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ORIGINAL ARTICLE

Preoperative modifiable risk factors in colorectal surgery: an observational cohort study identifying the possible value of prehabilitation

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ABSTRACT

Background: Colorectal cancer (CRC) is the second most prevalent type of cancer in the world. Surgery is the most common therapeutic intervention, and associated with 20–40% reduction in physiological and functional capacity. Postoperative complications occur in up to 50% of patients resulting in higher mortality rates and greater hospital costs. The number and severity of complications is closely related to patients' preoperative performance status. The aim of this study was to identify the most important preoperative modifiable risk factors that could be part of a multimodal prehabilitation program.

Methods: Prospectively collected data of a consecutive series of Dutch CRC patients undergoing colorectal surgery were analyzed. Modifiable risk factors were correlated to the Comprehensive Complication Index (CCI) and compared within two groups: none or mild complications (CCI <20), and severe complications (CCI ≥20). Multivariate logistic regression analysis was done to explore the combined effect of individual risk factors.

Results: In this 139 patient cohort, smoking, malnutrition, alcohol consumption, neoadjuvant therapy, higher age, and male sex, were seen more frequently in the severe complications group (CCI ≥20). Patients with severe complications had significantly longer hospital stay (16 vs. 6 days, $p < 0.001$). The risk for severe complications was increased in patients with ASA score III [adjusted odds ratio (OR) 4.4, 95% CI 1.04–18.6], and hemoglobin level <7 mmol/l (adjusted OR 3.3, 95% CI 1.3–8.2). Compared to having no risk factors, more than one risk factor increased OR of severe complications (crude OR 5.2, 95% CI 1.8–15).

Conclusion: This study revealed that the risk of getting severe complications increases with the number of risk factors present preoperatively. Several preoperative patient-related risk factors are modifiable. Multimodal prehabilitation may improve patients' preoperative status and should be tested in a multicenter randomized controlled trial. With an international consortium (Copenhagen, Montreal, Paris, Eindhoven) we initiated a randomized controlled trial (NTR5947).

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Colorectal cancer (CRC) is the second most prevalent type of cancer worldwide with over 800 000 new patients diagnosed yearly. The only way to cure this condition is by surgical removal of the tumor. Unfortunately, postoperative complications occur in up to 50% of patients and lead to a higher mortality rate, increased hospital costs, and a lower health-related quality of life (HRQoL) [1,2]. Even in the absence of complications, major surgery is associated with a 20–40% reduction in physiological and functional capacity, which can be measured by energy expenditure, endurance time, workload, and heart rate during maximum exercise [3]. In patients that need adjuvant chemotherapy an optimal functional capacity is mandatory and complications will often lead to a delayed start or cancelation of treatment.

Efforts to improve the recovery process have primarily focused on the intraoperative (e.g., minimally invasive surgery, afferent neural blockade) and postoperative period

(e.g., 'fast track' early nutrition and mobilization) [1,4]. The latter protocols have been designed to facilitate the return of functional activities and accelerate convalescence known as *rehabilitation*. However, the postoperative period may not be the best time to ask surgical patients to make significant changes in their lifestyle, as patients are tired and concerned about perturbing the healing process as well as being depressed and anxious as they await additional treatments for their underlying condition. The preoperative period may in fact be a better time to intervene in the factors that contribute to recovery. This may alleviate some of the emotional distress surrounding the anticipation of surgery and the recovery process [5].

Although some have used education to prepare patients for procedures [6], little has been developed to systematically improve patients' preoperative status. Many of the patient-related risk factors [e.g., anemia, diabetes mellitus (DM),

cigarette smoking] for postoperative complications have already been identified and might be modifiable prior to surgery to improve postoperative outcome measures (e.g., length of hospital stay, complication index, HRQoL) [1]. Poor physical performance capacity increases the risk of complications after major non-cardiac surgery and prolongs recovery after abdominal surgery [7]. The role of nutritional status and psychological wellbeing in surgical recovery may also not be underestimated and might be improved accordingly [8,9]. Standard consultation of a dietician and psychologist may enhance patients' preoperative status by improving their oral intake, offering nutritional supplements (i.e., multi vitamins, proteins) and strategies to cope with anxiety. The nutritional status of patients affected by CRC is directly influenced by the presence of cancer, and by other factors such as age, (neo)adjuvant cancer therapy, and stage of the disease. It is as well documented that patients awaiting major surgery experience anxiety concerning their upcoming operation, its outcome, and their course of healing and recovery [10].

All current evidence demonstrates there is a necessity – and opportunity – to enhance patients' preoperative functional status to improve postoperative outcome. *Prehabilitation* might offer the solution to preoperatively optimize patients' performance status to withstand intensive treatments as surgery [11,12]. Unfortunately, only small trials evaluated the impact of prehabilitation prior to colorectal surgery.

Currently, based on the literature, it is not exactly known how preoperative modifiable risk factors are distributed among CRC patients. This information would support any intervention in order to optimize patients' preoperative status. Therefore, the general aim of this study was to identify modifiable preoperative risk factors in colorectal patients and to investigate whether multimodal prehabilitation could be valuable to improve the preoperative status. For this purpose, we employed a prospective observational cohort study.

Methods

A consecutive series of Dutch CRC patients undergoing surgery with primary anastomosis collected from May 2015 until June 2016 in Máxima Medical Center (MMC) were analyzed. The MMC is a 543-bed community and teaching hospital situated in the southern part of the Netherlands serving a population of approximately 200 000 inhabitants.

Pre-, peri-, and postoperative data were extracted from the electronic patient files and perioperative registration data. Relevant patient-related risk factors that might be optimized prior to surgery to lower the risk of peri- and postoperative complications were identified by screening the literature: body mass index (BMI), ASA grade III, DM, current smoking and pack years >15, alcohol use >3 units/day, hemoglobin below 7 mmol/l, Short Nutritional Assessment Questionnaire (SNAQ) score >3, neoadjuvant chemo or radiotherapy, and oral corticosteroid use [13–15]. These factors were prospectively recorded by integrating the required information in the routine patient registration system.

Outcome

The primary outcome for this study was the CCI score. The CCI is a combined outcome measure of morbidity and mortality [16] and summarizes the postoperative wellbeing of the patient concerning complications based on the Clavien-Dindo classification. As a CCI score above 20 was depicted as clinically relevant morbidity [17], we used this cutoff point to dichotomize the data into a less severe and severe group. In addition, baseline characteristics were described separately for patients without any complications and mild complications [none or mild (CCI 0–<20)], and patients with severe complications or death [severe (CCI ≥20)].

Statistical analysis

Baseline characteristics were compared between different categories of CCI (none or mild and severe) using the Pearson χ^2 -test for categorical variables, the unpaired *t*-test for normally distributed continuous variables and the Mann-Whitney *U*-test for non-normally distributed continuous variables.

The influence of preoperative characteristics on the risk of severe postoperative complications was expressed as odds ratios (OR) with 95% CI as calculated by univariate logistic regression analysis. Multivariate logistic regression analysis was done to explore the combined effect of individual risk factors. We included all variables that were associated with severe postoperative complications in univariate analysis at a *p* value of <0.05 into the multivariate model.

To explore the effect of burden of risk factors on risk of severe complications, we included the number of risk factors in each patient as an independent covariate into the logistic regression analysis.

All analyses were done in SPSS version 22 (IBM Corp., Armonk, NY) and statistical significance was accepted at a two-sided *p* value <0.05.

Results

During the inclusion period 139 patients were prospectively analyzed. The mean CCI score was 8.7 (SD 14.5) (median 0, interquartile range 0–20.9), and 35% of the patients showed one or more postoperative complications as measured with the Clavien-Dindo scale. However, 65% of the patients had no complications at all (CCI = 0) (data not shown).

In the severe complications group, patients were on average older and more were male patients compared to patients in the none or mild complications group (Table 1). A significant proportion of patients had an ASA score higher than III (*p* = 0.03) and a hemoglobin level lower than 7 mmol/l (*p* < 0.01). Further, a SNAQ score higher than 3, high use of alcohol, and long term-smoking were reported more frequently in the severe complication group. The length of hospital stay was significantly higher in the severe complication group (16 vs. 6 days, *p* < 0.01). With increasing number of risk factors a higher proportion of patients had severe complications (Figure 1).

Table 1. Baseline characteristics according to severity of complications as indicated by the comprehensive complication index in a consecutive sample of 139 colorectal cancer patients, The Netherlands 2015–2016.

	Total group N = 139	None or mild CCI = 0 and <20 n = 100	Severe CCI ≥20 n = 39	p Value ^b
Age in years	69 (39–91)	68 (39–88)	72 (53–91)	0.086
Male sex	57%	53%	76%	0.146
BMI (kg/m ²)	25.1 (18–44)	26.1 (18–39)	25.6 (19–44)	0.511
BMI <20 or BMI ≥30	22%	27%	10%	0.103
Diabetes mellitus	12%	11%	13%	0.763
ASA grade				0.025
I	22%	26%	13%	
II	66%	66%	64%	
III	12%	8%	23%	
Current smoking	17%	16%	18%	0.781
Ever smoked	56%	54%	62%	0.421
Pack years	7 (0–70)	5 (0–70)	15 (0–60)	0.156
Alcohol use >3 units/day	16%	13%	23%	0.144
Hemoglobin <7 mmol/l	19%	12%	62%	<0.001
SNAQ ≥3	14%	12%	18%	0.359
Corticosteroids (present use, excluding inhalers)	3%	3%	3%	0.890
Neoadjuvant therapy	12%	11%	15%	0.478
Risk factors ^a				
0	24%	38%	15%	0.127
1	37%	39%	36%	0.045
>1	39%	23%	49%	0.011
Length of hospital stay	7 (5–11)	6 (5–7)	16 (11–25)	<0.001

Medians plus range and number plus column percentages (%) are presented for continuous and categorical variables, respectively. Univariate analysis was performed for all preoperative potential risk factors. ^aRisk factors are body mass index (BMI), ASA grade III, diabetes mellitus (DM), current smoking, number of pack years, alcohol use >3 units/day, hemoglobin below 7 mmol/l, Short Nutritional Assessment Questionnaire (SNAQ) score >3, neoadjuvant chemo or radiotherapy, and oral corticosteroid use; ^bnone or mild versus severe complication group. A p value <0.05 was considered statistically significant.

CCI: Comprehensive complication index.

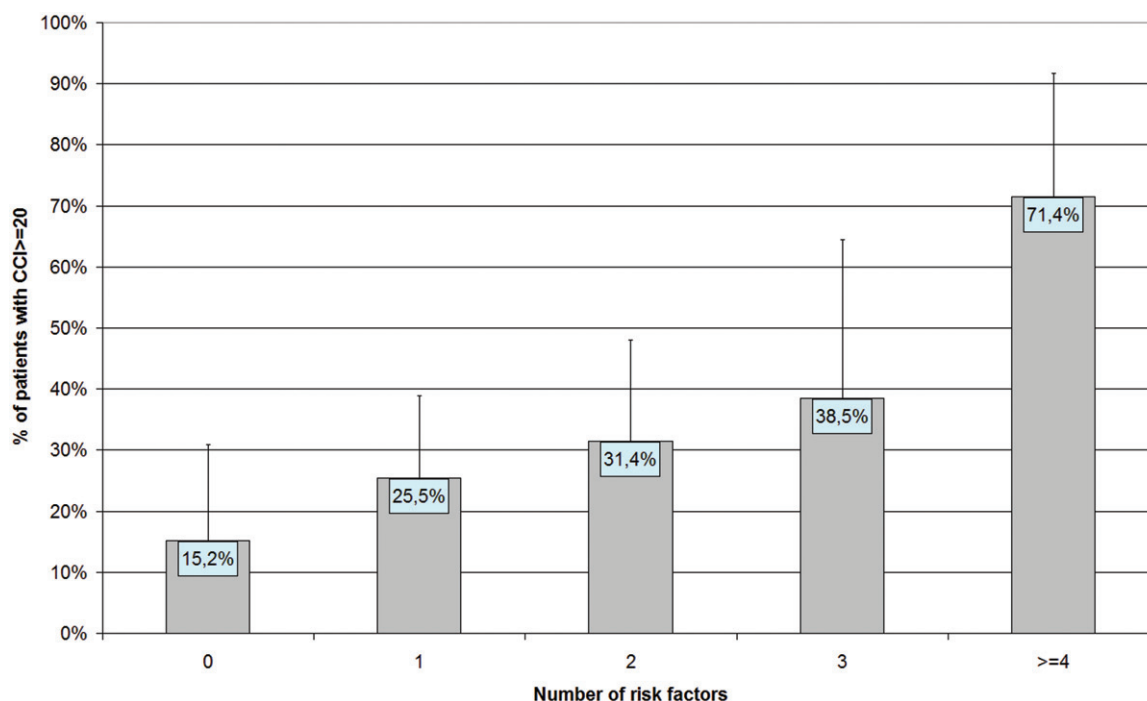


Figure 1. Percentage of colorectal cancer patients with severe postoperative complications (CCI score ≥20), related to the number of preoperative risk factors [ASA III, body mass index (BMI) <20/>30, pack years (PY) >15, alcohol (AH) >3 units/day, hemoglobin level (Hb) <7 mmol/l, Short Nutritional Assessment Questionnaire (SNAQ) >3, neoadjuvant therapy]. Y-bars indicate upper 95% confidence limits. Percentages are displayed within the bars.

In the univariate analysis patients with BMI <20 or 30+ had a lower OR (0.3, 95% CI 0.1–0.95) for severe complications, but this was not observed in the multivariate analysis (OR 0.3, 95% CI 0.1–1.1) (Table 2). In both univariate and

multivariate analysis OR for severe complications were increased with ASA grade III (adjusted OR 4.4, 95% CI 1.04–18.6) and hemoglobin level <7 mmol/l (adjusted OR 3.3, 95% CI 1.3–8.2). The OR for severe complications was

Table 2. Uni- and multivariate analyses of preoperative risk factors of severe postoperative complications (CCI ≥ 20) in a consecutive sample of 139 colorectal cancer patients, The Netherlands 2015–2016.

	None or mild vs. severe CCI <20 vs. CCI ≥ 20 Crude OR (95% CI) ^a	None or mild vs. severe CCI <20 vs. CCI ≥ 20 Adjusted OR (95% CI) ^b
Age (years)	1.0 (0.99–1.1)	–
Male	1.8 (0.8–3.8)	–
BMI (kg/m ²)	0.3 (0.1–0.95)	0.3 (0.1–1.1)
BMI <20 or BMI ≥ 30		
Diabetes mellitus	1.2 (0.4–3.7)	–
ASA grade (compared to ASA I)		
II	2.0 (0.7–5.7)	1.7 (0.6–5.0)
III	5.8 (1.5–22.6)	4.4 (1.04–18.6)
Current smoking	1.1 (0.4–3.1)	–
Pack years >15	2.0 (0.9–4.1)	–
Alcohol use >3 units/day	2.0 (0.8–5.2)	–
Hemoglobin <7 mmol/l	4.6 (1.9–11.1)	3.3 (1.3–8.2)
SNAQ ≥ 3	1.6 (0.6–4.4)	–
Corticosteroids (present use, excluding inhalers)	0.9 (0.1–8.4)	–
Neoadjuvant therapy	1.5 (0.5–4.3)	–
Number of risk factors (compared to 0) ^c		
1	2.3 (0.8–6.5)	–
>1	5.2 (1.8–15)	–

^aCalculated by using univariate logistic regression analysis; ^bmultiple logistic regression including all statistical significant variables from the univariate analysis; ^cwe did not include this variable into the multivariate analysis because it is constructed out of these variables.

BMI: body mass index; CCI: comprehensive complication index; SNAQ: Short Nutritional Assessment Questionnaire.

strongly increased with presence of more than one risk factors preoperatively [crude OR 5.2 (95% CI 1.8–15)] compared to patients without risk factors preoperatively (Table 2).

Discussion

This prospectively collected consecutive case series of CRC patients confirms the existence and distribution of potentially modifiable preoperative risk factors that are associated with postoperative complications as measured by the CCI score. We depicted a CCI score above 20 as clinically relevant morbidity [16,17]. For scores below 20, patients have not encountered any major events such as colorectal anastomotic leakage (CAL), prolonged ileus, nor a reoperation. This cutoff value is supported by the significantly increased length of hospital stay in the severe complication group. Factors like poor nutritional status, ASA score III, cigarette smoking, anemia (Hb <7 mmol/l), alcohol consumption >3 units/day, neoadjuvant therapy, DM, male sex, and higher age, have been all shown to be independent risk factors for complications in colorectal surgery [12–15]. In the present study sample ASA score III and hemoglobin level <7 mmol/l were found statistically significant risk factors whereas other factors were not statistically significantly associated with severe complications.

About 25–40% of all patients are undernourished on admission to the hospital [18], and in our cohort this was observed in 14% of patients. Moreover, malnutrition is further deepened during hospitalization and has been recognized as an independent risk factor of perioperative morbidity and severe postoperative complications [19]. Remarkably, in the present study population either underweight or obese patients actually had less severe complications. This might be explained by the small study population and the striking low number of patients with low hemoglobin levels within those

specific BMI groups. Despite this, malnutrition in general bears a significant association with postoperative mortality and cardiopulmonary complications after surgery [20]. Nutritional support is therefore still recommended, even in well nourished patients [18].

The average poor lifestyle (including physical inactivity, obesity, dietary pattern, smoking, and alcohol consumption behavior) of CRC patients, combined with the disease activity and change in metabolism results in a high rate of complications. Cigarette smoking and substantial alcohol consumption are well known risk factors for postoperative complications [15]. Smoking has a transient effect on the tissue microenvironment and a prolonged effect on inflammatory and reparative cell functions leading to delayed healing and complications. A period of 4–8 weeks smoking cessation prior to surgery has already been shown to significantly reduce postoperative complications and morbidity [21]. With about one-fifth of all patients as current smokers and alcohol consumers, a smoking and alcohol cessation program should be considered.

Next, our finding of low hemoglobin levels being associated with severe complications in CRC patients is in line with numerous other studies, and indicates that more focus should be put on presurgical management of anemia [22]. Patients should be screened preoperatively (at least four weeks before surgery) to identify insufficient hemoglobin levels (<7 mmol/l). In case of iron insufficiency, optimization of hemoglobin levels using iron injections is preferable [23]. Additionally, hyperglycemia is regarded as a predictor of complications of any type in colorectal surgical procedures [24]. In the present study cohort we were not able to investigate the glucose level in all of our patients. It might be of value to track patient's glucose level preoperatively as DM, hyperglycemia, and a high preoperative HbA1c are all independent risk factors of the worst complication in colorectal

surgery: CAL. Although DM may not be a modifiable risk factor in itself, the glucose level could be monitored and stabilized, and perioperative hyperglycemia could be prevented. Even in non-DM patients, perioperative hyperglycemia sustains a significantly higher risk of postoperative adverse events [25].

As seen in the present case series, the chance of severe complications rises with the addition of each risk factor. This indicates that a multimodal program could be favorable to tackle as many modifiable risk factors as possible in the individual (high) risk patient. Next to these factors, we also found a trend that with increasing clinical stage more patients had a CCI score higher than 20. Although our sample size is modest and thus results must be interpreted with caution, the factors identified as associated with complications do indicate the potential for improving patients' preoperative status. The addition of a multimodal prehabilitation program may enhance patients' preoperative performance status, might help them to recover faster and be less dependent on healthcare support during and after treatment [11,12]. As certain patients will undergo neoadjuvant treatment, it might be interesting to prehabilitate during this. Unfortunately, no evidence exists of prehabilitation programs or exercise training during neoadjuvant treatment, and therefore no suggestions can be given.

The first and largest randomized controlled trial on surgical prehabilitation compared two exercise regimens (intense exercise on a stationary bike vs. walking and deep breathing) for several weeks before colorectal surgery [11]. The primary outcome was functional walking capacity measured by the six-minute walk test (6MWT) between five and nine weeks postoperatively. Subgroup analysis identified that patients whose functional exercise capacity improved preoperatively, regardless of the exercise technique used, recovered well in the postoperative period. However, those patients who further deteriorated in the preoperative phase despite the exercise regimen were at greater risk for prolonged recovery after surgery. Poor preoperative physical function (fatigue, malnutrition, and physical performance) and presence of anxiety and depression were also significant confounding predictors of prolonged recovery [10,11]. These results suggest that exercise training alone, although it can improve the functional exercise capacity, is not sufficient to attenuate the surgical stress response in all patients. Therefore, to our opinion it is important to address factors that promote the beneficial adaptations to training like nutrition and coping behavior.

To improve both exercise capacity and nutritional state it is necessary to balance dietary intake against the energy use during exercise. High intensity training combined with supplemental whey proteins within one hour after training is recommended to achieve the ultimate improvement in functional capacity in a short time span of four weeks [9,12]. Nutritional supplementation four weeks before and after surgery has been shown to enhance preoperative functional walking capacity and recovery in patients undergoing colorectal resection for cancer [12]. Not only the nutritional status of patients should be optimal, but also the hemoglobin level. An improved hemoglobin level, combined with training, may lead to substantially better effects preoperatively, and will

lower the chance for severe complications as seen in this present cohort.

As the number and severity of complications appears to be closely related to patients' preoperative status, we believe the medical community has the responsibility to develop and test a multimodal intervention program targeting those problems. Current standard pre- and postoperative clinical care do not routinely include special nutrition, exercise, smoking cessation, and psychological support before surgery. Interventions used in studies on these parameters all have been proven to have a clinical relevant effect on the reduction of postoperative complications [12]. Although much of this is known, remarkably, it is not routine practice to implement this knowledge in daily clinical practice. If all these interventions are orchestrated in an innovative multimodal prehabilitation program, in our opinion it should be feasible to design a very effective intervention that might beneficially influence the outcome of this patient group.

Conclusion


This prospectively collected cohort study of 139 CRC patients revealed that potentially modifiable patient factors were prevalent and that the risk of severe postoperative complications increases with the number of risk factors present preoperatively. Multimodal prehabilitation may improve patients' preoperative status, which may be associated with improved outcomes of the operation, recovery, and adherence to further cancer treatment and rehabilitation. In order to obtain sufficient statistical power a multicenter randomized controlled trial should be performed. Such a study would be the first to systematically combine existing knowledge from a variety of different medical specialties and basic scientists into a prehabilitation protocol for CRC patients, focusing on modifiable preoperative risk factors, and improvement of functional capacity to lower the postoperative complication rate. With an international consortium (Copenhagen, Montreal, Paris, Eindhoven) such a randomized controlled trial (NTR5947) has been initiated.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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