Targets for improving patient outcomes after major gastrointestinal cancer surgery: the value of perioperative care

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Part I: Identification of Prognostic Factors for Postoperative Complications

Chapter 2

Preoperative Risk Factors for Major Postoperative Complications After Complex Gastrointestinal Cancer Surgery: A Systematic Review

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List of abbreviations

ACS NSQIP; American College of Surgeons National Surgical Quality Improvement Program, CD; Clavien-Dindo, CRP; C-Reactive Protein, DICA; Dutch Institute for Clinical Auditing, ERAS; Enhanced Recovery After Surgery

Abstract

Patients undergoing complex gastrointestinal surgery are at high risk of major postoperative complications (e.g., anastomotic leakage, sepsis), classified as Clavien-Dindo (CD) ≥ IIIa. Identification of preoperative risk factors can lead to the identification of high-risk patients. These risk factors can also be used to design personalized perioperative care. This systematic review focuses on the identification of these factors. TheMedline and Embase databases were searched for prospective, retrospective cohort studies and randomized controlled trials investigating the effect of risk factors on the occurrence of major postoperative complications and/or mortality after complex gastrointestinal cancer surgery. Risk of bias was assessed using the Quality in Prognostic Studies tool. The level of evidence was graded based on the number of studies reporting a significant association between risk factors and major complications. A total of 207 eligible studies were retrieved, identifying 33 risk factors for major postoperative complications and 13 preoperative laboratory results associated with postoperative complications. The present systematic review provides a comprehensive overview of preoperative risk factors associated with major postoperative complications. A wide range of risk factors are amenable to actions in perioperative care and prehabilitation programs, which may lead to improved outcomes for high-risk patients. Additionally, the knowledge of this study is important for benchmarking surgical outcomes.

Introduction

Postoperative complications can occur after every type of surgery, and can lead to increased morbidity and mortality, as well as increased hospital length of stay and healthcare costs [1]. Complex gastrointestinal surgery (e.g., colorectal, gastric and esophagus resections) is associated with high complication rates [2, 3]. A large number of studies have focused on reducing complications by improving surgical techniques; however, relatively few have addressed improving perioperative care. The latter contributes largely to the avoidance of complications and is responsible for shorter recovery time after surgery, together with less morbidity and increased survival. Some studies have suggested that perioperative care more accurately dictates outcomes and postoperative complications than surgery itself [4]. Perioperative care is currently being standardized in the form of enhanced recovery after surgery (ERAS) protocols, which provide guidelines for improved perioperative care. A meta-analysis by Vardhan et al. showed that the use of ERAS protocols reduces the rate of complications following major abdominal surgery by up to 50% [5]. The period of time before admission is used for screening for medical conditions that can negatively alter the surgical outcome (e.g., smoking and malnutrition). This can be particularly beneficial when the screening focuses on modifiable risk factors, which subsequently can be (partially) reversed (e.g., physical therapy, nutritional support).

Reduction of postoperative complications is also important in relation to long-term outcomes, especially in patients with cancer. The severity of complications is often graded using the Clavien-Dindo (CD) classification, a therapy-based complication severity classification [6]. It has been demonstrated that major complications (CD ≥ IIIa) are associated with postponement of adjuvant therapy and worse oncological outcomes, like local recurrences and shortened recurrence-free survival [7, 8]. The majority of studies addressing the prevention of postoperative complications have concentrated on operation-specific risk factors (e.g., anastomosis technique). However, for complex surgeries, the standard perioperative care protocols may not be adequate to reduce major complications for every individual patient.

Additionally, identifying risk factors for adverse outcomes is important for case-mix correction in benchmarking quality of care in nation-wide clinical auditing and surgical improvement programs, such as the Dutch Institute of Clinical Auditing (DICA) and American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) [9, 10].

This review focuses on the identification of preoperative risk factors for major postoperative complications (CD ≥ IIIa) after major abdominal surgery with the construction of an intestinal anastomosis, which includes esophagectomy, gastrectomy, and colorectal surgery. Since, these types of surgery have technical similarities and are all high risk procedures. Furthermore, this study aims to identify the strengths and possible improvements in ERAS protocols.

Methods

The study protocol for this systematic review was registered with the PROSPERO database (CRD42020198812). This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA).

Criteria for study eligibility

To evaluate the effect of preoperative factors on the incidence of major postoperative complications, studies were selected based on the type of surgery. Only studies addressing complex gastrointestinal cancer surgery (e.g., esophagectomy, gastrectomy, and colectomy), including the construction of an intestinal anastomosis, were selected. As an outcome, a study was required to report on the associations between major complications and an independent preoperative factor. Major complications were classified as CD ≥ IIIa or severe complications that were classified as such (e.g., anastomotic leakage, endoscopic intervention) [6]. Retrospective, prospective cohort studies, and randomized-controlled trials with full-text articles published in English or Dutch were assessed for eligibility. Case reports and case series (< 40 patients) were excluded. Only studies including adult patients (≥ 18 years of age) were selected, and animal studies were excluded.

Search method

The Medline and Embase electronic databases were searched to identify all relevant publications. Search terms included those from MeSH in PubMed and EMtree in Embase, as well as free text terms. Reference lists of identified studies will be checked for additional relevant studies. Included studies were restricted to those that were published between January 2005 and July 2021. Authors were contacted in case of full-text unavailability.

Study selection

Assessment of eligibility was performed independently by RB and RvK. Any disagreement regarding eligibility was resolved by discussion with MW as an arbitrator when necessary. The initial screening was based on title and abstract. Full texts were independently screened by two authors (RB and RvK). Again, disagreement was resolved by discussion with MW, who acted as an arbitrator. Study selection was performed using Endnote X9 (Clarivate Analytics, Philadelphia, PA, USA) and Rayyan QCRI (a mobile web app for systematic reviews).

Assessment of risk of bias

All eligible studies were independently assessed for potential risk of bias by RB and RvK, using the Quality in Prognostic Studies (QUIPS) tool for classification of prognostic factor studies [11]. Discrepancies were resolved by discussion, with MW as an arbitrator when necessary. The risk of bias in clinical trials was assessed in the following domains: study participation, study attrition, prognostic factor measurement, outcome measurement, adjustment bias, and statistical analysis bias. Each domain was graded as high, low, or unclear. The results of risk of bias screening are summarized in Supplementary File A.

Data extraction and management

Data extraction was performed by RvK, and subsequently verified by RB using a predefined, standardized form designed by RB and RvK. Any discrepancies were resolved through discussion.

Grading the level of evidence

The level of evidence regarding the association between a risk factor and major complications (CD ≥ IIIa) was scored using a grading system (Table 1) [12]. The score resulted from the number of studies conducting a multivariable analysis of the association and percentage of statistically significant results of these analyses.

Table 1 - Grading the level of evidence adapted from the grading score used by Lagarde et al. [12].

Level of evidence	Criteria
None	No significant evidence
Minor	Evidence significant from multivariable analysis form **one article**
Considerable	Evidence significant from multivariable analysis in **three or less** articles and/or in **less than 50%** of the articles describing this risk factor
Strong	Evidence significant from multivariable analysis in **more than three** articles and in **more than 50%** of all articles describing this risk factor
Very strong	Evidence significant from multivariable analysis **in ten or more** articles and **in more than 70%** of all articles describing this risk factor

Results

The literature search retrieved 207 eligible studies (Figure 1), all of which used an observational study design. An overview of the results reported in these studies on preoperative risk factors associated with major complications (i.e., CD ≥ IIIa) after major gastrointestinal cancer surgery is shown in Table 2, together with the type of surgery (lower or upper gastrointestinal surgery), and the level of evidence graded according to Table 1. The fourth column reports the number of studies, including the risk factor, in multivariable analysis and the percentage of significant results. This section is divided into six subsections: patient characteristics, comorbidities, intoxication, nutritional indicators, disease-related factors, and neoadjuvant therapy-related factors.

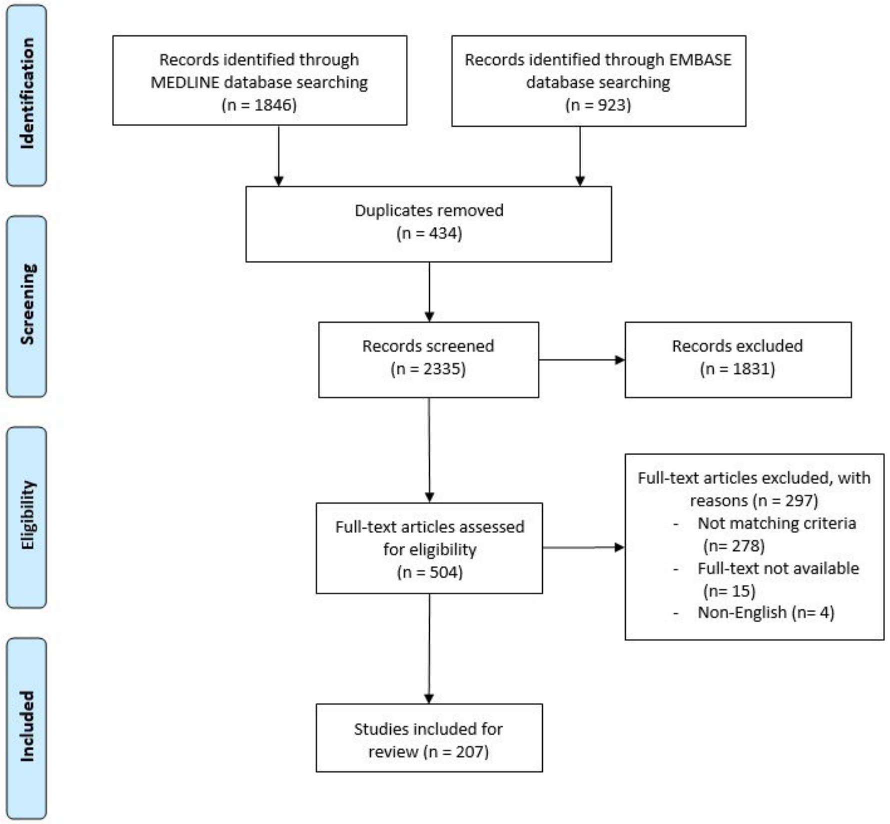

Figure 1 - PRISMA flowchart of study selection

Patient characteristics

Age and frailty

Age is an important risk factor. Many studies reported an independent association between older age and major complications and mortality (Table 2). The elderly are believed to exhibit less healing capacity, which leads to more postoperative complications [13, 14]. Another term reported in studies is "frailty", which is a physiological state of cumulative deficits (e.g., advanced age, poor physical performance), which render patients more susceptible to major complications [15]. In a large population-based retrospective cohort, Sparreboom et al. reported an association between frailty and anastomotic leakage [2]. Along with frailty, functional status, and activities of daily living dependency have demonstrated an association with postoperative complications and mortality (Table 2).

Table 2- This table represents all pre-operative risk factors for major complications (Clavien-Dindo (CD) ≥ IIIa) and mortality described in literature References used in this table are listed in Supplementary Information B. BMI= body-mass index; CD= Clavien-Dindo; HbA1c= glycated hemoglobin; Low= lower GI surgery; Up= upper GI surgery. *30-day mortality or in-hospital mortality.

Preoperative risk factors	Type of complications	Type of	Number of articles favoring (%)	Level of evidence	Reference(s)
Patient characteristics					
Age	Anastomotic leakage	Up & Low	10/22 (45)	Considerable	[2, 26, 66, 88-157]
	Intra-abdominal infection	Up	2/2 (100)	Considerable	
	Reoperation	Up & Low	2/2 (100)	Considerable	
	Venous thrombo-embolism	Up & Low	2/3 (67)	Considerable	
	Mortality*	Up & Low	17/20 (85)	Very strong	
	CD≥ IIIa	Up & Low	18/29 (62)	Strong	
Male gender	Anastomotic leakage	Up & Low	27/34 (79)	Very Strong	[2, 14, 26, 88, 89, 92, 95, 97, 102, 104, 105, 107, 111, 112, 114, 119-124, 126, 128, 129, 133, 137-140, 146, 149, 152, 156, 158-190]
	Pancreatic fistula	Up	1/2 (50)	Minor	
		Low	1/1 (100)	Minor	
	Intra-abdominal infection	Up & Low	3/5 (60)	Considerable	
	Reoperation	Up	1/1 (100)	Minor	
	Venous thrombo-embolism	Up	1/1 (100)	Minor	
	Mortality*	Low	5/6 (83)	Strong	
	CD ≥ IIIa	Up & Low	9/17 (53)	Strong	
American Society of Anesthesiologists (ASA) score	Anastomotic leakage	Up & Low	10/19 (53)	Strong	[2, 26, 88, 90, 91, 98, 99, 101, 102, 105, 110, 114, 120, 124, 126, 128-130, 133, 137-140, 144, 146, 148, 151-153, 162, 166, 170, 189, 191-196]
	Reintervention	Low	1/1 (100)	Minor	
	Mortality*	Up & Low	8/10 (80)	Strong	
	CD ≥ IIIa	Up & Low	6/15 (40)	Considerable	
	Mortality*	Up & Low	1/2 (50)	Minor	
Physical fitness	Anastomotic leakage	Low	1/2 (50)	Minor	[138, 160, 197, 198]
	CD ≥ IIIa	Up & Low	2/2 (100)	Considerable	
Frailty	Mortality	Up	2/2 (100)	Considerable	[92, 138, 153, 199]
	CD ≥ IIIa	Up & Low	2/3 (67)	Considerable	
Comorbidity					
Comorbidity	Anastomotic leakage	Up & Low	6/8 (75)	Strong	[2, 105-107, 129, 133, 146, 147, 149, 152, 162, 168, 200-203]
	Reoperation	Up & Low	2/2 (100)	Considerable	
	Respiratory failure	Up	1/1 (100)	Minor	
	Mortality*	Up & Low	3/3 (100)	Considerable	
	CD ≥ IIIa	Up	3/4 (75)	Considerable	

Table 2- Continued

Preoperative risk factors	Type of complications	Type of	Number of articles favoring (%)	Level of evidence	Reference(s)
	Anastomotic leakage	Up & Low	6/6 (100)	Strong	[136, 192, 193, 204-206]
Hypertension	Anastomotic leakage	Up & Low	2/3 (67)	Considerable	[135, 150, 155, 184, 207-209]
	CD ≥ IIIa	Up	3/3 (100)	Considerable	
	Anastomotic leakage	Up & Low	4/8 (50)	Strong	[100-102, 104, 114, 137, 140, 141, 154, 155, 170, 189, 190, 194, 202, 210-214]
	Acute respiratory distress syndrome (ARDS)	Up	1/1 (100)	Minor	
	Respiratory failure	Up	1/2 (50)	Minor	
	Mortality*	Up & Low	5/5 (100)	Strong	
	CD ≥ III	Up & Low	4/6 (67)	Strong	
	Anastomotic leakage	Up & Low	8/12 (75)	Strong	[100, 102, 104, 114, 117, 121, 131, 135-137, 154, 155, 158, 159, 170, 185, 194, 209, 210, 212, 213, 215-219]
	Duodenal stump fistula	Up	1/1 (100)	Minor	
	Respiratory failure	Up	1/1 (100)	Minor	
	Venous thrombo-embolism	Up	1/1 (100)	Minor	
	Mortality*	Up & Low	4/5 (80)	Strong	
	CD ≥ IIIa	Up & Low	8/11 (73)	Strong	
Chronic hepatic disease	Anastomotic leakage	Up	1/1 (100)	Minor	[102, 135, 140, 181, 215, 220, 221]
	Duodenal stump fistula	Up	1/1 (100)	Minor	
	Intra-abdominal infection	Up	1/1 (100)	Minor	
	Mortality*	Up & Low	2/2 (100)	Considerable	
	CD ≥ IIIa	Up	1/1 (100)	Minor	
Chronic kidney failure	Anastomotic leakage	Up	2/3 (67)	Considerable	[98, 102, 193, 209]
	Mortality*	Low	1/1 (100)	Minor	
Diabetes	Anastomotic leakage	Up & Low	9/18 (50)	Considerable	[26, 98, 104, 140, 158, 176, 182, 186, 194, 207, 208, 210, 212, 221-226]
	CD IV-V	Up	1/2 (50)	Minor	[100, 145]
Steroid use (chronically)	Anastomotic leakage	Up & Low	3/5 (60)	Strong	[98, 114, 129, 140, 165, 227, 228]
	Mortality*	Up & Low	2/2 (100)	Considerable	
Anti-coagulant therapy	Anastomotic leakage	Low	1/1 (100)	Minor	[189]
Prior abdominal surgery	Anastomotic leakage	Up & Low	3/5 (60)	Considerable	[2, 95, 142, 148, 167, 200]

Table 2- Continued

Preoperative risk factors	Type of complications	Type of	Number of articles favoring (%)	Level of evidence	Reference(s)
Intoxications					
Smoking	Anastomotic leakage	Up & Low	15/20 (75)	Very strong	[14, 25, 26, 98, 102, 114, 124, 129, 138, 142, 158, 160, 165, 166, 200, 201, 210, 220, 221, 229-232]
	Mortality*	Low	2/2 (100)	Considerable	
	CD ≥ IIIa	Up	2/2 (100)	Considerable	
	Anastomotic leakage	Low	4/6 (67)	Considerable	[124, 129, 138, 158, 166, 210, 232]
Nutritional indicators					
Overweight (BMI >25)	Anastomotic leakage	Up & Low	4/9 (44)	Considerable	[2, 49, 88, 94, 95, 104, 105, 111, 113-115, 122, 123, 133, 138, 146, 160, 163, 174, 180, 188, 195, 233-240]
	Pancreatic fistula	Up	2/2 (100)	Considerable	
	Intra-abdominal infection	Up & Low	3/5 (60)	Considerable	
	Reoperation	Up	1/1 (100)	Minor	
	Venous thrombo-embolism	Up & Low	1/3 (33)	Minor	
	Mortality*	Up & Low	2/4 (50)	Considerable	
	CD ≥ IIIa	Up	6/11 (55)	Strong	
Obesity (BMI >30)	Anastomotic leakage	Up & Low	6/7 (86)	Strong	[14, 114, 124, 140, 148, 165, 189, 207, 210, 233, 235, 238, 239, 241]
	Venous thrombotic-embolism	Up & Low	1/3 (33)	Minor	
	CD ≥ IIIa	Up & Low	1/3 (33)	Minor	
	Venous thrombo-embolism	Up & Low	1/3 (33)	Minor	
	CD ≥ IIIa	Low	1/1 (100)	Minor	
Sarcopenic obesity	CD ≥ IIIa	Up	1/1 (100)	Minor	[130]
Underweight (BMI <18,5)	Anastomotic leakage	Up & Low	1/2 (50)	Minor	[128, 184, 227, 235, 239]
Sarcopenia	Anastomotic leakage	Up & Low	2/3 (67)	Considerable	[242-247]
	Prolonged intubation	Up	1/1 (100)	Minor	
	CD ≥ IIIa	Up & Low	3/4 (75)	Strong	
Malnutrition/ preoperative weight loss	Anastomotic leakage	Up & Low	5/8 (63)	Strong	[106, 108, 114, 115, 130, 138, 140, 179, 210, 215, 248, 249] [144, 153, 198, 250]
	Duodenal stump fistula	Up	1/1 (100)	Minor	
	Mortality*	Up	2/2 (100)	Considerable	
	CD ≥ IIIa	Up	4/5 (80)	Strong	
High visceral fat area (VFA)	Anastomotic leakage	Up & Low	2/3 (100)	Considerable	[103, 234, 251-253]
	Intra-abdominal infection	Up	2/2 (100)	Considerable	
	Mortality*	Up	1/1 (100)	Minor	

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Table 2- Continued

Preoperative risk factors	Type of complications	Type of	Number of articles favoring (%)	Level of evidence	Reference(s)
Perineal Fat Surface area (PRF) ≥ 40 cm²	CD ≥ III	Low	1/1 (100)	Minor	[124]
Disease related risk factors					
Tumor stage/ tumor size	Anastomotic leakage	Up & Low	9/16 (56)	Considerable	[2, 49, 90, 91, 95, 104, 105, 110, 113, 119, 120, 123, 131, 133, 137, 139, 144-146, 148, 152, 153, 159-161, 164, 172, 173, 176-178, 187, 191, 216-219, 225, 254-260]
	Postoperative hemorrhage	Up	2/2 (100)	Considerable	
	Intra-abdominal infection	Up & Low	2/3 (67)	Considerable	
	Major adverse cardiac event (MACE)	Up	1/1 (100)	Minor	
	Mortality*	Up & Low	2/4 (50)	Minor	
	CD ≥ IIIa	Up	13/22 (59)	Strong	
Preoperative	Anastomotic leakage	Low	1/3 (33)	Minor	[2, 126, 139, 147, 184, 261, 262]
	Mortality*	Up & Low	2/3 (67)	Considerable	
	CD ≥ IIIa	Up	1/1 (100)	Minor	
Neoadjuvant therapy-related risk factors					
	Anastomotic leakage	Up	1/1 (100)	Minor	[53, 149, 207, 263, 264]
	CD ≥ IIIa	Up	1/2 (50)	Minor	
	Mortality*	Up & Low	1/2 (50)	Minor	
	Anastomotic leakage	Low	4/7 (57)	Strong	[2, 105, 166, 175, 196, 256, 265, 266]
	Chylothorax	Up	1/1 (100)	Minor	
	Intra-abdominal complication (CD≥ IIIa)	Low	1/1 (100)	Minor	
	Anastomotic leakage	Up & Low	2/3 (67)	Considerable	[113, 114, 133, 153, 164, 195, 259, 267]
	CD ≥ IIIa	Up & Low	2/4 (50)	Considerable	
	Mortality*	Up & Low	1/2 (50)	Minor	
	Anastomotic leakage	Up & Low	4/7 (57)	Strong	[2, 105, 138, 184, 237, 268, 269]
Preoperative laboratory tests					
	Anastomotic leakage	Up & Low	2/4 (50)	Considerable	[104, 108, 128, 184, 210]
Platelet count increased	Anastomotic leakage	Low	1/1 (100)	Minor	[165]
Platelet count decreased		Low	1/1 (100)	Minor	[171]
White blood cell count (WBC) increased	Anastomotic leakage	Up & Low	1/2 (50)	Minor	[143, 210, 224]
	Venous thrombo-embolism	Low	1/1 (100)	Minor	
Neutrophil-to-lymphocyte Ratio (NLR)	Anastomotic leakage	Low	1/2 (50)	Minor	[160, 270]

Table 2- Continued

Preoperative risk factors	Type of complications	Type of	Number of articles favoring (%)	Level of evidence	Reference(s)
C-reactive protein (CRP) increased	Anastomotic leakage	Up & Low	2/2 (100)	Considerable	[121, 128, 158, 178, 186]
	CD ≥ IIIa	Up	2/3 (67)	Considerable	
CRP/Albumin ration (CAR)	Anastomotic leakage	Low	1/1 (100)	Minor	[142]
Increased creatinine	Anastomotic leakage	Up & Low	1/2 (50)	Minor	[104, 117, 139, 140, 208, 216]
	Mortality*	Up	1/2 (50)	Minor	
	CD ≥ IIIa	Up	1/2 (50)	Minor	
Decreased estimated glomerular filtration rate (eGFR)	CD ≥ IIIa	Up	1/1 (100)	Minor	[159]
Serum albumin	Anastomotic leakage	Up & Low	5/8 (63)	Strong	[26, 104, 123, 128, 130, 137, 139, 140, 151, 164, 168, 178, 183, 189, 190, 216, 232, 250, 263, 266]
	Mortality	Up	2/3 (67)	Considerable	
	CD ≥ IIIa	Up	5/10 (50)	Considerable	
Total protein decreased	Anastomotic leakage	Low	3/3 (100)	Considerable	[14, 121, 189, 190, 210]
	CD ≥ IIIa	Up & Low	2/2 (100)	Considerable	
Albumin-to-fibrinogen ratio (AFR)	CD>IIIa	Up	1/1 (100)	Minor	[186]
Increased HbA1c	Anastomotic leakage	Up	1/1 (100)	Minor	[220]

Male sex

A wide variety of studies have confirmed that male sex is a risk factor for major postoperative complications. Several theories have been proposed to address this issue. Historically, the incidence of smoking and alcohol consumption in the male population has been higher. However, these confounding variables have not been measured in many studies and, therefore, their effect on males may be overestimated [16]. Another theory is that differences in cortisol-induced sex hormones change after surgically induced stress, which could render males more susceptible to postoperative complications [17]. A third theory is that the narrower pelvis of male patients can make surgery for tumors located in this region technically more difficult [2, 14].

American Society of Anesthesiologists score

One of the most studied risk indicators in the context of predicting postoperative complications is the American Society of Anesthesiologists (ASA) score. Multiple studies found an independent association between ASA score and a higher incidence of anastomotic leakage and major complications [2, 18, 19]. Furthermore, the ASA score is a reliable predictor of 30-day mortality (Table 2).

Preoperative inflammatory biomarkers

Several studies described an association between elevated levels of preoperative inflammatory biomarkers (e.g., white blood cell count, C-reactive protein [CRP]) and postoperative complications (Table 2). Similarly, the neutrophil-to-lymphocyte ratio, a proxy measure of inflammation status in the body, is independently associated with an increased risk for major complications (Table 2). The association between preoperative inflammation and complications, however, is not yet fully understood.

Serum albumin is a negative acute-phase protein. It decreases during inflammation due to increased capillary leakage [20]. It is also known as a nutritional biomarker reflecting malnutrition (Section 3.4.1). In the Glasgow Prognostic Score, an inflammation-based prognostic score for cancer prognosis, albumin and CRP are combined to predict perioperative complications [21]. Similarly, You et al. proposed the albumin/fibrinogen ratio as a predictor of major complications (Table 2). Fibrinogen is an essential protein in the coagulation cascade as well as an acute-phase reaction protein in the response to systemic inflammation [22].

Comorbidities

Patients with ≥ 1 comorbidities and those using ≥ 5 drugs per day are more susceptible to complications [23]. Several studies have demonstrated that heart failure, hypertension, and renal insufficiency are independently associated with major complications and anastomotic leakage (Table 2). Vascular disease, particularly arterial calcifications, is an important risk factor for major complications, especially anastomotic leakage (Table 2). Furthermore, the relationship between major complications and diabetes is well understood, whereas hyperglycemia induces microvascular damage, yielding a reduced capacity for anastomotic healing [24] (Table 2).

Intoxication

Smoking

A history of smoking is a risk factor for the occurrence of postoperative complications after major abdominal surgery (Table 2). In a large retrospective cohort study, Sharma et al. estimated the increased risk for major postoperative complications and mortality after smoking to be 30% [16]. Quan et al. reported that the number of pack-years significantly influenced the risk for major complications [25]. Smoking is believed to induce microvascular damage, leading to decreased healing ability of the anastomosis, thereby leading to an increased rate of anastomotic leakage [26].

Alcohol consumption

Several studies have shown that habitual use of alcohol (≥3 units per day) increases the risk for postoperative complications (Table 2). Alcohol causes alcohol-induced liver and pancreatic disorders, as well as impaired immune capacity, hemostasis, and surgical stress response [27, 28]. Alcohol cessation before elective surgery significantly decreased postoperative complications [27, 28].

Nutrition-related risk factors

Malnutrition/preoperative weight loss

Among cancer patients, 63% experience weight loss before treatment. In those with gastric and esophageal cancers, this figure has been reported to be as high as 79% to 83% [29, 30]. Absolute weight loss can be an indication of malnutrition, which can also be measured according to nutritional indexes (*e.g.*, Prognostic Nutritional Index, Nutritional Risk Screening). A more advanced stage of malnutrition leads to cancer anorexia-cachexia syndrome—a hypercatabolic state characterized by weight loss and sarcopenia—which occurs in 15% to 40% of cancer patients [31, 32]. Malnutrition and preoperative weight loss were significantly associated with major complications and mortality (Table 2). Lack of nutrients has been implicated in decreased function of the immune, respiratory and cardiac systems, as well as decreased healing function [33, 34] and further deterioration due to a more catabolic metabolic state [13]. Collectively, this leads to an increased incidence of infectious complications as well as anastomotic leakage (Table 2). Low preoperative serum albumin levels are independently associated with an increased risk for major complications (Section 3.1.4).

Sarcopenia

Sarcopenia refers to the loss of skeletal muscle volume and/or strength, which have a close relationship, and primarily originates from malnutrition (Section 3.4.1). Sarcopenia is especially prevalent in patients with esophageal and gastric cancers (up to 56%), but also in elderly patients [35-37]. As shown in Table 2, sarcopenia was independently associated with worse surgical outcomes. The relationship between sarcopenia and major postoperative complications and mortality is due to reduced healing capacity resulting from a lack of nutrients and, therefore, a catabolic state.

Overweight and obesity

Obese and overweight patients are at higher risk for postoperative complications and mortality after major gastrointestinal surgery (Table 2). There are multiple theories addressing the association between overweight and major complications. First, obese patients often exhibit a significantly increased number of comorbidities, including diabetes, hyperlipidemia, coronary artery disease, and hypertension [38, 39]. Second, overweight and obesity are associated with an increased incidence of anastomotic leakage believed to be caused by a preoperative inflammatory state and increased insulin resistance, leading to decreased healing capacity [40, 41]. Third, increased visceral fat in those undergoing abdominal surgery may lead to more complications due to more technical difficulties (e.g., thicker mesocolon, increased abdominal wall pressure leading to decreased intraoperative visibility) [39, 42], which in turn leads to longer operation time and greater transfusion requirements [19]. Some retrospective studies have explored the relationship between visceral fat area, body mass index, and the impact of excessive abdominal fat tissue on surgical outcomes. However, whether visceral fat area is a better parameter than body mass index remains controversial [43].

Disease-related risk factors

Preoperative tumor complications

Of all preoperative tumor complications, anemia and iron deficiency are the most common. The prevalence of any degree of anemia has been suggested to be 50% to 75% in patients with colorectal cancer [44, 45]. Anemia leads to decreased healing capacity. Therewithal, patients receiving preoperative transfusion exhibited an increased rate of postoperative complications [46]. Blood transfusions appear to induce an immunosuppressive effect; therefore, a policy restricting transfusion is recommended [47]. Local preoperative tumor complications (e.g., bowel obstruction and tumor perforation) are independently associated with major complications (Table 2), theoretically, due to greater technical difficulty caused by an inflammatory response of the abdominal cavity and by the frailty of the tissue used for anastomosis and/or the spill of gastrointestinal fluids.

Advanced tumor stage

Advanced tumor stage, including those from poorly differentiated cancer types, lead to more extensive resections and technically more demanding surgery, followed by more intraoperative organ damage and postoperative complications [42, 48]. Second, extensive lymph node dissections and additional splenic resection, especially in gastric and esophageal resections, are high-risk procedures [49, 50]. Additionally, larger tumors and more extensive resections lead to more non-radical resections [51]. Furthermore, patients with a higher tumor grade or TNM stage are more likely to exhibit a form of systemic immune-inflammation, which is also associated with major complications [52] (Section 3.1.4).

Neoadjuvant therapy-related factors

Neoadjuvant therapy aims to reduce tumor volume to achieve R0 resections and mitigate—if not eliminate—micrometastases and, eventually, cancer recurrence. However, the use of neoadjuvant therapy is also associated with an increase in postoperative complications caused by a diminished healing capacity of damaged tissue (Table 2). Additionally, a possible decrease in psychological performance after neoadjuvant therapy may lead to impaired postoperative recovery [53]. Preoperative radiotherapy in those treated for rectal cancer has a high prevalence of postoperative complications and anastomotic leakage (Table 2). After neoadjuvant therapy, patients also experience postoperative cardiopulmonary complications more frequently [54]. Patients unable to complete neoadjuvant therapy often experience increased postoperative complications, which may be a confounder due to poor underlying health conditions [55].

Discussion

Results of the present study provide a comprehensive and structured overview of the associations between preoperative risk factors and major complications and mortality following complex gastrointestinal cancer surgery. Our findings provide unambiguous evidence supporting the association between age and major postoperative complications, as well as for the association between anastomotic leakage and male sex and smoking. Furthermore, substantial evidence has been provided regarding the association between major postoperative complications and age, male sex, comorbidities, malnutrition, sarcopenia and overweight/obesity. This study also provides strong evidence supporting an association between different comorbidities, obesity, malnutrition, decreased serum albumin, more advanced tumor stages, neoadjuvant radiotherapy, neoadjuvant chemotherapy and the occurrence of anastomotic leakage. Furthermore, strong evidence exists for an association between 30-day mortality and male sex, higher ASA score, and cardiac comorbidity. This systematic review also shows that risk factors for postoperative major complications in lower – and upper gastrointestinal cancer surgery show a substantial overlap.

The identification of risk factors may afford opportunities to optimize perioperative care by managing preoperative risk factors, thereby decreasing the risk for postoperative complications and mortality. This may reduce healthcare costs, in contrast to major complications, which lead to an increase in healthcare expenditures [1]. The described associations may contribute to focused and personalized preoperative care by enrolling patients with certain risk factors (e.g., frailty and malnutrition) into prehabilitation programs. Subsequently, identification of high-risk patients may prompt closer postoperative surveillance. Additionally, the identification of high-risk patients may also influence decision making regarding treatment options, for example, a 'watch and wait' strategy after clinical complete response to neoadjuvant therapy [56, 57].

Preoperative care

In literature, several prehabilitation programs have been described for modifiable risk factors, acting on the associations between preoperative factors and postoperative complications (Table 3). Preoperative control/management of these factors could improve postoperative outcomes. For example, adequate preoperative glycemic control in diabetic patients should lead to less postoperative hyperglycemia, which is associated with postoperative infectious complications and, could therefore, decrease the complication rate [58]. Furthermore, several prehabilitation programs incorporating for instance physical resistance training and nutritional support have been described in the literature (Table 3). Theoretically, these prehabilitation programs should lead to a reduction in postoperative complications, although there is limited evidence to support this [59, 60]. A limitation—present in the majority of research investigating preoperative interventions—could be that prehabilitation is not specifically targeted at patient-specific risk factors. Physical endurance training in a population >70 years of age with ASA III-IV, led to a 20% reduction in complications [61], indicating that preoperative care should be tailored to and specified for patients targeting their risk factors. Smoking cessation, which leads to a significant reduction in postoperative complications, is such an example [25, 62]. Currently, growing interest of perioperative research is focused on the implementation and further improvement of ERAS protocols, which may lead to a reduction in overall complications by up to 50%, as shown in a meta-analysis [5]. However, studies included in this systematic review have been published during the period in which ERAS protocols have been gaining interested and were widely implemented. This means that perioperative care has been improved and optimization of risk factors (e.g., malnutrition, smoking cessation) is standard in daily practice [63]. Also standard in ERAS protocols for gastrointestinal surgery is nutritional support, this is important for patients to cope with the metabolic and physiological stress inflicted by gastrointestinal cancer surgery and increased protein requirements [64]. In addition to nutritional support the so-called "Immunonutrition" which entails nutritional supplements (e.g., arginine, omega-3 fatty acids) is being studied, this is thought to lead to a reduction of surgical stress [65](Table 3). In the light of ERAS protocols studies have shown that an abbreviated period (2 h versus 12 h) of fasting leads to significantly reduced time-to-first-stool and complete oral intake [66, 67]. In the ERAS protocol for lower gastrointestinal surgery, bowel preparation is an important point of discussion because this could lead to changes in electrolyte levels, metabolic imbalance, and dehydration, especially in elderly and/or frail patients [68]. The suggestion to omit this from the protocol, if possible, especially in frail patients, is supported by a meta-analysis that revealed an advantage to no-bowel preparation with regard to anastomotic leakage, intra-abdominal infections, and wound infections [69]. In this context the role of perioperative prophylactic antibiotics usage is studied, which may have a preventive effect on surgical site infections, anastomotic leakage and mortality [70].

Table 3 – Table includes actable or improvable risk factors and subsequent in literature described prehabilitation options to reduce the risk of postoperative morbidity. References used in this table are listed in Supplementary Information B.

Risk factors	Prehabilitation	Reference
Physical performance	Resistance training	[47, 59, 61, 271-275]
	Endurance training	
	Physical therapy	
	Breathing exercises	
	Nutritional support	
	Immunonutrition	
Pulmonary comorbidity	Preoperative inspiratory muscle training	[276-279]
Malnutrition	Nutritional support	[63-65, 280-283]
	Oral nutritional supplements	
	Immunonutrition	
Sarcopenia	Nutritional support	[275, 284, 285]
	Resistance training	
	Nutritional supplements	
Smoking	Smoking cessation	[16, 25, 62, 286]
Alcohol consumption	Alcohol cessation	[28]
Iron deficiency anemia	Intravenous iron supplementation	[287]
Dental plaque	Preoperative oral management by dentist	[288, 289]

Intraoperative techniques and care

Furthermore, ERAS protocols have been further improved intraoperative care in terms of: minimally invasive surgery, pain management, temperature management and fluid administration [71]. During the publishing of the included studies minimally invasive surgery has become more standard procedure. Other intra-operative ERAS-principles that have been studied and implemented such as goal-directed fluid administration and use of fewer use of intra-operative vasopressors have been independently associated with decreased postoperative complications [71-73]. Also intra-operative normothermia has been shown to have a positive effect on prevention of postoperative infections [74].

The use of opioid-sparing analgesia has been shown to increase recovery time, but no reduction in postoperative complications [75].

Postoperative care

With the current increase in data-driven approaches in healthcare, the risk factors reported in Table 2 could be assessed in analysis of large datasets, in which the development of artificial intelligence may play an important role. Machine learning models usually demonstrate similar performance for predicting medical outcomes compared with logistic regression [76]. With increasingly larger datasets, machine learning holds the potential to unravel subtle associations that are not—or cannot—be identified using classic regression approaches. For suspected low-risk patients, machine learning has been suggested to support early discharge decisions [77]. Suspected high-risk patients may benefit from closer postoperative surveillance. Earlier detection of deterioration in patients may reduce the severity of complications and lessen the incidence of failure-to-rescue [78]. A proposed method for augmented postoperative surveillance involves wearable devices for constant postoperative monitoring [79]. These devices continuously transmit vital signs that alert healthcare personnel in case of deterioration.

Benchmarking surgical outcomes

Reduction of postoperative complications can also be established by clinical auditing and benchmarking of surgical outcomes [80, 81]. Auditing is used to measure quality of care using structure, process, and outcome indicators [82, 83]. The information provided by this review can be used for fair comparison of outcomes between different hospitals and institutions, which can only be established when using robust casemix models.

Limitations

The present study had some limitations. First, it provided only an overview of the associations between preoperative risk factors and major complications. As such, additional evidence is needed to confirm that these risk factors are causally related to poor surgical outcomes. Second, heterogeneous patient populations and study designs may have hindered adequate interpretation of the study results. The included studies were all conducted in an observational manner, and most of them were designed retrospectively. There was a wide variety between risk factor reporting between studies, not all risk factors (e.g., renal disease, pulmonary comorbidity) were defined within the studies therefore making interpretation difficult. A similar reporting absence was seen in the implementation and usage of ERAS protocols within the included patient population. ERAS protocols have been widely implemented in surgery in recent years, that's why we limited our study period to 2005.This type of study is subjected to bias, although we suspect that due to the large number of studies, this bias was limited. However, all patients included in this study were preoperatively selected to be fit for surgery by expert opinion undergoing surgery, leading to allocation bias. This is a limiting factor for generalization of risk factor research in general. Although the present study provides an overview of all known risk factors, not all factors are described or necessarily applicable to every patient. Additionally, this study provides a theoretical overview; therefore, no quantitative effect of the specific risk factors is reported. An additional meta-analysis should be conducted to calculate the quantitative effects of each risk factor. Moreover, the inclusion of risk factors described in Table 2 was based on the significant outcomes in multivariable analysis. This selection was performed to minimize the risk of including confounding factors. However, this may have excluded risk factors studied in low-powered studies, which could also have led to the lack of research investigating risk factors. In the present study, both upper gastrointestinal and lower gastrointestinal cancer surgery were considered by examining esophageal, gastric, and colorectal resections in a large subset of patients undergoing these operations.

Conclusions

In conclusion, identification of improvable/modifiable risk factors exposes possibilities for augmentation of perioperative care, which may lead to improved surgical outcomes. Furthermore, the identified risk factors can lead to alteration and additions to already existing ERAS protocols, which have already resulted in improved perioperative care and reduction in complications [5, 63]. In addition, the identification of preoperative risk factors could lead to further improved and personalized perioperative care, thereby reducing major postoperative complications (e.g., risk factor-targeted prehabilitation). This study also contains important information to improve benchmarking of surgical outcomes in nation-wide clinical audits. The reduction of postoperative complications may prolong (recurrence-free) survival and lead to improved quality of life [84-87].

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Supplementary information A

Table S1 – Table showing the classification of study quality of all included studies using the QUIPS tool [1]. On the horizontal axis show the different assed domains per study. The vertical axis shows all included studies. The green bullet = little risk of bias, yellow = unclear risk of bias, red = high risk of bias.

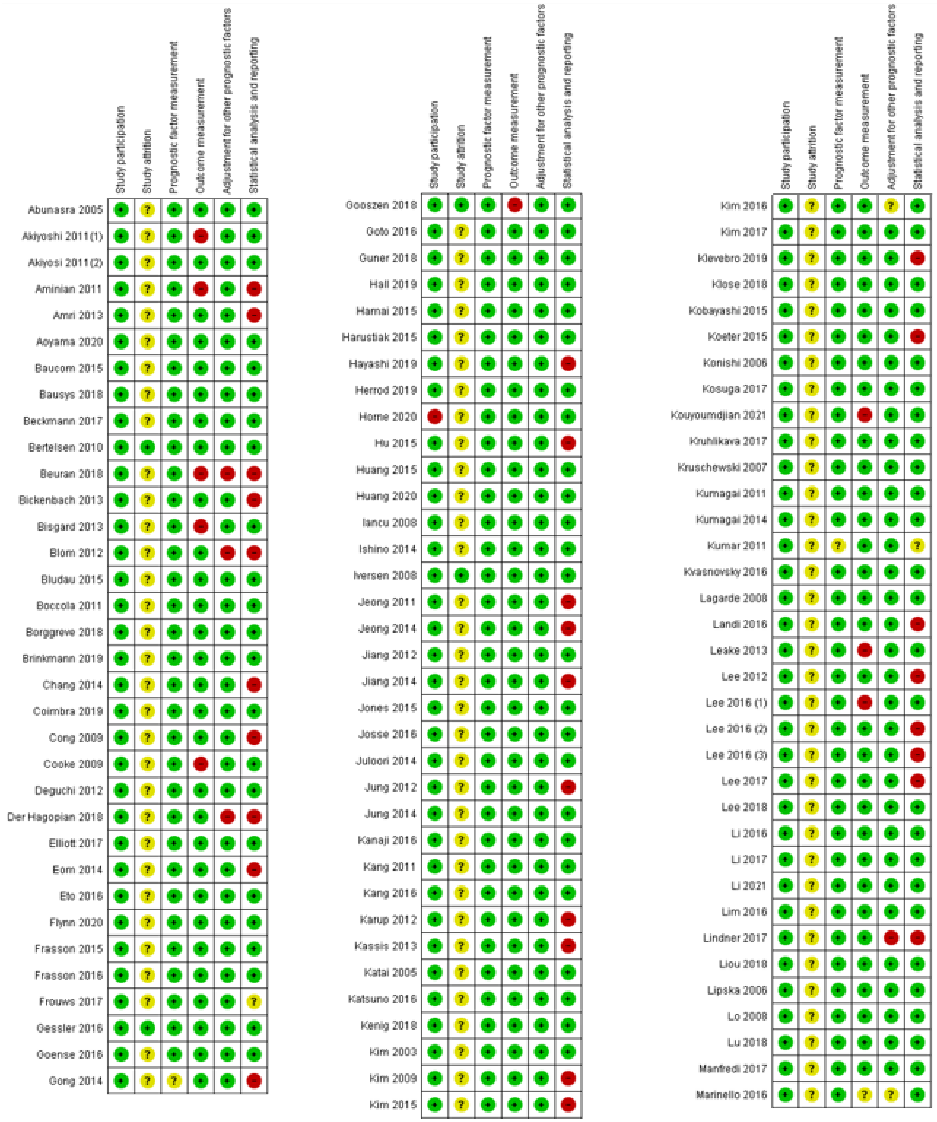
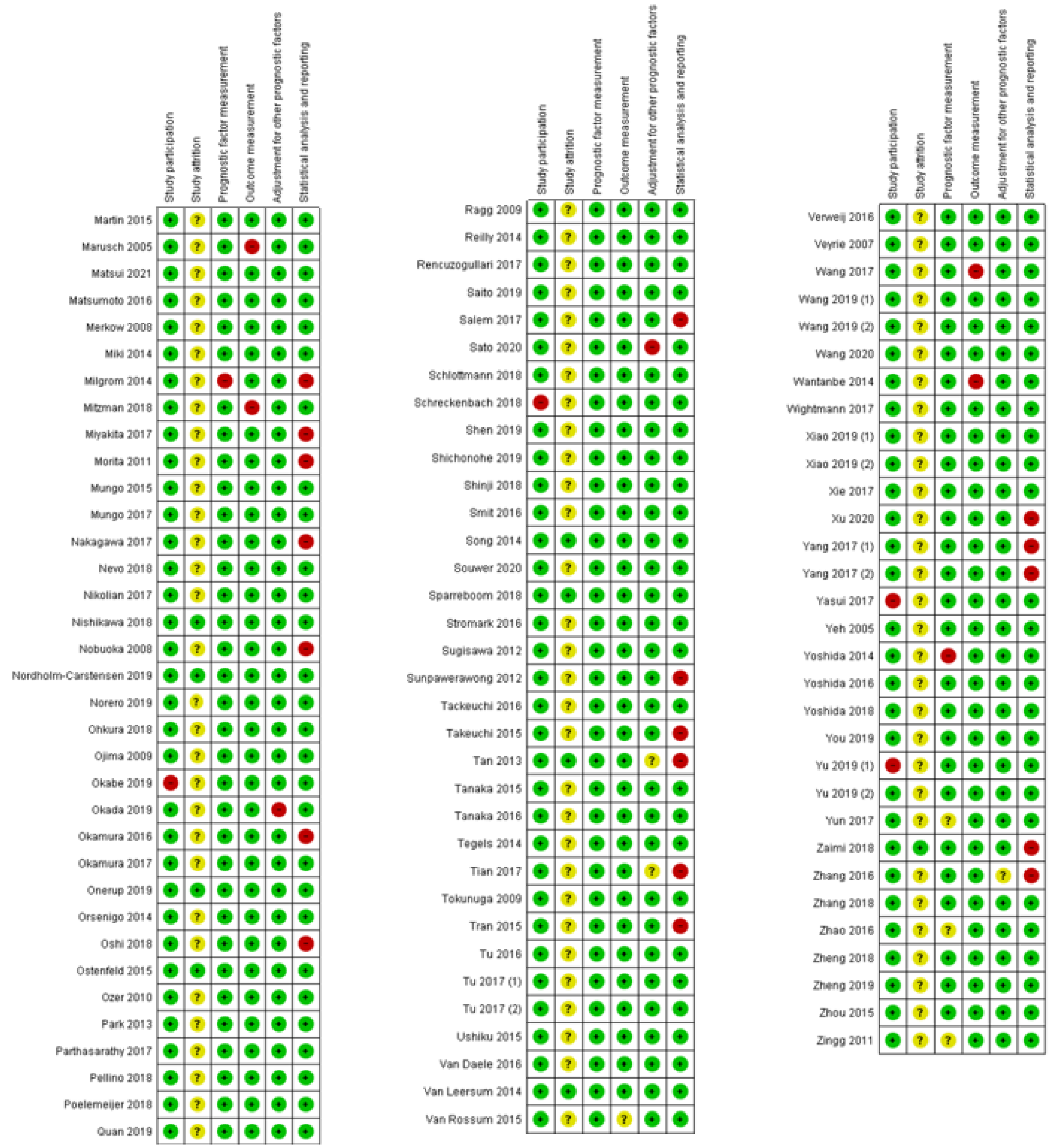


Table S1 –Continued



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Supplementary Information B

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