PREDICTION OF PHYSICAL OUTCOMES OF THE MULTIMODAL PREHABILITATION PROGRAMME IN PATIENTS WITH COLORECTAL CANCER (PREDICT PREHAB)

Name:	D.H. (Henri) van Dalen
Student number:	6211100
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Supervisor:	E.G.G. (Emiel) Verdaasdonk MD PhD
Institution (internship):	Jeroen Bosch Hospital
Lecturer:	J.M. (Janneke) de Man – van Ginkel RN PhD
Course:	Research Internship 2: Master's Thesis
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Institution:	Utrecht University

ABSTRACT

Title: Prediction of physical outcomes of the multimodal prehabilitation programme in patients with colorectal cancer (PREDICT PREHAB).

Background: Worldwide, colorectal cancer (CRC) has a high incidence. To reduce the postoperative complication rate after CRC surgery, prehabilitation was introduced. Prehabilitation is defined as “the process of enhancing functional capacity of the individual to better withstand the stressor of inactivity”. It is unknown which CRC patients benefit most of the prehabilitation programme.

Aim: To explore which patient factors can predict the physical outcome of a multimodal prehabilitation programme in preoperative patients with CRC.

Methods: A retrospective, single-centre, observational cohort study, including all patients who completed the multimodal prehabilitation programme prior to colorectal tumor resection between October 2018 and March 2020 in a Dutch teaching hospital. The primary study outcome was the change in the six minute walk test (6MWT). The secondary study outcome was the change in the leg press one repetition maximum (1RM). Logistic regression was performed to identify predictors for the physical outcome of the programme.

Results: In total, 89 patients were included in the data analysis. The median (IQR) change in the 6MWT and the 1RM were respectively 36 (39) meters and 21 (18) kilograms. The strongest predictor for a ≥50m change in 6MWT was alcohol consumption, corrected for American Society of Anaesthesiologists (ASA) grade. In the secondary outcome, the strongest predictor for a ≥20kg change in 1RM was the baseline 1RM, corrected for tumor location.

Conclusion and implications of key findings: There were no statistically significant predictors of a ≥50m change in 6MWT. The results of this study should be interpreted with caution because of the small sample size. Alcohol cessation should be kept as part of the prehabilitation programme. Patients with an average baseline 1RM, might benefit more of the programme.

Keywords: prehabilitation, colorectal cancer, physical fitness.

NEDERLANDSE SAMENVATTING

Titel: Voorspellen van fysieke uitkomsten van een multimodaal prehabilitatie-programma bij patiënten met darmkanker.

Achtergrond: Darmkanker komt wereldwijd veel voor. Om complicaties na darmchirurgie te verminderen, is prehabilitatie geïntroduceerd. Prehabilitatie is gedefinieerd als 'een proces om de functionele capaciteit van een individu te verbeteren zodat een periode van inactiviteit beter kan worden doorstaan. Het is niet bekend welke patiënten het meest profiteren van het prehabilitatie-programma.

Doel: Onderzoeken welke patiëntfactoren de fysieke uitkomst van een multimodaal prehabilitatie-programma bij preoperatieve patiënten met darmkanker kunnen voorspellen.

Methode: Een retrospectief, single-center, observationeel cohortonderzoek, waarin alle patiënten in een Nederlands ziekenhuis die tussen oktober 2018 en maart 2020, voorafgaand aan colorectale tumorresectie, het multimodale prehabilitatie-programma hebben voltooid. De primaire uitkomst van het onderzoek was de verandering in de zes minuten looptest (6MWT). De secundaire uitkomst was de verandering in de 'leg press one repetition maximum' (1RM). Er werd logistische regressie gebruikt om voorspellers van de fysieke uitkomst van het programma vast te stellen.

Resultaten: Er werden gegevens van 89 patiënten geanalyseerd. De mediane verandering in de 6MWT en de 1RM was respectievelijk 36 (IQR: 39) meter en 21 (IQR: 18) kilogram. De sterkste voorspeller voor een verandering van ≥50m in de 6MWT was alcoholgebruik, gecorrigeerd voor de American Society of Anaesthesiologists (ASA) klasse. Het uitgangsniveau van de 1RM was voor de secundaire uitkomst de sterkste voorspeller voor een verandering van ≥20kg in de 1RM gecorrigeerd voor tumorlocatie.

Conclusie en implicaties van de belangrijkste bevindingen: Er waren geen statistisch significante voorspellers voor een verandering van ≥50m in de 6MWT. Vanwege de kleine steekproefomvang moeten de resultaten van dit onderzoek voorzichtig worden geïnterpreteerd. Hulp bij het stoppen van alcoholconsumptie zou onderdeel van het prehabilitatie-programma moeten blijven. Patiënten met een gemiddeld 1RM uitgangsniveau lijken meer profijt van het programma te hebben.

Sleutelwoorden: prehabilitatie, darmkanker, fysieke conditie.

1. INTRODUCTION AND RATIONALE

In 2018, a total of 1,849,518 new cases of colorectal cancer (CRC) was reported worldwide (age standardised (world) incidence 19.7 per 100.000)[1]. In 2018, in the Netherlands, 14,921 new cases of CRC were reported (age standardised (world) incidence 37.8 per 100.000)[2]. CRC has a higher incidence among men than in women and 90 percent of the patients is over 55 years old[1,3,4]. The most common symptoms of CRC are a change in bowel habits, blood in the stool, abdominal pain, unintentional weight loss, and fatigue or weakness[5].

The standard curative treatment of CRC is surgical removal of the primary tumor[6]. Colorectal cancer surgery has a complication rate of 33-46.5%[7–11]. Rectal cancer surgery has an even higher complication rate, up to 37.9-49.3%[9,11]. On indication, patients with locally advanced rectal cancer receive radiotherapy or a combination of radiotherapy and chemotherapy as neoadjuvant therapy[6]. The most common postoperative surgical complications are wound complications, clinical anastomotic dehiscence, postoperative haemorrhage, stoma complications, and prolonged ileus[7]. The most common postoperative medical complications are venous thrombosis, and complications in the cardiorespiratory tract, urinary tract, neuropsychiatric tract and gastrointestinal tract[7]. Patient factors associated with higher complication rates are body mass index (BMI)[7], smoking and alcohol consumption[12], comorbidities[7,9], American Society of Anaesthesiologists (ASA) grade ≥3, male sex, age, neoadjuvant therapy, tumor location, and tumor stage (TNM)[9]. Additionally, anaemia and the number of risk factors[8], and poor physical condition[8,13] are patient factors associate with higher complication rates. The occurrence of complications often causes death[7] and is significantly associated with higher hospital costs[9].

In previous studies, prehabilitation significantly improved the perioperative physical condition in older patients undergoing colorectal surgery (measured with the six minute walk test (6MWT))[14,15], and the complication rate in older patients undergoing major abdominal surgery[16]. Prehabilitation is defined as the process of enhancing functional capacity to better withstand the stressor of inactivity[17]. Prehabilitation is prescribed to provide targeted interventions that improve a patient's health to reduce the incidence and the severity of current and future impairments[18]. Prehabilitation programmes nowadays usually have a multimodal approach, starting four weeks before surgery, focussing on physical training by a physiotherapist, nutritional training by a dietician, and in some reports also psychological training by a psychologist[13–15].

A previous multivariable model of predictors of recovery of walking after surgery measured with the 6MWT showed that recovery was significantly poorer in women, subjects aged ≥75, patients with complications, and patients with lack of believe in the role of fitness in recovery[19]. Another study conducted in patients with colorectal surgery for various reasons showed that responsiveness to the prehabilitation programme measured with the 6MWT was higher in men, patients with low baseline functional walking capacity, patients with high and moderate anxiety levels and patients with belief that fitness level affected recovery[20].

However, it remains unknown which patients with colorectal cancer benefit most of the prehabilitation programme. Therefore, the present cohort study was conducted to gain insight in the factors predicting the physical outcome of the prehabilitation programme measured with the 6MWT, in order to contribute to a more patient-tailored prehabilitation programme. The aim of this study was to explore which patient factors can predict the physical outcome of a multimodal prehabilitation programme in preoperative patients with colorectal cancer.

2. METHODS

Population and domain

A retrospective single-centre cohort study was conducted in a large Dutch teaching hospital, using data collected from October 2018 through March 2020 for the quality institute for oncological and palliative research and practice (in Dutch: Integraal Kankercentrum Nederland (IKNL)), and data collected for standard of care and evaluation of the prehabilitation programme (local electronic patient files). A cohort study design was suitable, as the patients were followed over a period of time and multiple variables have been measured[21]. The reporting of this study was guided by the Strengthening the Reporting of OBservational studies in Epidemiology (STROBE) checklist for observational studies[22].

Participants

Patients were referred to the prehabilitation programme and included in this study if they were: a) diagnosed with CRC; b) candidate for colorectal resection; c) at high risk for complications (defined by age ≥65 years and/or ASA grade ≥3); and d) wanted to voluntarily participate in the prehabilitation programme prior to colorectal resection. Patients were not referred to the prehabilitation programme if they were: a) in need for non-elective colorectal resection or; b) semi-elective colorectal resection in case of tumor obstruction; or c) if they were unable to read and/or understand Dutch.

Procedures

The prehabilitation programme which the patients in the present study cohort followed, consisted of an exercise programme, nutritional guidance, guidance on smoking and alcohol cessation, treatment of anaemia, and reducing polypharmacy (≥5 drugs/day) in a four-week period before surgery. The exercise programme had two components: high intensity training focussing on strength and condition, performed three times a week under supervision of a physiotherapist, and low intensity training without supervision in which patients were instructed to walk or bike four times a week for at least one hour. The nutritional guidance focussed on optimizing preoperative nutritional status, including a high-protein diet. A dietician assessed the patients' nutritional status and prescribed a personalised nutritional advice. For smoking and alcohol cessation help was offered at the outpatient clinic. Measurements regarding the nutritional status, and smoking and alcohol habits were performed by a dietician. Anaemia was treated with intravenous iron supplementation. To reduce polypharmacy, a geriatrician was consulted.

The primary study outcome was the change in the 6MWT in meters, calculated between the measurements by the physiotherapists at the start of the prehabilitation programme (t0) and at the end of the prehabilitation programme (t1). The change in the 6MWT was dichotomized to <50 meters and ≥50 meters as this change is found to be a moderate clinically important effect in another population of elderly patients[23]. The secondary study outcome was the change in the one repetition maximum (1RM) in kilograms, also calculated between the measurements at t0 and t1. The change in 1RM was dichotomized to <20kg and ≥20kg.

Data analysis

The total percentage of missing data was 8.3%. Missing data was highly concentrated to the post-test measurements of 6MWT and 1RM. Baseline measurements were more likely to be completed for all patients, as the data collection was embedded in daily practice and the prehabilitation programme suddenly ended due to restrictions regarding the COVID-19 pandemic. Multiple imputation was used to increase power and decrease the risk of bias of the primary analysis due to missing data[24]. The imputation consisted 5 imputation rounds[25]. Post-tests of 6MWT and 1RM were only imputed if the baseline test was performed. The baseline characteristics are presented for the original data only, using median and interquartile range (IQR) for non-normal distributed data. The imputed data was used for the primary and secondary analyses.

The primary analysis was performed as univariable logistic regression. The independent variables used as possible predicting factors for the change in 6MWT were the variables collected at t0 (age, sex, smoking, alcohol consumption, BMI, ASA grade, tumor location, TNM, comorbidities, neoadjuvant therapies, anaemia, baseline 6MWT, baseline leg press 1RM, and the number of risk factors). To explore if the number of present risk factors contributes to predicting the change in the physical outcome of the programme, this number was calculated out of the other baseline variables, counting one point for each variable with increased risk: age >70 years, male sex, current smoking, alcohol consumption >2 units per day, BMI <18,5 or ≥25 kg/m2, ASA grade ≥3, rectal tumor location, TNM 4, present comorbidities, present neoadjuvant therapies, and present anaemia (hemoglobin <6.8

mmol/L). Assumptions for logistic regression were checked visually. In case of nonlinearity with the log odds, continuous variables were transformed into categorical variables.

The secondary analysis was performed as multivariable logistic regression. To select the independent variables to include in the final multivariable model, a two-step procedure was handled. In the first step, four subsets of independent variables were made based on the following categories: demography (age, sex), lifestyle (smoking, alcohol consumption, BMI, and baseline 6MWT), CRC related (neoadjuvant therapies, tumor location and TNM), and comorbidity (comorbidities, ASA grade, and anaemia). The number of risk factors was not included as independent variable in multivariable logistic regression as this variable was constructed out of the other variables. The strongest associated independent variable of each category was selected as independent variable in the multivariable model. In the second step, the multivariable model was fitted, using a manual stepwise backward selection. The results of the univariable logistic regression analysis are presented for the pooled imputed data only, using Rubin's Rules (RR). The results of the multivariable logistic regression were pooled partly using RR and partly using the median *p* rule[26].

A statement that the study was not covered by the Medical Research Involving Human Subjects Act was obtained from the Medical Research Ethics Committee Brabant. The study was conducted according to the principles of the declaration of Helsinki (version October 2013). As the prehabilitation programme was part of the standard of care, it was subject to the Medical Treatment Contracts Act (In Dutch: Wet op de Geneeskundige Behandel Overeenkomst (WGBO)). All analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (Armonk, New York, USA: IBM corp.). Statistical significance was accepted at a *p* value of <.05.

3. RESULTS

In total, 99 patients were referred to the prehabilitation programme. The final data analysis included 89 patients. Reasons for not meeting the inclusion criteria were no diagnosis of CRC (n=7), not being at high risk for complications (age <65 and ASA grade <3) (n=2), and not being candidate for colorectal resection (n=1). The inclusion is summarized in figure 1.

Figure 1 around here

The median age was 75.07 years (IQR, 10) and 47 (52.8%) patients were men. The median BMI was 26.22 kg/m^2 (IQR, 5.22). ASA grade 2 or 3 was present in 83 (93.2%) patients, and 28 (31.5%) patients had anaemia. Primary colon carcinoma was present in 62 (69.7%) patients, and 77 (86.5%) patients consumed no alcohol or <2 units of alcohol/day. The number of risk factors was calculated for 82 patients, of whom 71 (86.6%) had a cumulative of 2-6 risk factors. The median baseline 6MWT was 450 meters (IQR, 128) and the median baseline 1RM was 116.5 kg (IQR, 41). The baseline characteristics are summarised in table 1.

<u>Table 1 around here</u>

The median post-test of the 6MWT was 484 meters (n=57, IQR 124). The median difference of the 6MWT between t0 and t1 was 36 meters (n=57, IQR 39). A total of 17 (29.8%) patients increased ≥50m in 6MWT. The median time between t0 and t1 was 28 days (IQR 10). The median post-test of the 1RM was 150 kg (n=59, IQR 68). The median difference of the 1RM between t0 and t1 was 21 kg (n=59, IQR 18). A total of 32 (54.2%) patients increased ≥20kg in 1RM. The median time between t0 and t1 was 29 days (IQR 10). The pre- and post-tests are summarized in table 2.

<u>Table 2 around here</u>

The median count of patients who increased ≥50m in 6MWT in the imputed datasets was 24 (31.2%). A univariable logistic regression analysis showed that sex, alcohol consumption, ASA grade, and tumor location were the strongest associated independent variables to improve ≥50m in 6MWT in each prespecified category. Women were less likely to improve ≥50m (OR, .368; 95% CI, .121–1.123; *p*=.079). Patients with an alcohol consumption of 2-6 units per day at baseline were more likely to improve ≥50m, compared to patients with no alcohol consumption at baseline (OR, 4.134; 95% CI, .873–19.573; *p*=.074). Patients with ASA grade 3-4 (OR, 2.298; 95% CI, .703–7.511; *p*=.164) and patients with rectal cancer were also more likely to improve ≥50m in 6MWT (OR, 2.711; 95% CI, .679–10.830; *p*=.152).

A multivariable logistic regression analysis with the strongest associated independent variables showed that the strongest predictor for a ≥50m change in 6MWT was alcohol consumption (*p*=.075). The odds-ratio (95% CI) to improve ≥50m for patients consuming 2-6 units of alcohol per day versus no alcohol consumption was 5.681 (1.038–31.079) (*p*=.045), adjusted for ASA grade. The results of the uni- and multivariable regression analysis are summarized in table 3.

<u>Table 3 around here</u>

The median count of patients to increase ≥20kg in 1RM in the imputed datasets was 49 (55.7%). A univariable logistic regression analysis of the secondary outcome showed that age, baseline 1RM, present anaemia, and tumor location were the strongest associated independent variables to improve ≥20kg in 1RM in each prespecified category. The odds to improve ≥20kg decreased per year of age (OR, .942; 95% CI, .864–1.028, *p*=.176). Patients with a baseline 1RM of 101-150kg were more likely to improve ≥20kg compared to patients with a baseline 1RM of ≤100kg (OR, 3.263; 95% CI, .920–11.570; *p*=.066). Patients with anaemia were less likely to improve ≥20kg (OR, .543; 95% CI, .213–1.385; *p*=.201) and patients with rectal cancer were more likely to improve (OR, 2.308; 95% CI, .735–7.243; *p*=.149).

A multivariable logistic regression analysis with the strongest associated independent variables of the secondary outcome showed that the strongest predictor for a ≥20kg change in 1RM was the baseline 1RM (*p*=.018). The odds-ratio (95% CI) to improve ≥20kg for patients with a baseline 1RM of 101-150kg versus ≤100kg was 3.539 (.908 – 13.787) (*p*=.067), adjusted for tumor location. The results of the uni- and multivariable regression analysis are summarized in table 4.

<u>Table 4 around here</u>

4. DISCUSSION

This study was conducted to provide insight in the factors predicting the physical outcome of the prehabilitation programme. The results of this study showed no statistically significant predictors for a change of ≥50m in 6MWT. A higher odd for improving ≥50m was seen for patients with an alcohol consumption of 2-6 units/day compared to patients who consume <2 units/day, corrected for ASA grade. The secondary outcome analyses showed that the baseline 1RM is a significant predictor for a change of ≥20kg in 1RM, corrected for tumor location. Patients with a baseline 1RM of 101-150kg were more likely to improve ≥20kg compared to a baseline 1RM of ≤100kg.

Alcohol is known for its adverse health effects and adverse effects on the cardiovascular system[27]. Therefore, a possible confounding factor is that patients who cut down alcohol consumption during the preoperative phase might relatively benefit more than patients who already did consume <2 units of alcohol per day. Alcohol cessation may thus be an important factor for patients with an alcohol consumption of ≥2 units/day, in order to acquire a better physical fitness. On the other hand, it is known that people who consume alcohol may be physically more active than non-drinkers[28] and might therefore be more responsive to training. Alcohol consumption or cutting down alcohol consumption has not previously been associated with a better response to a prehabilitation programme. Previous studies though have identified alcohol consumption as a risk factor for developing postoperative complications[8,12].

Previous research showed that responsiveness for change in 6MWT during a prehabilitation programme in a comparable population was negatively influenced by female sex, higher baseline 6MWT, anxiety and lack of belief that fitness level affected recovery[20]. Unfortunately, anxiety and belief in the programme have not been measured in our study cohort. In the present study, sex was the strongest demographic predictor for a ≥50m increase on the 6MWT in the univariable regression analysis, showing lower odds for female sex. Patient factors associated with poorer recovery of physical fitness after surgery measured with the 6MWT were female sex, age ≥75, high baseline values of 6MWT and higher BMI[19]. With regard to the secondary outcome in the present study, patients with an average baseline 1RM showed a better response to the current prehabilitation programme.

This study has several strengths and limitations. The first strength is the use of the 6MWT as primary study outcome. The 6MWT is a simple and low-cost, validated exercise test and is widely used as indicator for physical fitness for surgical patients[29–31]. A second strength is the use of a clinical relevant cut-off point, based on a moderate clinical difference of the 6MWT[23]. The third strength is the clinical relevance and actuality of the topic, finding ways to prevent colorectal surgery complications and reduce healthcare costs through patient-centred care. The first, and most important limitation of this study is the small sample size. Due to the restrictions regarding the COVID-19 pandemic, the count of post-test measurements was lower than expected. Also, the occurrence of a ≥50m increase in 6MWT was lower than expected, resulting in a lower event rate, compromising the number of events per variable. To increase the power of this complete case analysis, and reduce the risk of bias, a multiple imputation was performed[24]. Taking into account the broad 95% confidence intervals of the odds-ratios as seen in both the primary and secondary analyses of the primary and secondary outcome, the results may still be biased and the odds-ratios may be overestimated due to the small sample size[32]. Second, the study sample was not a random sample. Patients were selected for participation in the prehabilitation programme, based on a high complication risk. However, patient characteristics are comparable to other prehabilitation studies[8,13,19]. Finally, the voluntary aspect of the prehabilitation programme possibly tends to provide a sample with more motivated patients and patients with more belief that fitness level affects recovery. Hence, a random sample of patients will also be subject to this issue, as any prehabilitation programme will be on a voluntary basis.

Future research focussing on predicting patient factors for the response on prehabilitation programmes should contain larger samples, in order to provide more reliable results of regression analyses. Also, in a larger sample, a linear or multinomial logistic regression might be used to provide insight in those patients who did improve just not enough to reach the cut-off point. Results of linear or multinomial logistic regression analyses can be used to assess more indicators for adapting the prehabilitation programme and develop a more patient tailored prehabilitation programme. Furthermore, with a larger sample size, additional patient factors like anxiety and belief in the programme, and alcohol use at the end of the programme can be included as possible predictor variables. In order to enhance the prehabilitation programme, the physical tests could be used as a first indicator for adapting the training method (e.g. an extended training programme for patients with a low baseline 1RM and a small improvement during the training period or an abbreviated training programme for patients with an average baseline 1RM and a moderate improvement during the training period). As the physical tests are intermediate outcomes, it is also recommendable to gain insight in the predicting factors for the response to a prehabilitation programme in association with the peri- and postoperative complication rate and recovery.

In conclusion, based on the results of this small sample study, it is not possible to clearly identify patient factors with a greater probability to a better response on the prehabilitation programme. However, alcohol cessation should be kept as part of the prehabilitation programme and patients with an average baseline 1RM might benefit more of the prehabilitation programme.

5. REFERENCES

1. International Agency for Research on Cancer. World factsheet Globocan 2018 [Internet]. 2018 [cited 2019 Sep 10]. Available from: https://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf

2. International Agency for Research on Cancer. Colorectal cancer factsheet Globocan 2018 [Internet]. 2018 [cited 2019 Oct 9]. Available from: http://gco.iarc.fr/today/data/factsheets/cancers/10_8_9-Colorectum-fact-sheet.pdf

3. International Agency for Research on Cancer. The Netherlands factsheet Globocan 2018 [Internet]. 2018 [cited 2019 Sep 10]. Available from: http://gco.iarc.fr/today/data/factsheets/populations/528-the-netherlands-fact-sheets.pdf

4. Oncoline. Landelijke richtlijn colorectaal carcinoom [Internet]. 2014 [cited 2019 Sep 17]. Available from: https://www.oncoline.nl/colorectaalcarcinoom

5. NHS. Symptoms bowel cancer [Internet]. 2016 [cited 2019 Sep 24]. Available from: https://www.nhs.uk/conditions/bowel-cancer/symptoms/

6. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol. 2016;27(8):1386–422.

7. Alves A, Panis Y, Mathieu P, Mantion G, Kwiatkowski F, Slim K. Postoperative mortality and morbidity in French patients undergoing colorectal surgery: Results of a prospective multicenter study. Arch Surg. 2005;140(3):278–83.

8. van Rooijen S, Carli F, Dalton SO, Johansen C, Dieleman J, Roumen R, et al. Preoperative modifiable risk factors in colorectal surgery: an observational cohort study identifying the possible value of prehabilitation. Acta Oncol (Madr). 2017;56(2):329–34.

9. Govaert JA, Fiocco M, Van Dijk WA, Scheffer AC, De Graaf EJR, Tollenaar RAEM, et al. Costs of complications after colorectal cancer surgery in the Netherlands: Building the business case for hospitals. Eur J Surg Oncol. 2015;41(8):1059–67.

10. Biondo S, Parés D, Frago R, Martí-Ragué J, Kreisler E, De Oca J, et al. Large bowel obstruction: Predictive factors for postoperative mortality. Dis Colon Rectum. 2004;47(11):1889–97.

11. van der Sijp MPL, Bastiaannet E, Mesker WE, van der Geest LGM, Breugom AJ, Steup WH, et al. Differences between colon and rectal cancer in complications, short-

term survival and recurrences. Int J Colorectal Dis. 2016;31(10):1683–91.

12. Sørensen LT, Jørgensen T, Kirkeby LT, Skovdal J, Vennits B, Wille-Jørgensen P. Smoking and alcohol abuse are major risk factors for anastomotic leakage in colorectal surgery. Br J Surg. 1999;86(7):927–31.

13. Chen BP, Awasthi R, Sweet SN, Minnella EM, Bergdahl A, Santa Mina D, et al. Four-week prehabilitation program is sufficient to modify exercise behaviors and improve preoperative functional walking capacity in patients with colorectal cancer. Support Care Cancer . 2017;25(1):33–40.

14. Li C, Carli F, Lee L, Charlebois P, Stein B, Liberman AS, et al. Impact of a trimodal prehabilitation program on functional recovery after colorectal cancer surgery: A pilot study. Surg Endosc. 2013;27(4):1072–82.

15. Gillis C, Li C, Lee L, Awasthi R, Augustin B, Gamsa A, et al. Prehabilitation versus rehabilitation: A randomized control trial in patients undergoing colorectal resection for cancer. Anesthesiology. 2014;121(5):937–47.

16. Barberan-Garcia A, Ubré M, Roca J, Lacy AM, Burgos F, Risco R, et al. Personalised Prehabilitation in High-risk Patients Undergoing Elective Major Abdominal Surgery : A Randomized Blinded Controlled Trial. Ann Surg. 2018;267(1):50–6.

17. Topp R, Ditmyer M, King K, Doherty K, Hornyak J. The effect of bed rest and potential of prehabilitation on patients in the intensive care unit. AACN Clin Issues. 2002;13(2):263–76.

18. Silver JK, Baima J. Cancer prehabilitation: An opportunity to decrease treatment-related morbidity, increase cancer treatment options, and improve physical and psychological health outcomes. Am J Phys Med Rehabil. 2013;92(8):715–27.

19. Carli F, Charlebois P, Stein B, Feldman L, Zavorsky G, Kim DJ, et al. Randomized clinical trial of prehabilitation in colorectal surgery. Br J Surg. 2010;97(8):1187–97.

20. Mayo NE, Feldman L, Scott S, Zavorsky G, Kim DJ, Charlebois P, et al. Impact of preoperative change in physical function on postoperative recovery: Argument supporting prehabilitation for colorectal surgery. Surgery . 2011;150(3):505–14.

21. Euser AM, Zoccali C, Jager KJ, Dekker FW. Cohort studies: Prospective versus retrospective. Nephron - Clin Pract. 2009;113(3).

22. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)

statement: Guidelines for reporting observational studies. PLoS Med. 2007;4(10):1623–7.

23. Perera S, Mody SH, Woodman RC, Studenski SA. Meaningful change and responsiveness in common physical performance measures in older adults. J Am Geriatr Soc. 2006;54(5):743–9.

24. Donders ART, van der Heijden GJMG, Stijnen T, Moons KGM. Review: A gentle introduction to imputation of missing values. J Clin Epidemiol. 2006;59(10):1087–91.

25. Schafer JL. Multiple imputation: A primer. Stat Methods Med Res. 1999;8(1):3–15.

26. Eekhout I, Van De Wiel MA, Heymans MW. Methods for significance testing of categorical covariates in logistic regression models after multiple imputation: Power and applicability analysis. BMC Med Res Methodol. 2017;17(1):1–12.

27. Piano MR. Alcohol's Effects on the Cardiovascular System. Alcohol Res. 2017;38(2):219–41.

28. Piazza-Gardner AK, Barry AE. Examining physical activity levels and alcohol consumption: Are people who drink more active? Am J Heal Promot. 2012;26(3):95–105.

29. Cataneo DC, Kobayasi S, De Carvalho LR, Paccanaro RC, Cataneo AJM. Accuracy of six minute walk test, stair test and spirometry using maximal oxygen uptake as gold standard. Acta Cir Bras. 2010;25(2):194–200.

30. Moriello C, Mayo NE, Feldman L, Carli F. Validating the Six-Minute Walk Test as a Measure of Recovery After Elective Colon Resection Surgery. Arch Phys Med Rehabil. 2008;89(6):1083–9.

31. American Thoracic Society. ATS Statement : Guidelines for the Six-Minute Walk Test. Am J Respir Crit Care Med. 2002;166:111–7.

32. Van Smeden M, De Groot JAH, Moons KGM, Collins GS, Altman DG, Eijkemans MJC, et al. No rationale for 1 variable per 10 events criterion for binary logistic regression analysis. BMC Med Res Methodol. 2016;16(1):1–12.

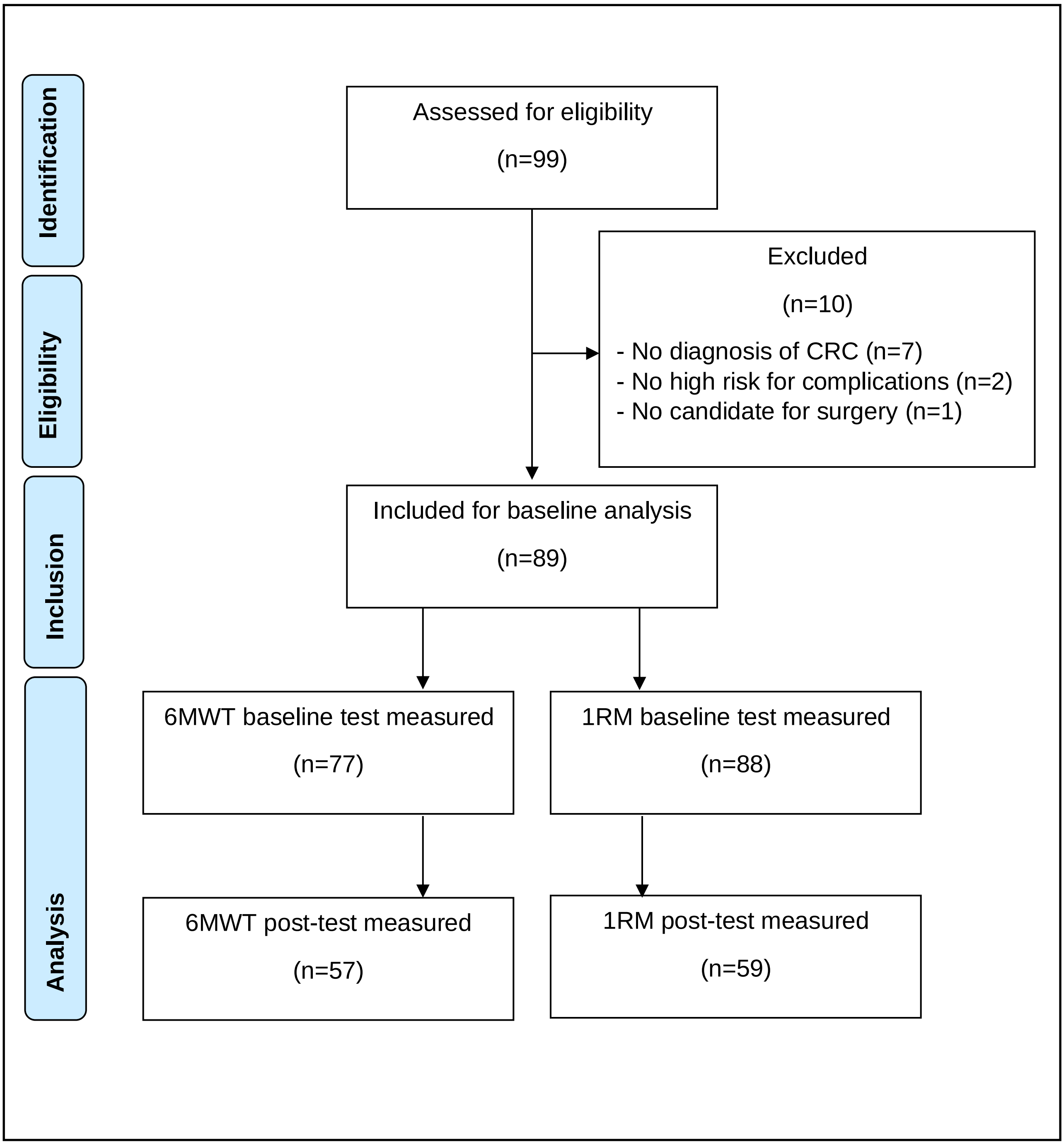

Figure 1 - STROBE flow chart

Table 1 – Baseline characteristics

Characteristic	No. of patients	Baseline data
Age, median (IQR), y	89	75.07 (10)
Minimum – Maximum		60-86
Age >70, *n* (%)		69 (77.5)
Male gender, *n* (%)	89	47 (52.8)
BMI, median (IQR), kg/m^2	89	26.22 (5.22)
Minimum – Maximum		18.00-54.01
BMI <18.5 or ≥25, *n* (%)		55 (61.8)
Smoking status, *n* (%)	89	
Never		31 (34.8)
Previous		50 (56.2)
Current		8 (9.0)
Alcohol consumption, *n* (%)	89	
No		44 (49.4)
Yes, <2 units/day		33 (37.1)
Yes, 2-6 units/day		12 (13.5)
Current, >6 units/day		0 (0.0)
ASA Grade, *n* (%)	89	
1		3 (3.4)
2		47 (52.8)
3		36 (40.4)
4		3 (3.4)
Tumor location, *n* (%)	89	
Colon		62 (69.7)
Rectum		27 (30.3)
TNM, *n* (%)	82	
1		24 (29.3)
2		24 (29.3)
3		29 (35.4)
4		5 (6.1)
Comorbidities present, *n* (%)	89	50 (56.2)
Anaemia present, *n* (%)	89	28 (31.5)
Neoadjuvant therapies given, *n* (%)	89	15 (16.9)
Number of risk factors*, *n* (%)	82	
1		4 (4.9)
2		7 (8.5)
3		14 (17.1)
4		18 (22.0)
5		22 (26.8)
6		10 (12.2)
7		3 (3.7)
8		4 (4.9)
Baseline 6MWT, median (IQR), m	78	450 (128)
Minimum – Maximum		90-686
Baseline leg press 1RM, median (IQR), kg	89	116.5 (41)
Minimum – Maximum		49-262

Abbreviations: IQR, interquartile range; y, years; kg, kilograms; m, meters; BMI, Body Mass Index; ASA, American Society of Anaesthesiologists; TNM, Classification of malignant tumors; 6MWT, six minute walk test; 1RM, one repetition maximum; * The number of risk factors was calculated out of the other baseline variables, counting one point for each variable with increased risk: age >70, male gender, current smoking, alcohol consumption >2 units per day, BMI <18,5 or ≥25, ASA grade ≥3, rectal tumor location, TNM 4, present comorbidities, present neoadjuvant therapies, and present anaemia.

Table 2 – Baseline- and post-tests of the 6MWT and 1RM

Characteristic	**Baseline test (t0)**	**Post-test (t1)**	**Difference (Δ t1-t0)**
6MWT, m	N=77	N=57	N=57
Median	450.0	484.0	36.0
IQR	128	124	39
Minimum – Maximum	90 – 686	188 – 676	-51 – 150
Difference ≥50m			
Yes, *n* (%)			17 (29.8)
Time between t0 and t1, d			
Median			28
IQR			10
Minimum – Maximum			11-50
Leg press 1RM, kg	N=88	N=59	N=59
Median	116.5	150.0	21.0
IQR	41	68	18
Minimum – Maximum	49 – 262	62 – 308	0 – 102
Difference ≥20kg			
Yes, *n* (%)			32 (54.2)
Time between t0 and t1, d			
Median			29
IQR			10
Minimum – Maximum			12-51
Abbreviations: 6MWT, six minute walk test; m, meters; IQR, interquartile range; d, days; 1RM, one repetition maximum; kg, kilograms.			

Table 3 – Uni- and multivariable regression analysis of ≥50m change in 6MWT

Characteristic	**Crude OR (95% CI)**	***p*-value***	**Adjusted OR (95% CI), model A (method enter)**	***p*-value***	**Adjusted OR (95% CI), model B**	***p*-value***
Constant			.238 (0.40 – 1.422)	.110	.200 (.056 - .707)	.014
Nagelkerke R square**			.189		.143	
Age, +1y	.952 (.873 – 1.038)	.261				
Constant	19.159					
Gender						
Male	Reference					
Female	.368 (.121 – 1.123)	.079	.521 (.156 – 1.744)	.288		
BMI <18.5 or ≥25		.226				
No	Reference					
Yes	1.974 (.655 – 5.945)					
Smoking status		.917				
Never	Reference					
Previous	1.432 (.231 – 8.866)	.699				
Current	1.508 (.261 – 8.697)	.646				
Alcohol consumption		.133		.223		.075
No	Reference					
Yes, <2 units/day	1.146 (.366 – 3.589)	.814	1.336 (.395 – 4.525)	.641	1.319 (.410 – 4.246)	.642
Yes, 2-6 units/day	4.134 (.873 – 19.573)	.074	4.131 (.730 – 23.377)	.108	5.681 (1.038 -31.079)	.045
Baseline 6MWT		.839				
≤300m	Reference					
301-400m	.576 (.072 – 4.626)	.602				
401-500m	.638 (.075 – 5.415)	.676				
501-600m	.572 (.063 – 5.164)	.616				
≥601m	.758 (.119 – 4.836)	.580				

Table 3 – Uni- and multivariable regression analysis of ≥50m change in 6MWT (continued)

ASA grade						
1-2	Reference					
3-4	2.298 (.703 – 7.511)	.164	2.353 (.576 – 9.605)	.226	2.888 (.765 – 10.896)	.114
Comorbidities present						
No	Reference					
Yes	1.617 (.407 – 6.430)	.477				
Anaemia present						
No	Reference					
Yes	.885 (.236 – 3.316)	.853				
Neoadjuvant therapies given						
No	Reference					
Yes	.770 (.160 – 3.696)	.740				
Tumor location						
Colon	Reference					
Rectum	2.711 (.679 – 10.830)	.152	1.447 (.472 – 4.440)	.280		
TNM		.797				
1	Reference					
2	.753 (.190 – 2.979)	.684				
3	.746 (.187 – 2.979)	.676				
4	.456 (.054 – 3.833)	.469				
Number of risk factors***						
0-4	Reference					
5-8	2.253 (.619 – 8.208)	.209				

*p-values for dichotomous and continuous variables are based on Rubin's Rules (RR). P-values for polychotomous variables are based on the median p rule (MPR). **Median of 5 imputed datasets. ***Number of risk factors was no candidate variable for multivariable analysis, as this variable is constructed out of the other variables. Abbreviations: y, year; BMI, Body Mass Index; 6MWT, six minute walk test; m, meters; ASA, American Society of Anaesthesiologists; TNM, Classification of malignant tumors.

Table 4 – Uni- and multivariable regression analysis of ≥20kg change in 1RM

Characteristic	**Crude OR (95% CI)**	**p-value***	**Adjusted OR (95% CI), model A (method enter)**	**p-value***	**Adjusted OR (95% CI), model B**	**p-value***
Constant			13.605 (.006 – 29194.276)	.494	.417 (.122 – 1.424)	.153
Nagelkerke R square**			.201		.188	
Age, +1y						
Constant	.942 (.864 – 1.028)	.176	.956 (.863 – 1.058)	.374		
Gender						
Male	Reference					
Female	.633 (.172 – 2.327)	.467				
BMI <18.5 or ≥25						
No	Reference					
Yes	1.595 (.480 – 5.295)	.430				
Smoking status		.222				
Never	Reference					
Previous	1.863 (.561 – 6.185)	.298				
Current	.658 (.112 – 3.867)	.641				
Alcohol consumption		.431				
No	Reference					
Yes, <2 units/day	1.833 (.556 – 5.801)	.319				
Yes, 2-6 units/day	1.612 (.306 – 8.489)	.564				
Baseline 1RM		.023		.030		.018
≤100kg	Reference					
101-150kg	3.263 (.920 – 11.570)	.066	3.308 (.790 – 13.852)	.098	3.539 (.908 – 13.787)	.067
≥151kg	2.990 (.540 – 16.564	.202	2.540 (.382 – 16.881)	.322	3.037 (.512 – 18.034)	.213

Table 4 – Uni- and multivariable regression analysis of ≥20kg change in 1RM (continued)

ASA grade						
1-2	Reference					
3-4	.595 (.159 – 2.223)	.415				
Comorbidities present						
No	Reference					
Yes	.603 (.232 – 1.563)	.295				
Anaemia present						
No	Reference					
Yes	.543 (.213 – 1.385)	.201	.969 (.300 – 3.126)	.957		
Neoadjuvant therapies given						
No	Reference					
Yes	1.931 (.559 – 6.672)	.298				
Tumor location						
Colon	Reference					
Rectum	2.308 (.735 – 7.243)	.149	2.464 (.602 – 10.088)	.201	2.545 (.718 – 9.022)	.144
TNM		.159				
1	Reference					
2	.379 (.102 – 1.406)	.145				
3	.567 (.151 – 2.133)	.395				
4	1.608 (.160 – 16.183)	.680				
Number of risk factors***						
0-4	Reference					
5-8	1.180 (.440 – 3.169)	.739				

*p-values for dichotomous and continuous variables are based on Rubin's Rules (RR). P-values for polychotomous variables are based on the median p rule (MPR). **Median of 5 imputed datasets. ***Number of risk factors was no candidate variable for multivariable analysis, as this variable is constructed out of the other variables. Abbreviations: y, year; BMI, Body Mass Index; 1RM, one repetition maximum; m, meters; ASA, American Society of Anaesthesiologists; TNM, Classification of malignant tumors.