P-value	**0.227**

Examples of individual patient cases

To demonstrate the potential functionality of the reference chart, three individual patient records were randomly extracted from the dataset and subsequently plotted into the chart (Figure 2). Patient A is a 58 years old female, BMI 24.1, who suffered from uterine cancer. She started around the 10th centile but demonstrated a better trajectory than was predicted, with her last SRT scoring between the 50th and 25th centile. Patient B is a 39 years old female, BMI 29.9, who suffered from breast cancer. Although her baseline SRT score was at the 90th centile, her aerobic capacity development did not meet the predicted level. In fact, her most recent SRT score was closer to the 75th centile, which is significantly lower than her initial score at the 90th centile. Patient C is a 67 years old female who also suffered from breast cancer. Her weight was 64.5kg and her length was not documented. The baseline SRT score for her was approximately at the 5th centile. Her aerobic capacity development aligned closely with predictions, as her most last SRT score also landed around the 5th centile.

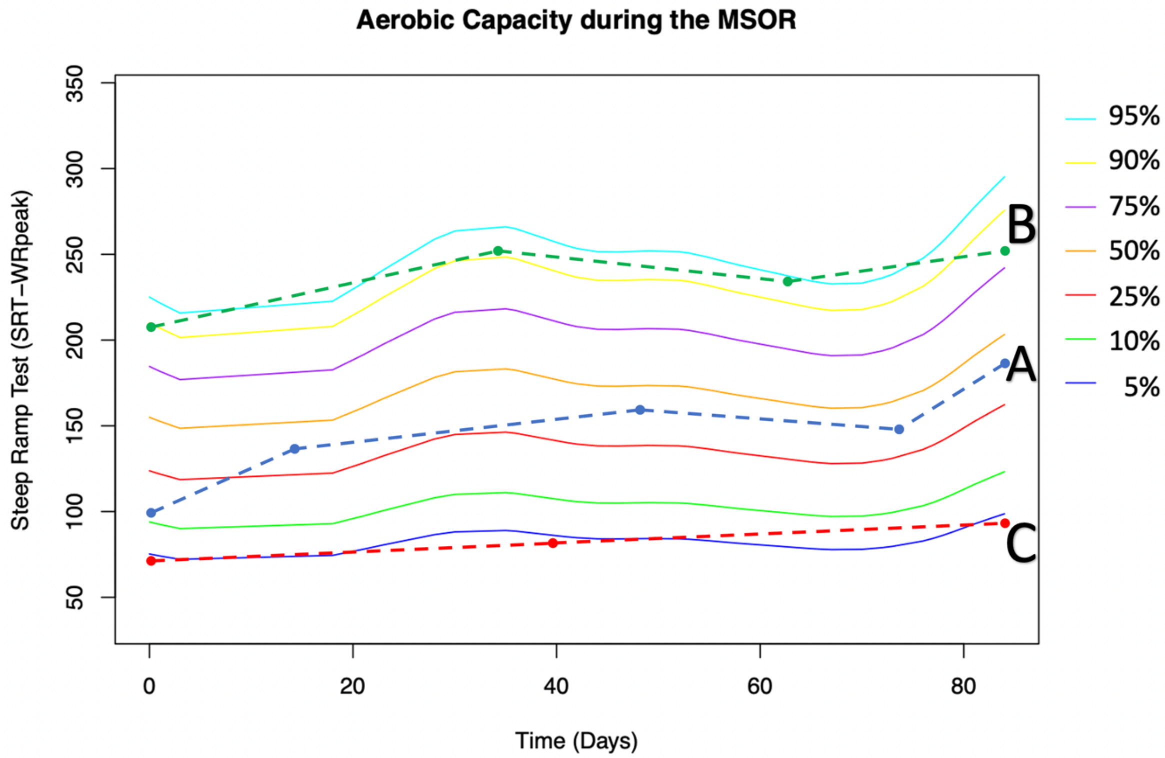

Figure 2: The aerobic capacity reference chart with three individual patient cases. SRT-WRpeak = Steep Ramp Test maximum achieved Watts.

DISCUSSION

This study aimed to develop a reference chart to monitor aerobic capacity of patients who have been treated for cancer, during a 12-weeks MSOR. The resulting reference chart showed improvement on all centiles, although the higher centiles showed greater improvement than the lower centiles.

To our knowledge, this is the first reference chart that enables clinicians to track aerobic capacity during the MSOR. This is considerably relevant as it can aid in tailoring the program's content to the individual patient. A tailored exercise plan may help boost motivation in cancer survivors[23]. Furthermore, the tool could be used in the personal goal setting of patients and to get feedback on their progress, also potentially boosting the motivation in cancer survivors[23,24]. All these factors combined can lead to an increase in the number of cancer survivors meeting the current physical activity guidelines[23-25].

The reference chart developed in this study demonstrates improvement on all centiles, suggesting that aerobic capacity is likely to improve over the course of the MSOR. This finding aligns with expectations, as previous evidence indicates that rehabilitation programs like the MSOR significantly enhance the aerobic capacity of cancer survivors[37]. Our reference charts reveals a more substantial improvement in aerobic capacity among patients with a higher baseline SRT, compared to those with a lower baseline SRT. This finding contradicts previous research and, which suggested that exercise has a greater impact on aerobic capacity in individuals with initially lower levels of aerobic capacity[38]. There could be several reasons for this contradictory result. One possibility is that the sample size in our study differ from those of previous research. Our study had fewer observations than, for example, the study developing a reference chart for monitoring cancer-related fatigue throughout a supervised exercise program, which used a total of 741 observations[26]. This makes our model more sensitive for outliers. Another possibility is that factors such as differences in patient demographics, type of cancer, treatment history and comorbidities contributed to the contradictory findings.

Although the improvement of 0.31 W/kg in the lowest percentile exceeded the MIC of 0.26 W/kg, it is important to acknowledge that the chart may be demotivating for patients with low baseline scores. This is due to the expectation that patients with lower initial scores show smaller improvements compared to those with higher baseline scores. Physical therapists can play a vital role in addressing this situation by explaining that even small improvements are expected and meaningful for patients with low baseline scores. Furthermore, they can emphasize that aerobic capacity is not the sole outcome that may improve. Strength, fatigue levels, and mental health are other aspects that can also show positive changes[6,19,37]. Therefore, highlighting the importance of patients adhering to their rehabilitation program.

The three example cases illustrate three potential scenarios where the reference chart could be useful. Patient A demonstrated a more favorable response to the MSOR than anticipated, as evidenced by her lower baseline SRT centile compared to her last SRT. However, her aerobic capacity remains below the 50th centile, indicating that over 50 percent of all participants have a better aerobic capacity. This result may suggest that it is appropriate to continue with the current treatment plan. Patient B demonstrated a higher aerobic capacity than most participants, starting with a baseline SRT around the 90th centile. However, her latest SRT score indicates a potential stagnation in improvement, as it is around the 75th centile. In this scenario, it may be appropriate for a clinician to intervene and collaborate with the patient to identify the underlying reasons for the stagnation in aerobic capacity and explore potential solutions to address it. Potential solutions could involve modifying the training intensity or frequency, adjusting the patient's personal goals, or exploring external factors that may be contributing to the stagnation. Patient C demonstrated a fairly predicted course of development of aerobic capacity, starting and ending around the 5th centile. Due to her baseline SRT being lower than nearly 95 percent of all participants, her predicted improvement of aerobic capacity was also low. Consequently, setting realistic goals with her clinician and tailoring the MSOR to focus on further improving her aerobic capacity could be of major importance[39].

This study has some strengths. First, the statistical method used to develop the reference chart is a widely employed method in similar studies[26,34–36]. This indicates that the reference chart is built upon a well-established and recognized approach, enhancing the credibility and validity. Second, the reference chart is directly applicable in daily practice as illustrated and explained in the paragraph above. Third, the positive outcomes of both the model's goodness-of-fit analysis and sensitivity analysis provide strong evidence for a valid, robust, and credible reference chart. Fourth, the data was already collected as part of usual medical care by a researcher not involved in patient care. This reduces the likelihood of volunteer bias or research eligibility criteria influencing the results.

This study has some limitations. First, the study's participants comprise a wide range of cancer types and corresponding treatments. The difference between men and women and various age groups and BMIs were also not taken into account in the analysis. Despite this variability, the cohort is analyzed as a whole to maximize the sample size, resulting in a more accurate analysis. However, it is important to consider that the type of cancer and treatment received or patient demographics may impact the results. For instance, a male with lung cancer who underwent a pneumonectomy may face more challenges in improving their aerobic capacity compared to a female with breast cancer who underwent a mastectomy. As more data is collected, personalized predictions and reference charts for aerobic capacity can be developed in the future for participants who share more similar characteristics.

Second, the analysis of the data did not consider any exercise modalities, such as the frequency and intensity of training. Understanding the various exercise modalities and their impact on the course of aerobic capacity could improve patient motivation and adherence to the exercise program. This is crucial, as maintaining higher levels of exercise could potentially lower the risk of cancer death and recurrence. In future research, it may also be beneficial to differentiate between exercise modalities when developing similar reference charts.

CONCLUSION

The reference chart developed in this study may a useful tool to monitor the aerobic capacity of patients who received treatment for cancer, during the MSOR. It provides help for clinicians in tailoring the program to the individual patient. The reference chart also aids patients in their goal setting and in getting feedback on their progress, potentially boosting their motivation. Patients with a higher baseline SRT seemed to improve more than patients with a lower baseline SRT. Future studies could focus on developing reference charts which distinguish between different patient characteristics such as type of cancer and treatment and between different exercise modalities.

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APPENDIX

N/A