Reshaping perioperative colorectal care

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From risk **identification** to risk **mitigation**

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Muriël Reudink

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on

General introduction and thesis outline

General introduction

Colorectal resection encompasses various types of surgery regarding the colon and the rectum. Colorectal surgery may be indicated for benign diseases (e.g. diverticular disease, inflammatory bowel disease, polyps, obstruction, volvulus, incontinence), and it is also the primary treatment for colorectal malignancies. Colorectal cancer (CRC) is one of the most common cancer types worldwide.[1] Coordinated by the National Institute for Public Health and the Environment (RIVM) a national screening program for CRC among Dutch citizens aged 55 to 75 years was implemented in 2014. In 2022, the National Cancer Registry recorded nearly 12.000 newly diagnosed patients in the Netherlands and it is expected that this number will increase to 14.300 in 2032.[2] The incidence rates of CRC are on the rise due to a growing aging population, sedentary lifestyle, unhealthy diet, obesity, tobacco use and excessive alcohol intake.[1]

Postoperative complications occur in up to one third of the patients undergoing colorectal surgery and associated risk is failure to rescue resulting in mortality, prolonged hospital stay, delayed recovery, diminished quality of life, impaired long term survival, and increased healthcare costs.[3,4] The occurrence of postoperative complications primarily depends on three key factors: 1) the degree of surgical stress, 2) the quality of surgical and perioperative care, and 3) the patient's preoperative condition.[5] For a clear comprehension of the main objectives of this thesis, these fundamental aspects will be introduced first.

Concerning the first aspect, surgical trauma triggers a complex set of changes within the body known as the 'surgical stress response', characterized by neuroendocrine and inflammatory-immune responses.[6] It is believed that this cascade of events serves as a mechanism of survival, by functionally stimulating the mobilization of energy stores.[7] However, an exaggerated or prolonged stress response contributes to reduced insulin sensitivity, representing a state of insulin resistance and concomitant hyperglycemia, which adversely affects postoperative recovery.[7-9] In addition to the extent of surgical trauma and the duration of surgery, several preexisting patient conditions such as cancer, malnutrition, obesity, and diabetes also contribute to the influence of surgery on the stress response.[6,10] Hence, modern perioperative care, referring to several aspects of patient care throughout the preoperative, intraoperative, and postoperative phases, has focused on interventions that act upon the stress response to surgery.

The quality of surgical and perioperative care has changed tremendously by the introduction of Enhanced Recovery After Surgery (ERAS), initially described by Kehlet and colleagues

in the 1990s.[11] Multiple meta-analyses have shown that enhanced recovery programs effectively reduce perioperative morbidity rates and hospital length of stay.[12-14] ERAS involves a multidisciplinary care bundle that incorporates evidence-based interventions throughout the entire perioperative period, with the aim of minimizing perioperative stress and accelerating recovery. Examples of these perioperative interventions include the prevention of intraoperative hypothermia, utilization of minimally invasive surgery, management of anemia, early initiation of enteral feeding and early mobilization in the postoperative phase, and preoperative education and counseling.[15] While some of these principles are relatively straightforward to implement in clinical practice, others, such as preoperative anemia management, present challenges due to the need for multidisciplinary teamwork and logistical complexities.[16] Although perioperative music is not part of current ERAS care, previous research suggests that it attenuates the stress response to surgery. [17]

The introduction of prehabilitation, focusing on the patient's preoperative condition, was the next revolutionary step in perioperative care. Prehabilitation complements ERAS and aims to optimize the patients' preoperative condition in order to increase their adaptive capacity to cope with surgery **(Figure 1).**[18] Multimodal prehabilitation involves a range of integrated interventions targeting modifiable risk factors, such as physical exercise, smoking and alcohol cessation support, nutritional support and protein supplementation, correction of medical conditions, and mental support.[19] Previous studies that investigated the effect of prehabilitation on outcome after colorectal surgery described an almost 50% reduction in complication rates[20,21], a reduced length of stay[22], and even an improved disease free survival.[23] In the Netherlands, accurate information on the use and content of prehabilitation programs is scarce.

Despite the abovementioned advances in perioperative care, there is room for improvement. More specifically, incidence rates of anastomotic leakage, a detrimental complication following colorectal surgery, have not been significantly reduced over the past few decades.[24] Worldwide, colorectal leak rates vary widely, with occurrences reported up to 20%.[24,25] Based on data of the Dutch Surgical Colorectal Audit over 2018, reported incidence rates in the Netherlands were 4.5% and 7.3% after colon and rectal resection, respectively.[26] Clinical presentation varies from occult leakage to the formation of intraabdominal abscesses, or in severe cases fecal peritonitis with multiorgan failure and finally death.[27] Most patients with anastomotic leakage require a reoperation in which the anastomosis will be sacrificed or repaired, and/or a permanent or temporary stoma needs to be created. Others can be conservatively treated by antibiotics, radiological or surgical drainage, and/or endosponge application, which might take several months.[28] Clearly, a long-lasting recovery is awaited.

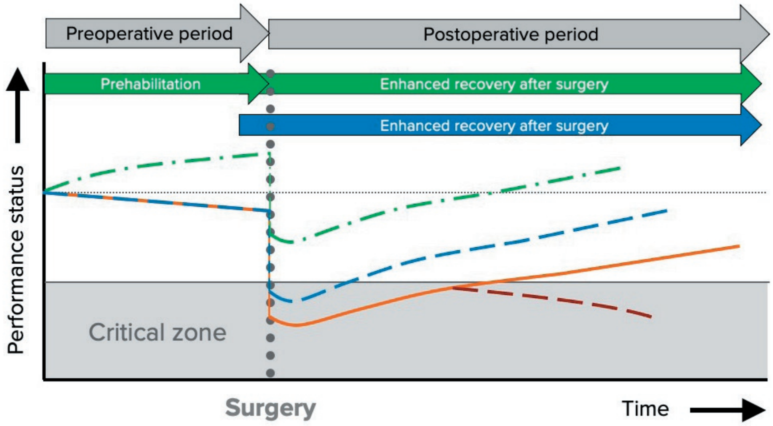

Figure 1. Along with the ERAS program (blue, dashed line), prehabilitation (green, dashed line) aims to increase a patient's performance status prior to surgery in order to reduce the risk of complications and length of hospital stay, and thereby accelerate recovery. Adapted (with permission) from Bongers BC, Dejong CHC, Dulk den M., European Journal of Surgical Oncology 47 (2021) 551-559 [18]

The exact etiology of anastomotic leakage is not well understood, but independent risk factors that have been identified in literature include male sex, higher American Society of Anesthesiologist (ASA)-classification, distal anastomosis close to anal verge, preoperative radiotherapy, and emergency surgery.[25,29] After early scientific work on these so called non-modifiable factors, attention turned to potentially modifiable factors such as (visceral) obesity, diabetes mellitus type 2, preoperative anemia, level of physical functioning, poor nutritional status, and duration of surgery.[25,30,31] Modifiable factors are important because they could potentially be changed in the perioperative setting. Some perioperative modifiable factors are extensively studied, others require further evaluation or are unidentified.[23] More knowledge and a better understanding which factors contribute to adverse postoperative outcomes like anastomotic leakage or other complications could facilitate the development of (new) perioperative strategies or interventions that might reduce surgical risks.

At last, postoperative recovery involves more than just complications. Whereas healthcare providers focus on postoperative morbidity and survival, patients mention resolution of symptoms, overcoming stress, and reacquirement of independency and joy as important recovery outcomes.[32] Long-term postoperative complaints such as frequent bowel movements, fecal incontinence, urgency difficulties, and sexual dysfunction, can severely affect quality of life and level of functioning.[33] It is essential to provide patients with detailed

information prior to surgery regarding the risks and expected course of recovery. To date, studies on the true impact of colorectal resection surgery on long-term health-related quality of life are lacking in literature.

Outline of this thesis

The main objectives of this thesis are 1) to identify and assess potentially modifiable risk factors for adverse outcome after colorectal resection, and 2) to explore perioperative methods and interventions targeting such risk factors. The findings of studies addressing these aims might help guide perioperative risk management strategies with the aim to improve surgical recovery.

Part 1 - Identification & assessment of modifiable risk factors

In Part 1 of this thesis, we aim to identify potentially modifiable risk factors for adverse outcome following colorectal resection surgery. The first section focuses on perioperative modifiable factors associated with colorectal anastomotic leakage. In **chapter 2** associations between anastomotic leakage and a number of items are investigated, collected by carrying out a second time-out procedure, in addition to the first that is performed before starting the procedure, in the operating theater just prior to the creation of the anastomosis (the LekCheck procedure). In **chapter 3** we further evaluate the identified association of intraoperative hyperglycemia and anastomotic leakage using the same LekCheck cohort data. Herein, we particularly address the patient's intraoperative blood glucose and its relation with anastomotic leakage, stratified for patients with and without diabetes mellitus. In **chapter 4** we again used data from the LekCheck study in order to further assess the identified association of preoperative anemia and anastomotic leakage. In addition, we discuss challenges in current initiatives. Furthermore, we focus on the metabolic syndrome, recognized as a modifiable condition, characterized by a cluster of interrelated metabolic abnormalities including hyperglycemia, visceral obesity, hypertension, and hyperlipidemia. Our hypothesis was that patients with metabolic syndrome might be at high-risk for metabolic distress around surgery and subsequently, for (severe) complications. **Chapter 5**, a systematic review and meta-analysis is presented on this topic. We describe the current best evidence on the impact of metabolic syndrome and preoperative hyperglycemia, as an individual component of metabolic syndrome, on short-term outcome after colorectal resection. In line with the shortcomings in the available literature as described in chapter 5, we are currently evaluating the effect of metabolic syndrome on postoperative outcome in patients diagnosed with CRC in a prospective, observational study, as described in **chapter 6**.

Part 2 - Perioperative optimization

In Part 2, we emphasize on perioperative methods and interventions targeting modifiable risk factors, aiming to improve postoperative recovery. To start, we focus on initiatives to inform and to better prepare patients before surgery. In **chapter 7,** we aim to gain insight into the impact of colorectal resection on the course of health-related quality of life from baseline (before start of treatment) up to 2 years after cancer diagnosis among a population-based sample of patients diagnosed with CRC. To provide a clear overview on health-related quality of life, the total cohort of patients is divided in patients undergoing right-sided colonic resection, left-sided colonic resection and rectal resection, respectively. As introduced before, prehabilitation is a strategy to optimize a patient's overall condition prior to surgery. The purpose of the study presented in **Chapter 8** is to investigate the current-state of prehabilitation practices in all Dutch hospitals for patients receiving surgery for CRC. This will be followed by **chapter 9**, an initiative to evaluate if it is feasible to implement music as part of standard perioperative care on a hospital-wide level, is presented.

Lastly, **chapter 10** covers a summary, general discussion, and future perspectives followed by an impact paragraph in **chapter 11**.

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Part 1

Identification and assessment of modifiable risk factors

chapter

two

LekCheck: A prospective study to identify perioperative modifiable risk factors for anastomotic leakage in colorectal surgery

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Abstract

Objective:

To assess potentially modifiable perioperative risk factors for anastomotic leakage in adult patients undergoing colorectal surgery.

Summary background data:

Colorectal anastomotic leakage (CAL) is the single most important denominator of postoperative outcome after colorectal surgery. To lower the risk of CAL, the current research focused on the association of potentially modifiable risk factors, both surgical and anesthesiological.

Methods:

A consecutive series of adult patients undergoing colorectal surgery with primary anastomosis was enrolled from January 2016 to December 2018. Fourteen hospitals in Europe and Australia prospectively collected perioperative data by carrying out the LekCheck, a short checklist carried out in the operating theater as a time-out procedure just prior to the creation of the anastomosis to check perioperative values on 1) general condition 2) local perfusion and oxygenation, 3) contamination, and 4) surgery related factors. Univariate and multivariate logistic regression analysis were performed to identify perioperative potentially modifiable risk factors for CAL.

Results:

There were 1562 patients included in this study. CAL was reported in 132 (8.5%) patients. Low preoperative hemoglobin (OR 5.40, $P < 0.001$), contamination of the operative field (OR 2.98, $P < 0.001$), hyperglycemia (OR 2.80, $P = 0.003$), duration of surgery of more than 3 hours (OR 1.86, $P = 0.010$), administration of vasopressors (OR 1.80, $P = 0.010$), inadequate timing of preoperative antibiotic prophylaxis (OR 1.62, $P = 0.047$), and application of epidural analgesia (OR, 1.81, P = 0. 014) were all associated with CAL.

Conclusions:

This study identified 7 perioperative potentially modifiable risk factors for CAL. The results enable the development of a multimodal and multidisciplinary strategy to create an optimal perioperative condition to finally lower CAL rates.

Introduction

Over the recent years, improved surgical techniques and enhanced recovery programs, early detection and treatment and higher surgeon caseloads have been proven effective to decrease the incidence and reduce the consequences of colorectal anastomotic leakage (CAL).[1,2] In addition, several preoperative, intraoperative, and postoperative risk factors for CAL have been identified.[3–5] Despite these advances, CAL remains a severe complication following surgery with a reported incidence ranging from 3 to 19% worldwide.[3] Leakage often results in a reoperation leading to a decreased health related quality of life and often a permanent stoma. Consequently, it increases hospital stay and health expenditures. CAL after colorectal surgery for cancer has a negative impact on the prognosis with regard to local recurrence and reduced survival rates.[6–9]

The exact risk factors of CAL remain unclear. Previous studies have revealed that patient-related factors, such as male gender and higher American Society of Anesthesiologist (ASA) score, are associated with CAL.[4,10–13] Also, intra-operative factors, such as operative time, and blood loss, are associated with higher leakage rates.[13] These risk factors, however, are mostly static and nonmodifiable. Recently, it has been suggested that some risk factors for CAL can actually be modified, as intraoperative temperature, blood pressure, and glucose levels may also contribute to the development of CAL.[14–17] However, it is still unknown what the optimal values for these factors are during perioperative care.

The prognostic value of potentially modifiable perioperative risk factors for CAL has not yet been examined. This is the first international prospective multicenter registration study where perioperative data is collected just prior to the creation of the anastomosis during colorectal surgery. We aimed to analyze the association between perioperative potentially modifiable risk factors and CAL.

Methods

Study design and patient population

Fourteen hospitals in the Netherlands, 1 hospital in Belgium, 1 in Italy and 1 hospital in Australia participated in the LekCheck study collecting data from January 2016 to December 2018. Adult patients undergoing surgery with the formation of a primary anastomosis for malign or benign indications were included. A multifactorial intraoperative checklist, the LekCheck, was

designed in 2016 by surgeons from 2 Dutch hospitals (VU Medical Center in Amsterdam and Máxima Medical Center in Veldhoven) and was supported by the Dutch Taskforce Colorectal Anastomotic Leakage (Acknowledgements). The study was approved by the Ethics Committee of the participating medical centers and all patients provided informed consent.

Data collection

The LekCheck contained 4 main topics including modifiable and nonmodifiable factors: 1) general condition of the patient (hemoglobin level, temperature, glucose, antibiotic prophylaxes), 2) local perfusion and oxygenation (blood loss, blood transfusion, oxygen saturation, mean arterial pressure, urine production, fluid suppletion, subjective clinical assessment of perfusion), 3) contamination, and 4) surgery related factors (duration of surgery, surgical procedure, approach, configuration, anastomotic technique and location, administration of vasopressors, intraoperative events, suture reinforcement, stoma type, surgeon fit to perform). All LekCheck items were prospectively collected by carrying out an additional time-out procedure in the operating theater just prior to the creation of the anastomosis during which both the surgeon and anesthesiologist were present. Baseline characteristics such as sex, age, body mass index (BMI), ASA classification score, diabetes, intoxications (smoking, alcohol use, steroid use), benign or malignant disease, detection by screening program, distance of the tumor to the anal verge, neoadjuvant therapy, and the Tumor-Node-Metastasis (TNM) stage according to the American Joint Committee on Cancer,[18] were recorded. Data of the presence of CAL, the diagnosis and treatment were determined and collected prospectively with a follow-up of 30 days postoperatively.

Definitions

Potentially modifiable LekCheck factors and their cut-off values for optimal intraoperative condition were extracted from a previously published review by our research group **(Table 1)**.[16] LekCheck values were dichotomized in order to create a composite score. Temperature below 36 degrees Celsius was considerate low. Hyperglycemia was defined as a glucose level above 109.8 mg/dL. Adequate timing of the administration of antibiotic prophylaxes was within 15 to 60 minutes prior to incision. Administration of vasopressors, the requirement of blood transfusion and the application of epidural analgesia were all classified as yes/no. A low preoperative hemoglobin (Hb) was defined by a concentration of less than 10.5 g/dL in males and less than 9.7 g/dL in females. Blood loss was collected by blood from suction bottles and/or drainage bags and was defined as 100mL or more. An oxygen saturation below 95% was considerate low. A low mean arterial pressure (MAP) was defined by 60 mm Hg or lower. Suboptimal intraoperative fluid management was defined by the administration of 1000mL or more per hour. Prolonged surgery was considered 3 hours

or more. Contamination was subjectively measured (yes/no), surgeons were instructed to report contamination as more than normal when the operated field was contaminated more than the regular loss of bowel content during a colorectal resection without bowel preparation. Intraoperative events were scored as yes/no and included: hypoxic events, hypertension, hypercarbia, bradycardia, hypotension, embolism, reanimation, more extensive resection than planned, serosa lesions, bladder and ureteral injuries, intraoperative bleeding, splenectomy or bleeding. Anastomotic location above the level of the peritoneal reflection was classified as colonic, below as rectal. Leakage was defined according to Reisinger: "clinically relevant anastomotic leakage is defined as extra luminal presence of contrast fluid on contrast-enhanced CT scans and/or leakage when relaparotomy was performed, requiring reintervention or treatment."[19]

Table 1. Perioperative modifiable factors and their cut-off values for optimal intraoperative condition.

Variable	Cut off values
Temperature	<36 degrees
Glucose	>109.8 mg/dL
Antibiotic prophylaxes	<15 or >60 min prior incision
Administration of vasopressors	Yes
Hemoglobin	<10.47 g/dL (male), <9.67 g/dL (female)
Blood loss	>100 mL
Blood transfusion	Yes
Oxygen saturation	<95%
Mean arterial pressure	<60 mm Hg
Fluid administration	>1000cc/h
Fecal contamination	Yes
Application of epidural analgesia	Yes
Duration of surgery	>3 h
Intraoperative event	Yes

Adapted from van Rooijen et al.: Intraoperative modifiable risk factors of colorectal anastomotic leakage: Why surgeons and anesthesiologists should act together. Int J Surg. 2016.[16]

Statistical analysis

Data were analyzed with Statistical Package for the Social Sciences software (SPSS 25-0, SPSS, Chicago, IL). First, descriptive statistics were used to analyze baseline characteristics. A 90% completeness of the LekCheck was considered successful, allowing a maximum of 2 variables as missing data. Categorical variables are expressed as proportions (%). Differences between patients with and without CAL were tested with Pearson's x^2 test. Continuous variables are expressed as mean (standard deviation) or medians (interquartile range) depending on skewness. Differences between continuous variables were tested with the Student t test (normal distribution) or the Mann–Whitney U test (skewed distribution). P values < 0.05 were considered statistically significant. Logistic regression analyses with CAL as primary outcome were performed to analyze associations with LekCheck factors. First, the associations were tested for single factors in a univariate analysis. Second, significant LekCheck factors (P < 0.10) were analyzed in a multivariate model, adjusting for other variables (baseline and surgery related) that differed significantly between patients with and without CAL. We performed a subgroup analysis to analyze patients according to anastomotic location (colon and rectum). In the multivariate logistic regression analysis 2-sided P values <0.05 were considered statistically significant. Results are reported as odds ratios (OR) and 95% confidence intervals (CIs).

Results

The LekCheck was performed in 1821 patients. Seventy-nine patients were excluded from the analysis due to incompleteness of data in the checklists (<90% complete) and for this study, 180 patients were excluded due to emergency surgery. A flowchart of the inclusion is shown in **Figure 1**.

Baseline characteristics

Cohort characteristics of the included patients for both groups (with and without anastomotic leakage) are summarized in **Table 2**. Of the 1562 included patients, 799 (51%) were male and the median age was 69 (range 21–95 yrs). Patients with CAL were significantly more often men (62% vs. 50%, P = 0.009), were more frequently ASA score ≥ 3 (34% vs. 24%, P = 0.009) and had diabetes mellitus more often (22% vs. 14%, P = 0.017). Furthermore, significantly more long-term smokers (>15 pack years) were present in the leakage group (31% vs. 2%, P = 0.011). If a tumor was present, the mean distance of the tumor to the anal verge was smaller in patients with CAL (12 vs. 15 cm, P = 0.009).

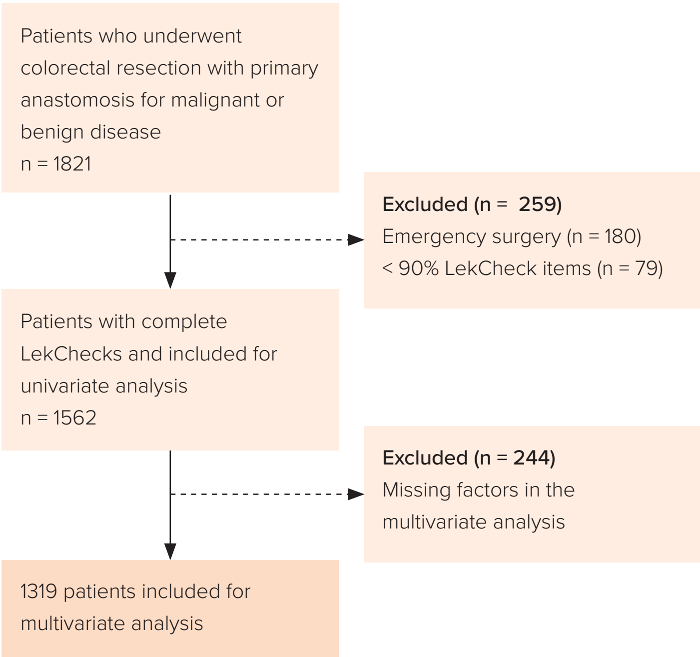

Figure 1. Flow diagram of study selection.

Surgical characteristics

The 1562 procedures that were performed were: 140 (9%) subtotal colectomies, 168 (11%) left colectomies, 526 (34%) right colectomies, 26 (2%) transverse colonic resections, 303 (20%) sigmoid resections, 349 (22%) rectum resections, and 50 (3%) reversals of Hartmann's procedures **(Table 3)**. The mean duration of surgery was significantly longer in patients with CAL (186 vs. 156 min, $P < 0.000$). A higher leakage rate was seen following a primarily open approach versus laparoscopic procedures (13% vs. 7.7%, $P = 0.007$). Likewise, if an intraoperative event occurred, the CAL rate increased (14% vs. 7.5%, $P = 0.001$). The distribution of type of anastomosis (end-to-end, end-to-side, side-to-end, side-to-side) can be found as supplemental data **(Supplementary Table A)**.

Table 2. Baseline characteristics of patient population (n = 1562)

Variable	Anastomotic leakage (n = 132)	Missing	No anastomotic leakage (n = 1430)	Missing	P value
Sex (male)	81 (62%)		718 (50%)		**0.009**
Age (years) *	71 (21-91)		68 (23-95)		0.162
< 70	64 (48%)		759 (53%)		
≥ 70	68 (52%)		663 (47%)		
Body-mass index ≥ 30 kg/m2	27 (20%)		241 (17%)		0.212
ASA classification					**0.009**
< 3	87(66%)		1075 (76%)		
≥ 3	45 (34%)		343 (24%)		
Diabetes mellitus	29 (22%)		204 (14%)	n = 12	**0.017**
Intoxications					
Current smoker	18 (14%)	n = 5	169 (12%)	n = 70	0.326
Pack years ≥ 15 years	40 (31%)	n = 4	301 (22%)	n = 43	**0.011**
Alcohol intake ≥ 3 units/d	14 (10%)	n = 4	121 (9%)	n = 2	0.244
Steroid use (excl. inhalers)	4 (4%)		36 (3%)	n = 14	0.449
Disease				n = 6	0.157
Malignant	113 (85%)		1163 (82%)		
Benign	19 (15%)		261 (18%)		
Diagnosed by screening program	48 (42%)	n = 18	476 (39%)	n = 238	0.361
Neoadjuvant therapy		n = 3		n = 74	0.195
None	111 (86%)		1192 (88%)		
5 x 5 radiotherapy	10 (8%)		92 (7%)		
Chemotherapy	3 (2%)		30 (2%)		
Chemoradiotherapy	5 (4%)		42 (3%)		
Distance of tumor from AV<15cm	37 (29%)	n = 6	267 (19%)	n = 22	**0.005**
Pathological TNM stage		n = 21		n = 284	0.158
I (T1-2N0M0)	52 (47%)		407 (36%)		
II (T3-4N0M0)	23 (21%)		324 (28%)		
III (T1-4N1-2M0)	27 (24%)		352 (31%)		
IV (T1-4N1-2M1)	9 (8%)		63 (6%)		

Abbreviations: ASA, American Society of Anesthesia score; TNM, tumor, node, and metastasis classification; AV, anal verge. Data are presented as number (%) or as medians (range) for categorical and continuous variables, respectively. Bold values have been found statistically significant (P < 0.05).

Outcome

While 214 (13.7%) patients had a clinical suspicion, CAL was confirmed in 132 patients (8.4%). The median time interval between surgery and the diagnosis of CAL was 5 days (IQR 3–8). The length of hospital stay was longer in the leakage group (20 vs. 6 d, P < 0.001). The overall 30-day mortality rate was 1.3% (21 of 1562), which was significantly worse in patients with CAL (5.6% vs. 0.9%, P = 0.001). Thirty-two (24%) of the 132 leakage patients, got some form of nonoperative treatment such as antibiotics (17%), insertion of a drain (8%), or both (6%). In total, 90 patients had a reintervention, among them: 4 (3%) patients received suture reinforcement of the anastomosis, 24 (18%) patients were treated by a deviating stoma alone, 37 (28%) patients by dismantling the anastomosis and installing a stoma and in 25 (19%) patients a complete new anastomosis was created. Treatment with an Endo-Sponge occurred in 10 (7.5%) patients after rectum resections.

Risk factors of colorectal anastomotic Leakage

Regarding the potentially modifiable factors low temperature, hyperglycemia, inadequate timing of preoperative antibiotic prophylaxis, administration of vasopressors, low preoperative hemoglobin, fluid supplementation of >1000 mL per hour, contamination of the operative field, application of epidural analgesia, duration of surgery of more than 3 hours, and intraoperative event were associated factors of CAL in the univariate analyses **(Table 4)**. The multivariate analysis revealed the following independent associated factors for CAL: low preoperative hemoglobin (OR 5.40, 95% CI 2.94–9.95, P < 0.001), contamination of the operative field (OR 2.98, CI 1.55–5.75, P < 0.001), hyperglycemia (OR 2.80, 95% CI 1.44–5.58, P = 0.003), duration of surgery of more than 3 hours (OR 1.86, 95% CI 1.18–2.95, P = 0.010), administration of vasopressors (OR 1.80, 95% CI 1.13–2.73, P = 0.010), epidural analgesia (OR, 1.81, 95% CI 1.15–2.84, P = 0.014), and inadequate timing of preoperative antibiotic prophylaxis (OR 1.62, 95% CI 1.03– 2.55, P = 0.047).

Table 3. Surgery related factors and risk for anastomotic leakage

	Anastomotic leakage (n = 132)		**No anastomotic leakage (n = 1430)**		**P value**
Variable		**Missing**		**Missing**	
Duration of surgery (minutes)	186 (32-385)	n = 4	153 (29-483)	n = 60	**0.000**
Surgical procedure					0.189
Subtotal colectomy	13 (9%)		127 (91%)		
Left hemicolectomy	16 (10%)		152 (90%)		
Right hemicolectomy	29 (5%)		497 (95%)		
Low anterior resection	37 (13%)		250 (87%)		
Sigmoid resection	30 (10%)		273 (90%)		
Transverse colon resection	1 (4%)		25 (96%)		
Rectum resection	4 (6%)		58 (94%)		
Reversal of Hartmann	2 (4%)		48 (96%)		
Surgical approach		n = 1		n = 15	**0.007**
Open	31 (23%)		209 (15%)		
Laparoscopy	90 (69%)		1132 (80%)		
Laparoscopy with conversion	10 (8%)		74 (5%)		0.223
Anastomotic location					**0.009**
Colon	91 (69%)		1123 (79%)		
Rectum	41 (31%)		307 (21%)		
Anastomotic configuration		n = 5		n = 40	**0.005**
End-to-end	35 (28%)		276 (20%)		
End-to-side	11 (7%)		94 (7%)		
Side-to-end	37 (30%)		304 (22%)		
Side-to-side	44 (35%)		716 (51%)		
Suture reinforcement	42 (32%)	n = 2	547 (40%)	n = 49	0.163
Anastomotic technique		n = 11		n = 123	0.189
Hand sewn	20 (17%)		272 (21%)		
Stapled	100 (82%)		997 (76%)		
Hand sewn and stapled	1 (1%)		38 (3%)		

Table continues on next page

Table 3 continued

	Anastomotic leakage (n = 132)		No anastomotic leakage (n = 1430)		P value
Variable		**Missing**		**Missing**	
Stoma type					0.082
Ileostomy	15 (94%)		103 (89%)		
Colostomy	1 (6%)		13 (11%)		
Goal directed therapy	29 (22%)	n = 1	277 (20%)	n = 40	0.307
Urine production in 1 h (mL)	95 (0 - 1180)		97 (0 – 1280)		0.395
Seniority of surgeon					0.189
Consultant surgeon	114 (86%)		1186 (82%)		
Fellow / register	18 (14%)		244 (17%)		
Fit to perform	119 (100%)	n = 13	1347 (99%)	n = 81	0.844

Data are presented as number (%) or as medians (range) for categorical and continuous variables, respectively. Bold values have been found statistically significant (P < 0.05).

2

Subgroup analyses (anastomotic location)

When colonic and rectal anastomoses were separately analyzed in multivariate analyses, associated factors for leakage of colonic anastomoses were low preoperative hemoglobin (OR 5.23, P < 0.001), contamination of the operative field (OR 4.03, P < 0.001), administration of vasopressors (OR 1.69, P = 0.04), hyperglycemia (OR 3.36, P = 0.009), and application of epidural analgesia (OR 2.08, P = 0.011). For rectal anastomoses, the following factors were significant: low preoperative hemoglobin (OR 5.02, P = 0.019), administration of vasopressors (OR 3.45, P = 0.012), and inadequate timing of preoperative antibiotic prophylaxis (OR 2.66, P = 0.026).

Subjective clinical assessment of perfusion

When the operating surgeon was asked to rate the local perfusion of the anastomosis on a scale from 4 to 10, the median score of the leakage group was 8 compared to a 9 for patients without CAL. The occurrence of CAL was significantly higher in patients rated with an ≤ 7 or lower (P < 0.001) **(Figure 2)**.

Table 4. Distribution of LekCheck factors and logistic regression analyses for anastomotic leakage.

		Univariate analysis*		Multivariate analysis**	
Variable	**No. (%)**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Temperature					
≥ 36 degrees	1229 (80%)	1		1	
< 36 degrees	306 (20%)	1.78 (1.16 - 2.74)	**0.008**	1.39 (0.85-2.29)	0.186
Glucose (mg/dL)					
≤ 109.8	39 (27%)	1		1	
> 109.8	1082 (73%)	2.79 (1.53 – 5.07)	**<0.001**	2.8 (1.44-5.58)	**0.003**
Antibiotics prophylaxes					
15 – 60 minutes	1102 (73%)	1		1	
< 15 or > 60 minutes	399 (27%)	2.08 (1.40 – 3.10)	**<0.001**	1.62 (1.03-2.55)	**0.037**
Administration of vasopressors					
No	928 (62%)	1		1	
Yes	579 (38%)	1.93 (1.30 – 2.87)	**<0.001**	1.8 (1.13-2.73)	**0.012**
Hemoglobin (g/dL)					
Male ≥ 10.5, female ≥ 9.7	1366 (94%)	1		1	
Male < 10.5, female < 9.7	92 (6%)	4.80 (2.80 – 8.23)	**<0.001**	5.4 (2.94-9.95)	**<0.001**
Blood loss (mL)					
≤ 100	1058 (69%)	1			
> 100	484 (31%)	1.06 (0.71 - 1.58)	0.753		
Blood transfusion					
No	1527 (98%)	1			
Yes	35 (2%)	1.44 (0.23 – 2.78)	0.745		
Oxygen saturation					
≥ 95%	1441 (94%)	1			
< 95%	86 (6%)	1.24 (0.59 – 2.59)	0.558		
Mean arterial pressure (mmHg)					
≥ 60	1496 (98%)	1			
< 60	32 (2%)	0.92 (0.21- 3.94)	0.800		
Fluid administration (mL/hour)					
≤ 1000	936 (76%)	1		1	
> 1000	303 (24%)	0.56 (0.33 – 0.96)	0.037	0.65 (0.34-1.24)	0.191

Table continues on next page

Table 4 continued

		Univariate analysis*		Multivariate analysis**	
Variable	**No. (%)**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Fecal contamination					
No	1407 (94%)	1		1	
Yes	89 (6%)	4.04 (2.31–67.04)	**<0.001**	2.98 (1.55-5.75)	**<0.001**
Epidural analgesia					
No	1011 (67%)	1		1	
Yes	487 (33%)	2.31 (1.56 - 3.40)	**<0.001**	1.81(1.15-2.84)	**0.010**
Duration of surgery (hours)					
≤ 3	1052 (70%)	1		1	
> 3	446 (30%)	2.19 (1.48 - 3.24)	**0.000**	1.86 (1.18-2.95)	**0.007**
Intraoperative event*					
No	1344 (86%)	1		1	
Yes	218 (14%)	1.94 (1.23 - 3.05)	**0.004**	1.15 (0.66-1.99)	0.622

Abbreviations: OR, odds ratio; CI, confidence interval. *Adjusted for: sex, American Society of Anesthesia score (ASA) ≥ 3, diabetes, pack years ≥ 15, distance of tumor from anal verge <15 cm, and anastomotic location. **Adjusted for: sex, American Society of Anesthesia score (ASA) ≥ 3, diabetes, pack years ≥ 15, distance of tumor from anal verge <15 cm, anastomotic location, and configuration, stoma type and surgical approach. Bold values have been found statistically significant (P < 0.05).

2

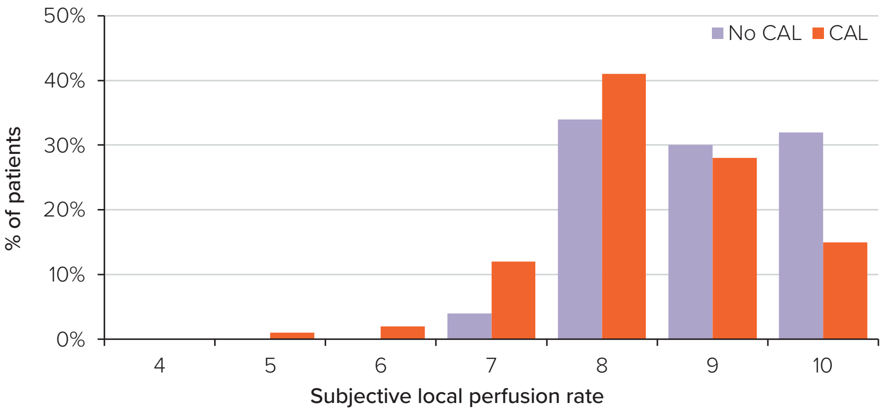

Figure 2. Differences in subjective local perfusion rates given by surgeons between patients without colorectal anastomotic leakage (CAL) (n = 1366) versus patients with CAL (n = 125).

Relation between numbers of risk factors and anastomotic leakage

The median number of the abovementioned 7 potentially modifiable risk factors for leakage was 3 in the leakage group compared to 2 in the nonleakage group ($P < 0.001$). In patients without any risk factors, the incidence of CAL was 2% versus 38% in patients with 6 risk factors present **(Figure 3).**

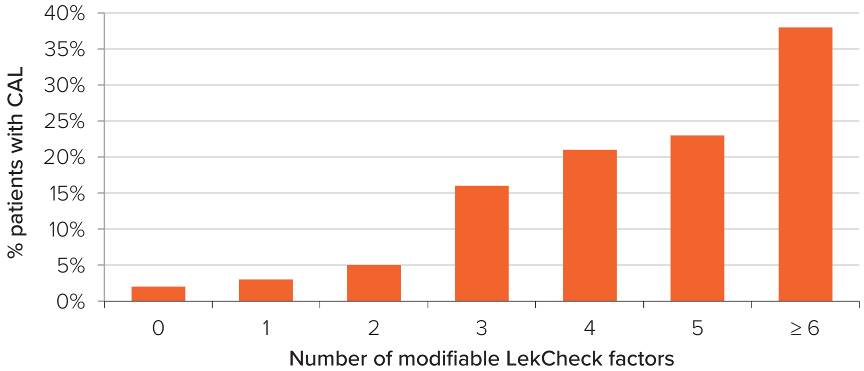

Figure 3. Percentage of patients with colorectal anastomotic leakage (CAL) related to the amount of perioperative potentially modifiable risk factors (low preoperative hemoglobin, contamination of the operative field, hyperglycemia, duration of surgery of more than 3 h, administration of vasopressors, inadequate timing of preoperative antibiotic prophylaxis, and application of epidural analgesia.

Discussion

This prospective multicenter study identified 7 perioperative potentially modifiable risk factors for CAL. Although no causal relationship has been demonstrated with this study, the patients in whom none of these risk factors were present (11% of our study population) had a remarkable low leakage rate of 2% versus 38% in patients with 6 risk factors present. Therefore, we do hypothesize that an integrated approach by both the surgical and anesthesiological teams to optimize the patient's perioperative condition might possibly lead to a decrease of CAL.

The present study showed an overall CAL rate of 8.5% (colon 7.5% vs. rectum 12%), a mortality rate of patients with CAL of 5.6% and a significantly longer length of hospital stay of 14 days in the leakage group. This is in concordance with the existing evidence of the leakage rates reported in previous studies and the Dutch national colorectal audit.[9,11,13,20]

With a prevalence of 6% in our overall study population, a low preoperative hemoglobin was the single most important contributor to CAL (OR 5.4, $P < 0.001$). This underlines the importance to optimize hemoglobin concentration as early as possible in the preoperative period. In order to achieve normohemoglobinemia in clinical practice, a multidisciplinary efficient approach is needed for early detection and treatment of anemia.[21–23] Preoperative suboptimal hemoglobin levels are mostly correctable in the preoperative phase and recent studies have shown that intravenous iron therapy increases hemoglobin level in case of iron deficiency anemia. Two major randomized controlled trials (RCT) in progress analyzing perioperative morbidity and mortality after active management of preoperative anemia should provide the answer whether this increase in hemoglobin level actually correlates with a reduction in complications.[24–26]

Perioperative hyperglycemia is clinically highly relevant since it was seen in 73% of our study population, that, interestingly enough, consisted of only 19% of patients with diabetes. Ziegler et al in 2012 suggested similar results concerning hyperglycemia.[27] Previously, a large cohort study also suggested that among non-diabetic patients, those with perioperative hyperglycemia have an increased risk of complications.[28] Whether perioperative hyperglycemia is caused by (undiagnosed) diabetes or surgical metabolic stress remains unclear.[29] However, except for protocols of cardiovascular surgery trials, strict intraoperative glycemic control regimens in surgical care are lacking. Although the present study does not show that optimization of glucose levels decreases the incidence of CAL, at the very least this parameter can be used for the prediction of the risk of a CAL. Next to this, preoperative plasma concentrations of glycosylated hemoglobin (Hb)A1c could be used to identify patients at higher risk of deprived glycemic control resulting in increased rates of postoperative complications.[30]

Contamination of the operative field was an independent risk factor for CAL, which is in accordance with previous studies that show its role in surgical site infections.[31] Although prevention of contamination is not always possible, intraoperative awareness could lead to significant decrease of its presence. Other means to reduce contamination might be the debated perioperative selective decontamination (SDD) of the digestive tract. A meta-analysis by Roos et al[31] reported a significantly lower incidence of CAL in patients who

received prophylactic SDD (3.3%) versus the control group (7.4%). On the other hand, a recently published study showed no effect of SDD on the CAL rate.[32]

Confirming the extensive amount of evidence on its influence on infectious complications, inadequate preoperative (<15 min or >60 min prior to surgery) antimicrobial therapy was also found to be a significant contributing factor to CAL.[33,34] The finding that such variety in timing of administration exists, accentuates that adherence to protocols is often challenging in daily practice.

Administration of vasopressors during surgery also showed to be an independent risk factor for CAL. This might be caused by vasoconstriction and ischemic effects of the vasopressor drugs at the anastomotic site.[35] Despite frequent perioperative use of these drugs, the exact role of vasopressors on the anastomotic healing process is not well studied in the literature. Interestingly, our results revealed that intraoperative mean arterial pressure rates did not differ significantly between patients with and without CAL. In line with this are the results found in a large study by Babazade et al., showing no clinical effect of intraoperative hypotension on the risk of infection after colorectal surgery.[36] However, in that study as in ours, the MAP rate was only collected intraoperatively, which does not allow us to draw conclusion of its effect in case of prolonged hypotension.

In the present study, patients who received intraoperative epidural analgesia were at almost a 2-fold higher risk of developing a CAL. When analyzing open resections separately, 18% of the patients receiving intraoperative epidural analgesia developed CAL compared to 8% of the patients receiving other forms of analgesia (P = 0.015). In laparoscopic surgery, this difference was not seen (10% vs. 8%, P = 0.378). Existing evidence about the effect of epidural analgesia on CAL is controversial.[17] Sympathetic activity and intestinal perfusion are important issues in this, however poorly understood.[37] A meta-analysis in 2001 did not show an impaired or increased risk on CAL.[38] The use of epidural analgesia remains equivocal and future research should focus on this topic to draw more valid conclusions.
As also reported in previous studies, nonmodifiable perioperative factors such as male gender[7,12], ASA greater than two[11], history of smoking[39], shorter distance of the tumor to anal verge[9,12] and open surgery[5] were all significantly related to a higher CAL rate in our study. Contradictory to other studies, a significant association between current smoking and anastomotic leakage was not found.[3] Smoking, and several other preoperative factors that were not analyzed in the current study (e.g. malnutrition, physical performance, psychological coping), enable preoperative risk prediction and are valuable in targeted multimodal prehabilitation programs.[40] Prehabilitation should play a crucial role in future research

focusing on optimization of suboptimal perioperative conditions. The LekCheck should not be inseparable from but rather be in accordance with preoperative optimization initiatives.

Several limitations of the current study are worth mentioning. The risk factors were collected by means of a 1-off intraoperative checklist. Since this is a snapshot of the actual situation at the time of the anastomosis, we do not have the data on the duration of the parameters collected such as the duration of vasopressor use or the duration of hypotension before its correction. Next to this, we are unaware of whether efforts were taken to optimize items prior or after the LekCheck during the final stage of the study when the operative teams became more aware of the risk factors scored. Checklists have a potentially beneficial effect on the measured outcome, due to the debated Hawthorne-effect. Inclusion numbers per hospital were too small to relate an observed reduction of present LekCheck factors to an actual decrease in CAL. Finally, it is important to point out that there is much debate about the definition of CAL since around the globe there is no generally accepted definition. We used Reisinger's definition,[19] although we know that this definition is quite strict and therefore we may have missed some anastomotic leaks in our analysis.

Conclusion

This study revealed 7 potentially modifiable intraoperative risk factors for CAL. This study shows that during optimal intraoperative conditions the incidence of CAL is very low. The LekCheck is a useful warning tool to identify suboptimal intraoperative conditions during colorectal surgeries. Future research should focus on modifying these suboptimal conditions by collaboration between the anesthesiologist and the surgeon. This is the subject of an ongoing multicenter study.

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Supplemental material

Supplementary Table A. The distribution of anastomotic configurations

Surgical procedure	End-to-end (n = 311)	End-to-side (n = 105)	Side-to-end (n = 341)	Side-to-side (n = 760)
Subtotal colectomy	20 (6%)	27 (26%)	22 (6%)	68 (9%)
Left hemicolectomy	25 (8%)	6 (6%)	26 (7%)	106 (14%)
Right hemicolectomy	38 (12%)	11 (10%)	7 (2%)	459 (60%)
Low anterior resection	95 (31%)	34 (32%)	122 (36%)	25 (3%)
Sigmoid resection	91 (29%)	21 (20%)	142 (42%)	41 (5%)
Transverse colon resection	6 (2%)	0 (0%)	0	20 (3%)
Rectum resection	21 (7%)	5 (5%)	16 (5%)	15 (2%)
Reversal of Hartmann	15 (5%)	1 (1%)	6 (2%)	26 (4%)

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Association between intraoperative blood glucose and anastomotic leakage in colorectal surgery

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Abstract

Background:

Perioperative hyperglycemia is a known risk factor for postoperative complications after colorectalsurgery. The aim of this study was to investigate whether intraoperative blood glucose values are associated with colorectal anastomotic leakage in diabetic and non-diabetic patients undergoing colorectal surgery.

Methods:

This is an additional analysis of a previously published prospective, observational cohort study (the LekCheck study). Fourteen hospitals in Europe and Australia collected perioperative data. Consecutive adult patients undergoing colorectal surgery with primary anastomosis between 2016 and 2018 were included. From all patients, preoperative diabetic status was known and intraoperative blood glucose was determined just prior to the creation of the anastomosis. The primary outcome was the occurrence of anastomotic leakage within 30 days postoperatively.

Results:

Of 1474 patients (mean age 68 years), 224 patients (15%) had diabetes mellitus, 737 patients (50%) had intraoperative hyperglycemia (≥126 mg/dL, ≥7.0 mmol/L), and 129 patients (8.8%) developed anastomotic leakage. Patients with intraoperative hyperglycemia had higher anastomotic leakage rates compared to patients with a normal blood glucose level (12% versus 5%, $P<0.001$). Anastomotic leakage rate did not significantly differ between diabetic and non-diabetic patients (12% versus 8%, $P=0.058$). Logistic regression analyses showed that higher blood glucose levels were associated with an increasing leakage risk in non-diabetic patients only.

Conclusion:

Incidence and severity of intraoperative hyperglycemia are associated with anastomotic leakage in non-diabetic patients. Whether hyperglycemia is an epiphenomenon, a marker for other risk factors, or a potential modifiable risk factor per se for anastomotic leakage requires future research.

Introduction

Perioperative hyperglycemia is common among patients undergoing major surgery and has a strong negative impact on postoperative outcome.[1] In colorectal surgery, perioperative hyperglycemia increases the risk on post-operative infections,[2] the length of hospital stay, and mortality rates.[3] In addition, it has recently also been established as an independent potentially modifiable risk factor for colorectal anastomotic leakage (CAL), the most feared complication after colorectal surgery.[4]

Reported CAL rates range between 5 and 19%.[5] When CAL is present, it often requires a reintervention.[6] CAL is associated with an increased mortality rate[7] and a decrease in long-term survival.[8] While previous studies focused on diabetes mellitus, an established non-adjustable risk factor for CAL,[9,10] the literature provides little information about the relationship between perioperative hyperglycemia and CAL.

Evidence suggests that perioperative hyperglycemia is caused by the trauma of major abdominal surgery[11] inducing a cascade of effects. This physiological response to injury, characterized by glycogenolysis, lipolysis, gluconeogenesis, a reduction in insulin sensitivity, and increased insulin resistance, is also known as "stress hyperglycemia".[11–13] Evidence-based enhanced recovery after surgery (ERAS) principles and guidelines attempt to blunt this stress response and avoid high blood glucose (BG) levels.[14,15] Despite these improvements in perioperative care, the clinical consequences of perioperative hyperglycemia are often overlooked. This study aimed to investigate whether intraoperative BG values, obtained at the moment of anastomosis creation, are associated with CAL after colorectal surgery in both diabetic and non-diabetic patients.

Materials and methods

Study design

This study is an additional analysis of the LekCheck study, a prospective observational international multicenter study designed by members of the Dutch Taskforce Colorectal Anastomotic Leakage. This study was conducted in fourteen hospitals (11 in the Netherlands, 1 in Belgium, 1 in Italy, and 1 in Australia). A detailed description of the study design and main results has recently been published.[4] Briefly, consecutive adult patients undergoing colorectal surgery with the formation of a primary anastomosis were

enrolled from January 2016 to December 2018. A multifactorial web-based checklist (www.naadlekkage.nl), including a range of perioperative values, was completed by the surgeon and the anesthesiologist during surgery as a time-out procedure just prior to the creation of the anastomosis. The study was approved by the Ethics Committee of each participating medical center (METC-2016.018), and informed consent was obtained from all patients. The current study is reported following the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.

Study population

Inclusion criteria of the LekCheck study consisted of adult patients (age ≥18 years), undergoing colorectal surgery with the formation of a primary anastomosis (with or without a diverting ileostomy/colostomy), for benign or malignant disease. Exclusion criteria were a >10% LekCheck missing data set and emergency surgery. For the current study, only patients with known preoperative diabetic status and a determined intraoperative BG level just prior to anastomotic creation were included for analysis.

Data characteristics and definitions

Data were collected by the coordinating investigators (D.H. and M.R.), who were not involved in patient care. Data were extracted from electronic patient files using a standardized data extraction form, which included baseline characteristics (sex, age, body mass index (BMI), American College of Anesthesiologists (ASA) classification, smoking status (pack years), diabetic status (classified as having diabetes controlled by diet, oral tablets, or insulin), corticosteroid use), disease-specific characteristics (indication for surgery, neoadjuvant treatment), and 30-day follow-up outcome data.

All intraoperative BG values were derived from one-off finger-prick measurements recorded immediately before anastomosis creation as part of the LekCheck procedure. For diabetic patients, intraoperative glycemic management was employed according to standard perioperative protocols. For non-diabetic patients, no intraoperative interventions were taken when glucose levels were elevated intra-operatively. Intraoperative hyperglycemia was defined as a BGlevel of≥126 mg/dL (≥7.0 mmol/L) according to the American Diabetes Association and World Health Organization guidelines,[16,17] assuming that the intraoperative status corresponds with a fasting state. BG concentrations were further divided in five subgroups using the following definitions: hypoglycemia <80 mg/dL (<4.4 mmol/L), normoglycemia 80–100 mg/dL (4.4–5.5 mmol/L), mildly elevated BG 101–125 mg/dL (5.5–7.0 mmol/L), hyperglycemia 126–200 mg/dL (7.0–11.1 mmol/L), and severe hyperglycemia >200mg/dL (>11.1 mmol/L).

The outcome of interest was CAL within 30 days postoperatively. CAL was defined according to Reisinger: "clinically relevant anastomotic leakage, defined as extraluminal presence of contrast fluid on contrast-enhanced CT scans and/or leakage when relaparotomy was performed, requiring re-intervention".[18] Intraoperative leak testing was performed by all participating centers to prevent technical insufficient anastomoses. Furthermore, all patients received standard perioper-ative care according to the ERAS principles.

Statistical analysis

Statistical analysis was performed using SPSS version 22 (SPSS Inc. Chicago, IL, USA). Categorical variables are presented as numbers and percentages. Means and standard deviations (SD) are used for parametric continuous variables. Non-parametric continuous variables are expressed with medians and interquartile ranges (IQR). CAL rates were compared between patients with and without hyperglycemia with-in the total study population, and for diabetic and non-diabetic patients separately. Additionally, univariable logistic regression analyses with CAL as outcome variable evaluated the association between BG levels and CAL. Results are reported as odds ratios (OR) and 95% confidence interval (CI). For multivariable analyses, confounders were chosen based on previous research4 or defined as variables that changed OR's by more than 10% (change-in-estimate). The following confounders were included: sex, diabetes, preoperative anemia, history of smoking, duration of surgery, surgical approach, administration of epidural analgesia, intraoperative blood loss, and contamination. Associations between BG levels and CAL were further separately tested in diabetic and non-diabetic patients. Finally, surgery and anesthesiological-related data were compared between (1) diabetic patients with and without hyperglycemia and (2) non-diabetic patients with and without hyperglycemia. Comparisons within diabetic and non-diabetic patients were tested for significance using the Pearson x2 test or the Fisher's exact test. A P value of < 0.05 was considered statistically significant.

Results

The LekCheck study evaluated a total of 1821 patients. Of these, 180 patients were excluded due to emergency surgery, and 79 patients were excluded because of ≥ 10% missing data. Additionally, 88 patients were excluded as diabetic status and intraoperative BG level were unknown **(Figure 1)**, resulting in a study population of 1474 patients (52% men, mean age 68 years) for the current analysis. A total of 224 patients (15%) were known to have diabetes, and 365 patients (25%) were obese (BMI >30 kg/m^2). **Table 1** shows the clinical baseline characteristics.

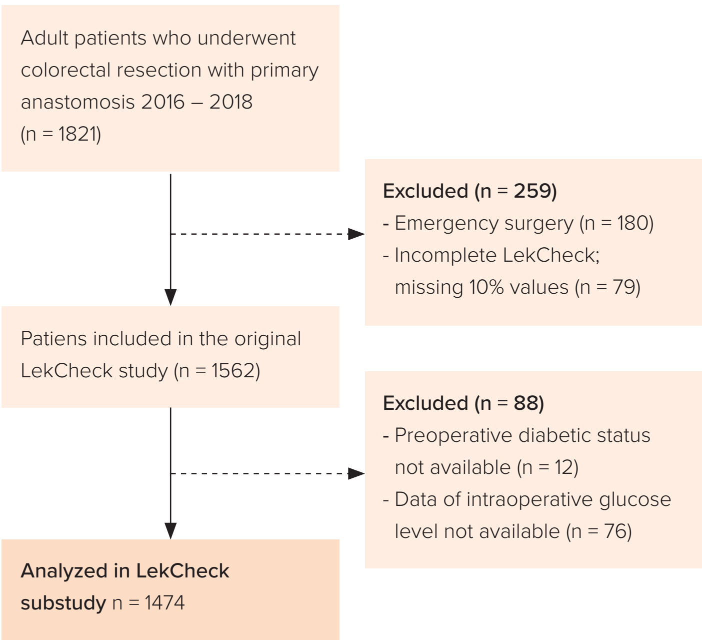

Figure 1. Flow diagram of study population according to inclusion and exclusion criteria.

Table 1. Baseline characteristics of the total study population.

	Total study population (n = 1474)
Age (years)[a]	68 (12)
Sex ratio (M:F)	770 : 704
Body mass index (kg/m^2)[a]	27 (4)
<25 kg/m^2	593 (41%)
25–30 kg/m^2	488 (34%)
≥ 30 kg/m^2	365 (25%)
Missing	28
American Society of Anesthesia classification	
I	228 (16%)
II	863 (59%)
III	359 (25%)
IV	18 (1%)
Missing	6
Diabetes	224 (15%)
Severe anemia[b]	53 (4%)
Missing	94
Current smoker	177 (13%)
Missing	73
Pack years ≥ 15 years	336 (28%)
Steroid use (excl. inhalers)	40 (3%)
Missing	4
Indication for surgery	
Malignant disease	1210 (82%)
Benign disease	261 (18%)
Missing	3
Neoadjuvant therapy	174 (12%)
None	1233 (88%)
5x5 radiotherapy	95 (7%)
Chemotherapy	33 (2%)
Chemoradiotherapy	46 (3%)
Missing	67

Values are numbers and percentages unless stated otherwise
[a] Values are means and standard deviations
[b] Hemoglobin level for male <10.47 g/dL (<6.5 mmol/L) and female <9.67 g/dL (<6.0 mmol/L)

3

Intraoperative blood glucose

Of the complete cohort, 737 patients (50%) had intra-operative hyperglycemia (≥126 mg/dL (≥7.0 mmol/L). Among them, 658 patients (89%) had a BG level of 126–200 mg/dL (7.0–11.1 mmol/L), whereas 78 patients (11%) had a BG level of >200 mg/dL (>11.1 mmol/L). Conversely, 171 patients (12%) had a BG level within normal ranges (80–100 mg/dL (4.4–5.5mmol/L), and a slightly elevated BG level of 101–125 mg/dL (5.5–7.0 mmol/L) was observed in 547 patients (37%). Only 20 patients, 1% of the complete study population, had in-traoperative hypoglycemia with a BG level of less than 80 mg/dL (<4.4 mmol/L). The distribution of BG levels of diabetic and non-diabetic patients is depicted in **Figure 2**. Although the incidence and severity of intraoperative hyperglycemia was higher in diabetic patients (80%) compared to non-diabetic patients, 45% of this latter population had intraoperative hyperglycemia (P<0.001).

Anastomotic leakage

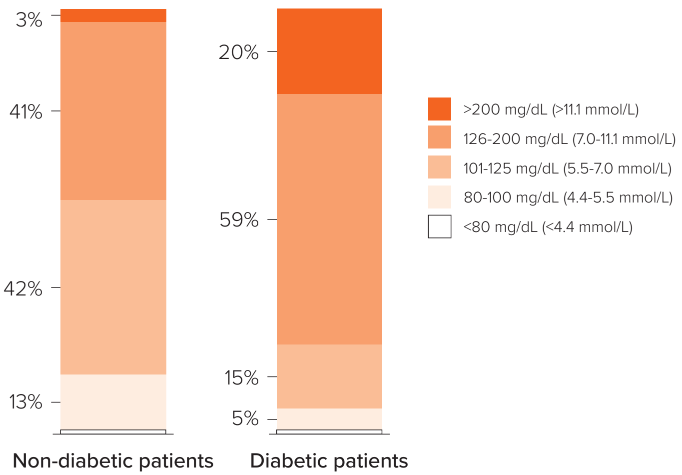

Figure 2. The distribution of blood glucose concentration levels for non-diabetic patients (n = 1250, 85% of total population) and diabetic patients (n = 224, 15% of total population).

A total of 129 patients (8.8%) developed CAL. Hyperglycemic patients had significantly higher CAL rates than normoglycemic patients (12% versus 5%, P<0.001). CAL rates did not significantly differ between diabetic and non-diabetic patients (12% versus 8%, P=0.058). As shown in **Figure 3a**, the risk of CAL in patients with an intraoperative BG level of 126–200 mg/dL (7.0–11.1 mmol/L) and ≥200 mg/dL (>11.1 mmol/L) were similar (12%). None of the

20 patients with intraoperative hypoglycemia developed CAL (subgroup is not shown). Additional logistic regression anal-yses showed that hyperglycemia (adj. OR 4.81, P=0.016) and severe hyperglycemia (adj. OR 4.70, P=0.046) were both independently associated with CAL. Results are visualized in **Table 2**.

Table 2. Logistic regression analysis of blood glucose (BG) subgroups for colorectal anastomotic leakage (CAL) among patients who underwent colorectal resection with primary anastomosis, stratified by diabetic status.

	Univariable OR (95% CI)	***P* value**	**Adjusted OR (95% CI)[a]**	***P* value**
Overall study population (n =1474)[b]				
BG <100 (<5.5)	1.00 (reference)		1.00 (reference)	
BG 100–125 (5.5–7.0)	1.37 (0.62–3.04)	0.433	2.44 (0.65–9.20)	0.189
BG 126–200 (7.0–11.1)	3.21 (1.52–6.80)	**0.002**	4.81 (1.34–17.29)	**0.016**
BG >200 (>11.1)	2.98 (1.11–8.04)	**0.031**	4.70 (1.03–21.50)	**0.046**
Without diabetes (n = 1250)[c]				
BG <100 (<5.5)	1.00 (reference)		1.00 (reference)	
BG 100–125 (5.5–7.0)	1.59 (0.65–3.92)	0.314	4.94 (0.63–38.65)	0.128
BG 126–200 (7.0–11.1)	3.98 (1.69–9.36)	**0.002**	11.99 (1.59–90.52)	**0.016**
BG >200 (>11.1)	5.12 (1.46–17.91)	**0.011**	16.97 (1.73–167.01)	**0.015**
With diabetes (n = 224)[d]				
BG <100 (<5.5)	1.00 (reference)		1.00 (reference)	
BG 100–125 (5.5–7.0)	0.77 (0.12–4.75)	0.768	0.93 (0.08–11.24)	0.956
BG 126–200 (7.0–11.1)	0.81 (0.16–3.95)	0.790	0.53 (0.06–4.63)	0.568
BG >200 (>11.1)	0.54 (0.10–3.32)	0.503	0.40 (0.04–4.57)	0.461

Values in parentheses are 95% confidence intervals
Blood glucose (BG) values are shown without units; mg/dL (mmol/L)
[a] Analyses are adjusted for sex, diabetes (in overall study population), preoperative anemia, history of smoking, duration of surgery, surgical approach, administration of epidural analgesia, blood loss, and contamination
[b] 1088 out of 1474 patients were included in the multivariable analysis
[c] 858 out of 1250 patients were included in the multivariable analysis
[d] 150 out of 224 patients were included in the multivariable analysis

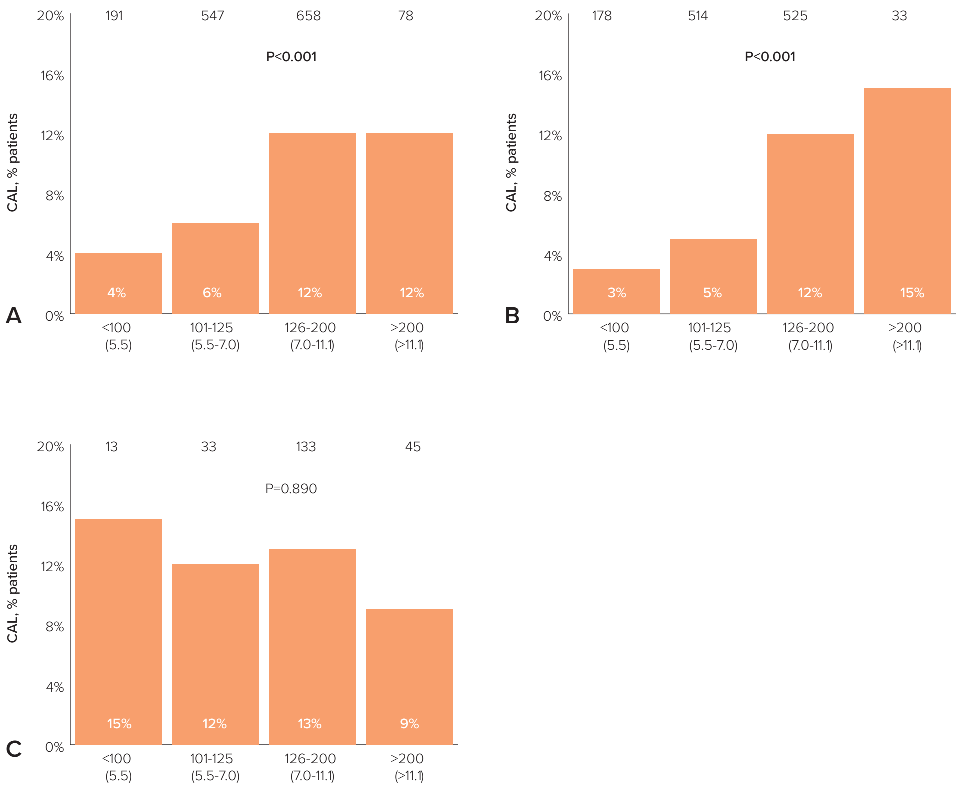

Figure 3. Risk of colorectal anastomotic leakage stratified by blood glucose subgroups in total study population (A) for non-diabetic patients (B) and for diabetic patients (C). Upper numbers (grey) are numbers of patients in subgroups. Glucose values are shown without units; mg/dL (mmol/L).

CAL Rates in diabetic and non-diabetic patients

Higher BG levels were seen in non-diabetic patients who developed CAL compared to those not having CAL (140 mg/dL (7.8 mmol/L) versus 126 mg/dL (7.0 mmol/L), P<0.001). Diabetic patients had higher BG levels compared to non-diabetic patients, but no difference was found between patients with or without CAL (156 mg/dL (8.7 mmol/L) versus 167 mg/dL (9.3 mmol/L), P=0.329).

When considering non-diabetic patients only, higher BG levels were associated with an increasing CAL risk (100–125 mg/dL (5.5–7.0 mmol/L) = 5% CAL versus 126–200 mg/dL (7.0–11.1 mmol/L) = 12% CAL versus >200 mg/dL (>11.1 mmol/L) = 15% CAL, P<0.001) **(Figure 3b)**.

In contrast, among diabetic patients, an increased risk of CAL was not observed (100–125 mg/dL (5.5–7.0 mmol/L) = 12% CAL versus 126–200 mg/dL (7.0–11.1 mmol/L) = 13%CAL versus >200 mg/dL (>11.1 mmol/L) = 9% CAL, P=0.890) **(Figure 3c)**. Multivariable logistic regression analyses among non-diabetic patients found that both hyperglycemia (adj. OR 11.99, P=0.016) and severe hyperglycemia (adj. OR 16.97, P=0.015) were independently associated with CAL. However, this association between intraoperative hyperglycemia (adj. OR 0.53, P=0.568) and severe hyperglycemia (adj. OR 0.40, P=0.461) and CAL was not observed in diabetic patients **(Table 2)**.

Patient-related factors

Of the non-diabetic patients, patients who had intraoperative hyperglycemia were older (68 versus 66 years, P<0.001), and a greater proportion had a BMI >30 kg/m^2 (26% versus 18%, P<0.001). Otherwise, there were no statistically significant differences in baseline data. Furthermore, among hyperglycemic patients, there was no significant difference in CAL risk in patients with or without obesity (14% versus 12%, P=0.628).

Surgical and anesthesiological-related factors

Among diabetic patients, less epidural analgesia was used (32% versus 49%, P=0.037), and more colorectal/ileorectal anastomoses (25% versus 11%, P=0.043) were performed in hyperglycemic patients compared to normoglycemic patients **(Table 3)**. Among non-diabetic patients, blood loss exceeding 100 mL and surgery exceeding 180 min were observed more often in hyperglycemic patients compared to normoglycemic patients (P<0.001). Also, intraoperative events occurred more often in hyperglycemic patients (16% versus 12%, P=0.020). Similarly to diabetic patients, less epidural analgesia was used in patients with hyperglycemia compared to normoglycemic patients (26% versus 38%, P<0.001). Participating hospitals recorded comparable leak rates, ranging from 6 to 13% in the hospitals that included more than 100 patients **(Supplementary Table A)**.

Table 3. Surgical and anesthesiological related factors for patients with and without diabetes.

	Diabetic patients			**Non-diabetic patients**		
	BG	BG	P	BG	BG	P
	<126 (<7.0)	≥126 (≥7.0)		<126 (<7.0)	≥126 (≥7.0)	
No. of patients	46 (21%)	178 (79%)		692 (55%)	558 (45%)	
Duration of surgery >180 minutes	11 (24%)	60 (35%)	0.200	148 (22%)	205 (38%)	**<0.001**
Missing	1	4		17	14	
Surgical approach			0.532			0.926
Open	9 (20%)	28 (16%)		102 (15%)	83 (15%)	
Laparoscopy	34 (74%)	137 (77%)		561 (81%)	438 (79%)	
Conversion	3 (7%)	13 (7%)		29 (4%)	35 (6%)	
Missing					2	
Contaminated field	3 (7%)	11 (6%)	0.918	29 (4%)	43 (8%)	**0.008**
Missing	1	2		5	4	
Anastomotic location			**0.043**			0.718
Ileocolonic/colocolonic	41 (89%)	134 (75%)		531 (77%)	433 (78%)	
Colorectal/ileorectal	5 (11%)	44 (25%)		161 (23%)	125 (22%)	
Stoma			0.673			0.237
Ileostomy	3 (7%)	12 (7%)		50 (7%)	46 (8%)	
Colostomy	0 (0%)	3 (2%)		8 (1%)	2 (1%)	
Temperature <36°	12 (26%)	36 (20%)	0.388	136 (20%)	111 (20%)	0.926
Antibiotic prophylaxisa	13 (30%)	4 (26%)	0.651	163 (24%)	121 (22%)	0.459
Missing	2	6		19	18	
Vasopressors	19 (42%)	87 (49%)	0.425	241 (35%)	212 (38%)	0.253
Missing	1			2	1	
Blood loss >100 ml	10 (22%)	42 (24%)	0.721	106 (15%)	136 (24%)	**<0.001**
Missing	3	16		79	54	
Blood transfusion	3 (7%)	11 (6%)	0.932	14 (2%)	7 (1%)	0.293
Epidural analgesia	22 (49%)	7 (32%)	**0.039**	262 (38%)	146 (26%)	**<0.001**
Missing	1	2		5	3	
Intraoperative event[b]	11 (24%)	33 (19%)	0.413	80 (12%)	90 (16%)	**0.020**

Data are presented as n (%) unless otherwise noted
Blood glucose (BG) values are shown without units; mg/dL (mmol/L)
A P<0.05 was considered statistically significant
[a] Refer to inadequate timing of administration of antibiotics; < 15 or > 60 min prior to surgery
[b] Intraoperative events include hypoxic events, hypertension, hypercarbia, bradycardia, hypotension, embolism, reanimation, more extensive resection than planned, serosa lesions, bladder and ureteral injuries, intraoperative bleeding, or splenectomy

Discussion

This study investigated the association between intraoperative BG levels and CAL in patients undergoing elective colorectal surgery. The incidence and severity of hyperglycemia is associated with a higher risk of CAL. Interestingly, however, this effect was observed in non-diabetic patients only. Intraoperative hyperglycemia occurred in nearly half (45%) of the non-diabetic patients, resulting in an almost five-fold higher risk of CAL. The results of the present study suggest a concise monitoring and optimization of intraoperative hyperglycemia regardless of the underlying mechanism.

The relationship between perioperative hyperglycemia and postoperative complications after colorectal surgery, specifically in non-diabetic patients, has been reported previously.[3,19–22] For example, Kotagal et al., reporting on 40,836 patients, showed a significantly higher risk on adverse events in hyperglycemic patients without diabetes,[19] and Margonis et al. reported that non-diabetic patients who developed hyperglycemia on the day of surgery had a six-fold increased risk of infectious complications after colorectal surgery.[20] Moreover, a study of 2628 patients undergoing colorectal resection reported that in non-diabetic patients the degree of hyperglycemia (measured within 48 h postoperatively) was associated with an increased risk of sepsis, reoperation, and length of hospital stay.[3] Our findings are in line with these results, and we suggest that more attention should be given to a fundamental understanding for this relationship, as a subject of future studies.

Although we have identified a significant association of intraoperative hyperglycemia, this by itself does not imply that it directly leads to CAL. Major surgery causes a change in glucose metabolism, including a reduction in glucose uptake and an increase in glucose production, also known as a state of insulin resistance.[23] Due to a glucose overload, cells produce oxygen free radicals, which in turn cause inflammation.[13,23] The results of the current study demonstrate that among non-diabetic patients, those presented with hyperglycemia were more likely to have undergone longer procedures with more blood loss and higher rates of intraoperative events, factors that may indicate greater levels of surgical stress. In contrast, these differences were not observed in diabetic patients, which may indicate that hyperglycemic non-diabetic patients were experiencing a higher surgical stress response causing higher intraoperative BG levels. Alternatively, some hypothesize that surgical stress may lead to a less prominent BG increase in diabetic patients compared to non-diabetic patients, given that insulin resistance is already present in diabetic patients.[19,20] Future research will be required to establish whether it is the magnitude of the stress response which creates an environment leading to a higher risk of CAL rather than high BG alone.

Given that non-diabetic patients who had intraoperative hyperglycemia were older and more frequently obese, an alternative explanation of our findings may be related to patients having prediabetes or undiagnosed diabetes. Prediabetes is characterized by blood sugar levels higher than normal values but not high enough to be considered as type 2 diabetes.[24] Prediabetes is associated with increased incidences of cardiovascular disease, obesity, dyslipidemia (elevated triglyceride and low high-density lipoprotein cholesterol), hypertension,[25] and microvascular dysfunction.[26] The combination of these comorbidities is defined as the metabolic syndrome.[27] The pathophysiology of these interrelated components is complex and not fully understood; however, excessive inflammation and impaired microvascular circulation are characteristically observed.[28] In theory, these events may contribute to a disturbed anastomotic healing. In a study of 120 patients without known diabetes undergoing major colorectal surgery, the prevalence of undiagnosed diabetes was 25%.[29] Preoperative diagnostics not captured in the current study, such as the glycosylated hemoglobin (Hb) A1c or the 2-h oral glucose tolerance test, can be used to identify patients with prediabetes or diabetic patients with poor preoperative glycemic control[30] and should be part of future CAL research. A comprehensive work-up to potentially diagnose new-onset diabetes to appropriately implement preoperative measures can be considered.

There are limited studies investigating strict glycemic control in patients undergoing colorectal surgery. In 2001, van den Berghe et al. were the first to undertake a randomized controlled study comparing conventional treatment versus strict glycemic control by tailored insulin therapy in a surgical intensive care unit. Morbidity and mortality rates were lower in the intervention group, independently from the patients' diabetic status.[31] Surprisingly, the NICE-SUGAR study group reported an opposite effect demonstrating increased mortality in surgical patients treated with intensive insulin therapy.[32] Therefore, these and other studies summarized in a Cochrane review showed that there is currently limited evidence to support tight perioperative glycemic control.[33] Recent research projects have focused on interventions including preoperative exercise and dietary instructions in order to prevent immobilization and starvation in an effort to optimize the patients perioperative glycemic state to improve postoperative outcomes.[12,34] In view of this, the time between oncological diagnosis and surgical treatment should be used to screen, monitor, and control the glycemic state, with the aim to lower perioperative hyperglycemia rates and prevent complications. This may be an initial simple first step prior to embarking upon measures aimed at complex intraoperative BG monitoring and correction.

The present study has several limitations. Firstly, the LekCheck study focused on the identification of perioperative factors related to CAL. BG was therefore consistently but one-

off recorded. However, it is known that BG levels fluctuate during and after surgery (glucose variability),[35] and intraoperative BG abnormalities may persist in the postoperative phase.[11,36] Unfortunately, in the current study, serum BG levels were not monitored postoperatively. This potential con-founder cannot be ignored, with anastomotic healing possibly influenced by glucose levels not measured postoperatively. Therefore, future studies should aim to expand glycemic monitoring also to the postoperative period. Additionally, BG was taken from capillary source by finger-prick testing.The accuracy of this type of intraoperative testing may be questioned in critical patients because several conditions (e.g., hypotension, edema, and anemia) can affect the BG values.[37] However, in view of the observational and multicenter nature of the study, we chose to use a minimally invasive and quick test which is generally used in routine clinical practice. Secondly, the LekCheck study was not powered to investigate the association between hyperglycemia and CAL in non-diabetic and diabetic patients separately. The fact that the current study found no association between hyperglycemia and CAL india-betic patients could therefore be a reflection of the limited sample size in this subgroup. Furthermore, the number of patients included in the logistic regression analyses was low due to missing data on confounding factors. This may have biased our estimates. Thirdly, nodistinction has been made between type 1 and 2 diabetic patients. Patients with diabetes type 1, often treated with insulin, might have received a more intensive regulation compared to patients with type 2. Finally, it was estimated that 50% of the participating hospitals used the corticosteroid dexamethasone, known to increase BG levels, with the aim to prevent postoperative nausea and vomiting,[38] but its use was not routinely recorded.

With the results of the current study, we hope to increase awareness and increase the interaction between the anesthesiologist, the surgeon, and the internal medicine doctor. Doing so, perioperative glycemic management should be the combined effort of all disciplines involved in colorectal perioperative care.

Conclusion

The current study shows an association between the incidence and severity of intraoperative hyperglycemia and the risk of a CAL in patients undergoing colorectal surgery. The fact that this effect was observed in non-diabetic patients only requires further investigation. Whether hyperglycemia per se is a modifiable risk factor for CAL or whether it is an epiphenomenon or a marker of other risk factors (e.g., greater surgical stress) leading to CAL is a focus of future research. Our results emphasize that routine perioperative glycemic screening and monitoring should be considered as a potential target for optimizing future care.

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chapter

four

The emerging role of preoperative anemia management

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Preoperative anemia and postoperative outcomes

Preoperative anemia is common among patients undergoing surgery for colorectal cancer, affecting 40% of the population.[1] According to the World Health Organization (WHO), anemia is defined as a condition in which the hemoglobin concentration is < 8 mmol/L (13 g/dL) in men and < 7.5 mmol/L (12 g/dL) in women.[2] Anemia prior to surgery is associated with fatigue[3], the risk of perioperative blood transfusions[4] and increased morbidity and mortality[5-7]. The multicenter LekCheck study, evaluating potentially modifiable perioperative factors associated with colorectal anastomotic leakage, reinforces these findings and demonstrated that preoperative anemia was the single most important contributor to anastomotic leakage.[8] These data were further explored in an additional analysis **(Table 1)**. Results indicate that patients with a preoperative hemoglobin level of less than 7 mmol/l have a one in four risk of developing anastomotic leakage.

Table 1. Distribution of hemoglobin levels and risk of colorectal anastomotic leakage (n = 1.458)

	N	%	Risk of CAL, N % (n = 124)	Univariate analysis OR (95% CI)	P value
< 6.5 mmol/L	121	8.3%	35 (28.9%)	8.73 (5.03 – 15.14)	**< 0.001**
6.5 - 6.9 mmol/L	99	6.8%	23 (23.2%)	6.49 (3.54 – 11.89)	**< 0.001**
7.0 - 7.4 mmol/L	154	10.6%	15 (9.7%)	2.31 (1.20 – 4.47)	**0.012**
7.5 - 7.9 mmol/L	184	12.6%	11 (6.0%)	1.36 (0.66 – 2.81)	0.400
8.0 - 8.4 mmol/L	294	20.2%	13 (4.4%)	0.99 (0.50 – 1.95)	0.982
≥ 8.5 mmol/L	606	41.6%	27 (4.5%)	1.00 (ref)	-

Abbreviations: CAL, colorectal anastomotic leakage; CI, confidence interval; OR, odds ratio

The challenges of preoperative anemia management

As briefly summarized above, preoperative anemia is recognized in literature as an important risk factor for poor surgical outcome. This realization has led to the development of multiple guidelines on perioperative strategies that address preoperative anemia and improve patient outcomes.[9,10] Yet, in clinical practice, anemia management in preoperative setting, is under-recognized and underappreciated. Presumably, due to a number of issues with regard to diagnosis and treatment.

Diagnostic approach

According to multiple guidelines, patients undergoing major abdominal surgery are advised to have their hemoglobin checked prior to surgery.[11,12] When a patient is considered anemic, further investigation is required in order to identify underlying causes. The latest Enhanced Recovery After Surgery (ERAS) guidelines, for instance, state that “all causes of anemia should be investigated appropriately and corrected”.[12] But what exactly does this mean? This lack of clear guidance has made translation into clinical practice difficult.

Anemia in patients with CRC is affected by multiple complex processes, frequently leading to iron deficiency (i.e. absolute and functional iron deficiency).[13,14] In some cases, anemia derives from less common mechanisms such as chronic kidney disease, vitamin B12 or folate deficiency, hemolysis or bone marrow disease. Regarding iron deficiency, main causes arise from gastro-intestinal tumor-induced blood loss, inadequate iron intake (both resulting in inadequate iron stores; absolute deficiency), and/or impaired iron homeostasis due to systemic inflammation. The latter causes functional iron deficiency, signifying insufficient iron mobilization or supply for erythropoiesis despite adequate iron stores.[13]

The diagnosis of iron deficiency anemia (IDA) in cancer patients can be demanding.[14,15] Next to serum ferritin, which in general reflects iron stores in the best way, standard laboratory tests include measurements of mean corpuscular volume (MCV), serum iron, transferrin, and serum iron/transferrin saturation (TSAT). The challenge is that serum ferritin, which is an acute phase protein, is not considered to be a good indicator for iron stores during inflammatory state. Whereas normally a cut-off value of < 30 µg/l indicates absolute iron deficiency, in cancer patients a cut-off value of < 100 µg/l is more appropriate.[13] Therefore, the use of modern indicators for IDA such as the transferrin/log(ferritin) ratio and reticulocyte hemoglobin, have proven to be useful when test results are inconclusive.[15,16]

In the Netherlands, there is a high variability in the diagnostic approach regarding anemia. Strikingly, results from physicians in 73 hospitals in the Netherlands (97%) demonstrated that in more than 60% of the hospitals, further laboratory investigation with iron variables (i.e. iron, ferritin, transferrin, transferrin saturation) was not performed.[17]

Treatment

As literature stresses the potential of anemia treatment for patients with CRC scheduled for surgery, scientific evidence on treatment strategies is limited. The success of treatment depends on several factors. First, it is important to treat underlying pathological conditions. In case of IDA, iron supplementation is recommended.[10,11] Intravenous iron, such as ferric carboxymaltose (a single dose of 1000 mg), is shown to be safe, more effective and better tolerated than oral iron.[18] Several studies have shown that the administration of intravenous iron in preoperative setting significantly increases hemoglobin concentrations and lowers blood transfusions perioperatively.[19-21] To date, evidence that preoperative anemia treatment improves perioperative outcome in terms of morbidity and mortality, is limited.[11] Recently, the results of the PREVENTT trial, showed no clinical benefit (no reduce in blood transfusion, mortality, in-hospital complications, length of hospital stay and benefits in quality of life) in giving intravenous iron preoperatively to anemic patients undergoing major abdominal open surgery.[19] Previous studies, investigating the treatment effect of intravenous iron, are limited by insufficient treatment interval (minimum of 10 days before surgery), which might have weakened results.[19,26] Currently, evidence from the FIT trial, a large multicenter randomized controlled trial, and the international prospective Double Check study is awaited.[22]

Secondly, close collaboration between (para)medical disciplines involved in colorectal care is essential. Perioperative anemia management is, per definition, multidisciplinary, and involves active participation of surgeons, anesthesiologists, gastroenterologists, oncologists, case managers, dieticians, clinical chemists, and nurses. For this reason, it is important to identify a key leader in each hospital responsible for the management.[17] Moreover, preoperative anemia management should be started as early as possible, preferable at the time of colonoscopy or once surgery is indicated. This may require a profound change in the colorectal care pathway.

There is still much debate about the role of iron supplementation for anemic patients with functional iron deficiency.[13] While most previous studies did not distinguish between absolute and functional IDA, the efficacy of iron supplementation seems highest in patients with absolute iron deficiency.[21] Some experts even have concerns about possible detrimental effects of iron supplementation on colorectal tumor growth. Hypothetical, cancer-related

anemia leading to impaired iron homeostasis could be a mechanism of the body to prevent tumor growth by the inhibition of cell proliferation.[23]

Since red blood cells have a 120-day lifespan, changes in iron status after iron treatment may not always be visible in the preoperative period when rechecking the hemoglobin concentration.[24] As reticulocytes mature in 2 or 3 days, measuring the hemoglobin content of reticulocytes is a fast, accurate, and inexpensive way to monitor the effect of iron treatment.[24]

In conclusion, the preoperative period is a potential window of opportunity to address anemia in patients with colorectal cancer. We recommend timely screening, specifically for underlying causes, as they require different management. With regard to IDA, more studies are needed to draw definite conclusions on the suggested benefits and potential risks of iron therapy.

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chapter five

Metabolic syndrome; associations with adverse outcome after colorectal surgery. A systematic review and meta-analysis

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Abstract

Background and objectives:
Increasing evidence shows that patients with Metabolic Syndrome (MetS) are at risk for adverse outcome after abdominal surgery. The aim of this study was to investigate the impact of MetS and preoperative hyperglycemia, as an individual component of MetS, on adverse outcome after colorectal surgery.

Methods:
A literature review was systematically performed according to the PRISMA guidelines. Inclusion criteria were observational studies that evaluated the relationship between MetS or preoperative hyperglycemia and outcomes after colorectal surgery (i.e. any complication, severe complication defined as Clavien-Dindo grade ≥ III, anastomotic leakage, surgical site infection, mortality and length of stay).

Results:
Six studies (246.383 patients) evaluated MetS and eight studies (9.534 patients) reported on hyperglycemia. Incidence rates of MetS varied widely from 7% to 68% across studies. Meta-analysis showed that patients with MetS are more likely to develop severe complications than those without MetS (RR 1.62, 95% CI 1.01–2.59). Moreover, a non-significant trend toward increased risks for any complication (RR 1.35, 95% CI 0.91–2.00), anastomotic leakage (RR 1.67, 95% CI 0.47–5.93) and mortality (RR 1.19, 95% CI 1.00–1.43) was found. Furthermore, preoperative hyperglycemia was associated with an increased risk of surgical site infection (RR 1.35, 95% CI 1.01–1.81).

Conclusion:
MetS seem to have a negative impact on adverse outcome after colorectal surgery. As a result of few studies meeting inclusion criteria and substantial heterogeneity, evidence is not conclusive. Future prospective observational studies should improve the amount and quality in order to verify current results.

Introduction

Colorectal surgery challenges the body to withstand major stress. Surgical trauma induces several physiological and metabolic changes, which negatively influences recovery.[1–3] It has been suggested that patients with Metabolic Syndrome (MetS), who are at increased risk of the development of cardiovascular disease[4], are also at high-risk for metabolic distress around surgery[5] and subsequently, for adverse outcome after abdominal surgery.[6]

MetS is characterized and defined by a cluster of interrelated metabolic abnormalities that include hyperglycemia, dyslipidemia, abdominal obesity and hypertension.[7] The worldwide prevalence of MetS is high, affecting around 25% of the adult population, and rates are increasing dramatically.[8] The pathophysiology of MetS is highly complex and not clear yet. According to many experts, insulin resistance and visceral obesity stand out as primary causes of MetS.[9–11]

Several individual components of MetS are well-established risk factors for adverse outcome after colorectal surgery.[12–15] Literature reporting on the relationship of the clustering of these components and adverse outcome after colorectal surgery is controversial. Moreover, the predictive value of hyperglycemia, as an individual component of MetS, remains insufficiently defined. Hence, the aim of the present systematic review and meta-analysis was to give an overview on the current best evidence on the impact of MetS and preoperative hyperglycemia, as an individual component of MetS, on short-term outcome after colorectal surgery.

Methods

Study design

A systematic literature review was performed and reported in line with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[16] and AMSTAR (Assessing the methodological quality of systematic reviews) guidelines. To define our research question, the CHARMS (checklist for critical appraisal and data extraction for systematic reviews of prediction modelling studies) was used[17] including the following key points: Population, Index prognostic factors, Comparison, Outcome, Timing and Setting (PICOTS).[18] A protocol was registered in the international prospective register of systematic reviews (PROSPERO registration number: CRD42020199913). Ethical approval was not required for this review article.

Search strategy

Electronic databases; MEDLINE (from PubMed), EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library were searched through 02-07-2020 for relevant studies. Key words were: 'metabolic syndrome', 'hyperglycemia', 'colorectal surgery', 'postoperative outcome'. Articles published before 1998 were not screened, since MetS was officially defined in 1998 by the World Health Organization.19 Duplicate studies were removed.

Study selection

Eligible articles were published peer-reviewed retrospective and prospective observational studies (e.g. cohort, cross-sectional and case-control studies) written in English. Inclusion criteria were studies that reported on adult human patients (18 years or older) who had undergone colorectal surgery for malignant or benign disease and evaluated the relationship between MetS (compared with non-MetS) or preoperative hyperglycemia (compared with normoglycemia) and adverse postoperative outcome. Studies were included if they had used a definition of MetS as stated by one or more of the following expert groups: 1) the World Health Organization (WHO)19, 2) the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI)10, 3) the International Diabetes Federation (IDF)11 and 4) the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III).20 One or more of the following measures to define hyperglycemia had to be used: 1) fasting plasma glucose (FPG), 2) oral glucose tolerance test, 3) hemoglobin A1c (HbA1c) according to the American Diabetes Association and WHO guidelines or 4) random blood glucose (BG). The cut-off value for hyperglycemia was not predefined; definitions were used as stated by the authors. Studies assessing one of the following outcomes: any complication, severe complication (defined as Clavien-Dindo grade III or higher), colorectal anastomotic leakage (CAL), surgical site infection (SSI), and mortality within 30–90 days after surgery and/or length of hospital stay (LoS) were included. Furthermore, studies were excluded if they were systematic or narrative reviews, meta-analyses, opinions, clinical guidelines, editorials, case reports or congress abstracts. Furthermore, studies evaluating intra- or postoperative hyperglycemia, studies reporting on glucose continuously instead of categorised or studies evaluating the impact of an individual component of MetS rather than the whole syndrome, were excluded. Inclusion and exclusion criteria are summarized in the supplemental data **(Supplementary Table A)**.

All retrieved articles were independently screened by two authors (M.R. and C.S.) for titles and abstracts. In case of uncertainty or disagreement, abstracts were discussed for consensus or were re-reviewed by a third reviewer (A.L.) until consensus was reached. The remaining

articles were independently read (full-text) by the same authors. Studies that fulfilled the inclusion criteria were hand-searched for additional articles in the final study selection.

Data collection

The following data were extracted from the included studies: name of first author, year of publication, country where the study was performed, study design, sample size, age, gender, number and proportion of cases (MetS or hyperglycemic patients) and controls (non-MetS or normoglycemic patients), definitions, surgery type, setting, outcomes and follow-up time.

Critical appraisal

The Newcastle-Ottawa Scale (NOS), a validated tool for evaluating the quality of non-randomized studies, was used to evaluate the methodological quality of the included studies.21 The NOS is based on three domains; selection (0–4 points), comparability (0–2), and outcomes of interest (0–3 points). A total score of 8–9 is considered as high, 6–7 as moderate, and ≤5 as low level of quality. Risk of bias was independently rated by two authors (M.R. and C.S.).

Statistical analysis

Outcomes were reported as incidence rates and proportions (for any complication, severe complication, CAL, SSI and mortality) or means/ medians with standard deviations/ interquartile range (for LoS). A meta-analysis was conducted if there were at least two compatible studies that reported on an outcome of interest. Heterogeneity across studies was assessed visually using forest plots and statistically using the chi-squared test, in which a P value < 0.10 was accepted to conclude presence of heterogeneity. Furthermore, the I 2 was calculated, which represents the proportion of total variance between studies that is explained by heterogeneity. Heterogeneity was defined as high (I2=75%-100%), moderate (I2=50–75%), low (I2=25–50%) or absent (I2=0–25%). Meta-analyses were performed with the use of the Mantel-Haenszel method to run the random and, fixed-effects model. The random-effects model was used in the presence of heterogeneity (either chi-squared test P < 0.10 or I2>75%). Data was pooled to calculate relative risks with 95% confidence interval (CI) on each outcome. A P value less than 0.05 was considered statistically significant. Sensitivity analyses were performed in order to examine the impact of including or excluding studies in the meta-analyses based on variance in follow-up time. Statistical analyses were performed using Review Manager software 5.4.

Results

Study selection

A total of 2.278 applicable records were initially identified after removal of duplicates. Based on titles and abstracts, 2.214 studies were excluded, remaining 64 studies to be assessed in full-text. Of those, thirteen studies met the inclusion and exclusion criteria. The reference lists of included studies were checked for additional relevant studies, not providing extra studies **(Figure 1)**.

Characteristics of studies that assessed MetS

As can be seen in **Table 1**, six studies reported on MetS.[22–27]. The majority of the included studies were retrospective observational studies reporting on both colon and rectal surgery. Two out of six studies were classified high-quality level and four studies as moderate level of quality. Risk of bias assessments are presented in Supplementary Table B. The combined study population was 246.383 patients (range 114–152.952 patients per study). Among the included studies, incidence rates of MetS varied widely from 7% to 68%, and multiple definitions of MetS were used. Three studies22–24 used the NCEP ATP III criteria and two studies[26,27] used the AHA criteria to define MetS. One study assessed MetS by using the NCEP ATP III, AHA and IDF criteria[25]. The highest prevalence of MetS (40–68%) was reported by studies that used the AHA criteria.

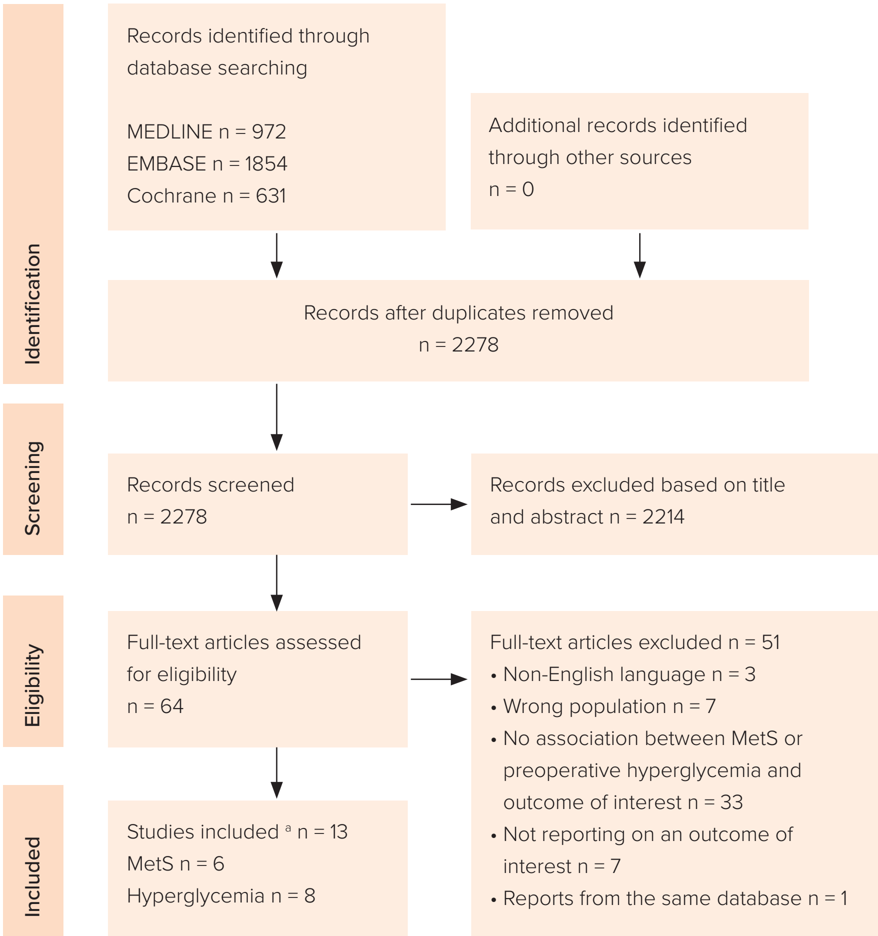


Figure 1. PRISMA Flow diagram [a] one study reported both on the association of MetS and hyperglycemia.

Table 1. Characteristics of studies that addressed metabolic syndrome and adverse outcome after colorectal surgery

Study, Year	Country	Design	Definition MetS a	Sample size	MetS cases, N (%)	Controls, N	Surgery type	Setting	Age [b]	Study quality [c]
Zarzavadjian et al. 2018 22	France	RCS	ATP III	1.236	85 (7%)	1.152	Colon	ND	64 (16-93)	7
Akinyemiju et al. 2018 23	USA	RCS	ATP III	152.952	10.543 (7%)	142.409	Colorectal	ND	ND	7
Shariq et al. 2019 24	USA	RCS	modified ATP III d	91.566	7.603 (8%)	83.963	Colorectal	Elective	66 (14)	9
Goulart et al. 2017 25	Portugal	PCS	ATPIII AHA IDF	134 e	46 (41%) ATPIII 79 (68%) AHA 71 (67%) IDF	67 38 35	Colorectal	Elective	68 (13)	7
Lohsiriwat. et al. 2010 26	Thailand	PCS	AHA	114	42 (37%)	72	Colorectal	Elective	61 (29-91)	7
Zhou et al. 2019 27	China	RCS	AHA	381	153 (40%)	228	Rectal	Elective	65 (16)	9

[a] National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III): three of the following conditions: abdominal obesity, elevated triglycerides, reduced high-density lipoprotein, hypertension, diabetes or glucose intolerance (fasting plasma glucose ≥ 110 mg)
American Heart Association/National heart, Lung and Blood Institute Scientific Stagement (AHA): three of the following conditions: abdominal obesity, elevated triglycerides, reduced high-density lipoprotein cholesterol, hypertension, diabetes or glucose intolerance (fasting plasma glucose ≥ 100 mg)
International Diabetes Federation (IDF): abdominal obesity plus two of the following conditions: elevated triglycerides, reduced high-density lipoprotein cholesterol, hypertension, or elevated fasting plasma glucose (≥ 100 mg/dL or diabetes type 2).
[b] values are in mean (SD) or median (range)
[c] scored according to the Newcastle-Ottawa Scale
[d] did not include dyslipidemia (i.e. elevated triglycerides, reduced high-density lipoprotein cholesterol) in MetS definition
[e] MetS could not be defined in all included study patients.
Abbreviations: MetS, metabolic syndrome, ND, not determined; PCS, prospective cohort study; RCS, retrospective cohort study

Metabolic syndrome and outcome

Any postoperative complication. All studies assessed any complication after surgery.[22–27] **(Table 2)** A significantly increased complication risk for patients with MetS was seen in three studies.[24, 26,27] All but one study could be included in meta-analysis, resulting in a total sample size of 93.431 patients. Pooled analysis demonstrates a higher complication rate for patients with MetS **(Figure 2a)**, however, this difference was not statistically significant (RR 1.35; 95% CI: 0.91–2.00, P = 0.13). Heterogeneity was high (I2 = 85%, P < 0.01). One study, not included in the meta-analysis reported a 7% decreased odds of postoperative complications for patients with MetS (significance not determined).[23]

Table 2. Summary of outcomes of studies that addressed metabolic syndrome and adverse outcome after colorectal surgery.

Study	Follow-up	Outcome of interest	Outcome measures
Zarzavadjian et al. [22]	≤ 90 days	Any complication	Incidence rate (%)
		Severe complication	Incidence rate (%)
		Anastomotic leakage	Incidence rate (%)
		Mortality	Incidence rate (%)
		Length of stay	Median
Akinyemiju et al. [23]	ND	Any complication	Adjusted OR (95% CI)
		Mortality [a]	Adjusted OR (95% CI)
Shariq et al. [24]	≤ 30 days	Any complication	Incidence rate (%), adjusted OR (95% CI)
		Surgical site infection	Incidence rate (%), adjusted OR (95% CI)
		Mortality	Incidence rate (%), adjusted OR (95% CI)
		Length of stay	Mean (SD), adjusted OR (%) b
Goulart et al. [25]	≤ 30 days	Any complication	Incidence rate (%)
		Anastomotic leakage	Incidence rate (%)
Lohsiriwat. et al. [26]	≤ 30 days	Any complication	Incidence rate (%), adjusted OR (95% CI)
		Mortality	Incidence rate (%)
		Anastomotic leakage	Incidence rate (%)
		Length of stay	Mean
Zhou et al. [27]	≤ 30 days	Any complication	Incidence rate (%), adjusted OR (95% CI)
		Severe complication	Incidence rate (%)
		Anastomotic leakage	Incidence rate (%)
		Mortality	Incidence rate (%)
		Length of stay	Median (IQR)

Abbreviations: CI, confidence interval; IQR, interquartile range; ND, not determined; OR, odds ratio; SSI, surgical site infection; SD, standard deviation [a] In-hospital mortality. [b] Adjusted OR presented for prolonged length of stay, defined as length of stay above 75[the] percentile.

5

Severe complication. Two studies[22,27] comprising 1.617 patients, reported the incidence of severe complications. Meta-analysis using the fixed-effects model shows that patients with MetS are significantly at higher risk of severe complications compared to patients without MetS (RR 1.62, 95% CI: 1.01–2.59, P = 0.04, I^2 = 59%, P = 0.12) **(Figure 2b)**.

Anastomotic leakage. Four studies[22,25–27] involving 1.844 patients were included in the analysis regarding the association of MetS and CAL. All four studies did not find a significant association between MetS and CAL. Meta-analysis shows a higher risk of CAL for patients with MetS (RR of 1.67 and 95% CI: 0.47–5.93; **Figure 2c**), but this difference was not statistically significant. Heterogeneity was moderate (I^2 = 65%, P = 0.04).

Surgical site infection. Only, Shariq et al.[24] evaluated SSI and found MetS to be an independent predictor of superficial (OR = 1.46, 95% CI, 1.32–1.60, P < 0.001) and deep SSI (OR = 1.40, 95% CI, 1.15–1.70, P < 0.001).

Mortality. Five studies evaluated mortality.[22–24,26,27] Three studies could be included in the meta-analysis, giving a total sample size of 93.183 patients for evaluation. The pooled analysis shows a higher risk of mortality for patients with MetS (RR of 1.19, 95% CI: 1.00–1.43, P = 0.06), however this difference was not statistically significant **(Figure 2d)**. Heterogeneity was not observed (I^2 = 0%, P = 0.78). No patients died in the study of Lohsiriwat et al.[26] Akinyemiju et al. [23] did not report incidence rates, but observed a lower odds of in-hospital mortality for patients with MetS (OR: 0.41, 95% CI: 0.35–0.49).

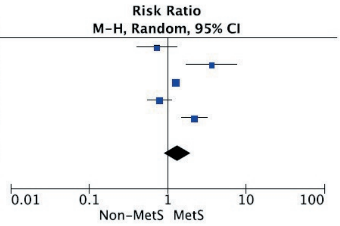
Length of stay. Four studies compared LoS for patients with and without MetS.[22,24,26,27] An estimation of an overall pooled effect could not be assessed. A significantly longer LoS for patients with MetS was reported by Lohsiriwat et al.[26] (11.2 versus 8.1 days, P = 0.006) and Shariq et al. [24] (for laparoscopic procedures 6.0 versus 5.5 days, P < 0.001, for open procedures 9.1 versus 8.5 days, P < 0.001). The remaining two studies observed comparable LoS between patients with and without MetS (7 versus 7 days, P = 0.721 and 14.4 versus 14.0 days, P = 0.264).[22,27]

Sensitivity analyses. While the majority of the studies reported on 30-day postoperative outcome, one study had a 90-day follow-up.[22] After exclusion of this study, the pooled risk estimates increased little for any complication (RR from 1.35 to 1.58) and CAL (RR from 1.67 to 2.82) (**Supplementary Figure 1a–c**). Risk estimates for any complication and CAL were similar when using incidence rates of MetS according to the AHA or IDF criteria for Goulart et al.[25]

a

Study or Subgroup	MetS Events	MetS Total	Non MetS Events	Non MetS Total	Weight	Risk Ratio M-H, Random, 95% CI
Goulart et al. 2017	12	46	24	67	16.7%	0.73 [0.41, 1.30]
Lohsiriwat et al. 2010	17	42	8	72	13.5%	3.64 [1.72, 7.71]
Shariq et al. 2019	2150	7603	18681	83963	26.5%	1.27 [1.22, 1.32]
Zarzavadjian et al. 2018	23	85	397	1151	21.8%	0.78 [0.55, 1.12]
Zhou et al. 2019	53	153	36	228	21.5%	2.19 [1.51, 3.18]
Total (95% CI)		**7929**		**85481**	**100.0%**	**1.35 [0.91, 2.00]**
Total events	2255		19146			

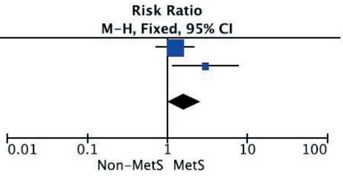
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 26.42$, df = 4 ($P < 0.0001$); $I^2 = 85\%$
Test for overall effect: Z = 1.51 (P = 0.13)



b

Study or Subgroup	MetS Events	MetS Total	Non MetS Events	Non MetS Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Zarzavadjian et al. 2018	12	85	130	1151	78.8%	1.25 [0.72, 2.16]
Zhou et al. 2019	12	153	6	228	21.2%	2.98 [1.14, 7.77]
Total (95% CI)		**238**		**1379**	**100.0%**	**1.62 [1.01, 2.59]**
Total events	24		136			

Heterogeneity: $Chi^2 = 2.41$, df = 1 ($P = 0.12$); $I^2 = 59\%$
Test for overall effect: Z = 2.01 (P = 0.04)



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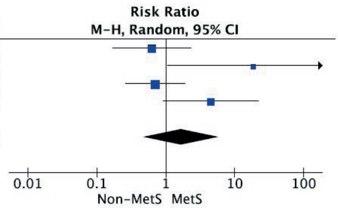
c

Study or Subgroup	MetS Events	MetS Total	Non MetS Events	Non MetS Total	Weight	Risk Ratio M-H, Random, 95% CI
Goulart et al. 2017	3	46	7	67	28.7%	0.62 [0.17, 2.29]
Lohsiriwat et al. 2010	5	42	0	72	13.2%	18.67 [1.06, 329.50]
Zarzavadjian et al. 2018	4	85	77	1151	33.0%	0.70 [0.26, 1.88]
Zhou et al. 2019	6	153	2	228	25.0%	4.47 [0.91, 21.86]
Total (95% CI)		**326**		**1518**	**100.0%**	**1.67 [0.47, 5.93]**
Total events	18		86			

Heterogeneity: $Tau^2 = 1.02$; $Chi^2 = 8.51$, df = 3 ($P = 0.04$); $I^2 = 65\%$
Test for overall effect: Z = 0.79 (P = 0.43)



d

Study or Subgroup	MetS Events	MetS Total	Non MetS Events	Non MetS Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Shariq et al. 2019	126	7603	1165	83963	98.9%	1.19 [1.00, 1.43]
Zarzavadjian et al. 2018	1	85	7	1151	0.5%	1.93 [0.24, 15.54]
Zhou et al. 2019	0	153	1	228	0.6%	0.50 [0.02, 12.09]
Total (95% CI)		**7841**		**85342**	**100.0%**	**1.19 [1.00, 1.43]**
Total events	127		1173			

Heterogeneity: $Chi^2 = 0.50$, df = 2 ($P = 0.78$); $I^2 = 0\%$
Test for overall effect: Z = 1.91 (P = 0.06)

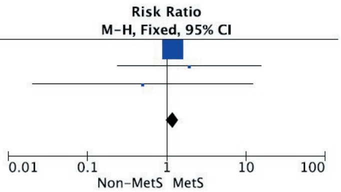


Figure 2. Forest plot showing the relationship between MetS and any complication **(a)**, severe complication (Clavien-Dindo III-IV) **(b)**, colorectal anastomotic leakage **(c)** and mortality **(d)**. Abbreviations: CI, confidence interval; M-H, Mantel Haenszel; MetS, metabolic syndrome; Fixed, fixed-effects modelling, Random; random-effects modelling. For **(a)** and **(c),** incidence rates of MetS according to the ATPIII criteria are shown for Goulart et al. [25]

Characteristics of studies that assessed preoperative hyperglycemia

Summarized in Table 3, eight studies reported on preoperative hyperglycemia.[25,28–34] Three out of eight studies were classified high-quality level and five studies as moderate level of quality **(Supplementary Table B)**. The study of Goulart et al. [25] reported on both MetS and hyperglycemia as a component of MetS and was therefore also evaluated in this section. Overall, a total of 9.534 patients were included; 13% had hyperglycemia as defined by various measures and cut-off values. Six out of eight studies reported a mixed population of diabetic and non-diabetic patients. Gustafsson et al. [28] included only non-diabetic patients and Goh et al. [30] only diabetic patients. Four studies used random BG measurements with cut-off values more than or 140 or 180 mg/dL [29,31–33], two studies used FPG values of more than 126 mg/dL 34 and 100/110 mg/dL 25, and two studies used HbA1c with predefined cut-off values of more than 6% and more than 8% [28, 30], to define hyperglycemia. The timing to define preoperative hyperglycemia varied widely. Three studies used values within 90 days of surgery [29,30,33], three studies defined hyperglycemia within 1 day before surgery [25,28,31] and two studies did not report timing.[32,34]

Preoperative hyperglycemia and outcome

Table 4 shows a summary of outcomes regarding studies evaluating preoperative hyperglycemia. While most studies reported on 30-day postoperative outcome, one study had a 90-day follow-up [33] and the study by Goh et al. [30] did not report follow-up time. Except for the two studies that evaluated SSI, studies were not compatible enough in terms of measures and outcomes. Data was therefore ineligible for statistical pooling.

Any postoperative complication. Of the two studies that reported on overall complication rate[25,28], Gustafsson et al. showed a threefold increased risk of overall postoperative complications (OR 2.9, CI 95% 1.1–7.9, P = 0.037), while Goulart et al. found no significant difference between hyperglycemic and normoglycemic patients.

Severe complication. Goh et al. [30], evaluating only diabetic patients with considerably increased HbA1c levels, observed an almost threefold higher risk of CD grade ≥2 (adj. OR 2.479, CI 1.041–5.905, P = 0.040), but not a significantly higher risk of severe complications (CD grade ≥3).

Anastomotic leakage. Two studies that evaluated CAL as outcome did not find an association with preoperative hyperglycemia.[25,33] In the study of Gustafsson et al.[28], two patients developed anastomotic leakage, both with preoperative levels of HbA1c within normal range (≤6.0%) (significance not determined). Jiang et al.[34] observed that hyperglycemic patients had a significantly higher risk of intestinal complications (i.e. leakage, intestinal obstruction, bleeding or peritonitis (14% versus 8%, P = 0.002).

Table 3. Characteristics of studies that addressed preoperative hyperglycemia and adverse outcome after colorectal surgery

Study, Year	Country	Study design	Population	Definition hyperglycemia	Sample size	Elevated glucose, N (%)	Normal glucose, N	Surgery type	Setting	Age [a]	Study quality[b]
Chen et al. 2019[33]	USA	RCS	DM & Non-DM	BG > 180 mg/dL	755	85 (11%)	670	Colorectal	Elective	57 (45-67)	9
Gachabayov et al. 2018[31]	USA	RCS	DM & Non-DM	BG > 140 mg/dL	690	113 (16%)	577	Colorectal	Elective	61 (15)	7
Goh et al. 2016[30]	Singapore	RCS	DM II	HbA1c > 8%	149 c	31 (24%)	99	Colorectal	Elective & semi-urgent	67 (11)	6
Gustafsson et al. 2009[28]	Sweden	PCS	Non-DM	HbA1c > 6%	120	31 (26%)	89	Colorectal	Elective	66 (31-90)	8
Jiang et al. 2019[34]	China	RCS	DM & Non-DM	FPG ≥ 126 mg/dL	1.876	248 (13%)	1628	Colorectal	Elective & urgent	64 (21-98)	9
Silvestri et al. 2017[32]	Italy	RCS	DM & Non-DM	BG > 180 mg/dL	687 c	17 (3%)	665	Colorectal	Elective & urgent	71 (19-93)	7
Ziegler et al. 2017[29]	USA	RCS	DM & Non-DM	BG > 140 mg/dL	5.123 c	694 (16%)	3588	Colon	Elective	ND	6
Goulart et al. 2017[25]	Portugal	RCS	DM & Non-DM	FPG ≥110 mg/dL	134 c	48 (42%)	65	Colorectal	Elective	68 (13)	7
				FPG ≥100 mg/dL		58 (50%)	59				

Abbreviations: BG; blood glucose, DM, diabetes mellitus; FPG fasting plasma glucose; HbA1c, hemoglobin A1c; ND, not determined; PCS, prospective cohort study; RCS, retrospective cohort study

[a] Values are in mean (SD) or median (range)

[b] Scored according to the Newcastle-Ottawa Scale

[c] Preoperative hyperglycemia could not be defined in all included study patients.

Table 4. Summary of results showing relation between preoperative hyperglycemia and outcome after colorectal surgery

Study	Follow-up	Any complication	Severe complication	Anastomotic Leakage	Surgical Site Infection	Mortality	Length of stay
Chen et al. [33]	≤ 90 days	ND	ND	No significant association (OR 1.33, CI 95% 0.50 - 3.54). No incidence rates	ND	ND	ND
Gachabayov et al. [31]	≤ 30 days	ND	ND	ND	↑SSI (28% versus 23%, significance ND)	ND	ND
Goh et al. [30]	ND	ND	A significant association with CD grade ≥2 or above (adj. OR 2.479, CI 1.041 - 5.905), but not with CD grade ≥3 (adj. OR 1.496, 95% CI 0.450-4.978) a	ND	ND	Mortality was not observed	ND
Gustafsson et al. [28]	≤ 30 days	↑ overall complications (45% versus 25%, OR 2.9, CI 95% 1.1-7.9, P=0.037).	ND	↑ CAL (6% versus 0%, significance ND)	ND	Mortality was not observed	No significant difference (8.5 (5.4) versus 7.3 (5.6) days).
Jiang et al. [34]	≤ 30 days	ND	ND	↑ Intestinal complications (14% versus 8%, p =0.002) b	ND	ND	ND
Silvestri et al. [32]	≤ 30 days	ND	ND	ND	↑ SSI (41% versus 19%, OR 2.91, 95% CI 1.04 - 7.72, P=0.03)	ND	ND
Ziegler et al. [29]	≤ 30 days	ND	ND	ND	ND	↑ Mortality (7% versus 3%, significance ND)	ND
Goulart et al. [25]	≤ 30 days	No significant difference in complication rate c	ND	No significant difference in CAL rate c	ND	ND	ND

[a] in-hospital complication rates [b] Intestinal complications include intestinal obstruction, leakage or bleeding, or peritonitis. [c] Incidence rates are only shown for hyperglycemic patients. Abbreviations: Adj, adjusted; BG, blood glucose; CAL, colorectal anastomotic leakage; CD, Clavien-Dindo; CI, confidence interval; DM, diabetes mellitus; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; LoS, length of stay; ND not determined; OR, odds ratio; SSI, surgical site infection [c] Preoperative hyperglycemia could not be defined in all included study patients.

Surgical site infection. Two studies comprising 1.377 patients, reported the incidence of SSI. As can be seen in **Figure 3,** meta-analysis using the fixed-effects model shows that patients with preoperative hyperglycemia are significantly at higher risk of SSI compared to patients with normoglycemia (RR 1.35, 95% CI 1.01–1.81, P = 0.04, I2 = 60%, P = 0.11). [31,32]
Mortality. Mortality was reported by three studies, two did not observe mortality[28,30] and one study demonstrated higher mortality rates for hyperglycemic patients (7% versus 3%, P = 0.03).[29]
Length of stay. Lastly, only one study compared LoS in non-diabetic patients, and did not find a significant difference (8.5 (5.4) versus 7.3 (5.6) days, p = 0.482) between hyperglycemic and normoglycemic patients.[28]

Study or Subgroup	Hyperglycemia Events	Hyperglycemia Total	Normoglycemia Events	Normoglycemia Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gachabayov et al. 2018	32	113	132	577	87.1%	1.24 [0.89, 1.72]
Silvestri et al. 2018	7	17	129	665	12.9%	2.12 [1.18, 3.83]
Total (95% CI)		**130**		**1242**	**100.0%**	**1.35 [1.01, 1.81]**
Total events	39		261			
Heterogeneity: $Chi^2 = 2.53$, df = 1 (P = 0.11); $I^2 = 60\%$						
Test for overall effect: Z = 2.04 (P = 0.04)						

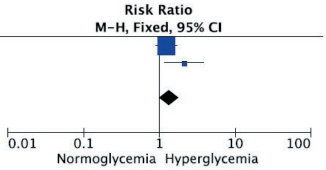


Figure 3. Forest plot showing the relationship between preoperative hyperglycemia and surgical site infection. Abbreviations: CI, confidence interval; M-H, Mantel Haenszel; Fixed, fixed-effects modelling.

5

Discussion

The purpose of the present systematic review and meta-analysis was to summarize the available evidence on the impact of MetS and preoperative hyperglycemia, as an individual component of MetS, on short-term outcome after colorectal surgery. The prevalence of MetS in patients undergoing colorectal surgery is high, exceeding 35% in half of the included studies. The pooled results show that patients with MetS are more likely to develop severe complications after colorectal surgery than those without MetS. Data on other outcomes including CAL, SSI and mortality are less clear and cannot be answered safely by this study. This lack of clear findings is likely due to shortcomings in the existence of only a handful of studies. Nevertheless, these analyses do demonstrate a non-significant trend toward increased risk ratios. Data on the association of preoperative hyperglycemia, as an individual component of MetS, and adverse outcome demonstrates a negative impact on SSI for hyperglycemic patients.

The number of studies that investigated the relationship of MetS and adverse outcome after colorectal surgery is scarce and results are controversial. Only six studies have determined outcomes following colorectal surgery.[22–27] The recorded prevalence of MetS in the six included varied from 7% to 68%. This substantial range in prevalence could explain the inconsistency in showing risks. In general, studies using the AHA criteria to define MetS found a positive association with adverse outcome[26,27], whereas studies using the NCEP ATP III did not.[22,23,25] Furthermore, several studies used modified criteria to define MetS. It is hard to retrieve lipid profiles, waist circumference or FPG levels from retrospective studies, because these are in general not often assessed preoperatively. Together, this emphasizes the need for prospective cohort studies in order to draw definite conclusions on the prevalence of MetS and to adequately compare study results.

Common problems in patients with MetS are endothelial dysfunction and chronic low-grade inflammation.[7] These conditions may not only cause problems in colorectal surgery, but also in several other surgical procedures. In liver surgery, for instance, Bayani et al. found not only an association between MetS and increased postoperative complications - specifically a 70% higher risk of superficial SSI - but also a more than 2-fold increased risk of mortality.[35] In a systematic review and meta-analyses evaluating patients undergoing orthopedic surgery, MetS was a risk factor for postoperative all-cause complications, SSI, urinary tract infection and 30-day re-admissions.[36] Furthermore, Glance et al. reporting on 310.208 patients undergoing non-cardiac surgery, showed substantial higher rates of postoperative complications, including adverse cardiac events, sepsis and wound infections.[6] Taken together with our findings, these observations support the importance of MetS as a risk factor for poorer prognosis after various forms of surgery.

From the perspective of pathophysiology, assuming the prominent role of insulin resistance, treatment of MetS should be aimed at improving insulin sensitivity. Clinical strategies to reduce MetS include energy restriction, macronutrient manipulation (carbohydrate restriction, enrichment in unsaturated fatty acids) and exercise regimens.[38] The preoperative period could optimally be used to carry out these strategies in terms of multimodal prehabilitation including interventions such as exercise, smoking and alcohol cessation, nutritional support and psychological support.[39] Multimodal prehabilitation aims to improve functional capacity and consequently, reduce surgery-associated morbidity and mortality[40], but could also provide as a strategy to modify abnormalities regarding MetS. To date, the impact on MetS has not been studied. However, it has been well established that insulin resistance can be improved by exercise and dietary interventions.[41, 42] In an era of a rapidly increasing prevalence of MetS worldwide, it is paramount to improve the knowledge in this subject.

The impact of preoperative hyperglycemia as a single component of MetS on outcome after colorectal surgery cannot be answered clearly by our study. This is due to high heterogeneity in hyperglycemia cut-off values, assessment methods and a heterogeneous range of complications reported by the included studies. Nevertheless, this study demonstrates a significant increased SSI risk for hyperglycemic patients, with and without diabetes, having a random glucose value of more than 140 or 180 mg/dL. Accordingly, preoperative glycemic screening may be advisably in perioperative care.

There are several limitations in the present study. First, considering that this systematic review comprises only observational studies, the quality of evidence using the Grading of Recommendations Assessment, Development, and Evaluation rating has to be considered very low.[43] Second, results of the included studies were substantially heterogeneous. Most likely due to the variety of definitions of MetS and hyperglycemia that were used and, subsequently, the wide range of prevalences. Unfortunately, we were unable to evaluate the predictive value by MetS definition as only one study stratified analyses by definition. Third, studies reporting on single complications such as CAL and mortality are often underpowered to detect a statistical difference. It might be better to evaluate clinically relevant postoperative morbidity, as determined by a composite outcome measure that summarizes frequency and severity of postoperative outcome. Concerning future research studies, adequately powered studies are needed to draw definitive conclusions. Ultimately, randomized controlled trials should investigate the potential benefit of preoperative interventions to modify metabolic abnormalities.

Conclusion

In conclusion, both MetS and preoperative hyperglycemia, as an individual component of MetS, seem to have a negative impact on short-term adverse outcome after colorectal surgery. As a result of relatively few studies meeting inclusion criteria and high heterogeneity across studies, evidence is not conclusive. Nevertheless, the present data offers surgeons, who are often not trained to identify metabolic disorders, food for thought. The identification of MetS is nowadays not part of routine preoperative screening, but might guide preoperative treatment strategies in order to enhance recovery and reduce complications.

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Supplementary material

Supplementary Table A. Inclusion and exclusion criteria based on CHARMS checklist [17]

Inclusion criteria	*Exclusion criteria*
Study type	
• Published peer-reviewed retrospective and prospective observational studies (e.g. cohort, cross-sectional and case-control studies)	• Interventional studies, systematic reviews, narrative reviews, meta-analyses, opinions, clinical guidelines, editorials, case reports, congress abstracts
Population	
• Adult patients (≥18 years of age)	• Patients < 18 years of age
• Patients who underwent colorectal, colonic or rectal surgery	• Minor procedures (day surgical procedures)
• Indication for surgery; malignant or benign disease	
Index prognostic factor	
• Studies reporting the relationship between MetS (compared with non-MetS) or preoperative hyperglycemia (compared with normoglycemia) • MetS defined by the NCEP ATP III, AHA, WHO or IDF criteria • Hyperglycemia defined by one or more of the following measures: FPG, OGTT, HbA1c, random BG	• Studies reporting on an individual component of metabolic syndrome rather than the syndrome
Outcome	
• Studies reporting on one of the following outcomes: any complication, severe complication, CAL, SSI, mortality or LoS.	
Timing	
• Hyperglycemia had to be defined before surgery • Follow-up information within 30 to 90 days after surgery	• Studies reporting on intraoperative and postoperative glycemic measurements.
Setting	
• Elective and emergency surgery	

Abbreviations: AHA/NHLBI, American Heart Association/National heart, Lung and Blood Institute Scientific Stagement; BG, blood glucose; CAL, colorectal anastomotic leakage; FPG, fasting plasma glucose; HbA1c, hemglobin A1c; IDF, International Diabetes Federation; LoS, Length of stay; MetS, Metabolic syndrome; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; OGTT, oral glucose tolerance test; SSI, Surgical site infection; WHO World Health Organisation

5

Supplementary Table B. Risk of bias of included studies (n = 13)

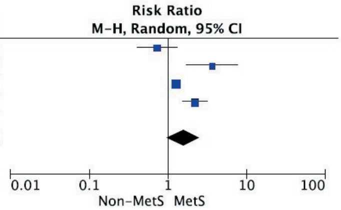
	Selection (0-4)				Comparability (0-2)	Outcome (0-4)			Total count
Metabolic Syndrome									
Zarzavadjian et al. [22]	•	•	•	•		•	•	•	7
Akinyemiju et al. [23]	•	•	•	•	• •	•			7
Shariq et al. [24]	•	•	•	•	• •	•	•	•	9
Goulart et al. [25] [a]	•	•	•	•		•	•	•	7
Lohsiriwat. et al. [26]	•	•	•	•	• •		•	•	7
Zhou et al. [27]	•	•	•	•	• •	•	•	•	9
Preoperative hyperglycemia									
Chen et al. [33]	•	•	•	•	• •	•	•	•	9
Gachabayov et al. [31]	•	•	•	•		•	•	•	7
Goh et al. [30]		•	•	•	• •	•			6
Gustafsson et al. [28]		•	•	•	• •	•	•	•	8
Jiang et al. [34]	•	•	•	•	• •	•	•	•	9
Silvestri et al. [32]	•	•	•	•		•	•	•	7
Ziegler et al. [29]	•	•	•	•			•	•	6

The Newcastle-Ottawa Scale (NOS) score, based on three domains; selection (0-4 points), comparability (0-2) outcomes of interest (0-3 points). A total score of 8-9 is considered as high, 6-7 as moderate and ≤ 5 as low level of quality.
[a] This study reported on both MetS and hyperglycemia as a component of MetS

a

Study or Subgroup	MetS Events	MetS Total	Non MetS Events	Non MetS Total	Weight	Risk Ratio M-H, Random, 95% CI
Goulart et al. 2017	12	46	24	67	21.9%	0.73 [0.41, 1.30]
Lohsiriwat et al. 2010	17	42	8	72	18.0%	3.64 [1.72, 7.71]
Shariq et al. 2019	2150	7603	18681	83963	32.7%	1.27 [1.22, 1.32]
Zhou et al. 2019	53	153	36	228	27.3%	2.19 [1.51, 3.18]
Total (95% CI)		**7844**		**84330**	**100.0%**	**1.58 [0.98, 2.54]**
Total events	2232		18749			

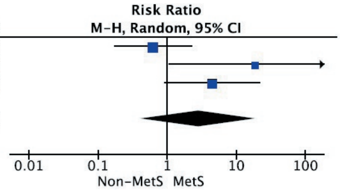
Heterogeneity: Tau² = 0.18; Chi² = 19.35, df = 3 (P = 0.0002); I² = 84%
Test for overall effect: Z = 1.88 (P = 0.06)



b

Study or Subgroup	MetS Events	MetS Total	Non MetS Events	Non MetS Total	Weight	Risk Ratio M-H, Random, 95% CI
Goulart et al. 2017	3	46	7	67	40.2%	0.62 [0.17, 2.29]
Lohsiriwat et al. 2010	5	42	0	72	23.1%	18.67 [1.06, 329.50]
Zhou et al. 2019	6	153	2	228	36.7%	4.47 [0.91, 21.86]
Total (95% CI)		**241**		**367**	**100.0%**	**2.82 [0.43, 18.61]**
Total events	14		9			

Heterogeneity: Tau² = 1.87; Chi² = 6.59, df = 2 (P = 0.04); I² = 70%
Test for overall effect: Z = 1.08 (P = 0.28)

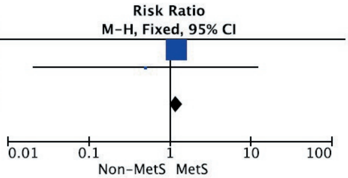


5

c

Study or Subgroup	MetS Events	MetS Total	Non MetS Events	Non MetS Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Shariq et al. 2019	126	7603	1165	83963	99.4%	1.19 [1.00, 1.43]
Zhou et al. 2019	0	153	1	228	0.6%	0.50 [0.02, 12.09]
Total (95% CI)		**7756**		**84191**	**100.0%**	**1.19 [0.99, 1.43]**
Total events	126		1166			

Heterogeneity: Chi² = 0.29, df = 1 (P = 0.59); I² = 0%
Test for overall effect: Z = 1.87 (P = 0.06)



Supplementary Figure 1. Sensitivity analyses excluding the study of Zarzavadjian Le Bian et al. [22] based on length of follow-up. Forest plot showing the relationship between MetS and any complication (a), anastomotic leakage (b), and mortality (c). Abbreviations: CI, confidence interval; M-H, Mantel Haenszel; MetS, metabolic syndrome; Random; random-effects modelling.

chapter six

Protocol of a prospective, observational study to assess the effects of metabolic syndrome on outcome after colorectal cancer surgery

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Submitted

Abstract

Background:

Controversial evidence exists regarding the impact of metabolic syndrome, a condition recognized as potentially modifiable, on postoperative outcome in patients undergoing surgery for colorectal cancer (CRC). The aims of this study are to investigate the impact of metabolic syndrome and its individual components on short-term and long-term postoperative outcome among a consecutive sample of patients scheduled for CRC surgery.

Methods and design:

In this prospective, observational study, consecutive adult patients scheduled for elective CRC surgery will be eligible for participation. The study will run at Máxima MC in the Netherlands from February 2022. Patients will be screened preoperatively for metabolic syndrome defined by the presence of three of the five following criteria: abdominal obesity, elevated triglycerides, low high-density lipoprotein cholesterol, hyperglycemia, elevated blood pressure. Patients who are on antidiabetic, hypolipidemic or antihypertensive drug treatment will also meet the criteria for individual components. Postoperative complications that occur up to 30 days after surgery will be classified according to Comprehensive Complication Index (CCI). The primary outcome of this study is the proportion of patients with clinically relevant postoperative morbidity (CCI ≥ 21.0). Other short-term outcomes include: Length of hospital stay, days at Intensive Care, discharge destination, readmission, and mortality. Impact on health-related quality of life and survival will be evaluated at 1 year after surgery.

Discussion:

With the results of this study, we hope to draw definite conclusions on the prevalence of metabolic syndrome and its impact on postoperative outcome in patients with CRC. If metabolic syndrome proves to be a useful clinical tool for risk stratification, the next step will be the development of specific preoperative targets in order to improve outcomes.

Trial registration:

This study is registered in Research Registry (identifying number: researchregistry7481) and was approved by the Medical Ethics Committee of Máxima MC, Eindhoven, the Netherlands (N21.097).

Introduction

The prevalence of metabolic syndrome is increasing rapidly worldwide[1], affecting around 25% of the European population nowadays.[2] A growing body of evidence has shown that patients with metabolic syndrome undergoing major abdominal surgery are at higher risk for adverse outcomes such as postoperative complications, delayed recovery, and mortality.[3-6] Metabolic syndrome is the name for a group of interrelated conditions: hyperglycemia, dyslipidemia, abdominal obesity, and hypertension.[7] The condition is recognized as potentially modifiable. Yet, in the context of perioperative colorectal care, the impact of metabolic syndrome is poorly investigated.

Although the pathogenesis and underlying mechanisms are still poorly understood, insulin resistance and obesity are suggested to play an important role in causing metabolic syndrome.[8] The syndrome is accompanied by high levels of proinflammatory cytokines and endothelial dysfunction[1], having potential harmful effects (i.e. poor tissue healing) perioperative. Identification of metabolic syndrome can improve preoperative risk stratification and might serve as an opportunity to optimize a patients' condition prior to surgery. It is hypothesized that affected patients might benefit from preoperative strategies to improve insulin sensitivity prior to surgery (e.g. multimodal prehabilitation).[6]

To date, there are several shortcomings in the scarce existing literature on the impact of metabolic syndrome on outcome after colorectal surgery. The prevalence of metabolic syndrome among patients undergoing colorectal surgery varies widely in previous studies (7% to 40%), mainly due to the existence of several definitions of metabolic syndrome.[4,9-11] Using large databases, both Shariq et al. and Glance et al. found metabolic syndrome to be an independent predictor of 30-day postoperative complications. However, they could only evaluate a modified definition of metabolic syndrome (substitution of obesity for abdominal obesity and exclusion of lipid profile) due to the retrospective design of their studies.[4,9] Conversely, Akinyemiju et al. concluded a 7% lower odds of postoperative complications among CRC patients with metabolic syndrome. However, this database comprised only in-hospital postoperative complications, potentially explaining the inconsistency in showing risks.[10] Furthermore, most studies are limited by small sample sizes and the inability to evaluate outcomes beyond 30 days after surgery.[12,13]

Therefore, the aims of the present study are (1) to determine the impact of metabolic syndrome among a consecutive sample of patients scheduled for CRC surgery on short-term and long-term postoperative outcome and (2) to investigate if individual components of metabolic syndrome contribute to specific risks.

Materials and methods

Study design and setting

This study is a prospective, observational, cohort study performed at the Department of Surgery of Máxima MC (MMC) in Veldhoven, a teaching hospital in the southern part of the Netherlands. Patient enrollment will start in February 2022 and run until patient inclusion is completed. The study was reviewed and approved by the Medical Ethics Committee and Institutional Review Board of MMC, Veldhoven, The Netherlands (registration number: N21.097) on December 2021. Significant protocol amendments will be communicated with the ethics committee and research registry.

Ethical considerations and declarations

The study will be conducted in compliance with the principles of the Declaration of Helsinki. Patients will be informed about the study during a preoperative visit to their nurse specialist or case manager in the outpatient clinic. Patients are included only after written informed consent or consent by the opt-in method (for using data for research and education) has been obtained.

Study population

Inclusion criteria are as follows: (1) consecutive patients aged 18 years or older; (2) with pathologically confirmed or a strong suspicion of malignancy of the colon and/or rectum; (3) planned for elective surgery; and (4) informed consent or consent by opt-in form. Patients will be excluded in case the postoperative pathology results do not confirm CRC diagnosis.

Data collection

Over the past decades, various definitions with newer clinical criteria related to metabolic syndrome (measures and cut-off points) have been published by a number of expert groups (e.g. World Health Organization (WHO)7, American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI)[14], National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III)[15], International Diabetes Federation (IDF)[16]). In order to unify definitions, common criteria were agreed by a joint scientific committee in 2009.[8] In the present study, these unified criteria **(Table 1)** will be used to define metabolic syndrome, as the presence of three of the following five criteria: 1) waist circumference equal or greater than 94 cm in men and equal or greater than 80 cm in women, 2) serum triglyceride (TG) concentration of 1.7 mmol/L or greater, 3) high-density lipoprotein cholesterol (HDL-c) concentration of less than 1.0 mmol/L for men or less than 1.3 for women, 4) fasting plasma glucose (FPG) of 5.6 mmol/L or greater, 5) systolic blood pressure of 130 or greater mmHg or diastolic blood pressure of 85 mmHg or greater. Patients who are on antidiabetic, hypolipidemic or antihypertensive drug treatment will also meet the criteria for the individual component.

Identification of metabolic syndrome is embedded in our preoperative colorectal care pathway with no additional interventions. Abdominal obesity will be evaluated by waist circumference, as it is considered a good indicator for abdominal obesity and a simple anthropometric method to use in clinical practice.[17] Waist circumference will be measured in standing position, at the end of a normal expiration, with a tape around the abdomen at the level of the superior border of the iliac crest, as per National Institutes of Health (NIH) recommendations.[18] The measuring tape should be parallel to the floor and should not compress the skin. To assess dyslipidemia and hyperglycemia, FPG, HDL-c, and TG concentrations will be collected from preoperative laboratory tests. When FPG is 7.0 mmol/L or higher (in patients without diabetes mellitus), patients will be referred to their general practitioner to repeat the FPG test on a second day. For diabetic patients, perioperative glycemic management will be employed according to standard hospital protocol. If the patient has a TG of 6 mmol/L or higher, he or she will be referred to an internal medicine physician for further evaluation. Blood pressure will be measured at baseline by a physiotherapist or a nurse specialist according to standard of care.

Table 1. Clinical criteria for diagnosis of metabolic syndrome, using the unified criteria of AHA/NHLBI and IDF as agreed in the Joint Scientific Statement.[8] The presence of any 3 of 5 components constitutes the diagnosis.

Main components	Measure	Cut-off points
Abdominal obesity	Waist circumference	≥ 94 cm (men) or ≥ 80 cm (women) a
Hypertriglyceridemia	Triglycerides	≥ 1.7 mmol/L or on drug treatment b
Low HDL-c	HDL-c	< 1.0 mmol/L (men) or < 1.3 (women) or on drug treatment b
Hyperglycemia	FPG	≥ 5.6 mmol/L or on drug treatment b
Hypertension	Blood pressure	≥ 130 mmHg (systolic) and/or ≥ 85 mmHg (diastolic) or on drug treatment b

[a] According to references for the European population.
[b] Patients who are on antidiabetic, hypolipidemic or antihypertensive drug treatment will also meet the criteria for the individual component. Abbreviations: FPG, fasting plasma glucose, HDL-c, High-density lipoprotein cholesterol.

Apart from the metabolic syndrome components as described above, baseline patient and tumor characteristics; age, sex, body-mass index, American College of Anesthesiologists (ASA) classification, history of smoking, pathological tumor node and metastasis (TNM) stadium, tumor location, neoadjuvant treatment (radiotherapy, chemotherapy or chemoradiotherapy), adjuvant therapy, and information regarding prehabilitation will be collected. All patients receive perioperative care according to the Enhanced Recovery After Surgery (ERAS) principles[19] and multimodal prehabilitation is standard preoperative care in our institute.[20] Furthermore, surgery-related factors; date and type of surgery, duration of surgery, surgical approach (minimally invasive versus open), diverting stoma placement and type of anastomosis will be collected. Short-term outcome is restricted to 30 days after the index surgery and include: postoperative complications (i.e. anastomotic leakage, ileus, intra-abdominal abscess, wound complications (dehiscence or infection), bleeding, cardiopulmonary complications, urinary tract infection, and thromboembolic complications), length of stay in Intensive Care Unit (ICU), length of hospital stay (LoS), readmission, discharge destination, and mortality. Anastomotic leakage is defined as clinically relevant leak that requires active intervention including administration of therapeutic antibiotics and/or radiological (or endoscopic) drainage and/or surgical reoperation (i.e. grade B/C).[21] Fluid collections, (presacral) abscesses, and fistulae will also be classified as anastomotic leakage. Long-term outcome is restricted to 1 year after the index surgery and include survival and health-related quality of life (HRQoL). HRQoL will be collected via the Prospective Dutch Colorectal Cancer (PLCRC) cohort[22], in which the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core module (EORTC QLQ) -C30 and -C29 (version 3.0) was used.[23] All data will be prospectively collected using an electronic case report form in an online database system ‘Research Manager’ **(Table 2)**.

Table 2. Collection of study data.

	Preop	Surgery	30 days follow-up	1 year Follow-up
Patient and tumor characteristics				
Age (years)	x			
Sex	x			
Body-mass index (kg/m2)	x			
ASA classification	x			
History of smoking	x			
Tumor location	x			
Neoadjuvant treatment	x			
Metabolic Syndrome information				
Waist circumference (cm)	x			
Systolic and diastolic blood pressure (mmHg)	x			
Laboratory assessments: HDL-c, TG, FPG	x			
Drug treatment for diabetes mellitus	x			
Drug treatment for dyslipidemia	x			
Drug treatment for hypertension	x			
Metabolic Syndrome score (1 – 5)	x			
Surgery-related factors				
Date of surgery		x		
Type of surgery		x		
Surgical approach		x		
Duration of surgery		x		
Diverting stoma		x		
Type of anastomosis		x		
Pathological information				
TNM stage			x	
Postoperative outcome				
Postoperative complications			x	
CCI score			x	
Length of stay in ICU			x	
Discharge destination			x	
Readmission			x	
Length of hospital stay			x	
Mortality			x	x
Health-related quality of life				x
Other				
Adjuvant therapy			x	x

Abbreviations: ASA, American College of Anesthesiologists; CCI; Comprehensive Complication Index; FPG, fasting plasma glucose; HDL-c, High-density lipoprotein cholesterol; ICU, Intensive Care Unit; preop, preoperative; TG, Triglycerides

Study endpoints

Main study endpoints

The primary endpoint is the proportion of patients with clinically relevant postoperative morbidity, as determined with a Comprehensive Complication Index (CCI) score ≥ 21.0. CCI is a composite outcome measure that summarizes the frequency and severity of all postoperative complications in a continuous score from 0 (no complication) to 100 (death).[24] The score is based on the Clavien-Dindo classification system[25] and can easily be calculated using www.assessurgery.com. By using a composite measure of CCI ≥ 21.0, all clinically relevant complications (at least one complication Clavien-Dindo grade II or higher) are combined in one endpoint.

Secondary study endpoints

Secondary endpoints include: CCI median (or mean) and standard deviation (or interquartile range), individual postoperative complications, admission to the Intensive Care Unit (ICU), length of stay in ICU (days), LoS (days), discharge destination, total number of unplanned readmissions, and mortality within 30 days after the index operation. Median (or mean) and standard deviation (or interquartile range) of number of metabolic syndrome components (metabolic syndrome score ranges 1 – 5).

Other study endpoints

Long-term outcomes include survival and HRQoL at baseline and 1 year after colorectal surgery.

Safety

Due to observational study design, there are no risks associated with participation.

Sample size calculation

The sample size calculation is based on the primary aim of the study, to detect a difference in the proportion of patients with clinical relevant postoperative morbidity, as determined according to a CCI score of 21 or above. Based on previous research from our own hospital data, a CCI ≥ 21 occurred in 28% of the CRC patients undergoing surgery.[26] We furthermore evaluated data on postoperative complications of patients with and without metabolic syndrome undergoing CRC surgery from data of Loshirawat et al..[13] For the present study, the expected percentage of patients with a CCI score ≥ 20 is 35% versus 20% for patients with and without metabolic syndrome, respectively. Based on these proportions, a sample size of 276 patients (138 per group) was calculated to detect a difference of at least 15%, with a

power of 0.80 and an alpha of 0.05 (two-sided test). To account for possible dropouts (10%), we intent to recruit 304 patients or more, at least 152 per group. We will continue including patients until both groups have reached this number. In MMC, approximately 150 CRC patients undergo elective surgery each year. The prevalence of the metabolic syndrome in Dutch patients is estimated to be up to 30%.[27] With a known age-associated increase[2], the prevalence of patients with metabolic syndrome undergoing surgery for CRC is expected to be higher. Therefore, it is assumed that patient enrollment will be completed in two to three years.

Statistical analysis

Data will be analyzed using Statistical Package for the Social Sciences version 22 (SPSS Inc. Chicago, IL, USA). First, the prevalence of metabolic syndrome will be calculated within the total study population. Second, outcomes of patients with metabolic syndrome will be compared to outcomes of patients without the metabolic syndrome. Baseline categorical data will be presented as numbers with percentages and will be compared using a chi-square test or Fisher's exact test. Continuous variables will be expressed with means and standard deviations (SD) or medians and interquartile ranges (IQR) for respectively parametric and non-parametric data, and will be compared using the Student's t test or Mann-Whitney U test as appropriate. The primary endpoint (the proportion of patients with a CCI score above 20) will be tested with logistic regression analysis. Secondary endpoints will be analyzed using logistic regression analysis (for dichotomous outcomes) or linear regression analysis (for continuous outcomes). For multivariable analyses, covariates were chosen based on previous research or defined as variables that differed significantly between patients with and without a CCI score above 20. Crude and adjusted odds ratios (OR) with 95% confidence interval (CI) and p value will be reported. A $p < 0.05$ will be considered statistically significant.

Discussion

Surgery is the cornerstone of treatment for CRC, however, the intervention poses a substantial risk of postoperative complications (in up to 30% of the patients).28 Identification of potentially modifiable risk factors for adverse postoperative outcome seems clear, but there is still a paucity of data in this field. Only a handful of studies has focused on the impact of metabolic syndrome on postoperative outcome after colorectal surgery. These studies lack long-term prospectively collected comparative data. While a few reports found a higher

risk of adverse postoperative outcome among patients with metabolic syndrome9-11, other studies did not.[12,29] Whether metabolic syndrome is an adequate tool for risk stratification remains controversial and yet unknown. In an era of an alarmingly increasing prevalence of metabolic syndrome worldwide, it is crucial to improve the quantity and quality of knowledge on this topic.

In addition to the need for detecting high risk surgical patients, metabolic syndrome (and its individual components) could also serve as a target for optimization. Major contributors to the development of insulin resistance are excessive circulating fatty acids, mainly derived from visceral adipose tissue.[1] Effective treatment includes lifestyle interventions such as physical exercise, nutritional optimization (in combination with weight loss), and smoking cessation and/or pharmacological management. Future studies are needed to demonstrate if these treatment goals can be achieved preoperatively and if optimization has a positive effect on postoperative outcome.

In summary, this study is a prospective cohort study that aims to evaluate the impact of metabolic syndrome on adverse outcome after CRC surgery. The next step will be to act on this in a preemptive way with specific preoperative targets. This ultimate goal requires a change in culture and behavior of both the patient and health care provider. As of this moment, we first should know specific risks when faced with a patient with metabolic abnormalities.

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Part 2

Perioperative optimization

chapter

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Evaluating the longitudinal effect of colorectal surgery on health-related quality of life in patients with colorectal cancer

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Abstract

Background and objectives:

Surgery for colorectal cancer (CRC) negatively affects health-related quality of life (HRQoL). Addressing shortcomings in literature, the purpose of this study was to evaluate the impact of surgery for CRC on the course of HRQoL from baseline up to 2 years after diagnosis.

Methods:

In this prospective, population-based study, patients with newly diagnosed CRC were included between 2016 and 2019. HRQoL was assessed by the EORTC QLQ-C30 questionnaire over time both between and within subgroups of patients that underwent right-sided colonic, left-sided colonic, and rectal resection using linear mixed model analyses.

Results:

The study included 415 patients of whom 148 patients underwent right-sided colonic (36%), 147 left-sided colonic (35%), and 120 rectal resections (29%). Overall, HRQoL scores restored to baseline level 1 year after diagnosis. The impact of surgery seems to be more prominent in patients who underwent rectal resection, as they experienced more pain and had worse role and social functioning scores 4 weeks after surgery. Finally, among patients who underwent left-sided and rectal resection, physical functioning did not return to baseline level during follow-up.

Conclusion:

This study shows several differences (between-group and within-group) in HRQoL according to surgery type and offers perspective, which patients may need additional support in the care pathway.

Introduction

Colorectal cancer (CRC) is one of the four most common cancers in the world making it a major public health issue.[1] Health-related quality of life (HRQoL) is negatively affected by CRC and it is being compromised further by the treatment modalities and associated adverse effects.[2] Incidence of CRC is increasing and patients tend to be diagnosed at a younger age. While new treatment options improve the overall survival rates[2], an increasing amount of cancer survivors face persistent problems after primary treatment and live with this chronic disease.[3] As a result, quality of life has become an important outcome of surgery, the cornerstone for CRC treatment in current clinical practice. For some patients, a complicated, prolonged recovery due to treatment morbidity accompanied by a decline in HRQoL is not outweighed by the benefits of curation.[4]

A number of studies have been published assessing HRQoL in patients with CRC. Some include assessment of quality of life only after treatment[5–7], others include baseline assessment but have a relatively short follow-up period of up to 6 months post- operatively.[8–10] Baseline assessment is necessary to interpret HRQoL results reported postoperatively and thus to determine the impact of treatment. Moreover, considering the fact that a substantial group of patients are likely to receive adjuvant treatment, a follow-up period of 6 months will not represent the final HRQoL results. Only few studies have been published with both baseline and long term follow-up results[11–13], however, these studies included patients with rectal cancer only. To address these shortcomings, this study aimed to evaluate the course of HRQoL from baseline up to 2 years after diagnosis in patients with CRC undergoing surgery. Insight into the impact of CRC surgery on the course of HRQoL may help professionals to prepare and inform patients more optimally.

Methods

Study design

The current study is a secondary analysis of the ongoing PROCORE study; a prospective, population-based study in which patients with newly diagnosed CRC were included between 2016 and 2019. Longitudinal data is being collected on baseline (before start of treatment), 4 weeks postoperatively, and 1 and 2 years after diagnosis via PROFILES (Patient-Reported Outcomes Following Initial treatment and Longterm Evaluation of Survivorship), a registry containing data of the psychosocial and physical impact on cancer treatment.[3]

The PROCORE study was ethically approved by the Medical Research Ethics Committees United (reference number NL51119.060.14). The current study is reported following the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.

Population

Patients were recruited from four hospitals in the Netherlands: Catharina Hospital in Eindhoven, Elisabeth-TweeSteden Hospital in Tilburg, Elkerliek Hospital in Helmond, and Máxima Medical Center in Veldhoven. Inclusion criteria consisted of adult patients with a pathologically confirmed diagnosis of CRC as a primary tumor. Patients were excluded in case of a previously diagnosed different cancer, except for basal cell carcinoma of the skin. Furthermore, patients unable to read or write the Dutch language or with cognitive impairments were excluded as well. Patients were eligible for the current analysis if they underwent surgical resection for CRC, completed the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire—Core module (EORTC QLQ-C30)[14] at baseline and at least one follow-up moment.

Data collection

CRC patients were informed and included before start of treatment by a case manager or research nurse. All patients provided written informed consent. Questionnaires could be filled out in paper-and-pencil versions or online via the PROFILES registry, according to patient preference.

PROFILES data were linked to data from the Netherlands Cancer Registry (NCR). Sociodemographic data (i.e., gender, age) and clinical information (e.g., tumor staging according to the American Joint Committee on Cancer 8th Edition, and neoadjuvant treatment) were obtained from the NCR. Questionnaires at baseline included questions regarding general characteristics (e.g., smoking status, educational level, and self-administered comorbidity questionnaire[15]). Information regarding the surgical treatment (e.g., type, surgical approach, stoma, and length of hospital stay) were collected from the Dutch ColoRectal Audit (DCRA), a national audit performed by the Dutch Institute of Clinical Auditing (DICA) in which information on all patients undergoing surgery for CRC is recorded.[16]

For the current study, surgical procedures were divided into (1) right-sided colonic resection (terminal ileum, cecum, ascending colon, hepatic flexure, and transverse colon), (2) left-sided colonic resection (descending colon, splenic flexure, and sigmoid colon), and (3) rectal

resection. Patients undergoing local excision, proctocolectomy, or subtotal colectomy were excluded due to the inability to divide into one of the subgroups.

Health-related quality of life

HRQoL was assessed using the EORTC QLQ-C30 (version 3.0). The EORTC QLQ-C30 contains five functioning scales (physical, role, social, emotional, and cognitive functioning), a global quality of life scale, three symptom scales (fatigue, pain, and nausea/vomiting), and six single items (appetite loss, constipation, diarrhea, dyspnea, sleep disturbance, and financial impact). Participants scored items in an ordinal four or seven-point Likert scale. The scores were converted into a scale ranging from 0 to 100 according to the EORTC scoring manual.[17] Higher scores on the functional scales and global QoL indicate better functioning and health status, while higher scores on the symptom scales indicate more symptoms.

For the current study, we included all functioning and global quality of life scales and selected the symptom scales and single items which were relevant for CRC patients in particular: fatigue, pain, sleep disturbance, constipation, and diarrhea.

Statistical analysis

Statistical analysis was performed using SPSS version 22 (SPSS Inc.). Baseline demographic and clinical characteristics were compared between patients that underwent right-sided colonic resection, left-sided colonic resection, and rectal resection. Categorical variables were compared between groups using χ^2 or Fisher's exact tests. Continuous variables were compared with one-way analysis of variance (ANOVA) or Kruskal-Wallis test, according to distribution of data. We evaluated changes in quality of life from baseline until 2 years after diagnosis by comparing scores of patients that underwent right-sided colonic resection, left-sided colonic resection, and rectal resection, both between and within groups. Linear mixed model (LMM) analyses were performed with the selected EORTC QLQ-C30 scales as continuous dependent variables. We used a maximum likelihood estimation and an unstructured covariance matrix with a two-level structure (i.e., patients and repeated time points). Time was analyzed as an independent categorical variable with four levels (i.e., baseline, 4-week, 1-year, and 2-year follow-up). Random intercepts on patient-level were included in the models to take into account the intrasubject correlation between repeated measures. Analyses were adjusted for possible confounders which were selected as follows: baseline variables which were statistically different between groups or factors known to affect quality of life described in the literature. Values were derived from descriptive statistics.

Differences were based upon analyses adjusted for confounders. Clinical relevance of the changes of EORCT QLQ-C30 scores was assessed for both between[18] and within groups[19] using previously published minimal important differences. A P = 0.05 or less was considered statistically significant.

Results

Baseline questionnaires were completed by 477 of 713 (67%) patients eligible for participation in the PROCORE study. Of these, 14 patients had no surgical treatment and were therefore excluded for the current study. Seven patients were excluded from analyses due to surgery type (local excision, proctocolectomy, or subtotal colectomy). Finally, baseline EORTC QLQ-C30 was not completed by six patients and 35 patients did not complete this questionnaire during at least one of the follow-up moments resulting in 415 patients included for analysis **(Figure 1)**.

Baseline characteristics

Table 1 shows the baseline demographic and clinical characteristics of 148 patients who underwent right-sided colonic resection (36%), 147 patients who underwent left-sided colonic resection (35%), and 120 who underwent rectal resection (29%). Significant differences were found between groups for age, time between diagnosis and completion of baseline questionnaire, number of comorbid conditions, tumor stage, (neo)adjuvant therapy, surgical approach, and stoma.

Between-group differences in HRQoL on different time points

At baseline, patients scheduled for right-sided resection reported worse physical (p = 0.030) and role functioning (P = 0.008) compared with patients scheduled for left-sided resection **(Figure 2)**. Furthermore, they were more fatigued than patients scheduled for left-sided (P < 0.001) or rectal resection (P < 0.001), but reported less diarrhea (P = 0.007, P = 0.016, respectively). Finally, the scores on the insomnia scale were worse for patients scheduled for right-sided resection compared with rectal resection (P = 0.035) **(Figure 3)**.

Four weeks postoperatively, patients who underwent rectal resection scored significantly worse on the role functioning scale compared with right-sided resection (P = 0.039), on the social functioning scale compared with both groups (P = 0.001, P = 0.005), and had a higher level of pain compared with patients who underwent right-sided resection (P = 0.049). Scores did not significantly differ between groups 1 year after diagnosis. Finally, after 2 years of

follow-up, patients who underwent left- sided resection scored significantly worse compared with the other two groups on the insomnia (P = 0.031, P = 0.039) and constipation (P < 0.001, P = 0.016) scales. All changes between groups except the change in physical functioning scale were clinically relevant.

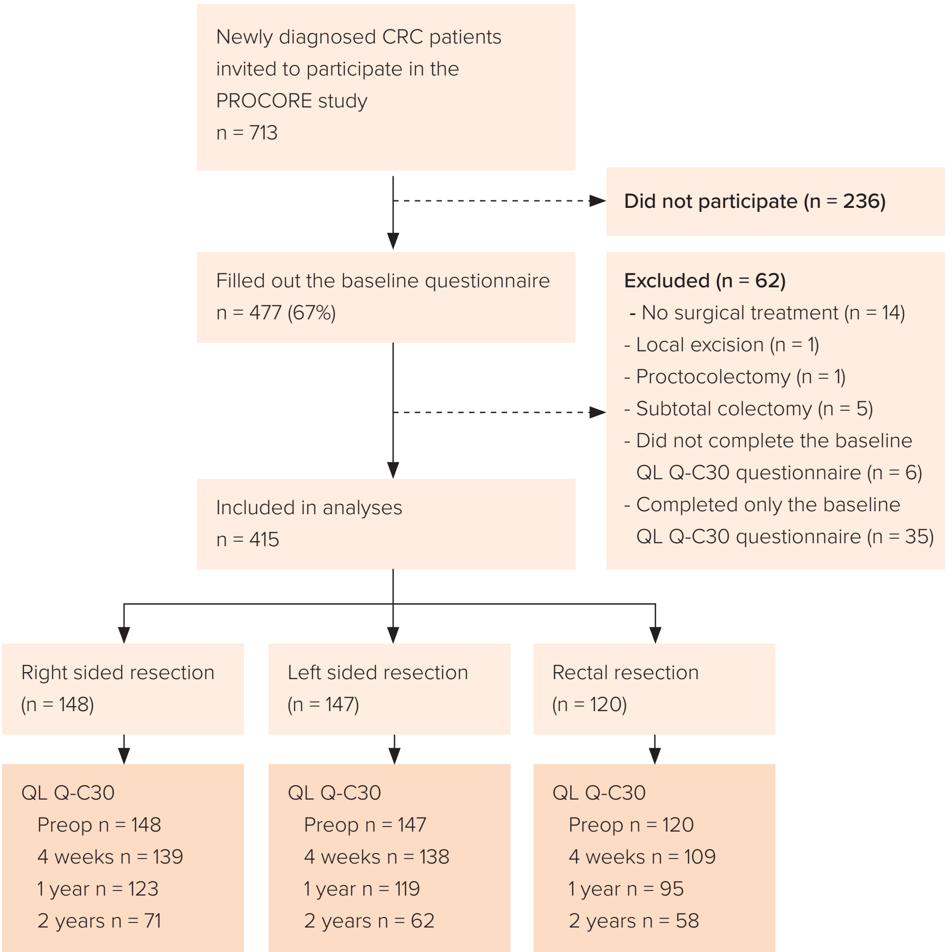

Figure 1. Flowchart of the study

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Table 1. Baseline demographic and clinical characteristics of all patients that underwent colonic or rectal resection for colorectal cancer (n = 415)

Variable	All respondents (n = 415)	Right-sided resection (n = 148)	Left-sided resection (n = 147)	Rectal resection (n = 120)	P value
Age at baseline (years)					**0.003**
≤ 70	248 (59.8%)	76 (51.4%)	86 (58.5%)	86 (71.7%)	
>70	167 (40.2%)	72 (48.6%)	61 (41.5%)	34 (28.3%)	
Gender (male)	249 (60.0%)	85 (57.4%)	89 (60.5%)	75 (62.5%)	0.692
Time between diagnosis and baseline (days)	21 [15-28]	21 [15-27]	19 [13-26]	24 [18-35]	**0.008**
Highest level of education[a]					0.344
Low	4 1(9.9%)	12 (8.1%)	18 (12.2%)	11 (9.2%)	
Medium	265 (63.9%)	89 (60.1%)	99 (67.3%)	77 (64.2%)	
High	105 (25.3%)	44 (29.7%)	30 (20.4%)	31 (25.8%)	
Missing	4 (1%)	3 (2.0%)	0 (0%)	1 (0.8%)	
BMI (kg/m2)					0.362
< 25	147 (35.4%)	53 (35.8%)	47 (32.0%)	47 (39.2%)	
25 - 30	161 (38.8%)	57 (38.5%)	55 (37.4%)	49 (40.8%)	
≥ 30	102 (24.6%)	35 (23.6%)	44 (29.9%)	23 (19.2%)	
Missing	5 (1.2%)	3 (2.0%)	1 (0.7%)	1 (0.8%)	
ASA grade					0.055
I-II	354 (85.3%)	119 (80.4%)	131 (89.1%)	104 (86.7%)	
III-V	58 (14%)	29 (19.6%)	16 (10.9%)	13 (10.8%)	
Missing	3 (0.7%)	0 (0%)	0 (0%)	3 (2.5%)	
Smoking					0.542
Current smoker	45 (10.8%)	18 (12.2%)	12 (8.2%)	15 (12.5%)	
Former smoker	241 (58.1%)	83 (56.1%)	84 (57.1%)	74 (61.7%)	
Non-smoker	118 (28.4%)	43 (29.1%)	46 (31.3%)	29 (24.2%)	
Missing	11 (2.7%)	4 (2.7%)	5 (3.4%)	2 (1.7%)	
Number of comorbid conditions					**0.012**
0	116 (28%)	29 (19.6%)	50 (34.0%)	37 (30.8%)	
1	135 (32.5%)	46 (31.1%)	46 (31.3%)	43 (35.8%)	
≥ 2	162 (39%)	73 (49.3%)	50 (34.0%)	39 (32.5%)	
Missing	2 (0.5%)	0 (0%)	1 (0.7%)	1 (0.8%)	

Table continues on next page

Table 1 continued

Variable	All respondents (n = 415)	Right-sided resection (n = 148)	Left-sided resection (n = 147)	Rectal resection (n = 120)	P value
Tumor stage (pTNM)					**0.004**
I	126 (30.4%)	48 (32.4%)	47 (32.0%)	31 (25.8%)	
II	115 (27.7%)	51 (34.5%)	42 (28.6%)	22 (18.3%)	
III	157 (37.8%)	44 (29.7%)	53 (36.1%)	60 (50.0%)	
IV	10 (2.4%)	1 (0.7%)	4 (2.7%)	5 (4.2%)	
Unknown	7 (1.7%)	4 (2.7%)	1 (0.7%)	2 (1.7%)	
(Neo)adjuvant therapy	150 (36.1%)	35 (23.6%)	48 (32.7%)	67 (55.8%)	**<0.001**
Radiotherapy only	29 (7.0%)	0 (0%)	0 (0%)	29 (24.2%)	
Chemotherapy only	88 (21.2%)	33 (22.3%)	48 (32.7%)	7 (5.8%)	
Chemo and radiotherapy	33 (8.0%)	2 (1.4%)	0 (0%)	31 (25.8%)	
Surgical approach					**0.002**
Laparoscopy	381 (91.8%)	139 (93.9%)	142 (96.6%)	100 (83.3%)	
Open	25 (6.0%)	8 (5.4%)	5 (3.4%)	12 (10.0%)	
TaTME	4 (1.0%)	0 (0%)	0 (0%)	4 (3.3%)	
Missing	5 (1.2%)	1 (0.7%)	0 (0%)	4 (3.4%)	
Stoma (yes)	73 (17.6%)	1 (0.7%)	3 (2.1%)	69 (57.5%)	**<0.001**
Diverting	47 (11.3%)	0 (0%)	1 (0.7%)	46 (38.3%)	
End	25 (6.0%)	1 (0.7%)	2 (1.4%)	22 (18.3%)	
Unknown	1 (0.2%)	0 (0%)	0 (0%)	1 (0.8%)	
Length of hospital stay					0.090
<10 days	357 (86.0%)	134 (90.5%)	127 (86.4%)	96 (80.0%)	
≥10 days	39 (9.4%)	11 (7.4%)	11 (7.5%)	17 (14.2%)	
Missing	19 (4.6%)	3 (2.0%)	9 (6.1%)	7 (5.8%)	

Note: Values are in frequencies (percentages) or median [IQR].
Bold values have been found statistically significant ($P < 0.05$).
[a] Level of education: low (no or primary school); medium (lower general secondary education or vocational training); high (pre-university education, high vocational training, university).
Abbreviations: ASA, American Society of Anesthesiologists; BMI, Body Mass Index; IQR; interquartile range, kg, kilograms; m, meters; pTNM, pathological tumor node and metastasis stage; TaTME, Transanal Total Mesorectal Excision.

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Changes in HRQoL over time (within-group differences)

Right-sided colonic resection. For patients who underwent right-sided resection, global health status, social functioning, and scores of the insomnia and constipation scales remained stable after 4 weeks compared to baseline but significantly improved after 1 and 2 years of follow-up **(Figure 2)**. A significant drop in scores at 4-week follow-up was observed in physical and role functioning, however, scores returned to baseline at 1-year follow-up. Emotional functioning was lowest at baseline but continued to improve from that point until the follow-up after 2 years. Furthermore, more fatigue and diarrhea symptoms were reported 4 weeks after right-sided resection, however, scores normalized to baseline levels or improved further at 1-year follow-up. Finally, cognitive functioning and pain scores did not change significantly over time **(Figure 3)**. All changes were of clinical relevance.

Left-sided colonic resection. Global health status remained stable compared to baseline 4 weeks after left-sided resection, but significantly improved at 1-year follow-up. Deterioration in physical functioning, cognitive functioning, fatigue, and pain was seen 4 weeks postoperatively **(Figure 2 and 3**). These scores remained significantly lower than baseline score at 1 and 2-year follow-up. However, mean changes from baseline to 1 and 2 years of follow-up for physical functioning were not clinically relevant. Furthermore, role functioning and social functioning scores deteriorated significantly after left-sided resection, but returned to baseline level at 1-year follow-up. For emotional functioning, scores were lowest at baseline and continued to improve during follow-up up to 1 year. A slight decrease in scores after 2 years of follow-up was not clinically relevant. Scores for constipation initially remained stable after left-sided resection but deteriorated at 2 years of follow-up. Patients experienced less complaints of diarrhea over time in the follow-up until 2 years. Finally, scores did not change significantly over time for insomnia **(Figure 3)**.

Rectal resection. Global health status, role functioning, social functioning, pain, and insomnia initially deteriorated after rectal resection. However, scores improved and restored to baseline level after 1 year of follow-up **(Figure 2 and 3)**. For physical functioning, cognitive functioning, and fatigue symptoms the course was quite similar, however, scores did not recover to baseline level. Similar to the other two groups, emotional functioning was lowest at baseline but continued to improve during follow-up after 4 weeks postoperatively and after 1 year. Patients undergoing rectal resection experienced less constipation-related symptoms at 1 year of follow-up compared with baseline. Finally, diarrhea-related symptoms diminished over time after rectal resection. All reported changes were clinically relevant.

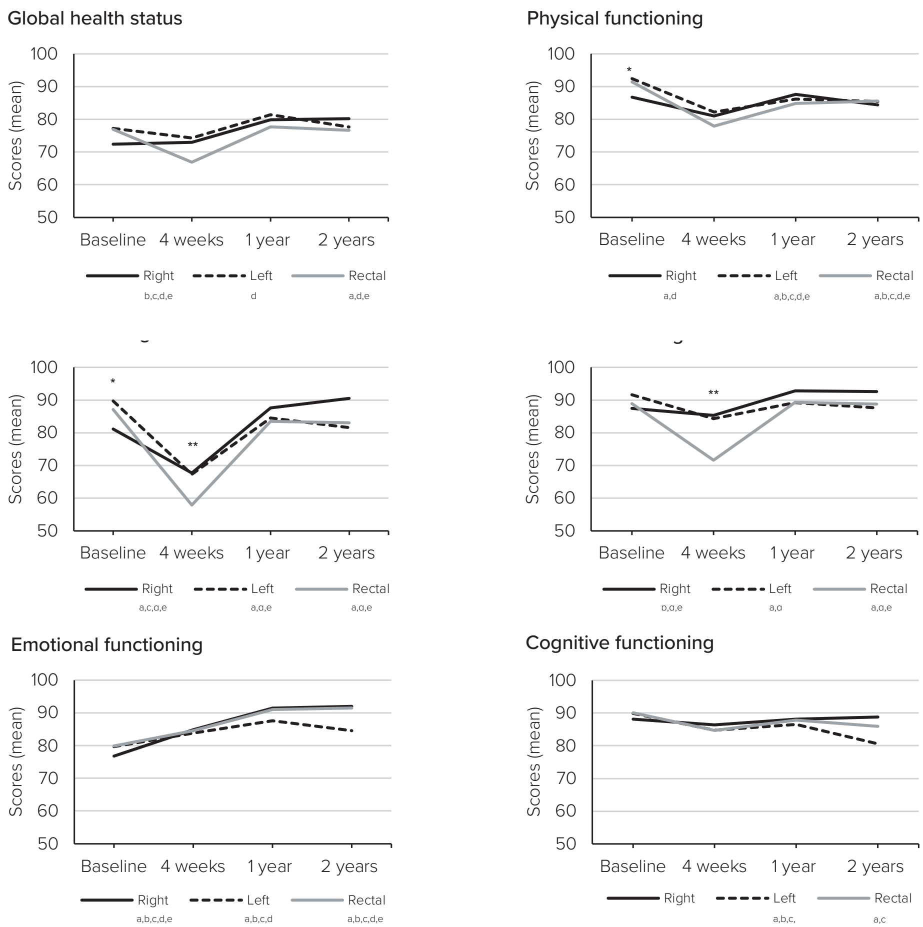

Figure 2. Health-related quality of life function scores over time measured with the European Organization for Research and Treatment of Cancer QLQ-C30 questionnaire for subgroups (right-sided, left-sided, and, rectal resection). A higher score means better functioning/global health status. For a more visually suitable display of the results, the scale ranges from 50 to 100. The actual scale ranges from 0 to 100. Between-group analyses: *significant difference between patients that underwent right-sided and left-sided resection. **significant difference between patients that underwent right-sided and rectal resection. ***significant difference between patients that underwent left- sided and rectal resection. Within-group analyses: [a]significant difference baseline, 4-week follow-up; [b]significant difference baseline, 1-year follow-up, [c]significant difference baseline, 2-year follow-up; [d]significant difference 4-week, 1-year follow-up; [e]significant difference 4-week, 2-year follow-up. Analyses were adjusted for: age, time between diagnosis and baseline, number of comorbid conditions, tumor stage, (neo)adjuvant therapy, surgical approach, and stoma

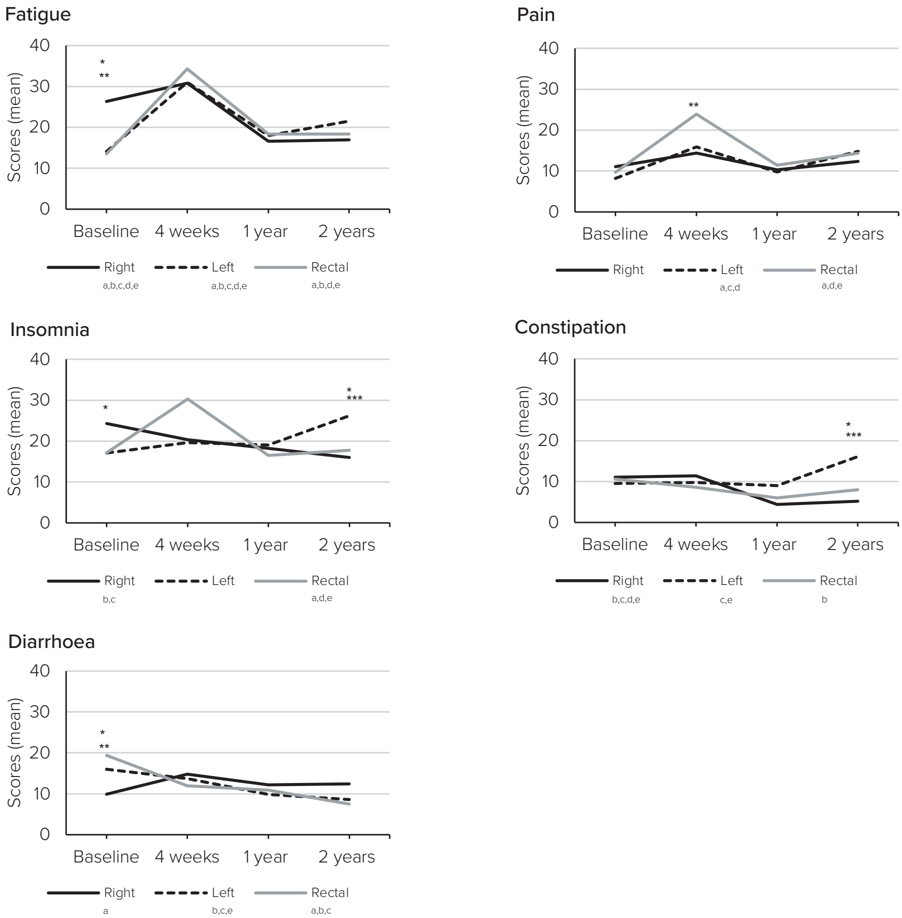

Figure 3. Health-related quality of life of single items and scales over time measured with the European Organization for Research and Treatment of Cancer QLQ-C30 questionnaire for subgroups (right-sided resection, left-sided resection, and rectal resection). A lower score means less symptoms. For a more visually suitable display of the results, the scale ranges from 0 to 40. The actual scale ranges from 0 to 100. Between-group analyses: *significant difference between patients that underwent right-sided and left-sided resection. **significant difference between patients that underwent right-sided and rectal resection. ***significant difference between patients that underwent left-sided and rectal resection. Within-group analyses: [a]significant difference baseline, 4-week follow-up; [b]significant difference baseline, 1-year follow-up; [c]significant difference baseline, 2-year follow-up; [d]significant difference 4-week, 1-year follow-up; [e]significant difference 4-week, 2-year followup. Analyses were adjusted for: age, time between diagnosis and baseline, number of comorbid conditions, tumor stage, (neo)adjuvant therapy, surgical approach, and stoma

Discussion

The current study evaluates HRQoL in patients with CRC and presents the impact of surgery on the course of HRQoL. In general, we found that HRQoL deteriorated at 4 weeks after surgery but restored approximately to baseline level at 1 year after diagnosis in most of the domains. Comparing results within patients that underwent right-sided colonic, left-sided colonic, and rectal resection over time, mean changes were largest in patients undergoing rectal resection. Notable results are discussed below.

HRQoL scores seemed to be most affected in patients undergoing rectal surgery. Recovery in HRQoL was less advanced 4 weeks postoperatively compared with the other subgroups suggesting that the amount of recovery is more extensive in this population. These findings are in agreement with those of Andersson and colleagues, who reported similar scores at 4 weeks after surgery[11] and are perhaps declared by dysfunctional bowel symptoms associated with rectal surgery, such as fecal incontinence, frequent bowel movements, emptying, and urgency difficulties.[7] The current study found the greatest differences in role and social functioning, and pain; scales that are closely related to bowel functioning according to previous studies.[7,20] In contrast to colonic procedures, tissue damage after rectal surgery is relatively high and patients often have a comprehensive perineal wound, which likely causes significant problems. Taken together, patients with rectal cancer should be informed about the more extensive recovery and additional support postoperatively may be indicated. 7

Around diagnosis, patients who underwent right-sided resection reported more fatigue symptoms and worse physical functioning compared with the other two groups. This finding might be due to anemia often present in patients diagnosed with a tumor in the right-sided colon.[21] Assessment of hemoglobin was not part of the PROCORE study protocol, therefore, this possible confounder could not be accounted for in the analyses. Patients should be screened routinely for anemia in the preoperative period and in case of insufficiencies be addressed to optimize hemoglobin levels and there- with possibly associated fatigue symptoms.[22]

Considering physical functioning, for patients who underwent left-sided or rectal resection, scores did not return to baseline levels after 2 years of follow-up. A systematic review by Hamaker et al. showed similar results.[4] Physical functioning could be optimized using rehabilitation programs. Even better, the preoperative period may be more suitable to introduce interventions that improve a patient's functional capacity because the condition is generally better compared to the direct postoperative period.[23] A multimodal prehabilitation

program (i.e., involving physical exercise, nutritional support including protein supplementation, lifestyle behavioral changes such as smoking and alcohol cessation, anemia correction, and mental support) diminishes the inevitable deterioration due to surgery and limits the extent.[24] Furthermore, because patients initiate the program in the preoperative period, continuation of such interventions are more easily resumed in the postoperative period. Prehabilitation enables patients to return more rapidly to baseline physical functioning.

An improved functional capacity both pre and postoperatively enables patients to maintain a certain level of independence; to continue to carry out daily activities in both personal and professional setting. Role functioning, the scale with most extreme changes over time in this study, reflects these daily activities and is, therefore, an important domain for the patient. Informing the patient about the impact of surgery on daily life activities is essential and furthermore, encourages initiatives such as prehabilitation.

Strengths of the current study are the large population-based sample size and the prospective collection of data containing both preoperative and long-term postoperative HRQoL values of a validated questionnaire. This study also has several limitations. First, we intended to include postoperative complications in our LMM analyses since this is expected to impact HRQoL to a great extent. However, since these data were not available, this was not possible. Instead, we considered to include length of hospital stay (< of ≥10 days) as a surrogate measure since a longer admission is generally caused by complications occurring in the direct postoperative period. Another confounder one could assume to be included in the analyses is American Society of Anesthesiologists (ASA)-classification. Instead, we included number of comorbidities, which was significantly different between groups, as a confounder. We think that this is a better indicator of preoperative health status since comorbidities that might negatively impact HRQoL are included in this variable and do not contribute to a higher ASA-classification. Second, conclusions from our HRQoL findings after 2 years of follow-up should be made with caution due to the ongoing nature of the study. Based on the current data, we believe however that HRQoL does not change significantly after 1 year of follow-up. Third, laparoscopy is widely implemented in the Netherlands and standard surgical approach in most surgeries (91% in the current study). However, since not all countries have similar rates of laparoscopic approach in CRC, generalization of the study results should be done with caution. Finally, although analyses were corrected for multiplicity within the various scales and items, we did not impose a corrected P value between those scales and items. Since we believe all scales and items can be interpreted separately, additional correction for multiplicity is unnecessary.

The results of this study enable specialists to inform patients about the impact of surgery on HRQoL domains in general and specified by surgery type. It helps patients to conceive realistic expectations. This crucial information should be communicated with the patient beside standard information regarding surgery procedure and risk of complications and is to date perhaps somewhat underexposed in the consultation room. Additionally, such results offer perspective which patients need additional support in what period of the cancer pathway and enable professionals to act accordingly.

The current study found that patients generally recover to baseline level somewhere between 4 weeks postoperatively and 1 year after diagnosis. However, full recovery after for example 8 weeks or 8 months obviously affects the impact on the patient's life. Therefore, assessing quality of life more frequently in the direct postoperative period will provide insight in the recovery rate and may be addressed in future studies. Furthermore, nonmedical factors that affect quality of life (i.e., social determinants of life) should be included in future studies in this direction.

Conclusions

The results of the current study enable clinicians in daily clinical practice to inform CRC surgical patients on the course of specific HRQoL domains up to 2 years after diagnosis. Furthermore, this study offers recommendations for potential strategies such as anemia correction or (p)rehabilitation to optimize specific HRQoL domains. In addition to other clinical treatment outcomes (e.g., survival, postoperative complications), HRQoL directly affects the patient and should therefore be discussed thoroughly on a routine basis.

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Prehabilitation for patients with colorectal cancer: a snapshot of current daily practice in Dutch hospitals

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Abstract

Background:

Multimodal prehabilitation programmes are increasingly being imbedded in colorectal cancer (CRC) pathways to enhance the patient's recovery after surgery. However, there is no (inter)national consensus on the content or design of such a programme. This study aimed to evaluate the current practice and opinion regarding preoperative screening and prehabilitation for patients undergoing surgery for CRC throughout the Netherlands.

Methods:

All regular Dutch hospitals offering colorectal cancer surgery were included. An online survey was sent to one representative colorectal surgeon per hospital. Descriptive statistics were used for analyses.

Results:

Response rate was 100% (n = 69). Routine preoperative screening of patients with CRC for frailty, diminished nutritional status and anaemia was the standard of care in nearly all Dutch hospitals (97%, 93% and 94%, respectively). Some form of prehabilitation was provided in 46 hospitals (67%) of which more than 80% addressed nutritional status, frailty, physical status and anaemia. All but two of the remaining hospitals were willing to adopt prehabilitation. The majority of the hospitals offered prehabilitation to specific subgroups of patients with CRC, such as the elderly (41%), the frail (71%) or high-risk patients (57%). There was high variability in the setting, design and content of the prehabilitation programmes.

Conclusion:

Whereas preoperative screening is sufficiently incorporated in Dutch hospitals, standardised enhancement of the patient's condition in the context of multimodal prehabilitation seems to be challenging. This study presents an overview of current clinical practice in the Netherlands. Uniform clinical prehabilitation guidelines are vital to diminish heterogeneity in programmes and to produce useful data to enable a nationwide implementation of an evidence-based prehabilitation programme.

Introduction

Preoperative risk screening prior to surgery is standard of care in the Netherlands. Once surgery is indicated, patients are referred to the preoperative screening outpatient clinic to be evaluated on general health under supervision of anaesthesiologists. Adequate screening is crucial to identify deficiencies. The interventions prescribed in this setting should be distinguished from the concept of prehabilitation. Prehabilitation not only addresses deficiencies but refers to interventions in the preoperative period to improve overall functional capacity prior to surgery and consequently, improve outcome and allow quicker recovery postoperatively[1]. It has been shown to reduce length of hospital stay[2] and complication rate[3-5], and even resulted in an improved disease-free survival.[6] Additionally, a recently published paper concluded that a prehabilitation programme has turned out to be cost-effective with regard to health-care costs.[7]

Prehabilitation is often used in colorectal cancer (CRC) treatment since colorectal resection is associated with high morbidity rates.[8] Furthermore, the treatment interval (diagnosis to treatment) generally comprises several weeks.[9] CRC slowly develops over time and treatment initiation is less hasty than in other types of cancer.[10] In the Netherlands, the government recommends to initiate treatment within five weeks after pathological confirmation of CRC diagnosis in 80% of the patients and within seven weeks in 100%.[11] This interval could optimally be used to proceed through a multimodal prehabilitation programme.

Awaiting more conclusive evidence about its effectiveness from ongoing trials, prehabilitation is already being implemented. There is consensus that prehabilitation should ideally be multimodal, containing various interventions such as exercise, nutritional support and protein supplementation, smoking and alcohol cessation, anaemia correction, and psychological support.[12] Beside the multimodal design, there is no (inter)national consensus on the content and design of such a programme. Furthermore, the implementation of a multidisciplinary programme proved to be difficult in practice as it involves many professionals and may be accompanied by logistic and financial difficulties.

Increased awareness of the potential benefit of prehabilitation has led to the recognition of the need to facilitate prehabilitation in Dutch hospitals. The ultimate goal of leading stakeholders (e.g. the Dutch Society for Surgery, the Dutch Healthcare Authority and insurance companies) is to implement a national and uniform evidence-based protocol. To evaluate the current daily practice in the Netherlands, we conducted a national survey among CRC surgeons with the aims of 1) assessing preoperative screening in general to

enable distinction from interventions as part of a prehabilitation programme, 2) evaluating surgeons' knowledge and opinions on prehabilitation, and 3) collecting information on the general design of prehabilitation programmes in the Netherlands.

Methods

Study design and data collection

This study was conducted by the Department of Surgery of Máxima MC (MMC), a large teaching hospital in Veldhoven, the Netherlands. MMC is experienced in the conduct of research on prehabilitation (PREHAB trial: international, multicentre randomised controlled trial for patients with CRC (Netherlands Trial Register NL5784); non-randomised pilot study for patients with non-small cell lung cancer, (Netherlands Trial Register NL8080)). Furthermore, MMC has implemented multimodal prehabilitation programmes in several cancer care pathways.

An online electronic survey **(Supplementary file 1)** was developed by the authors and included questions about 1) the general use of preoperative screening, 2) the surgeon's knowledge and opinions on prehabilitation, and 3) the general design of prehabilitation programmes in the surgeon's hospital. Additionally, colorectal surgeons were asked if they were interested in implementing prehabilitation in their hospital and if they would accept a potential delay of surgery for that purpose. The survey was built using the online survey software of SurveyMonkey© (SVMK Inc., San Mateo, California, United States of America). An answer to each question was mandatory before the participant could proceed to the next. All questions required multiple choice or checkbox answers. Preoperative screening and prehabilitation domains were predefined by the authors and included nutritional status, frailty (according to the Geriatric 8 (G8) screening tool[13]), physical status, mental health status, intoxications, anaemia, and polypharmacy. In case other domains were used, participants were asked to elaborate on their answers. The survey was tested by three independent colorectal surgeons of MMC and was adjusted based on the feedback received. The dataset generated and analysed during the current study is available from the corresponding author on request.

Study setting and population

In 2020, approximately 17.4 million inhabitants lived in the Netherlands with a life expectancy of 81.4 years, which is slightly higher compared to the mean life expectancy in Europe.[14,15] In total, 143 general, academic, private and paediatric hospitals were located throughout the Netherlands, with 2.7 million admissions in 2020.[16] Hospital-related expenses comprised approximately 29.1 billion euros in 2019.[17] Medical insurance is mandatory and inhabitants are generally registered with a local general practitioner, who serves as a gatekeeper.

The incidence of CRC is relatively high in the Netherlands compared to other European countries, with 60.8 new cases per 10.000 inhabitants.[18] In 2019, 6.511 patients with colonic cancer and 2.621 patients with cancer located in the rectum underwent surgical resection, mainly laparoscopically- or robotic-assisted (colon cancer: 82.3%; rectal cancer: 79%).[19]

In the Netherlands, preoperative assessment prior to surgery is standard care. Once the indication for surgery is made, patients are referred to the outpatient preoperative screening clinic. Routine preoperative screening generally comprises of risk assessment (e.g. American society of Anaesthesiologists classification (ASA), metabolic equivalent of task score (METs)), nutritional assessment (e.g. short nutritional assessment questionnaire (SNAQ), malnutrition universal screening tool (MUST)), routine blood work (e.g. hemoglobin, kidney function), and frailty screening (e.g. G8, Fried frailty index (FFI)). Furthermore, enhanced recovery after surgery (ERAS) programmes have been implemented in the majority of hospitals.

All regular Dutch hospitals offering CRC surgery were included. The study population comprised of one oncological surgeon per hospital. We used our own network to select participants. Based on our information, these surgeons were considered to be experts in the field of CRC surgery and were involved and well aware of their hospital's policy. Nevertheless, in case a surgeon indicated that he or she was not suited to participate in our study, we intended to approach a second surgeon. We selected all Dutch academic, teaching and non-teaching hospitals for the current study. All surgeons received the first invitation for the survey in July 2020 and received subsequent reminders between August and October 2020. Results were handled anonymously. Ethical approval was deemed not necessary for this study.

Statistical analyses

Data were analysed using SPSS version 22 (SPSS Inc. Chicago, IL, USA). Descriptive statistics were used to present data. Qualitative analyses were performed for data from comments or open questions.

Results

Participation rate

Seventy-four hospitals were deemed eligible for participation in this study. Two hospitals were excluded because they were either children's hospitals or outpatient clinics. Three hospitals were excluded because surgery for CRC was not being offered. This resulted in 69 unique hospitals **(Figure 1).** A total of 69 representative surgeons responded to the survey resulting in a response rate of 100%. Forty-three surgeons responded after the first invitation with the remaining 26 surgeons responding after a reminder.

Preoperative screening

The use of preoperative screening in patients with CRC in various domains is presented in **Figure 2.** Screening for nutritional status, frailty, and anaemia was implemented in nearly all Dutch hospitals. Additional domains reported by the respondents included fall risk and geriatric assessment, evaluation of the patient's domestic environment, comorbidity assessment, and evaluation in general by the surgeon in the outpatient clinic. When preoperative screening revealed deficiencies in the screened domains, interventions were applied by default to address these deficiencies in only half of the hospitals (n=34, 48.6%).

The surgeon's knowledge and opinion on prehabilitation

The term prehabilitation was understood by 98.6% of the respondents and the majority (82.6%) believed a prehabilitation programme should have a multimodal design **(Table 1).** According to 53.6% of the respondents, multimodal was defined as at least two interventions. Several respondents suggested another definition of multimodal being as many interventions as needed based on the patient's baseline assessment.

Current practice: the global design of prehabilitation programmes

Displayed in **Table 2**, a total of 46 Dutch hospitals (66.7%) had implemented some form of prehabilitation for patients scheduled for CRC surgery. Twenty-two hospitals (31.9%) had not implemented a prehabilitation programme for CRC at the time the survey was conducted. Of

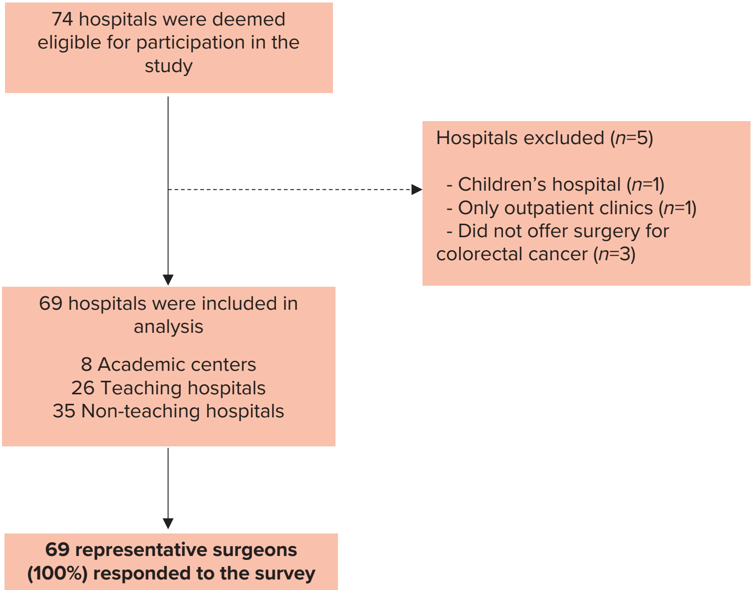

Figure 1. Flow diagram of included Dutch hospitals.

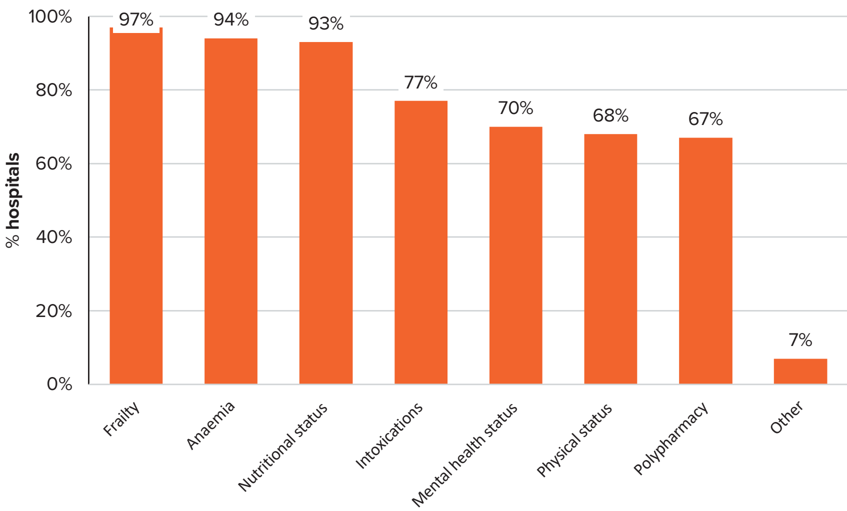

Figure 2. Current practices on preoperative screening for patients with colorectal cancer in the Netherlands, according to respondents (n=69).

these, twenty hospitals (91%) were intending or willing to adopt such a programme and only two respondents declared that they do not intend to implement a prehabilitation programme since they were not convinced by the benefits of this concept.

The majority of hospitals offered prehabilitation to more than one subgroup with elderly, frail patients being targeted most often. Only 17.4% of the hospitals did not focus on subgroups and offered prehabilitation to all patients with CRC. All prehabilitation programmes included more than one intervention. Polypharmacy and mental health status were underrepresented domains in the programmes. The interventions were offered both for the home as well as a structured, individualised programme tailored for the individual patient in 26 (56.5%) hospitals. Eleven surgeons (23.9%) responded that the programme was not structured or standardised but consisted of individualised interventions based on the patient's needs. The majority of the interventions were being outsourced to primary care facilities.

Treatment interval

Finally, we had asked the surgeons whether or not they were willing to extend time from pathological diagnosis to surgery (treatment interval) in order to facilitate prehabilitation. Nearly half of the respondents were willing to perform surgery after a maximum of six weeks or eight weeks after diagnosis, and 29.0% of the respondents was willing to extend time to surgery as long as necessary to optimise the patient's condition **(Figure 3).**

Table 1. General questions regarding prehabilitation, according to respondents (n=69)

	N (%)
Are you familiar with the term "prehabilitation"?	
Yes	68 (98.6%)
No	1 (1.4%)
What do you mean by prehabilitation?	
Any intervention	10 (14.5%)
Multimodal programme	57 (82.6%)
Other	1 (1.4%)
Missing*	1 (1.4%)
What do you mean by multimodal?	
At least two interventions	37 (53.6%)
At least three interventions	14 (20.3%)
Other	17 (24.6%)
Missing*	1 (1.4%)

* One respondent did not complete the survey and accounts for the missing value.

Table 2. The global design of prehabilitation programmes for patients with colorectal cancer

	Hospitals that provide prehabilitation (n=46)	**Hospitals that are interested in the implementation of prehabilitation (n=20)**
	N (%)	**N (%)**
Do you/would you triage patients before start of a prehabilitation programme?		
Yes	37 (80.4%)	18 (90.0%)
No	9 (19.6%)	2 (10.0%)
What (sub-) groups (would) qualify for prehabilitation?*		
All patients with CRC	8 (17.4%)	7 (35.0%)
Frail patients with CRC	33 (71.7%)	13 (65.0%)
Elder patients with CRC	19 (41.3%)	9 (45.0%)
High-risk patients with CRC	26 (56.5%)	11 (55.0%)
Patients with diseases other than CRC	9 (19.6%)	8 (40.0%)
What domains are/would be included in the hospital's prehabilitation programme for CRC? [b]		
Nutritional status	45 (97.8%)	20 (100%)
Frailty	39 (84.8%)	16 (80.0%)
Physical status	39 (84.8%)	18 (90.0%)
Mental status	22 (47.8%)	15 (75.0%)
Intoxications	27 (58.7%)	15 (75.0%)
Anaemia	38 (82.6%)	20 (100%)
Polypharmacy	19 (41.3%)	14 (70.0%)
Other	1 (2.2%)	1 (5.0%)
What is/would be the design of the interventions?*		
Advices for home	28 (60.9%)	9 (45.0%)
A structured,standardised programme equal for all patients	6 (13.0%)	0 (0.0%)
A structured,individualised tailored programme	34 (73.9%)	20 (100%)
Other	11 (23.9%)	0 (0.0%)
In what setting is/would the programme being/be offered?*		
Hospital-based	24 (52.2%)	6 (30.0%)
In primary care facilities	39 (84.8%)	19 (95.0%)
In the gym	14 (30.4%)	6 (30.0%)
Home-based	32 (69.6%)	16 (80.0%)

[a] Three hospitals not included: two respondents were not intending to implement prehabilitation within the near future and one is missing.
[b] Check box questions; more than one answer allowed.
Abbreviations: CRC, colorectal cancer; N, number of respondents.

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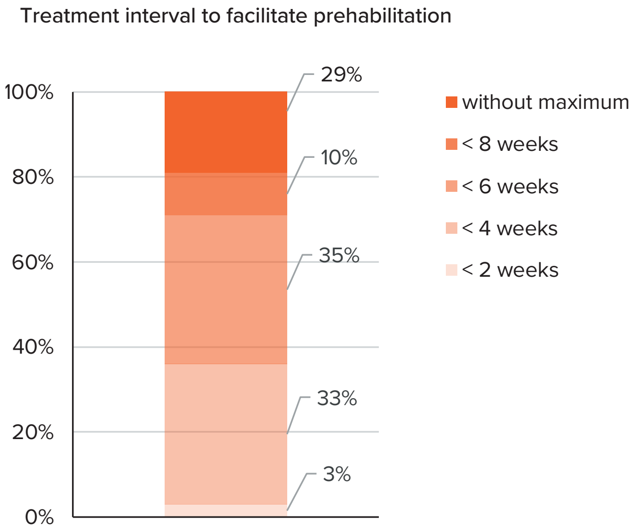

Figure 3. Opinion about interval from diagnosis until surgical treatment to facilitate prehabilitation

Discussion

This study assessed the current state of prehabilitation for patients with CRC in Dutch hospitals. Preoperative screening is sufficiently incorporated in Dutch hospitals. However, it is remarkable that this does not translate into acting on deficiencies accordingly and moreover, to interventions in the preoperative period that improve the patient's condition. In the Netherlands, the concept of prehabilitation has nowadays been incorporated by 67% of the hospitals, but there is high variability in the design of the programme and the setting in which prehabilitation is being offered.

Prehabilitation is an upcoming phenomenon; a concept rapidly embraced by health care facilities worldwide. In general, preoperative optimisation consists of screening, assessment and interventions[1,20] addressing modifiable risk factors with the aim to improve the patient's condition. Main domains in the programme focused on physical, nutritional and mental health status.[1] Additionally, addressing lifestyle behaviour and, in CRC, anaemia correction may be included in the programme. Combining interventions in a multimodal programme results in a synergistic effect.[12]

Preoperative screening

Factors that are traditionally being screened in the preoperative period such as age, gender and ASA classification, cannot be optimised. In contrast, risk factors that are modifiable have been studied thoroughly.[21,22] The present study shows that current preoperative screening methods in the Netherlands include various domains. The high screening rates for frailty and malnutrition can be explained by the fact that these domains are imposed by a national safety programme focused on the frail elderly.[23] Additionally, haemoglobin is routinely being screened according to the 4-5-6 rule (haemoglobin levels of 4-5-6 mmol/L) included in the Dutch blood transfusion guideline.[24] However, this rule does not take into account the underlying causes of anaemia and correction thereof. Despite current recommendations of anaemia management in the latest ERAS guidelines[25], translation into clinical practice is still inconvenient.[26]. A recently published study by Bosker et al. reported preoperative anaemia in approximately 20% of the Dutch patients undergoing right-sided colonic resection and a similar amount receiving blood transfusion postoperatively.[27] Since anaemia is a major risk factor for postoperative complications, e.g. colorectal anastomotic leakage[28] and worse survival[29,30] ,preoperative optimisation is of great importance. Without an intervention, screening of risk factors like this is futile.

Prehabilitation in Dutch hospitals

The results from this study revealed that nearly all respondents (97%) were familiar with the concept. Some form of prehabilitation has already been implemented in two thirds of the Dutch hospitals. As mentioned before, the programme should be multimodal. This was also clearly reported by our respondents (82.6%). The majority of the programmes were carried out in primary care facilities. Even though supervision is provided in both in-hospital and primary care setting, the latter minimises the potential travel burden. However, for high-risk patients for example, in-hospital exercise may be more appropriate. In the near future, triage will enable professionals to distinguish subgroups with an indication for in-hospital, primary care or home-based exercises.

Logistical and financial challenges

There are several challenges regarding the implementation of prehabilitation in routine clinical practice and financial factors should be taken into account. Prehabilitation is not included in the health insurance policy in the Netherlands. Furthermore, implementing a prehabilitation programme is time consuming. The multimodal design of the programme involves many disciplines and all departments have their own board of directors and own budget. Redesigning the care pathway with a programme that suits all departments is

challenging. More importantly, in order to minimise the burden for patients, departments need to cooperate quickly and accurately in order to harmonise all appointments for the patient. We would therefore advise hospitals with the intention to implement such a programme to adjust and adopt one of the protocols that already have been published.[31]

Interventions to improve mental health status

A domain underrepresented in current prehabilitation programmes in the Netherlands is mental health status. From a practical perspective, this domain is as important as the nutritional and/or exercise intervention since a good mental health status (and consequently motivation) is necessary to complete an intensive programme. However, it remains unclear from the existing evidence which psychological interventions are most effective with regard to surgical outcomes (postoperative complications, length of stay, mortality) or patient-reported outcomes.[32] Optimal information provision, maximal involvement of the patient within their own cancer pathway, relaxation techniques and cognitive therapy (insight in the patient's coping strategy) may form the base for psychological interventions. While it may seem intuitive to mentally prepare patients before surgery, interventions are difficult to design. When indicated, intensive guidance by a trained psychologist may be beneficial.

Treatment interval

The majority of the respondents (34.8%) was willing to postpone surgery with a maximum of six weeks after pathological confirmation of diagnosis to optimise the patient's condition with prehabilitation. Furthermore, 29.0% of the respondents stated that for an individual patient, when necessary, there should be no limit to the period needed to optimise the patient's condition. A recently published systematic review concluded that there is a safe window to prehabilitate patients with colon cancer within eight weeks from diagnosis.[9]

Limitations

One of the key strengths of this study is that we have collected a comprehensive range of data (e.g. opinions, beliefs, and values) from all hospitals in the Netherlands that perform CRC surgery. In order to get a complete overview, open answers were allowed when no other option would suffice. It was difficult to organise the answers and to capture the actual practice regarding content and design of prehabilitation programmes for some hospitals. We chose to collect responses of only one surgeon performing surgery for CRC to represent his/her hospital in order to prevent a high variety in responses within hospitals. We expected the responses of surgeons who were aware of the details regarding the hospitals' policy on prehabilitation to be more accurate than the information of surgeons that were selected randomly. Moreover, assessment of the consensus of different health care providers within

hospitals was not one of our goals. However, this might limit the validity of the responses and might introduce bias. Another limitation is that in order to limit the length of the survey, details of the programmes on measures and tests for screening and assessment were not included. Furthermore, not all modifiable risk factors, such as glycaemic status, were included in the survey. However, including those variables in the current study would perhaps have resulted in cluttered results, but are beyond the scope of this study. Even though this survey was designed to evaluate the current clinical practice regarding prehabilitation in the Netherlands, our findings could be of interest for other countries worldwide.

Conclusions

In conclusion, this study presents a high variability in prehabilitation practices in CRC care. Whereas preoperative screening is sufficiently incorporated in Dutch hospitals, optimising patients in the context of multimodal prehabilitation seems to be challenging. Uniform clinical guidelines of such programmes enable comparison and further implementation of prehabilitation programmes across all countries.

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Supplementary material

Supplementary file 1: The national survey about prehabilitation for patients with colorectal cancer.

1. What is the name of your hospital? *The purpose of this question is to document responses. This information will be handled strictly confidential and won't be used for publication.*

Preoperative optimisation

"The next part is about the preoperative work-up of patients with CRC in your hospital. Specifically, it is about preoperative screening and intervention(s) as part of standard care."

2. Does your hospital screen patients with CRC preoperatively as part of standard care on the following domains? (multiple selections possible)
   - ☐ Nutritional status
   - ☐ Frailty
   - ☐ Physical status
   - ☐ Mental status
   - ☐ Intoxications
   - ☐ Anaemia
   - ☐ Polypharmacy
   - ☐ Other:

3. Is an intervention applied when scores on a particular domain are insufficient? *Example of interventions include but are not limited to the following domains: nutritional status, frailty, physical status, mental status, intoxications, anaemia, polypharmacy.*
   - o Yes, an intervention is always applied whenever this is deemed necessary regarding one or more domains
   - o An intervention is not always applied even though results are insufficient based on screening of one or more domains
   - o An intervention is not applied

Prehabilitation

4. Are you familiar with the term "prehabilitation"?
   - o Yes
   - o No

If yes, *"there is no universally accepted definition of prehabilitation. Large variations of content and design of prehabilitation programmes have been reported in the literature. Clearly, there is need for a generally accepted definition and we are interested in your opinion."*

If no, *"the term prehabilitation refers to interventions in the preoperative period to improve functional capacity prior to surgery and consequently, improve outcome and fasten recovery postoperatively. Prehabilitation often consists of a multimodal, structured program. Examples include but are not limited to the following: nutritional support, smoking cessation, mental support, anaemia correction."*

5. What do you mean by prehabilitation?
    - o Any preoperative intervention for optimisation
    - o A structured, preoperative multimodal programme for optimisation
    - o Other:

6. What do you mean by multimodal? *Examples include but are not limited to the following: nutritional support, smoking cessation, mental support, anaemia correction.*
    - o At least two interventions
    - o At least three interventions
    - o Other:

7. Does your hospital offer a prehabilitation programme to patients with CRC?
    - o Yes, please go to question 8
    - o No, please go to question 13

"The next part is about prehabilitation of patients with CRC in your hospital."

8. What (sub)groups qualify for prehabilitation? (multiple selections possible)
    - ☐ All patients with CRC
    - ☐ Frail patients with CRC
    - ☐ Elder patients with CRC
    - ☐ High-risk patients with CRC
    - ☐ Patients with diseases other than CRC

9. Do you triage patients before start of a prehabilitation programme?
   - o Yes
   - o No

10. What domains are included in the hospital's prehabilitation programme for CRC? *(multiple selections possible)*
    - ☐ Nutritional status
    - ☐ Frailty
    - ☐ Physical status
    - ☐ Mental status
    - ☐ Intoxications
    - ☐ Anaemia
    - ☐ Polypharmacy
    - ☐ Other:

11. What is the design of the interventions? *(multiple selections possible)*
    - ☐ Advice for home
    - ☐ A structured, standardised programme equal to all patients
    - ☐ A structured, individualised programme tailored for each patient
    - ☐ Other:

12. In what setting is the programme being offered? *(multiple selections possible)*
    - ☐ Hospital-based, *please go to question 21*
    - ☐ In primary care facilities, *please go to question 21*
    - ☐ In the gym, *please go to question 21*
    - ☐ Home-based, *please go to question 21*

13. What is the reason that you are not providing prehabilitation for patients with CRC in your hospital?
    - o We never thought of that
    - o Due to logistic reasons
    - o Due to financial reasons
    - o Other:

14. Would you like to offer a prehabilitation programme to patients with CRC?
    - o Yes, *please go to question 16*
    - o No

15. What is the reason not wanting to offer prehabilitation to patients with CRC? *(multiple selections possible)*
    - ☐ Due to financial reasons
    - ☐ Due to logistic reasons
    - ☐ I could not convince my colleagues of the benefit
    - ☐ I am not convinced of the benefit
    - ☐ Other:

16. What (sub)groups would qualify for prehabilitation? (multiple selections possible)
    - ☐ All patients with CRC
    - ☐ Frail patients with CRC
    - ☐ Elder patients with CRC
    - ☐ High-risk patients with CRC
    - ☐ Patients with diseases other than CRC

17. Would you triage patients with CRC before the start of a prehabilitation programme?
    - o Yes
    - o No

18. What domains would be included in the hospital's prehabilitation programme for CRC? *(multiple selections possible)*
    - ☐ Nutritional status
    - ☐ Frailty
    - ☐ Physical status
    - ☐ Mental status
    - ☐ Intoxications
    - ☐ Anaemia
    - ☐ Polypharmacy
    - ☐ Other:

19. What would be the design of the interventions? *(multiple selections possible)*

☐ Advice for home
☐ A structured, standardised programme equal to all patients
☐ A structured, individualised programme tailored for each patient
☐ Other:

20. In what setting would the programme be offered? *(multiple selections possible)*

☐ Hospital-based
☐ In primary care facilities
☐ In the gym
☐ Home-based

21. How should prehabilitation be financed?

o Patients finance their own prehabilitation
o The insurance companies reimburse the costs
o The hospitals finance the programme
o Other:

"According to national guidelines, the time interval between diagnosis of CRC and surgical treatment is five to six weeks in the Netherlands. This time can be used for prehabilitation."

22. Would you postpone surgery in order to optimise the patient's condition preoperatively?

o Yes, up to a maximum of two weeks from pathologic diagnosis
o Yes, up to a maximum of four weeks from pathologic diagnosis
o Yes, up to a maximum of six weeks from pathologic diagnosis
o Yes, up to a maximum of eight weeks from pathologic diagnosis
o Yes, as long as it takes
o No, I would not postpone the surgery

chapter

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Implementation of perioperative music in day care surgery

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Abstract

Background:

Perioperative music can have beneficial effects on postoperative pain and perioperative opioid requirement. This study aims to assess the implementation feasibility of music in day care surgery through adherence to implementation, as well as its effects.

Methods:

This implementation study employed a prospective single-center study design. Perioperative music was implemented as part of standard surgical care during day care surgery procedures. The music intervention consisted of preselected playlists. Primary outcome was adherence to implementation. Barriers and attitudes towards music of patients and perioperative care providers were evaluated. Furthermore, the effects of music were assessed through a matched cohort analysis. This study was registered with the Netherlands Trial Register (NL8213).

Results:

From January to April 2020, a total of 109 patients received the music intervention and 97 were analyzed after matching to retrospective controls. Adherence rate to the music intervention was 92% preoperatively, 81% intraoperatively, and 86% postoperatively, with 83% of patients satisfied with the preselected music, and 93% finding music to be beneficial to surgical care. All health care providers believed perioperative music to be beneficial (63%) or were neutral (37%) towards its use. Postoperative pain was not significantly different (mean numeric rating scale 0.74; the music intervention group versus 0.68; control group, $P = 0.363$). Although not statistically significant, postoperative opioid requirement in the music group was lower (30% versus 40%, $P = 0.132$).

Conclusion:

Perioperative music implementation in day care surgery is feasible with high adherence rates, patient satisfaction levels, and positive attitudes of health care providers towards its use.

Introduction

Perioperative music can have a beneficial effect on preoperative anxiety and postoperative pain[1,2], reduce intraoperative sedative and postoperative opioid medication requirement[3], and attenuate the physiological stress response to surgery in adult surgical patients.[4] Therefore, it is an attractive non-pharmacological intervention that fits into current perioperative fast-track surgery patient care, especially since no deleterious effects of perioperative music are known.[3] However, music is still not part of daily perioperative care.

Currently, the most well-known fast track protocols are collectively known as the Enhanced Recovery After Surgery (ERAS) protocols, which primarily aim to attenuate the stress response and reduce opioid requirement.[5,6] Such new care protocols take years to become part of active daily practice and repetitive evaluation and reimplementation is necessary to maintain its beneficial effects.[7,8] Implementation research that assesses contextual factors and barriers at the level of the patient, physician, surgical team, and organization can ultimately influence implementation in daily practice and therefore the outcome of an intervention.[9]

The aim of this study is to analyze the implementation feasibility of perioperative music in day care surgery through adherence to implementation. Secondary outcome measures consisted of (1) patient reported experience, (2) barriers and facilitators of implementation, as well as attitudes of perioperative health care providers towards the use of perioperative music. Finally, the effect of perioperative music was evaluated, which included postoperative pain, medication requirement, and postoperative in-hospital complication rate.

Methods

The study was approved by the Medical Research Ethics Committee of the Máxima Medical Center, Veldhoven, the Netherlands (L19.117/N19.102) and was prospectively registered with the Netherlands Trial Register (NL8213). The current study is reported following the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.

Study design

This implementation study employed a single-center study design with prospective included patients matched to a retrospective control group. Perioperative music was implemented as part of standard surgical care during day care surgery procedures. Patients undergoing day care surgery are both admitted to and discharged from the same ward, which minimized logistical problems during initiation of the implementation. All adult patients scheduled for elective day care surgery from January 2020 to April 2020 were eligible for inclusion. Patients were excluded if they had severe hearing impairment, defined as no verbal communication possible. Furthermore, patients with insufficient knowledge of the Dutch or English language to understand the study documents were excluded as well.

Included patients received music before, during, and after surgery according to the predefined implementation protocol. The implementation protocol was developed by a multidisciplinary implementation team, with representatives of the surgical and anesthesiological department, as well as the nursing group, operation room assistants, and the management. Regular meetings of the implementation team every eight weeks were conducted throughout the study. Before implementation start, perioperative health care providers were asked if they were ready to change routine practice through interviews at staff meetings. In our regular team meetings, members were asked for their feedback on the implementation process in order to overcome barriers that arise at different levels in the health care system **(Figure 1)**.

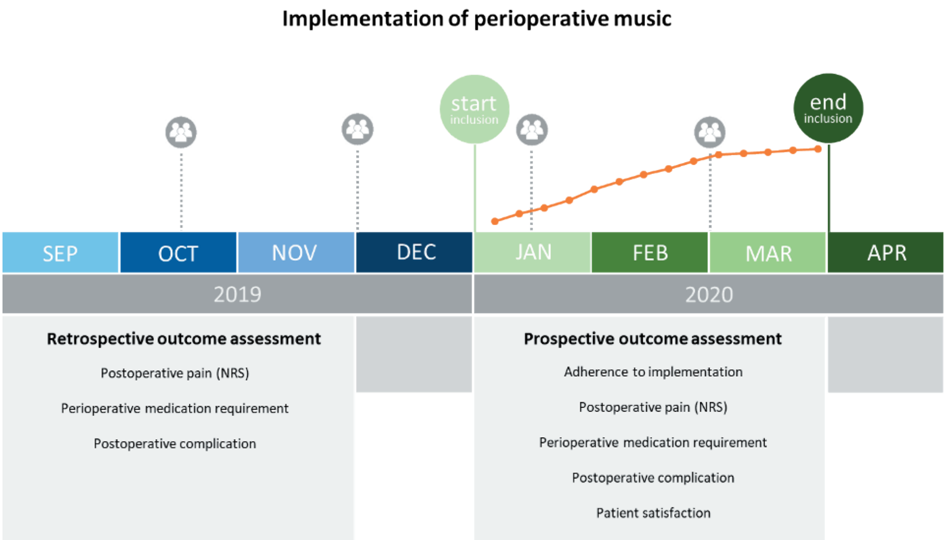

Figure 1. Timeline detailing study events in day care surgery patients. Regular meetings of the implementation team every eight weeks were conducted throughout study (grey dotted lines). NRS: Numeric Rating Scale.

Music intervention

The music intervention was provided by using a Lenova Tab E7 and disposable headphones. Patients were able to choose from different music genres. A preselected list of playlists was used based on recommendations from literature[1], with patients being allowed to choose their own preferred music. The lists included the following genres: blues/jazz (4:30 h), classical (5:02 h), pop (9:10 h) and Dutch songs (5:50 h). The music intervention was started after admission to the surgical ward and continued throughout the surgical procedure until discharge from hospital. In regards to copyright concerning music, Buma Association and Stemra Foundation gave permission to use the preselected music for research purposes.

Outcome measures

The primary outcome measure was adherence to implementation, calculated as the percentage of performed music interventions relative to the number of total possible interventions. Previous studies investigating the implementation of ERAS principles have defined success of implementation when 80% of adherence is obtained.[10] Secondary outcome measures consisted of patient reported experience, assessed through a custom-made satisfaction questionnaire. Furthermore, the effect of perioperative music was investigated. A matched-cohort analysis was conducted to compare outcomes of patients who received the music intervention and patients who did not (patients that underwent surgery prior to implementation start). Evaluated outcomes were postoperative pain (11-point Numeric Rating Scale (NRS) in which 0 implies no pain and 10 implies the worst pain possible), intraoperative and postoperative opioid medication requirement (converted to morphine equivalents (ME), with 1mg ME = 1mg of parenteral morphine[11], and in-hospital postoperative complication rate **(Figure 1)**. Demographic and clinical characteristics were prospectively collected from the electronic patient database. Finally, a custom-made questionnaire was distributed to perioperative health care providers to evaluate the implementation after inclusion end.

Statistical analysis and blinding

Prospectively included patients undergoing the music intervention were matched according to surgical procedure first, and (if possible) age at surgery, in a one to one ratio to patients who underwent day care surgery prior to implementation start (September–November 2019). If insufficient pre-test controls were available, matching was eased on type of surgery.

Statistical analysis was performed using SPSS version 22 (SPSS Inc. Chicago, IL, USA). Categorical variables were summarized as absolute number and percentage. Continuous data were presented as mean and standard deviation (SD) if normally distributed, and median and interquartile range (IQR) if not. Normality of data was assessed using the Kolmogorov-Smirnov test and visually in QQ plots. Continuous variables were compared using an independent samples student's T-test or a Mann-Whitney U-test, as appropriate. Discrete variables were compared using a Fisher's exact test or Chi-Square test. Two tailed testing was used with statistical significance inferred at $P < 0.05$. In case of five percent missing data or more, both a case complete analysis and missing data imputation using the median and lower and upper interquartile ranges.[12] No sample size calculation was performed, as a predefined inclusion period was chosen for this implementation study. Due to the nature of the intervention, participating patients could not be blinded to the intervention. Perioperative health care providers were also not blinded, given the implementation study design. All data was collected by the coordinating investigator (M.R.) or research assistants, who were not blinded to the intervention.

Results

From 1 January 2020 to 1 April 2020, 110 patients were assessed for eligibility and gave written informed consent. Of these, 109 patients participated and completed the music intervention protocol. One patient could eventually not listen to music due to a technical problem of the music device. Twelve patients could not be matched according type of surgery and age because insufficient controls were available from the retrospective patient cohort. Therefore, effect analysis was performed of 97 matched patients.

Adherence to implementation and patient satisfaction

Of the 110 patients, 59 (54%) filled out the custom-made satisfaction questionnaire. A total of 54 patients (92%) listened to music in the preoperative period, 48 patients (81%) intraoperatively and 51 patients (86%) in the postoperative period. Median patient satisfaction on a visual analogue scale was 8, with 6 patients (10%) giving the maximum score of 10 when surveyed **(Figure 2)**. Median rating score for satisfaction did not change after imputation of missing values. Fifty-five patients (93%) considered the music intervention to be beneficial to perioperative patient care, 56 (95%) would like to listen to music again if they would be operated again in the future.

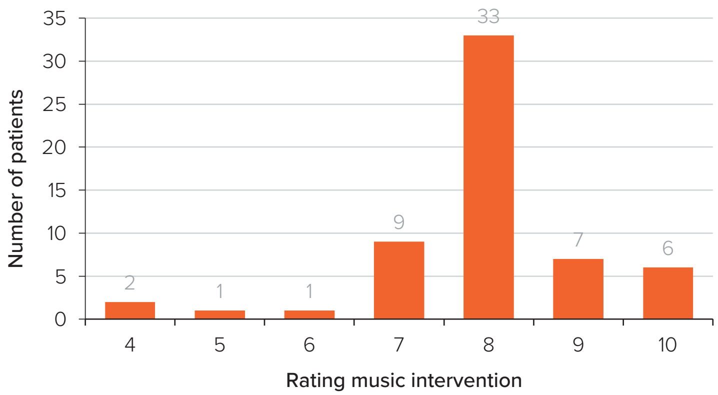

Figure 2. Music intervention rated by patients that completed the satisfaction questionnaire (n=59). For a more visually suitable display of results, satisfaction scores range from 4 to 10. Actual scores ranges from 1 to 10.

Shown in **Table 1**, 49 patients (83%) were satisfied with the preselected music. Two patients (3%) additionally stated that they preferred their own choice of music (in addition to preselected music playlists). The majority of the patients (90%) was satisfied with the information provided by staff regarding the music intervention. The quality of the medium (tablet and headphone) was rated 'bad' or 'poor' by one third of the patients. Fourteen patients (24%) mentioned the volume of the headphones being too low. Finally, the self-control of the music device was rated 'fair', 'good' or 'excellent' by nearly all patients (95%). Four patients (7%) experienced technical difficulties with the tablet. 9

Table 1. Ratings of several factors regarding patient satisfaction (n=59)*

	Bad	Poor	Fair	Good	Excellent
Music genres	0 (0%)	5 (9%)	5 (9%)	41 (69%)	8 (14%)
Songs	1 (2%)	4 (7%)	4 (7%)	45 (76%)	5 (8%)
Information provided by staff	1 (12%)	2 (3%)	3 (5%)	40 (68%)	13 (22%)
Quality of medium	4 (7%)	14 (24%)	10 (17%)	31 (53%)	0 (0%)
Self-control device	2 (3%)	2 (3%)	14 (24%)	38 (64%)	3 (5%)

*59 of 110 patients filled out the custom-made satisfaction questionnaire.

Attitudes and barriers towards perioperative music implementation

Table 2 represents the results of the questionnaire that assessed attitudes and barriers towards the implementation of perioperative music of perioperative health care providers at the end of the study period (n = 54). Most of the respondents were medical doctors (31%), surgeon assistants (17%) or day-care nurses (15%). The majority of respondents reported that they usually spend little extra time (0–10 min) on the music intervention. All respondents were either convinced or neutral about the positive impact of perioperative music on the patient (respectively 63% and 37%). Six respondents (11%) reported that the music should not negatively influence patient communication at crucial moments, especially during the time-out procedure in the operating room. The majority of the respondents (74%) thought perioperative music should be standard perioperative care, whereas four respondents (7%) stated that patients should always be able to choose freely.

Demographic and perioperative characteristics

No differences in age (50 (16) versus 51 (18) years, P = 0.707) and sex (female 55% versus 59%, P = 0.562) were found between patients in the music intervention and control group **(Table 3)**. Although not statistically different, patients in the control group had a higher CCI score[13] (median 1 (0–6) versus 2 (0–9), P = 0.285). The majority of surgeries that were performed for both groups consisted of abdominal, plastic and gynecological surgical procedures. Duration of surgery (47 (31) versus 43 (34) min, P = 0.131) and time spend on the recovery ward (53 (22) versus 52 (18) min, P = 0.562) were comparable between groups. The majority of patients received general anesthesia (74% in the music intervention group versus 84% in the control group, P = 0.113).

Effect of perioperative music implementation

Postoperative pain did not differ significantly between the music intervention group and retrospective matched control group (mean music NRS 0.74 (1.26) versus 0.68 (0.90), P = 0.363) **(Table 4)**. Although total amount of opioid requirement did not differ significantly (2.53mg ME (6.24) versus 3.33mg (2.47), P = 0.511), it seemed that less patients who received the music intervention required postoperative opioids (30% versus 40%, P = 0.132) **(Table 5)**. Only one patient (1%) in the intervention group experienced postoperative bleeding after breast surgery, a complication which was unrelated to the music intervention.

Table 2. Results of questionnaire that assessed attitudes and barriers towards the implementation of perioperative music among perioperative health care providers (n = 54)

Questions	**Answers**	**n (%)**
Sex	Male	14 (26%)
	Female	40 (74%)
What is your occupation?	Day-care nurse	8 (15%)
	Recovery nurse	3 (6%)
	Nurse anesthetist	6 (11%)
	Surgeon assistant	9 (17%)
	Medical doctor	17 (31%)
	Resident not in training	2 (4%)
	Resident in training	7 (13%)
	Preoperative screening assistant	2 (4%)
How much extra time do you spend on the music intervention?	0-10 min	41 (76%)
	10-20 min	2 (4%)
	20-30 min	0 (0%)
	20-30 min	0 (0%)
	NA	8 (15%)
	Other	3 (5%)
Do you believe that the patient experiences a positive effect of the music intervention?	Yes	34 (63%)
	Neutral	20 (37%)
Does the music intervention impair you to do your own work?	Yes	7 (13%)
	Neutral	16 (30%)
	No	31 (57%)
How likely are you to recommend the music intervention to others?*	1-2	0 (0%)
	3-4	1 (2%)
	5-6	12 (23%
	7-8	29 (54%)
	9-10	12 (23%)
Do you think music should be standard perioperative care?	Yes	40 (74%)
	No	8 (15%)
	NA	2 (4%)
	Other	4 (7%)

NA not applicable. *Scores range from 1 (not at all likely) to 10 (extremely likely).

9

Table 3. Demographic and clinical characteristics of patients receiving the perioperative music intervention (n=97) and patients in the control group (n=97)

	Music intervention group (n = 97)	**Control Group (n = 97)**	**P value**
Age (years)	50 (16)	51 (18)	0.707
Sex, male	44 (45%)	40 (41%)	0.562
Body-mass index (kg/m2)	25.7 (4.6)	26.1 (5.4)	0.556
ASA-classification			0.155
I - II	86 (89%)	80 (82%)	
III-IV	10 (10%)	17 (18%)	
Missing	1	0	
Charlson comorbidity index (CCI)	1 (0-6)	2 (0-9)	0.285
Surgery type			0.875
Abdominal surgery	27 (28%)	25 (26%)	
Gynecology	16 (17%)	16 (17%)	
Orthopedics and trauma surgery	11 (11%)	13 (13%)	
Plastic surgery	21 (22%)	19 (20%)	
Urology	10 (10%)	9 (9%)	
Vascular surgery	5 (5%)	5 (5%)	
Other *	7 (7%)	10 (10%)	
Duration of surgery (min)	47 (31)	43 (34)	0.131
Time on recovery (min)	53 (22)	52 (18)	0.562
Anesthesia type			0.113
General	72 (74%)	81 (84%)	
Other (spinal, regional, local, sedative)	25 (26%)	16 (16%)	

Values are in numbers (percentages), mean (standard deviation) or median (interquartile range).
* Other: ear, nose and throat, oral, breast or neurosurgery. Abbreviations: ASA, American Society of Anesthesia score

Table 4. Postoperative pain scores of patients receiving the perioperative music intervention (n = 97) and the control group (n = 97)

	Music intervention group (n = 97)		**Control group (n = 97)**		**P value**
NRS*	**n (%)**		**n (%)**		
Maximum NRS	88	1.07 (1.55)	94	1.19 (1.54)	0.455
First NRS	88	0.48 (1.30)	94	0.32 (0.78)	0.671
Second NRS	77	1.05 (1.46)	83	1.14 (1.56)	0.755
Mean NRS	88	0.74 (1.26)	94	0.68 (0.90)	0.636

For a more suitable display of results pain scores are in mean (standard deviation), differences are based upon nonparametric tests.
*Numeric Rating Scale (NRS) ranges from 0 to 10.

Table 5. Intraoperative and postoperative analgesic medication requirement of prospective (n = 97) and retrospective cohort (n = 97)

	Music intervention group (n = 97)	**Control group (n = 97)**	**P value**
Intraoperative analgesic medication requirement			
Sufentanil	66 (68%)	78 (80%)	**0.049**
µg	25.00 (13.13)	20.00 (11.25)	0.990
Morphine	5 (5%)	5 (5%)	-
mg	8.00 (5.00)	5.00 (4.00)	0.496
Remifentanil	8 (8%)	3 (3%)	0.121
mg	0.81 (0.54)	1.20 (-)	0.149
Alfentanil	4 (4%)	8 (8%)	0.233
mg	0.75 (1.28)	0.45 (0.68)	0.343
Postoperative analgesic medication requirement			
Total recovery	15 (15%)	25 (26%)	0.076
ME (mg)	5.86 (5.87)	3.33 (1.67)	0.139
Total ward	16 (16%)	17 (18%)	0.848
ME (mg)	2.53 (1.85)	2.53 (0.00)	0.106
Total recovery + ward	29 (30%)	39 (40%)	0.132
ME (mg)	2.53 (6.24)	3.33 (2.47)	0.511

Values are in numbers (percentages) or in medians (interquartile range).
Abbreviations: ME, morphine equivalent.
Bold values have been found statistically significant (P < 0.05).

Discussion

Perioperative music has beneficial effects on postoperative pain[1], opioid requirement[3], and attenuates the physiological stress response to surgery.[4] Although these are important objectives of the fast track recovery protocols in current surgical patient care[6], music is still not part of routine perioperative care. As the true effect of an intervention depends partly on whether or not it can be successfully implemented, the aim of this study was to evaluate the implementation feasibility of music in day care surgery through adherence to implementation, as well as its effects.

Implementation was deemed successful, given that adherence was over 80%. Furthermore, patient satisfaction was high and the attitude of health care providers towards the perioperative music intervention was positive, with minimal time and effort (less than 10 min) required by the latter to perform the intervention. A potential improvement point were the headphones used, which consisted of low-quality, disposable, overear headphones. As they were already standardly provided to each admitted patient, these headphones were considered to be safe for patient use and also reduced costs. Given the implementation success, we have continued to provide perioperative music and have procured headphones that offer improved audio quality. Furthermore, these are easy to clean and reusable, with the latter being important in an era of increased consumption and waste production by hospitals.[14]

Although several systematic reviews and meta-analyses have previously described the positive role of music on pain and analgesia needs[1,3,15], no statistically significant beneficial effects on postoperative pain and opioid requirement were observed in the current study. Several reasons seem apparent for the lack of results. No sample size calculation was performed, given that the primary outcome measure was implementation adherence. Therefore, this study was not adequately powered to evaluate a significant clinical effect. Furthermore, implementation was performed in day care surgery, as this was considered to involve straightforward surgical procedures minimizing logistical planning issues in the hospitals' infrastructure. Postoperative pain levels and opioid requirement are usually low, making it hard to find a clinically relevant, beneficial effect in the first place. However, it should be noted that a trend towards less patients needing postoperative opioids when listening to perioperative music was observed. Previous research revealed that regional anesthesia, compared to general anesthetic techniques, decreases postoperative pain. This could also possibly explain the finding that more patients in the control group required more postoperative opioids since a higher proportion of patients in the control group received

general anesthesia.[16] Especially in light of the current opioid epidemic[17], music could be an attractive non-pharmacological additive to opioid-free analgesia, which is unfortunately limited studied.[18]

This study has several strengths and limitations. Various key factors of implementation were thoroughly assessed in this study, taking into account both the opinions of surgical patients and staff alike. Unfortunately, not all patients filled out the postoperative satisfaction questionnaire due to either being drowsy or forgetting about it altogether, which was to be completed in the recovery ward before returning to the surgical ward. However, imputation of missing values according to common statistical methods did not change the outcome, even when the lowest quartile scores were used for imputation. Therefore, we do not believe that the true values would be different. The duration of the music intervention was not truly evaluated through a comprehensive music report. In theory this could mean that the actual adherence was either underreported or over reported. Moreover, the COVID-19 pandemic, which started to spread in the Netherlands at the end of February 2020, limited patient inclusion and the final sample size. Finally, due to the nature of the music intervention, patients and health care providers were not blinded. However, a previous report observed blinding in surgical trials to be the case in only three percent of studies published in high impact journals.[19]

This implementation study of perioperative music in day care surgery observed a high adherence rate, an easy applicability, high patient satisfaction levels both with the perioperative music intervention and the preselected music as well, a positive attitude of health care providers towards the music intervention, and a trend towards a reduced postoperative opioid requirement need. This success has led to an expansion towards other surgical procedures, improvement of the music devices, the provision of music streaming services for surgical patients, and perhaps more importantly, a role model for other Dutch hospitals. Future studies should further evaluate implementation of perioperative music and its effect during more complex surgical procedures, which will also involve more care providers and possibly increase barriers to implementation.

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chapter

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Summary
Discussion
Future perspectives

Summary

In **Part 1** of this thesis, we aimed to identify potentially modifiable risk factors for an unfavorable outcome after colorectal resection. As discussed in **chapter 1**, the general introduction of this thesis, identification of modifiable risk factors could improve perioperative management strategies, and ultimately lower complication rates and enhance functional recovery after surgery. It is one thing to identify modifiable factors, to actually modify them is another. In **Part 2**, we emphasized on perioperative methods and interventions targeting modifiable risk factors, aiming to improve postoperative outcomes.

Part 1 - Identification & assessment of modifiable risk factors

Chapter 2 focuses on modifiable risk factors for colorectal anastomotic leakage, one of the most detrimental complications following colorectal resection. We describe the multicenter prospective LekCheck study in which we evaluated the prognostic value of perioperative modifiable factors for colorectal anastomotic leakage in 1.562 patients undergoing colorectal resection. In this study, perioperative values were obtained by a comprehensive checklist, carried out in the operating room just prior to the creation of the anastomosis. The prevalence of anastomotic leakage was 8.5%. Seven potentially modifiable factors were independently associated with colorectal anastomotic leakage, namely: severe anemia (male <7, female <6.5 mmol/L), hyperglycemia (>6 mmol/L), fecal contamination of the operative field, administration of vasopressor agents during surgery, inadequate timing of antibiotic prophylaxis, duration of surgery, and application of epidural analgesia. Patients that present with any of these risk factors have a higher change of anastomotic leakage (38%) compared to patients without risk factors (2%). These findings underscore the urgent need for new perioperative strategies that act upon these potentially modifiable factors.

In the LekCheck study, intraoperative blood glucose was measured by a single assessment, just prior to the creation of the anastomosis. We found that hyperglycemic patients had significantly higher colorectal anastomotic leakage rates than normoglycemic patients (12% versus 5%). In **chapter 3**, we further evaluated this finding. We performed an additional analysis of the LekCheck data and investigated the association between intraoperative blood glucose levels and colorectal anastomotic leakage, in both diabetic and non-diabetic patients. The incidence of intraoperative hyperglycemia in non-diabetic patients was 45%, compared to 79% in diabetic patients. Only in non-diabetic patients, the incidence and severity of hyperglycemia was associated with anastomotic leakage. This finding suggests that clinicians should consider concise perioperative glycemic screening and monitoring in all patients requiring colorectal resection and not just only for diabetic patients. Whether

intraoperative hyperglycemia per se is a risk factor for colorectal anastomotic leakage or whether it is a marker of other risk factors (e.g., greater surgical stress, undiagnosed (pre) diabetes) leading to anastomotic leakage remains incompletely understood, as hyperglycemic non-diabetic patients were likely to have undergone more laborious procedures and were more frequently obese.

Preoperative anemia is a well-known risk factor for poor outcome after colorectal surgery. In chapter 2 we found that anemia was the single most important contributor to colorectal anastomotic leakage. Therefore, this finding was further explored in an additional analysis presented in **chapter 4**, in conjunction with a thorough narrative review summarizing considerations on the management of preoperative anemia in colorectal surgery. The finding that 25% of the patients with a preoperative hemoglobin level of less than 7 mmol/l developed anastomotic leakage, calls for action. As recommended by current guidelines, preoperative screening should be done as early as possible, specifically for the underlying causes of anemia, as they require different treatment. Patients undergoing surgery for colorectal cancer (CRC), the vast majority of indications, are at high risk for iron deficiency anemia, predominantly due to gastro-intestinal blood loss, reduced iron intake, and impaired iron homeostasis. To date, the efficacy and potential risks of iron supplementation for this group of patients are still unclear and future studies should address knowledge gaps in the upcoming years.

In an attempt to provide the rationale behind hyperglycemia as a potentially modifiable risk factor, we further focused on metabolic conditions leading to glucose intolerance. **Chapter 5** describes a systematic review on the impact of metabolic syndrome (defined by a cluster of factors including hyperglycemia, visceral obesity, hypertension, and hyperlipidemia) and hyperglycemia (as an individual component of metabolic syndrome) on outcome after colorectal surgery. The number of studies was very limited and mostly of retrospective design. Prevalence of metabolic syndrome in patients undergoing colorectal surgery is high, exceeding 35% in half of the included studies. A meta-analysis confirmed that patients with metabolic syndrome are at higher risk of severe complications (defined as Clavien-Dindo grade III or higher). Furthermore, patients with preoperative high blood glucose levels have a higher risk of surgical site infections compared to their non-hyperglycemic counterparts. The predictive value of metabolic syndrome on other outcomes, such as mortality, anastomotic leakage, and length of hospital stay, could not be assessed, due to inconclusive data and large heterogeneity in the total body of evidence. Nonetheless, given the high, and at present still increasing prevalence of metabolic syndrome across patients undergoing colorectal surgery, it is important to improve the quantity and quality of knowledge on this topic.-

Studies reporting on serious, but relatively infrequent complications, such as colorectal anastomotic leakage and mortality, are often underpowered to detect a statistical difference. Therefore, we developed a study protocol of a prospective observational study to assess the effects of metabolic syndrome on outcome after colorectal surgery, which is presented in **Chapter 6**. Postoperative complications that occur up to 30 days after surgery will be classified according to Comprehensive Complication Index (CCI). As a primary outcome, we choose to evaluate clinically relevant postoperative morbidity, as determined by a (CCI) score of 21 or more. Other short-term outcomes include: number and type of complications up to 30 days postoperatively, length of hospital stay, days at Intensive Care, discharge destination, and readmission rate. Impact on health-related quality of life (measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core module -C30 and -C29) and survival will be evaluated at 1 year after surgery.

Part 2 - Perioperative optimization

In the past few years, health-related quality of life (HRQoL) has become an important outcome after CRC surgery. However, studies on the true impact of colorectal resection surgery on HRQoL in general, and specified by surgery type, are lacking in literature. In **chapter 7**, we evaluated a prospective collection of data containing both preoperative and up to 2-year postoperative HRQoL values, in 415 patients undergoing right-sided colonic, left-sided colonic, and rectal resection for CRC. In general, HRQoL deteriorated at 4 weeks after surgery but improved approximately to baseline level at 1 year after diagnosis. The impact of surgery on HRQoL seemed to be greatest in patients who underwent rectal resection, as they had lowest scores 4 weeks after surgery. Physical functioning did not return to baseline level during follow-up in patients who underwent left-sided and rectal resection. During consultations, frequent monitoring of quality of life, at least in the first year of follow- up, is advised in order to identify deficits and act on these accordingly.

New developments in perioperative care focus on the role of multimodal prehabiliation. The presence of multimodal prehabiliation in the Netherlands is unclear. **Chapter 8** of this thesis presents a questionnaire study in which the current practice and opinion regarding prehabilitation for patients undergoing surgery for CRC throughout the Netherlands was evaluated. We conducted a national survey among CRC surgeons. It appeared that some form of prehabilitation was provided in 46 hospitals (67%). There was high variability in the setting, design and content of the programmes. Based on our findings, we concluded that there is need for evidence-based prehabilitation guidelines in order to enable nationwide and effective implementation.

In the light of the above mentioned approaches targeting modifiable risk factors, there has been increasing scientific interest in the use of music in surgery in recent years. **Chapter 9** documents a single-center pilot study, investigating the implementation of a multidisciplinary music intervention throughout the entire perioperative period of elective day care surgery procedures. We provided a tablet with pre-selected music playlists and a disposable headphone device to 109 patients waiting for surgery. Implementation of a perioperative music intervention was successful (i.e. given that adherence was over 80%), and based on our experience relatively easy. Ninety-three percent of the participants found music to be beneficial to perioperative surgical care but our music delivery methods (e.g. choice of headphone and mobile device) require improvement. The music intervention was well accepted by our health care team. Additionally, quantitative data on postoperative pain and opioid requirement was analyzed by using a matched retrospective patient cohort. There were no significant differences in postoperative pain and opioid requirement between the music and control group, however, this pilot study was not powered to detect a difference in postoperative outcome. Nevertheless, the high patient satisfaction of the present music intervention alone might warrant broad implementation.

General discussion

The potential to improve perioperative care involving patients undergoing colorectal resection has been a hot topic in clinical science for decades. As explained in the introduction of this thesis, the quality of surgical care has evolved over the years by the introduction of new operative techniques and advances in perioperative management such as enhanced recovery principles and better preoperative evaluation to assess risks. These evolutions have contributed to a significant decrease in complications, shorter hospitals stay, and reduced healthcare costs.[1,2] Not to forget, perioperative care is nowadays the collective responsibility of a team of healthcare professionals. Nevertheless, there are still many challenges to overcome. The results of the studies described in this thesis recognize new possibilities for change across the perioperative colorectal trajectory. We focused on the identification and assessment of potentially modifiable risk factors for adverse outcome following colorectal surgery and explored several perioperative strategies that aim for improvements.

Recognizing modifiable risk factors: a key approach in managing complications

Despite abovementioned advances in surgical and perioperative care, anastomotic leakage after colorectal resection surgery remains a great challenge. Over time, we do have better diagnostic tools and imaging techniques for early detection of anastomotic leakage, allowing for earlier intervention.[3,4] Also, research explored new, less invasive treatment options for anastomotic leakage, such as endoscopic vacuum therapy and image-guided percutaneous drainage.[5,6] Alongside these developments, in **chapter 2, 3, and 4** we reported on risk factors, particularly those that might be modifiable prior to or around surgery, to further reduce the occurrence of colorectal anastomotic leakage. Several preoperative, intraoperative and postoperative potentially modifiable risk factors for anastomotic leakage and other unfavorable outcomes after colorectal surgery were previously reported.[7-12] In line with other studies[9], in **chapter 2** we found an association between low preoperative hemoglobin concentration and the occurrence of colorectal anastomotic leakage. Preoperative anemia has also been reported to significantly increase the risk of other postoperative morbidity and mortality.[13,14] Whilst the exact causal relationship between anemia and the development of leakage or other adverse outcomes remains partially unclear, there is increasing scientific attention underlining the importance of optimization.[15] Presurgical correction of anemia has been described in literature since many years and it is core to multiple guidelines of a number of scientific societies.[1,16,17] Assessment on anemia and differentiation between underlying causes should be done as soon as possible before surgery. When anemia is caused by iron-deficiency, intravenous (iv) supplementation of iron is considered an effective and safe treatment leading to an improvement in hemoglobin concentration.[18,19] Despite recommendations, anemia management is still poorly employed worldwide due to the following pitfalls and research gaps. The previously performed, few, randomized clinical trials investigating iv iron therapy reported conflicting results or did not demonstrate a clear clinical benefit for the patient with respect to a reduction in perioperative red blood cell transfusions, complications or mortality rates.[19-22] In light of the limitations of these trials, including the lack of iron deficiency as an inclusion criterion, statistical under-powering, and heterogeneity in timing of treatment, further trials are required to increase the limited and conflicting evidence in this field.

According to a substantial body of literature, perioperative hyperglycemia in patients with and without diabetes could negatively impact outcomes after colorectal surgery.[23-25] Remarkably, patients without known diabetes seem to be at greater risk of complications compared to patients with diabetes.[23,24,26] In **chapter 3**, similar results are reported. Intraoperative hyperglycemia was seen more in patients with diabetes, but only in patients

without a previous diagnosis of diabetes the presence and magnitude of hyperglycemia was associated with colorectal anastomotic leakage. To date, these findings are not well understood. They can be explained by several possible mechanisms. First, with the release of several hormones and inflammatory cytokines, surgery causes metabolic abnormalities including insulin resistance, impaired insulin production, increased lipolysis, reduced glucose utilization, and increased glucose production, all leading to a rise in blood glucose level.[27] Hyperglycemia in patients without diabetes might be a marker or epiphenomenon of a more severe stress or inflammatory response.[23,26] In other words, hyperglycemia itself may not have a causal influence on a higher rate of complications. At this point, it is difficult to label intraoperative hyperglycemia as a modifiable risk factor, as it may not necessarily be avoidable during complex surgical procedures. Nonetheless, perioperative glucose monitoring can be used as diagnostic indicator to identify those at risk. Secondly, the higher rate of complications among hyperglycemic patients without diabetes might be related to the presence of undiagnosed diabetes. A previous systematic review has shown that non-diabetic patients with elevated glycated hemoglobin (HbA1c) levels before surgery have a higher complication rate after colorectal surgery.[28] As part of preoperative risk assessment, it may be worth considering routine HbA1c screening to detect patients with undiagnosed (pre)diabetes, as they might benefit from optimization strategies prior to surgery.[29] Thirdly, patients with diabetes could benefit from careful perioperative glycemic monitoring and treatment.[26] Whether intraoperative hyperglycemia is the underlying cause of postoperative complications or an epiphenomenon of other primary contributing factors could not be determined with the results of the study in **chapter 3**. Future research is required to clarify these mechanisms.

As described in the introduction of this thesis, metabolic syndrome is recognized as a potentially modifiable condition. We hypothesized that patients with metabolic syndrome might be at high-risk for complications after colorectal resection surgery, and the need to clarify this arose. The systematic review and meta-analysis in **chapter 5** indicates that only a handful of studies has focused on this topic. Currently available evidence shows a tendency towards an increased risk of complications after colorectal surgery in these patients, although our findings contain substantial heterogeneity in outcomes and definitions, leading to limited comparability. Since there is an alarmingly increasing prevalence of metabolic syndrome worldwide (estimated approximately 25-35 %)[30,31], we encourage further research in this field. In **chapter 6**, a study protocol is presented of a prospective observational cohort study that aims to evaluate the impact of metabolic syndrome among a consecutive sample of patients scheduled for CRC surgery on short-term and long-term postoperative outcome. An important concern emerged during the development of this research protocol. Visceral adipose tissue,

located in the abdominal cavity surrounding internal organs, is believed to be one of the primary contributors to the development of metabolic syndrome.[32] Based on the definition of metabolic syndrome, waist circumference level is used as a diagnostic criterion33, but does this accurately reflect visceral obesity? Computed tomography (CT) or magnetic resonance imaging (MRI) scans with local software analyzing body composition are considered as being the gold standard to measure the amount of visceral fat. Manual segmentation of visceral fat within images is time consuming and requires trained staff, both contributing to overall high expense. In my opinion, future focus should be given to the implementation of alternative easier methods like automatic segmentation for measuring body composition in routine clinical practice.[34,35]

Perioperative optimization strategies

The second part of this thesis focused on several perioperative methods and interventions targeting modifiable risk factors, aiming to improve postoperative recovery. As discussed in the general introduction of this thesis, preparedness for surgery starts with providing patients with information about the upcoming procedure, alternative treatment options, and expected outcomes. In other words, our responsibility is to empower patients, enabling them to manage their own health. In addition to outcomes such as complications and survival after colorectal surgery, patient-centered outcomes like quality of life and health status have become increasingly important over the years.[36] There is a deficit in literature comparing the impact of different surgical procedures for CRC on quality of life with both baseline and long term follow-up results.[37-41] In **chapter 7**, our objective was to gain insight in the impact on health-related quality of life (HRQoL) in patients undergoing right-sided, left-sided and rectal resection surgery from the initial baseline assessment before surgery, up to two years after the diagnosis of CRC. First, we concluded that patients who underwent left-sided colonic and rectal resection colorectal surgery do not return to their preoperative physical function level even after 2 years of follow-up. Our findings are in agreement with the outcomes of a systematic review, showing a permanent loss in physical capacity after CRC surgery.[42] These data suggest that patients undergoing CRC surgery may need additional support during their perioperative trajectory, perhaps by the use of prehabilitation and rehabilitation interventions. Second, we found that effects of surgery appear to be more significant in patients who underwent rectal resection, as they reported more pain and role- and social functioning problems four weeks after surgery. Another study focusing on patients undergoing surgery for rectal cancer reported similar highly affected HRQoL scores at four weeks postoperatively.[43] In contrast to colonic procedures, dysfunctional bowel symptoms, such as fecal incontinence, frequent bowel movements, emptying, and urgency difficulties, are more observed in patients undergoing rectal procedures and likely result in lower

HRQoL scores.[39] Informing the patient about the impact of surgery on the patient's daily life is essential, it helps patients to conceive realistic expectations. Despite the availability of well validated patient reported outcome measures (PROM) tools to asses quality of life, there is a lack of use in routine clinical practice.[44] Computer-based collection and visualization of PROMs (by using dashboards, graphics) could make it easy to see changes in patients, interpret outcomes and address them accordingly. It could make medical consultations more effective and efficient. One of the future challenges lies in the implementation and utilization of such advanced information technology systems in clinical setting.

Over the past two decades, prehabilitation has become popular in perioperative care research.[45] Prehabilitation focuses on the potential to improve the patient's physiologic reserve and functional capacity prior to surgery.[46] As shown in **figure 1**, integration of prehabilitation with Enhanced Recovery After Surgery (ERAS) interventions, can influence outcomes through mediation of the surgical stress response.[47] The preoperative period seems an opportune time to improve the overall condition of the patient and previous studies have demonstrated significant benefits including fewer complications, a decrease in length of hospital stay, prolonged survival, fewer costs and improved quality of life.[48-52] Three recently published randomized controlled trials on multimodal prehabilitation for patients scheduled for colorectal surgery found a reduction of up to 50% in postoperative complication rate.[48,50,53] Multimodal prehabilitation refers to a program that includes two or more interventions focusing on physical exercise, nutrition, emotional strength, and cessation of smoking and/or alcohol consumption.[54] Also, management of comorbidities (e.g. anemia and (pre)diabetes as discussed in the former paragraphs) and medication take part in prehabilitation programs.[29,55,56] Single interventions might not directly affect specific complications, but combining interventions could result in better outcomes.[54]

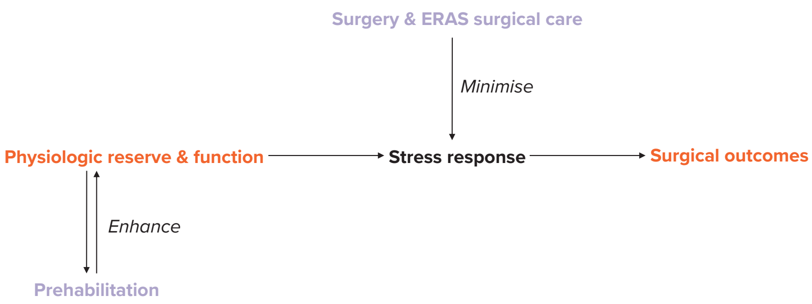

Figure 1. How Enhanced recovery after surgery (ERAS) and prehabilitation interventions can influence surgical outcomes (adapted with permission from C. Gillis, O. Ljungqvist, F. Carli, British Journal of Anaesthesia, volume 128, issue 3, march 2022, pages 434-448)[47]

However, there are still some issues regarding prehabilitation limiting worldwide implementation. In the Netherlands, prehabilitation is nowadays being performed in 46 hospitals (67%) involving patients planned for elective CRC surgery (**chapter 8**). Pointing to the first issue, the results of this chapter indicate there is practice variation. Until May 2023, content and design of multimodal prehabilitation have not yet been clearly defined in Dutch guidelines.[57] Secondly, there is conflicting evidence who might benefit the most from prehabilitation. Some researchers suggest that prehabilitation should be executed only to high-risk patients[51,58], while others recommend a tailored or individualized program for all patients.[59] This should be further investigated in future work in order to align on this. Thirdly, prehabilitation requires active engagement of the patient, which sometimes poses a challenge. The feasibility of prehabilitation programs before CRC surgery is still questionable, as only a small part of the potentially eligible patients actually participates and completes the program in the majority of feasibility studies.[60] The greatest barrier to participation in hospital prehabilitation is related to the transport of (elderly) patients back and forth.[61] Therefore, further investigation should explore the effectiveness of home- or community based programs, ideally supervised by a local physical therapist. In the Netherlands there is a wide availability of highly educated physical therapists acting in first line practices. A national network of physical therapists committed to prehabilitation is currently being set up. This is important because patients require (tele)monitoring to enable adjustment of their training program in accordance with the goals that have (not) been achieved.[62] A few studies have demonstrated that such home-or community based programs are feasible and well accepted by patients.[51,62,63] Meanwhile, we should not wait but instead enlarge perioperative care networks of trained primary care professionals.

As modern perioperative care has focused on interventions that act upon the stress response to surgery, there might be room for perioperative music in ERAS protocols. Previous research suggests that perioperative music attenuates the stress response to surgery by lowering cortisol levels and thereby insulin resistance and hyperglycemia.[64] Other studies have furthermore shown that music has a significant beneficial effect on postoperative pain and anxiety.[64-66] Data demonstrating the effect of perioperative music on postoperative complications are, however, lacking. Music is not (yet) part of daily perioperative practice in the majority of Dutch hospitals. In the last chapter of this thesis we present a real-life experience of a clinical perioperative pathway improvement at Máxima Medical Center in the Netherlands: implementing a music intervention during the perioperative period, guided by a multidisciplinary team of health care professionals (**Chapter 9**). We found that patients responded positively to the music intervention and for caregivers, it was easy applicable and not time-consuming, indicating successful implementation. For the benefit of the patient,

it is necessary to adjust our routine behavior and change current perioperative pathways. The Dutch Guideline Database recently published recommendations for the use of music in perioperative practice.[67]

Future perspectives

The current knowledge on modifiable risk factors for adverse outcomes following colorectal surgery poses important considerations for future management. One can imagine that the complexity involved in overseeing and managing all these different perioperative factors might lead to challenges. Nowadays, perioperative interventions such as ERAS and prehabilitation are collaborative approaches involving multiple professionals. However, in the near future, shouldn't there be one central coordinator for the entire perioperative period? Such perioperative coordinator could serve as the central hub in the organization, by tracking individual patients and the entire process in a manageable way. Furthermore, this person would have the ultimate responsibility for development of protocols, continuous monitoring of outcomes, and implementation of new perioperative interventions into clinical practice.

From the patient's perspective, there is much to oversee as well. How can we make sure that patients keep track of all perioperative opportunities and feel responsible for their own improvements? Maximizing adherence to perioperative programs is highly important as it leads to improved outcomes.[61] A potential quality improvement for future care could be the implementation of interactive preoperative (prehabilitation) classrooms, where patients can be extensively educated about their perioperative journey.[68] This approach offers several advantages, including the opportunity to share experiences with other patients and the potential to enhance motivation for lifestyle improvements by increasing the awareness of the benefits. Furthermore, in a world in which digital technology has become indispensable, smartphones and tablets are very likely to play a crucial role by offering medical information (e.g. videos, podcasts) and reminders (to ensure optimal compliance) on digital applications at various stages throughout the perioperative trajectory. Data of wearables such as smart watches or other devices with sensors to track vital signs, activity and sleep patterns can be integrated into these applications.[69] Such devices provide personalized insights, encouraging patients to achieve lifestyle goals. Furthermore, wearable devices can assist in continuous monitoring in home-based prehabilitation programs in order to evaluate progress. At least, advanced sensors measuring blood glucose levels might also be beneficial in the early

detection of complications such as colorectal anastomotic leakage, surgical site infections or other complications. These advancements in technology clearly present challenges as a wide variety of patients (with e.g. differences in age and literacy) should understand how to use these new technologies. Future studies must demonstrate the adoption and use of such digital advancements. Other hurdles are related to accuracy and privacy of data, both necessitating further validation and investigation.[70]

Also, artificial intelligence (AI) may play a significant role in discovering novel predictive factors for specific complications by analyzing large volumes of data and determining associations that cannot be identified by traditional statistical research methods.[71] To date, there are many prediction models available or being developed to predict the likelihood of complications after colorectal surgery[72,73], but they are not commonly used in clinical practice and require further development and validation. Ultimately, the evidence of future studies should gain the trust of caregivers to implement machine learning methods in clinical practice. Collaboration among healthcare providers and software developers is fundamental in achieving this.

Lastly, I believe that poor outcomes may not always be prevented by either the quality of the patient (having modifiable and unmodifiable risk factors) or the quality of the surgeon. Sometimes adverse outcomes may just be inevitable due to factors such as the complexity of the procedure or availability of healthcare resources.

The studies described in this thesis have provided new insights into the management of modifiable risk factors for adverse surgical outcomes throughout the perioperative period. Areas for improvements in current perioperative practices have been identified as has been described in the discussion section. In parallel, this thesis illustrates the complexity of perioperative colorectal care. Several questions remain unanswered and new questions are created. In the mission to improve outcomes of patients undergoing colorectal resection surgery, we should further optimize preventive strategies in the context of perioperative care and ensure implementation in daily practice.

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chapter

elev

ven

In this chapter a reflection is presented on the scientific, societal and economic impact of the results of the research described in this thesis. For whom the findings are relevant will also be discussed.

Scientific impact

The knowledge acquired from this thesis on modifiable risk factors for adverse outcome following colorectal resection surgery (**chapters 2,3,4,5**) is crucial for further development of perioperative optimization strategies. For instance, the LekCheck findings have paved the way for the development of a new perioperative protocol in colorectal surgery, addressing modifiable risk factors, which will be evaluated in the DoubleCheck study. Moreover, the LekCheck study resulted in a broad network of clinicians and researchers, both in the Netherlands and internationally, likely leading to future research projects. At the same time, several thesis results were utilized in the development of the recently published Dutch Prehabilitation Guidelines1, allowing for consistent implementation of prehabilitation throughout the Netherlands (**chapter 2,3,4,8**). The present thesis also highlighted novel insights regarding the course of patient-reported outcome measures following surgery for colorectal cancer (**chapter 7**). The results enable clinicians involved in colorectal cancer care to better inform patients about the longitudinal impact of surgery on specific health-related quality of life domains. Finally, our successful implementation of a music intervention during the complete perioperative period of elective day care surgery procedures can be the start for others to adjust their perioperative practice (**chapter 9**). Implementation studies like ours, hold significance as there remains a large gap between scientific evidence and everyday clinical practice. The scientific relevance of this thesis is further addressed by the fact that all chapters, except one, have been published in peer-reviewed international journals listed on PubMed. Additionally, the publications have already been cited multiple times according to Google Scholar. Furthermore, the findings of this thesis were presented at various national and international congresses and meetings.

Societal relevance

As evident from several studies in the current thesis, perioperative care is a shared responsibility of a team of healthcare professionals. In numerous ways, this thesis highlights the importance of multidisciplinary collaboration in enhancing outcomes following colorectal surgery. The joint effort in completing the LekCheck tool not only assists in identifying patients at risk for colorectal anastomotic leakage but also leads to intensified intraoperative interaction and collaboration within the surgical team. The management of modifiable comorbidities, such as anemia, hyperglycemia, and other metabolic abnormalities, during the perioperative period necessitates the collaboration of multiple healthcare professionals,

including anesthesiologists, dietitians, physiotherapists, sports physicians, endoscopists, internists, oncologists, geriatricians, nurses, and surgeons. It is essential for them to function as a team, pooling their expertise and experience to gain a comprehensive understanding of patient conditions. In this way, with its emphasis on multidisciplinary treatment, our research can be an accelerator of interprofessional collaboration which at present is an important focus point of health policy and innovation in The Netherlands.[2] Next to this, multidisciplinary collaboration ensures continuity of care throughout the preoperative, intraoperative, and postoperative phases, enabling effective implementation and integration of health concepts like Enhanced Recovery After Surgery (ERAS) and prehabilitation. Moreover, it is hoped that this thesis will motivate healthcare professionals and software developers to collaborate more closely in the near future. For instance, by enabling electronic collection of patient-reported outcome measures, like quality of life, throughout the perioperative period. Such solutions fit well with current focus points on e-health of the Dutch Ministery of Health, Welfare, and Sport.[3] By enhancing information technology, perioperative care can further revolutionize.

At the patient level, colorectal surgery, whether with or without complications, can have a detrimental impact on the lives of patients, their families, and caregivers. It is important to consider that not all patients have equal opportunities to face the challenges that surgery brings, due to several factors, including socioeconomic situation and overall health status. Adequate preoperative risk stratification, followed by tailored optimization strategies can help unify the chances of fast and full recovery. For significant impact, hospital culture should promote ERAS principles and a healthy lifestyle in every possible way. For instance, we have a common room in our hospital clinic ward of Máxima Medical Center where patients can eat together, interact and share experiences which each other, and do physical exercises, or other activities during hospitalization.

Perioperative management of modifiable risk factors could hypothetically even result in long-term changes of lifestyle. This is in line with today's motto of the Dutch Ministry of Health, Welfare, and Sport: 'Everyone healthy, fit and resilient'.[4] The Dutch National Prevention Agreement "Nationaal Preventieakkoord", which was launched in 2018, focuses on three main goals: 1) smoke-free generation, 2) reduce excessive alcohol consumption (from 9% form 5%), and 3) reduce obesity (from 50% to 38%).[5] With our results on modifiable risk factors, we want to encourage the Dutch government in achieving these challenging goals for 2040.

Economic relevance

The economic impact of complications after surgery of the colon or rectum is enormously. Where the average cost for a patient without complications is €9.226, the average cost for minor and severe complications increase by €2.403 and €17.906 respectively.[6] In case of anastomotic leakage, the average cost is €33.486, which is nearly three times higher compared to patients without anastomotic leakage.[6] Severe complications often lead to an extended recovery period, resulting in delayed return to work, and increased pressure on caregivers, also leading to a rise in costs. By targeting modifiable risk factors in colorectal surgery, complications could be reduced or prevented, hospital activities could be reduced, and hospital days could be shortened. To assess the cost-effectiveness of perioperative optimization strategies with management of modifiable risk factors, return on investment calculations should be made. Multimodal prehabilitation appears to be a cost-effective intervention, with costs-savings of over €1.200 per patient.[7] Given that the annual number of patients undergoing surgery for colorectal cancer in The Netherlands is 10.5000, savings of €12.8 million are generated over one year, and this rises to €64.3 million over a five-year period.[1]

Target population

The findings of this thesis are important for patients undergoing colorectal surgery as well as for healthcare professionals involved in their perioperative care. However, this knowledge is not confined to colorectal surgery alone; it has relevance across other surgical fields as well. Many modifiable risk factors for complications are not exclusive to colorectal surgery. Approaches aimed at mitigating modifiable risk factors in one surgical pathway might be effective in other surgical specialties' pathways. A perioperative coordinator could play a crucial role in sharing knowledge and facilitating the adaption and implementation of protocols. It is hoped that the insights on perioperative modifiable risk factors, along with recommendations for further development of optimization strategies outlined in this thesis, will inspire other researchers and clinicians, alike.

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Appendices

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Nederlandse samenvatting

In Deel I van dit proefschrift beschrijven we meerdere studies waarin we op zoek zijn gegaan naar potentieel beïnvloedbare risicofactoren voor een ongunstige uitkomst na colorectale resectie. Zoals beschreven in **hoofdstuk 1**, de algemene introductie van dit proefschrift, zou de identificatie van beïnvloedbare risicofactoren kunnen bijdragen aan de ontwikkeling van betere perioperatieve behandelstrategieën. Hiermee hopen we het risico op complicaties te verlagen, de impact van complicaties te verminderen en het herstel na een operatie te bevorderen en bespoedigen. Het herkennen van beïnvloedbare factoren is één ding, het daadwerkelijk beïnvloeden of verbeteren is iets anders. Daarom beschrijft deel II van dit proefschrift verschillende perioperatieve interventies gericht op het beïnvloeden van risicofactoren om het postoperatieve beloop te verbeteren.

Deel 1 - Identificatie en beoordeling van modificeerbare risicofactoren

Hoofdstuk 2 richt zich op beïnvloedbare risicofactoren voor naadlekkage, thans de meest gevreesde complicatie na een colorectale resectie. We beschrijven de multicenter prospectieve LekCheck-studie waarin we de prognostische waarde van perioperatieve beïnvloedbare factoren voor naadlekkage hebben onderzocht in 1.562 patiënten die een colorectale resectie ondergingen. In deze studie werden perioperatieve waarden verkregen door middel van een uitgebreide checklist die werd afgenomen in de operatiekamer, vlak voor het aanleggen van de colorectale anastomose. De prevalentie van naadlekkage was 8.5%. Zeven potentieel beïnvloedbare factoren waren onafhankelijk geassocieerd met naadlekkage, namelijk: ernstige anemie (mannen < 7 mmol/l, vrouwen < 6,5 mmol/L), hyperglykemie (>6 mmol/L), fecale verontreiniging van het operatieveld, toediening van vasopressiva tijdens de operatie, niet adequaat toedienen van antibiotische profylaxe, duur van de operatie en toepassing van epidurale analgesie. Bij patiënten zonder deze risicofactoren was het naadlekkage percentage significant lager in vergelijking met patiënten met deze risicofactoren (respectievelijk 2% en 38%). Deze bevindingen onderstrepen de behoefte aan nieuwe behandelstrategieën gericht op het optimaliseren van deze specifieke risicofactoren.

In de LekCheck studie werd de bloedglucose spiegel gemeten middels een enkele meting tijdens de operatie. De bevinding dat patiënten met hyperglykemie vaker een naadlekkage ontwikkelden dan patiënten zonder hyperglykemie (12% versus 5%) is verder onderzocht in een aanvullende analyse van de LekCheck data in **hoofdstuk 3**. Hierbij is onderscheid gemaakt tussen patiënten met en zonder diabetes. De incidentie van hyperglykemie tijdens de operatie was bij patiënten zonder diabetes significant lager dan bij patiënten met diabetes

(respectievelijk 45% en 79%). Alleen bij patiënten zonder diabetes was de incidentie en ernst van hyperglykemie geassocieerd met naadlekkage. Deze bevindingen suggereren dat we niet alleen de bloedglucose spiegel bij patiënten met diabetes perioperatief routinematig moeten controleren en behandelen, maar dat een perioperatief hyperglykemie protocol voor alle patiënten die een colorectale resectie ondergaan van waarde zou kunnen zijn. Het blijft vooralsnog echter onduidelijk of hyperglykemie tijdens de operatie een risicofactor of een marker voor een andere risicofactor (bijv. meer chirurgische stress, niet-gediagnosticeerde (pre)diabetes) voor naadlekkage is, aangezien de niet-diabetici met hyperglykemie tijdens de operatie vaker een moeizame ingreep ondergingen en overgewicht hadden.

Preoperatieve anemie is een bekende risicofactor voor postoperatieve complicaties na colorectale chirurgie. Zo bleek uit de resultaten van hoofdstuk 2 dat preoperatieve anemie een belangrijke onafhankelijke voorspeller is voor naadlekkage na colorectale chirurgie. Deze bevinding is verder onderzocht in **hoofdstuk 4**. In totaal ontwikkelde 25% van de patiënten met een preoperatief hemoglobinegehalte lager dan 7 mmol/l een naadlekkage. Omdat anemie een relatief corrigeerbare aandoening is, wordt het gezien als een potentieel belangrijke component in prehabilitatie programma’s. Daarom hebben we in dit hoofdstuk ook de overwegingen voor de behandeling van preoperatieve anemie bij colorectale chirurgie samengevat. Conform de huidige richtlijnen, dient anemie zo vroeg mogelijk vastgesteld te worden in het preoperatieve traject. Vervolgonderzoek omvat ten minste onderzoek naar de mogelijke onderliggende oorzaken van anemie, aangezien deze een andere behandeling vereisen. Patiënten met een colorectaal carcinoom lopen een hoog risico op anemie door ijzertekort, voornamelijk als gevolg van gastro-intestinaal bloedverlies, verminderde ijzerinname en verminderde ijzerhomeostase. Tot op heden zijn de potentiële risico’s en de werkzaamheid van ijzersuppletie voor deze groep patiënten onduidelijk en belangrijke pijlers voor vervolgonderzoek.

In een poging hyperglykemie als potentieel beïnvloedbare risicofactor beter te begrijpen, hebben we ons ook gericht op metabole aandoeningen die leiden tot verminderde glucosetolerantie. **Hoofdstuk 5** betreft een systematisch literatuuronderzoek en meta-analyse waarin de impact van het metabool syndroom (gedefinieerd als een cluster van hyperglykemie, visceraal obesitas, dyslipidemie en hypertensie) en preoperatieve hyperglykemie (als individuele criteria van het metabool syndroom) op uitkomsten na colorectale chirurgie is onderzocht. Het aantal geïncludeerde studies was zeer beperkt en meestal retrospectief opgezet. De prevalentie van het metabool syndroom bij patiënten die colorectale chirurgie ondergaan was hoog, de helft van de geïncludeerde onderzoeken

toonde een prevalentie van meer dan 35%. Een meta-analyse toonde dat het metabool syndroom geassocieerd was met ernstige complicaties na operatie (Clavien-Dindo score van 3,4 of 5). Verder hadden patiënten met hyperglykemie voor de operatie een hoger risico op postoperatieve wondinfecties in vergelijking met patiënten zonder hyperglykemie. De voorspellende waarde van metabool syndroom op andere uitkomsten zoals mortaliteit, naadlekkage en ziekenhuisopnameduur, kon niet goed worden beoordeeld omdat de resultaten niet eenduidig waren en er grote heterogeniteit was tussen de studies. Gezien de hoge, en momenteel nog steeds toenemende prevalentie van het metabool syndroom bij patiënten die colorectale chirurgie ondergaan, is het belangrijk om de kwantiteit en kwaliteit van kennis over dit onderwerp te verbeteren.

Eerdere studies die complicaties beschrijven die relatief weinig voorkomen, zoals naadlekkage en mortaliteit, hebben vaak onvoldoende power om een statistisch verschil te detecteren. In **Hoofdstuk 6** wordt een onderzoeksprotocol beschreven voor een prospectieve, observationele studie die de impact onderzoekt van het metabool syndroom op het postoperatieve beloop na colorectale chirurgie. Complicaties die zich voordoen tot 30 dagen na de operatie zullen worden geëvalueerd met de Comprehensive Complication Index (CCI). Als primaire uitkomst hebben we gekozen voor klinisch relevante postoperatieve morbiditeit; een CCI-score van 21 of hoger. Daarnaast onderzoeken we ook andere uitkomsten zoals: aantal en type complicaties in de eerste 30 dagen postoperatief, opnameduur in het ziekenhuis, opnameduur op de Intensive Care, ontslagbestemming, en heropname. De impact op de gezondheidsgerelateerde kwaliteit van leven (EORTC QLQ-C30 en C29 vragenlijsten) en overleving zal 1 jaar na de operatie worden geëvalueerd.

Deel 2 - Perioperatieve optimalisatie

De laatste jaren is de gezondheidsgerelateerde kwaliteit van leven een belangrijke uitkomst na een operatie voor darmkanker. In de literatuur ontbreekt echter vaak informatie over het verloop van deze kwaliteit van leven na een operatie. Het doel van de studie in **hoofdstuk 7** was het prospectief onderzoeken van de invloed van het type chirurgie op de kwaliteit van leven van darmkanker patiënten vanaf baseline tot 2 jaar na de diagnose. De onderzoekspopulatie bestond uit 3 groepen met in totaal 415 patiënten; 148 patiënten die een rechtszijdige colonresectie hadden ondergaan, 147 patiënten die een linkszijdige colonresectie hadden ondergaan en 120 patiënten die een rectumresectie hadden ondergaan. Over het algemeen was de gemeten kwaliteit van leven van patiënten 1 jaar na diagnose weer terug op het baseline niveau. Bij patiënten die een linkszijdige colon- of een rectale resectie ondergingen, keerde het fysiek functioneren niet meer terug naar het baseline niveau tijdens de follow-up. Verder lijkt de operatie het meeste impact op de

gezondheidsgerelateerde kwaliteit van leven te hebben bij patiënten die een rectumresectie ondergingen, aangezien zij de laagste scores hadden 4 weken na de operatie. Dit onderzoek geeft aan dat de gezondheidsgerelateerde kwaliteit van leven, in ieder geval in het eerste jaar van follow-up, regelmatig gemonitord dient te worden om tekorten te signaleren en hierop in te kunnen spelen middels extra ondersteuning in het zorgtraject.

Nieuwe ontwikkelingen in de perioperatieve zorg richten zich onder andere op multimodale prehabilitatie. In hoeverre prehabilitatie in Nederlandse ziekenhuizen wordt toegepast bij patiënten die een electieve colorectale resectie moeten ondergaan, is onduidelijk. In **Hoofdstuk 8** presenteren we een vragenlijstonderzoek waarin de huidige praktijk en opvattingen over prehabilitatie voor patiënten die een operatie ondergaan voor een colorectaal carcinoom werden uitgevraagd. Van alle Nederlandse ziekenhuizen bleek in 46 ziekenhuizen (67%) enige vorm van prehabilitatie toegepast te worden in de colorectale perioperatieve zorg. Verder vonden we een grote variatie in de opzet en inhoud van de programma's. Op basis van onze bevindingen concluderen we dat er behoefte is aan een evidence-based richtlijn om landelijke en effectieve implementatie mogelijk te maken.

De laatste jaren is er een toenemende wetenschappelijke belangstelling voor het gebruik van muziek bij operaties. **Hoofdstuk 9** betreft een pilotstudie waarin we de implementatie van een muziek interventie in de perioperatieve periode onderzoeken bij patiënten die een electieve operatie ondergingen in de dagbehandeling. De interventiegroep bestond uit 109 patiënten die voorgeselecteerde muziek aangeboden kregen middels een tablet en koptelefoon. De implementatie was succesvol (meer dan 80% werd geheel volgens protocol doorlopen), relatief eenvoudig en werd goed ontvangen door ons zorgteam. Drieënnegentig procent van de deelnemers vond muziek een positieve toevoeging voor de perioperatieve chirurgische zorg. Verder concludeerden we dat de keuze voor devices om muziek af te spelen (koptelefoon, tablet) geoptimaliseerd moeten worden. Een aanvullende analyse met behulp van een gematched retrospectief patiënt cohort liet geen significante verschillen zien in pijnbeleving postoperatief en opiaatgebruik tussen de interventiegroep en controlegroep. Deze pilotstudie had echter onvoldoende power om een statistisch verschil te detecteren in postoperatieve uitkomst. Desalniettemin, de hoge patienttevredenheid in deze studie rechtvaardigt verdere implementatie van muziekinterventie in perioperatieve zorg.

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About the author

Muriël Reudink, daughter of Andrea Henriette Mulder and Harry Reudink, was born on the 29th of June 1991 in Enschede (Overijssel), the Netherlands. She is the elder sister of Luuk. After graduating high school (VWO at Stedelijk Gemeenschap Zuid, Enschede) she enrolled in Human Movement Sciences at the Rijksuniversiteit Groningen. Following the completion of her propaedeutic degree and driven by a fascination for the relationship between physical activity and health, she started medical school in 2010 and obtained her bachelor's degree in 2013. During her studies, she joined medical sorority 'Usus Cognitus', went to Spain and Nicaragua for medical internships, and organized a Medical Sciences Summer School.

For her research internship, she focused on the possibilities to implement a prehabilitation program for patients undergoing abdominal surgery. Together with surgeons and researchers dr. C.I. Buijs and prof. dr. J.M. Klaase, she laid the basis for this thesis. Her final year electives were spent at the abdominal surgery and rehabilitation departments of the University Medical Center Groningen. She completed her medical degree in 2018 and moved to Utrecht for her work as a surgical resident doctor (not in training) at the Diakonessenhuis Utrecht.

Her persistent interest in improving perioperative management strategies brought her to the Máxima Medical Center in Veldhoven and the Maastricht University Medical Center, where she started as a PhD candidate at the colorectal surgery department. Under supervision of prof. dr. L.P.S. Stassen, prof. dr. J.M. Klaase, dr. G.D. Slooter, and dr. R.M.H. Roumen, she conducted research on perioperative modifiable risk factors for adverse outcome after colorectal surgery; of which this thesis is the result.

In 2023 she took a new challenge; Muriël currently works as a general practitioner in training. She is living with Frank in Amersfoort. She loves nature and doing sports, so in her free time, you can find her on the trails in the Province of Utrecht or on (mini) expeditions abroad.