Risk prediction models for postoperative outcomes of colorectal cancer surgery in the older population - a systematic review

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Risk prediction models for postoperative outcomes of colorectal cancer surgery in the older population - a systematic review

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ABSTRACT

Background: An increasing number of patients with Colorectal Cancer (CRC) is 65 years or older. We aimed to systematically review existing clinical prediction models for postoperative outcomes of CRC surgery, study their performance in older patients and assess their potential for preoperative decision making.
Methods: A systematic search in Pubmed and Embase for original studies of clinical prediction models for outcomes of CRC surgery. Bias and relevance for preoperative decision making with older patients were assessed using the CHARMS guidelines.
Results: 26 prediction models from 25 publications were included. The average age of included patients ranged from 61 to 76. Two models were exclusively developed for 65 and older. Common outcomes were mortality ($n = 10$), anastomotic leakage ($n = 7$) and surgical site infections ($n = 3$). No prediction models for quality of life or physical functioning were identified. Age, gender and ASA score were common predictors; 12 studies included intraoperative predictors. For the majority of the models, bias for model development and performance was considered moderate to high.
Conclusions: Prediction models are available that address mortality and surgical complications after CRC surgery. Most models suffer from methodological limitations, and their performance for older patients is uncertain. Models that contain intraoperative predictors are of limited use for preoperative decision making. Future research should address the predictive value of geriatric characteristics to improve the performance of prediction models for older patients.

1. Introduction

Older patients make up the majority of (new) patients with colorectal cancer (CRC), and for this heterogeneous population, risks and benefits of treatment must be weighted at an individual level [1–4]. Prediction models can be used to facilitate this process and estimate the outcomes of treatment. Morbidity and mortality are important outcomes to discuss when deciding upon cancer treatment, but for older patients with cancer quality of life and retaining functional independence are also important outcomes [5].

The aim of this systematic review was to study existing clinical prediction models that were developed to predict postoperative outcomes of CRC surgery. Quality and accuracy of the prediction models in older patients were studied. Furthermore, their usefulness for preoperative decision making in older patients was evaluated.

Abbreviations: ACPGBI, The Association of Coloproctology of Great Britain and Ireland; ACS, The American College of Surgeons; AFC, the *French* Association for *Surgery*; ASA, American Society of Anesthesiologists; BH 2012, Barwon Health 2012 model; CCF, Cleveland Clinic Foundation; CLS, Colon leakage score; COLA score, Contamination, Obesity, laparotomy and ASA Grade score; CR, Colorectal; CR-BHOM, Colorectal The Biochemistry and Haematology Outcome Model; CRC, Colorectal Cancer; CrOSS, Colorectal preOperative Surgical Score; IRCS score, Identification of Risk in Colorectal Surgery score; I-score, Ileus Score; JSCCR, Japanese Society for Colon and Rectal Cancer; LARS, the Low Anterior Resection Syndrome; NNIS, the National Nosocomial Infections Surveillance (Japan); N-RIC, NNIS - risk index category; NSQIP, N*ational Surgical Quality Improvement Program*; POSSUM, The Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity; PROCOLE, Prognostic Colorectal Leakage.

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2. Methods

2.1. Search Strategy and Article Selection

This systematic review is reported following the recommendations set forth by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [6]. A literature search was performed on 1 November 2018, in the electronic databases Pubmed and Embase. The search contained the following key elements: "colorectal", "surgery" and "prediction" or "risk model" or "nomogram". No limits in age, language or publication date were included in the search. The full search strategies are shown in Appendix A. Inclusion criteria for prediction modelling studies were as follows; the study's main goals included the development of a prediction model for postoperative outcomes of colorectal (cancer) surgery. The final prediction model included more than one variable, and the model's performance was reported as an Area Under the Curve (AUC) or C-statistic/index. It was mandatory that pre- or intraoperative predictors were included in the published prediction model. Studies examining the validity of a prediction model outside the development population (the study population on which the prediction model was developed), without calibration or model update, were not eligible for inclusion in this review. Neither were reviews, editorials and conference abstracts.

Predefined outcomes of interest were any postoperative morbidity (for example, complications, readmission, hospital stay, functional and quality of life outcomes) and postoperative mortality up to 12 months.

All titles and abstracts of the studies retrieved by the search were addressed by two reviewers (ETDS and EB), to determine which studies warranted further examination. Articles in other languages then English, German, French or Dutch were excluded. The following studies were excluded based on title and abstract: treatment options other than colorectal surgery, no original research, non-human studies, only a subgroup of patients (e.g. only lung metastasis or liver metastasis), the inclusion of postoperative variables in the final model or the outcome of interest was not postoperative morbidity of mortality. All potentially relevant articles were subsequently screened as full text by two authors (ETDS and EB).

In the case a model update was published, the updated model was included in the review, but study information of the original study model was used when applicable. Furthermore, references of included publications were cross-referenced to retrieve any additional relevant citations. Finally, only studies that had a score chart or nomogram published or online/offline calculator made available were eligible for data-extraction.

2.2. Data Extraction and Quality Assessment

The CHecklist for critical Appraisal and data extraction for Systematic Reviews of prediction Modelling Studies (CHARMS) was used for data extraction [7]. For each included study, the following data were independently extracted by two investigators (ETDS, EB): Study date, data source (cohort, case-case control, randomized trial or registry data), study population (age, gender, tumour stage and type of surgery), outcome of interest, number of outcome events reported, predictors included in the final model. The final model's performance was assessed based on its discrimination (AUC of the c-statistic/index, sensitivity and specificity to calculate a Likelihood Ratio) and calibration (accuracy of the predicted risk versus the observed risk, and reported by Hosmer-

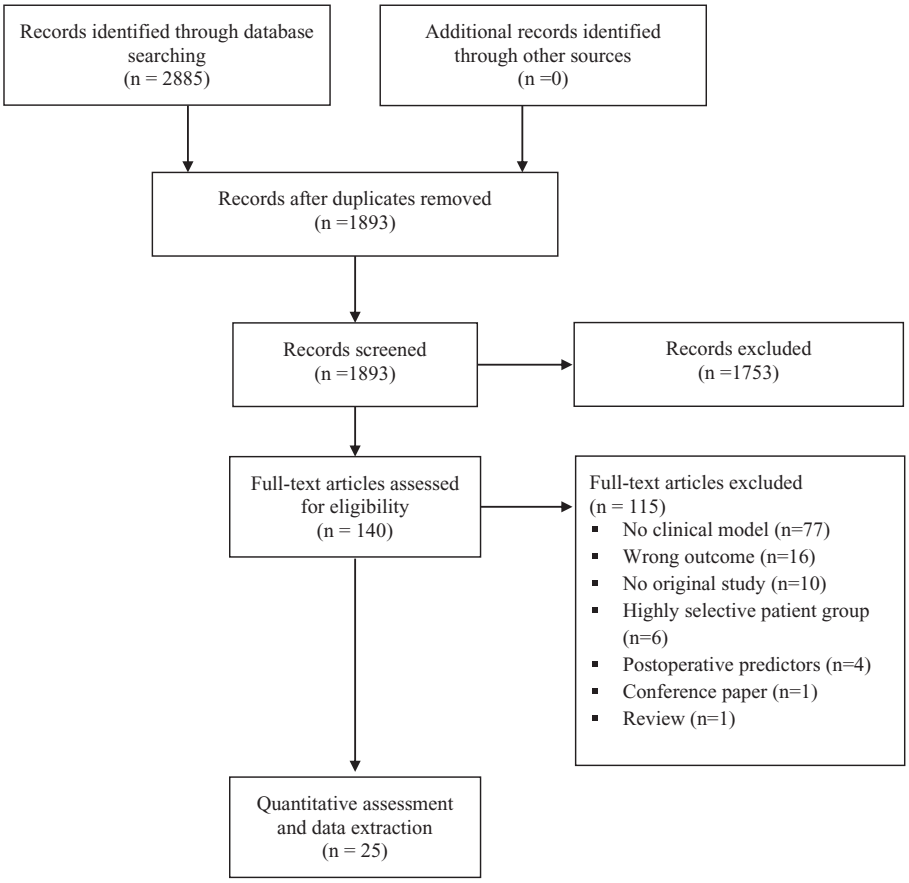

Fig. 1. PRISMA Flow Diagram.

Table 1
Characteristics of the 25 selected prediction modelling studies.

First Author [reference]	Cohort years	Model "name"	Outcomes	Type of surgery	Single or multicenter or /data source	Pro/retrospective	Tumour stages	No. of patients	Mean Age (range)	Patients >65[a] of >70[b]
Tekkis et al. [10] UK	1993–2001	CR-POSSUM	In-hospital mortality	CR surgery (37.2% CRC)	Multicenter ($n = 15$)	Pro	I-IV	6883	NR	37%[b]
Fazio et al. [11] USA	1976–2002	CCF-CRM	30-day mortality	CRC surgery	Single Center	Pro	I-IV	5053	Median 66 (18–98)	50%[a]
Slim et al. [12] France	2002	AFC Index	In-hospital mortality	CR surgery (CRC 70%)	Multicenter ($n = 81$)	Pro	NR	1421	NR	46%[a]
Cohen et al. [13] USA	2005–2007	ACS-NSQIP	1. 30-day mortality 2. 30-day overall and severe morbidity	CR surgery (49% CRC)	ACS-NSQIP database	Pro	I-IV	28,863/ 3037 (V)	Mean 61.8 (SD 15.9)	NR
Farooq et al. [14] UK	2001–2007	CR-BHOM	1. 30-day mortality 2. Major morbidity	CRC surgery	Single centre	Pro	NR	704	Median 74 (24–98)	NR
Dekker et al. [15] The Netherlands	2005–2006	CLS	Anastomotic Leakage	Left-sided CRC	Single center	Meta-analysis	NR	121	Median 66 (25–93)	NR
Richards et al. [16] UK	1997–2007	Revised ACPGBI	30-day mortality	Curative CRC surgery	Single centre	Pro	I-III	423	NR	67%[a]
Gervaz et al. [17] Switzerland	2008–2010	COLA-score	1. SSI – superficial 2. SSI - deep	CR surgery	Multicenter ($n = 24$)	Pro	NA	543	NR	NR
Kiran et al. [18] USA	2005–2007	Elderly ACS-NSQIP	30-day mortality	CR surgery (% CRC NR)	ACS-NSQIP database	Pro	I-IV	235,407	Non-elderly 52.8 Elderly (70 +)78.4	35%[b]
Pasic et al. [19] Bosnia and Herzegovina	2009–2011	–	Anastomotic leakage	CR surgery	Single center	Retro	NR	119	Mean 62 (33–87)	NR
Van der Sluis et al. [20] The Netherlands	1990–2011	IRCS	In-hospital mortality	CRC surgery	Single center	Pro	I-IV	2856	NR	49%[b]
Frasson et al. [21] Spain	2011–2012	Anastomoticleak.com	Anastomotic leakage	CRC surgery	Multicenter ($n = 52$)	Pro	I-IV	3193	Median (63–79)	NR
Hu et al. [22] China	2010–2014	–	Anastomotic leakage	Laparoscopic Rectal cancer surgery	Single center	Pro	I-IV	1968	Mean 61 (27–83)	NR
Kong et al. [23] Australia	2008–2010	CrOSS	In-hospital mortality	CRC surgery	Single center	Pro	I-IV	894	NR	50%[b]
Vather et al. [24] Australia	2012–2014	I-score	Prolonged postoperative ileus	CR surgery (28% CRC)	Single center	Pro	NR	351	Mean 67 (SD 23)	NR
Watanabe et al. [25] Japan	2005–2010	N-RIC derived study model	SSI	CR surgery (88% CRC)	Single center	Retro	I-IV	538	65.5 (20–98)	NR
Murray et al. [26] USA	2006–2012	Preop ACS-NSQIP	30-day mortality	Elective CRC surgery	ACS-NSQIP database	Pro	I-IV	59.968	Median 67 (IQR 56–77)	NR
Rojas-Machando et al. [27] Spain	2003–2010	PROCOLE	Anastomotic leakage	CRC surgery	Single center	Retro	I-III	123	NR	NR
Bailey et al. [28] USA	2009–2010	–	Post-acute care discharge	CRC surgery without postoperative complications	NY and California database	Pro	I-IV	32,942	NR	NR
Rencuzogullari et al. [29] US	2012–2014	ACS-NSQIP	Anastomotic leakage	65+ CRC surgery	ACS-NSQIP database	Pro	I-III	10,392	Mean 74.9 (SD 7.1)	All
Zang et al. [30] China	2007–2012	–	Major Perioperative Cardiac Events	CRC surgery	Single center	Retro	I-IV	1899	NR	NR
Battersby et al. [31] UK/ Denmark	2009–2014	POLARS Score	LARS (EORTC) score	Elective rectal surgery (PME/TME)	Multi center	Retro	I-IV	1401	Mean 64.9 (29–92)	NR
Fieber et al. [32] USA	2008–2011	–	Multiple admissions within the year after CRC surgery	Elective CRC surgery	SID and SPARCS database	Pro	I-IV	14,780	Median 69 (IQR 58–77)	47[b]
Hoshino et al. [33] Japan	2010–2013	JSCCR	Anastomotic leakage	Rectal surgery (LAR <10 cm	JSCCR database	Pro	I-IV	936	Mean/ Median NR	29%[b]
Shen et al. [34] China	1998–2013	SCSECC SSISECC	Surgical complications SSI	65+ CRC surgery	Single center	Retro	I-IV	1008	Median 74 (65–99)	49% 75+

Pro/retro pro- or retrospectively collected data; SD, standard deviation; IQR, interquartile range; PME, partial mesorectal excision; TME, total mesorectal excision.

Lemeshow (H-L) test value, observed/expected ratio or calibration plot).

For all studies, we searched for external validation studies in the Pubmed and Embase databases.

Clinical predictors were classified into demographic-, comorbidity- (including American Society of Anesthesiologists Classification (ASA) score, Body Mass Index (BMI)) biochemical- (electrolytes and albumin), geriatric- (falls, functional dependency, independency (i) Activities of Daily Living (ADL), cognition) and non-geriatric predictors (all others, including weight loss).

2.3. Quality Assessment

The methodological quality of each study was independently assessed by two reviewers (ETDS, EB). The CHARMS checklist was also used to assess the risk of bias and applicability concerns. Applicability refers to the extent to which the prediction model is useful for older patients with CRC [7]. The intended use is for preoperative shared decision making with older patients. Therefore, predictors need to be available preoperatively. In Appendix A and B, the criteria for quality assessment and applicability are described. These criteria were adapted from a systematic review of asthma prediction models by Smit et al. [8] We defined a prediction tool representative for the average older patient with CRC, when at least 30% of the study population was 65 years or older. In European countries and the US, more than half of all patients with CRC are 65 years or older [9].

In case of a model update; the model development studies were reviewed to assess the method of predictor selection.

2.4. Data Synthesis and Analysis

We describe study characteristics and the outcomes of interest, the predictors of each model and the model's performance. Furthermore, the quality (bias and applicability) of the prediction model studies was described.

3. Results

3.1. Study Characteristics

The literature search identified 2885 citations (1899 from Medline and 1100 from Embase), of which 992 were duplicates. Details on the search and final study selection are shown in Fig. 1. After exclusion of 2957 publications, 25 publications with 26 prediction models were included in this review [10–34]. Cross-referencing yielded no additional results.

The characteristics of 26 prediction models (Shen et al. reported two models) [34] are summarised in Table 1. Four publications were adaptions or previously earlier published prediction models [35–38].

Publication years ranged from 2003 to 2018; seven studies originated from the United States (USA), four from the United Kingdom (UK) including one collaboration with Denmark and three from China. Other countries were Australia, Bosnia Herzegovina, France, Japan, the Netherlands, Spain and Switzerland.

Table 2A
Predictors for mortality.

Author	Outcome	Predictors							
		Age	Gender	Tumour stage[1]	Comorbidity	Geriatric predictors	Biochemical predictors	Operative urgency (or mode of admission)	"Other predictors"
Tekkis et al. [10]	In-hospital mortality	√	–	√	CHD, Respiratory status	–	Haemoglobin, WBC, Sodium, Potassium, Urea,	√	ECG, Blood Pressure, Pulse, GCS, No of. procedures, Blood loss, Peritoneal Soiling
Fazio et al. [11]	30-day mortality	√	–	√	ASA score	–	Hematocrit	√	CR resection
Slim et al. [12]	90-day mortality	√	–	–	Neurological deficit			√	Weight loss
Cohen et al. [13]	1. 30-day mortality 2. 30-day overall morbidity 3. 30-day severe morbidity	√	–	√	COPD, Dyspnea	Functional dependency	Creatinine, Albumin, PT time	√	BMI, Sepsis, Indication for surgery, Surgical extent, Wound Class
Farooq et al. [14]	1. 30-day mortality 2. Major morbidity	√	–	–	–	–	Urea, Sodium, Albumin	√	
Richards et al. [16]	30-day mortality	√	–	√	ASA score	–		√	Operative procedure[2]
Kiran et al. [18]	30-day mortality	√	–	√	ASA score, Renal failure or dialysis	Functional dependency	Albumin	√	
Van der Sluis et al. [20]	In-hospital mortality	√	–	√	CHD, Pulmonary failure	–		√	–
Kong et al. [23]	In-hospital mortality	√	–	–	CHD	–	Albumin	√	–
Murray et al. [26]	30-day mortality	√	–	√	ASA score, Renal failure, Ascites, CHD	Functional dependency	Albumin	–	–

√Predictor included, — Predictor not included. BMI, body mass index,[1] Disseminated cancer or actual tumour stage; GCS, Glasgow Coma Scale; PT time, partial thromboplastin time; WBC, white blood cell count [2];Type of surgery; CR, colorectal; CHD, congestive heart disease including signs of heart failure.

There was some heterogeneity between the study cohorts and related interventions; patient cohorts included patients with CRC and patients with colorectal surgery (including those with noncancer indications). The most frequently studied intervention was resectional colorectal surgery; in the study of Dekker et al. [15] the studied intervention was left-sided colorectal surgery and in the studies of Hu et al. [22], Battersby et al. [31] and Hoshino et al. [33] only rectal surgery was studied.

The study populations for the 25 studies originated from single centres (13), multicenter studies (5) and registry data or administrative data (7). In the majority of the studies (19 out of the 25) data were collected prospectively. Two prediction model studies used a meta-analysis to select predictors for the final model instead of a primary database [15,27].

3.1.1. Patients and Outcomes

The number of patients that were included ranged from 119 to 23,5407. Average age ranged from 61 to 76 years. Two models were exclusively developed for patients of 65 and over [29,34].

Of the 26 models, ten models studied mortality as an outcome and seven anastomotic leakages (Table 1). Two models with mortality as an outcome were also developed to predict major complications or major morbidity [13,14]. Deep organ space infections, wound disruptions, stroke, renal failure and sepsis were considered major complications and anastomotic leakage, abscess, bleeding or postoperative bowel obstruction as major morbidity in these studies. No models focused on quality of life or postoperative functional dependency.

3.1.2. Predictors

For model development, predictors were mostly selected based on their statistical significance (with $p < .10$ or $p < .05$) with a corresponding weight (OR), before constructing the final model [10–14,16–26,28–30,32–34]. For three models, the choice of predictors depended exclusively on the research of the literature or clinical experience [15,27,31]. The median number of predictors included was 6 (range 4–22). In Table 2(A-C), predictors in the different prediction models are depicted, categorised by outcome (mortality, anastomotic leakage and "other outcomes") which include all other surgical complications including ileus, post-acute care discharge, cardiac events and readmission.

Age, ASA score, tumour stage, operative urgency, and albumin were common predictors for mortality and anastomotic leakage. Six models included parameters such as weight loss [12,29,31] and functional status or dependency [13,18,26]. Thirteen out of 26 prediction models included intraoperative predictors such as laparoscopic surgery, surgical extent, peritoneal contamination, distance of the anastomosis, duration of surgery, and intraoperative complications such as blood loss [10,15,17,19,21,22,24,25,28–31,34]. The proportion of studies that included intraoperative predictors were higher in models with anastomotic leakage as an outcome (5 out of 7) [15,19,21,22,29] and the "other outcomes" summarised in Table 2C [17,24,28,30,34]. In contrast, only one model for postoperative mortality included intraoperative predictors in their final model [10].

3.2. Applicability Concerns

Shown in In Table 3, are the applicability concerns for participant selection, predictors and outcomes for the different studies where they are judged based on their applicability for preoperative shared decision making with older patients.

Applicability concerns related to the population were raised for the studies of Pasic et al. [19] and Rojas [27]. These studies did not describe their study population in detail or did not include >30% older patients.

Table 2B
Predictors for anastomotic leakage.

Author	Outcome	Predictors							
		Age	Gender	Tumour stage[1]	Comorbidity	Geriatric predictors	Biochemical predictors	Operative urgency (or mode of admission)	"Other predictors"
Dekker et al. [15]	Anastomotic leakage	√	√	–	–	–		√	BMI, Intoxication, Neoadjuvant therapy, Distance of anastomosis, Blood Loss, Additional procedures, Duration of surgery
Pasic et al. [19]	Anastomotic leakage		–	–	ASA score	–		–	Rectal tumours, Duration of surgery, Blood transfusion
Frasson et al. [21]	Anastomotic leakage	–	√	–	Oral Anticoagulants	–		–	BMI, Intraoperative complication, Serum protein, Hospital size (No of beds)
Hu et al. [22]	Anastomotic leakage	–	√	–	Diabetes	–		–	Distance of anastomosis, Blood Loss
Rojas-Machando et al. [27]	Anastomotic leakage	–	√	–	ASA score, Diabetes, CV Disease, Respiratory Disease, Renal Disease, Hepatic Disease, Steroid use	–	Hemoglobin, WBC, Albumin,	√	Intoxications, Neoadjuvant treatment, Concurrent presented pathologies, Additional surgery, Mechanical anastomosis
Rencuzogullari et al. [29]	Anastomotic leakage	-[a]	√	–	ASA score, Diabetes, COPD Steroid use			√	Weight loss, Open Wound/ Wound infection, Duration of surgery
Hoshino et al. [33]	Anastomotic leakage	–	√	–	–	–	Albumin	–	Tumour location, Tumour diameter, Additional surgery

√ predictor included, — predictor not included. BMI, body mass index,[1] Stage IV (disseminated) cancer or actual tumour stage; WBC, white blood cell count [2];Typ of surgery (colectomy, ostomy ect); CHF, congestive heart disease including signs of heart failure. [1]ntoxication include alcohol abuses and smoking.

[a] Model development for patients of age ≥ 65.

All the outcomes were considered relevant for older patients, all the non-mortality outcomes such as anastomotic leakage, surgical complications, LARS symptoms, multiple admissions (health care usage) could result in delayed recovery and decrease in quality of life. That also included surgical site infections. Due to the inclusion of intraoperative predictors, there were applicability concerns for preoperative decision making for thirteen studies [10,15,17,19,21,22,24,25,28–31,34]. The CR-POSSUM model for postoperative mortality [10] includes a intraoperative collected physiological score that cannot be calculated preoperatively. Inclusion of predictors such as intraoperative blood loss and duration of surgery [15,19,25,29,30,34], intraoperative complications [21], the distance of the anastomosis to the anal verge [15,22] limits the applicability for preoperative decision making.

3.3. Technical Analysis and Performance

Tables 4A-C shows the technical analysis and performance of all model.

For mortality (Table 4A), the reported discrimination (AUC) of the models during model development ranged from 0.68 to 0.91. However, eight studies did not report confidence intervals [11–14,16,18,23,26]. The internal validation methods that were reported were random-split [10,11,18,26], cross-validation [13], two studies reported external validation [16,20].

Additional external validation studies were found for the following models: CR-POSSUM [39–42], CCF-CRM [43], AFC Index [44], CR-BHOM [41], revised ACPGBI [45], and IRCS [42]. Discrimination ranged from 0.56–0.89. However, calibration was considered poor except for the CR-BHOM and AFC model. Calibration could not be judged for the ACS-NSQIP model [13]. The performance of the CR-POSSUM [10] and CR-BHOM [14] models in a cohort of 991 Portuguese octogenarians were AUC 0.74 and 0.65, and poor and good calibration, respectively [41].

For the anastomotic leakage models (Table 4B), discriminaton of the models ranged from 0.63 to 0.95 (in the development cohort). Discrimination in the development phase did not apply to the studies of Dekker et al. [15] and Rojas-Machado et al. [27] because of their meta-analysis approach for model development. Remarkably, the study of Pasic et al. reported an AUC of 1.0 (validation) without a confidence interval in a small study population of 40 patients [19].

Additional external validation studies were found for the CLS [27,46], anastomoticleak.com [46], and ACS-NSQIP anastomotic leakage model [46]. In these studies, AUC ranged from 0.58–0.80. Calibration could not be judged for the ACS-NSQIP anastomotic leakage model and JSCCR model.

For the "other" outcomes, the methodological and model performance analysis is shown in Table 4C. Of note, the discriminatory performance of the COLA-score model varied across the countries France, England and Switzerland (AUC 0.60–0.64), with poor calibration in all three cohorts.

Online calculators can be found for the CR-POSSUM [10], ACS-NSQIP [13,26,29] and ACPGBI models [16]. Other modes of presentation were a formula, chart or nomogram.

Table 2C
Predictors for Surgical Site Infections (SSI) and other outcomes.

Author	Outcome	Predictors							
		Age	Gender	Tumour stage[1]	Comorbidity	Geriatric predictors	Biochemical predictors	Operative urgency (or mode of admission)	"Other predictors"
Gervaz et al. [17]	1. SSI – superficial 2. SSI - deep	–	–	–	ASA score, Obesity	–	–	–	Contamination class. Laparotomy
Vather et al. [24]	Prolonged postoperative ileus	–	√	–	–	–	Albumin,	–	Open Surgery, Operation difficulty, Wound Size, RBC transfusion
Watanabe et al. [25]	SSI	–		–	ASA score	–	–	–	Wound Classification, Duration of surgery, Laparoscopic surgery
Bailey et al. [28]	Post-acute care discharge	√	√	–	No. comorbid conditions	–	–	√	Open surgery, New Ostomy, ≥ 1 admission in the previous year
Zhang et al. [30]	Major Perioperative Cardiac Events	√		–	Kidney Disease, Coronary Artery Disease, CHD	–	Hematocrit, Albumin	–	Intoxication (smoking), Blood Pressure, RBC transfusion
Battersby et al. [31]	LARS (EORTC) score	√	√	T-stage	–		–	√	Weight loss, TME Ostomy, Neoadjuvant Radiotherapy
Fieber et al. [32]	Multiple admissions within the year after CRC surgery	–		–	Elixhauser index	–	–	√	No of admission in the previous year, Primary Payer Health Insurance
Shen et al. [34]	Surgical Complications	-[a]		–	–	–	–	–	Bowel obstruction, Laparoscopic Surgery, Blood Loss, Classification of the incision, Intraoperative low body temperature
Shen et al. [34]	SSI	-[a]		–	–	–	C reactive protein, Electrolyte Imbalance	–	BMI, Bowel Obstruction, Thickness subcutaneous fat, Laparoscopic surgery, Blood Loss, Classification of the incision, Intraoperative low body temperature, faecal contamination

√ Predictor included, — predictor not included. BMI, body mass index; CHD, congestive heart disease; RBC, red blood cell.
[a] Model development for patients of age ≥ 65.

Table 3
Applicability concern based on the CHARMS checklist.

	Applicability Concern		
	Participant selection	Predictors	Outcome
Mortality			
Tekkis et al. [10]	L	M	L
Fazio et al. [11]	L	L	L
Slim et al. [12]	L	L	L
Cohen et al. [13]	L	L	L
Farooq et al. [14]	L	L	L
Richards et al. [16]	L	L	L
Kiran et al. [18]	L	L	L
Van der Sluis et al. [20]	L	L	L
Kong et al. [23]	L	L	L
Murray et al. [26]	L	L	L
Anastomotic leakage			
Dekker et al. [15]	L	M	L
Pasic et al. [19]	M	M	L
Frasson et al. [21]	L	M	L
Hu et al. [22]	L	M	L
Rojas-Machando et al. [27]	H	L	L
Rencuzogullari et al. [29]	L	M	L
Hoshino et al. [33]	L	L	L
Other outcomes			
Gervaz et al. [17]	L	M	L
Vather et al. [24]	L	M	L
Watanabe et al. [25]	L	L	L
Bailey et al. [28]	L	L	L
Zhang et al. [30]	L	M	L
Battersby et al. [31]	L	L	L
Fieber et al. [32]	L	L	L
Shen et al. [34]	L	M	L

CHARMS; checklist for Critical Appraisal and Data Extraction. for Systematic Reviews of Prediction Model Studies. Criteria. listed in the Appendix B. L, low concern; M. moderate concern; H, high concern.

3.4. Critical Appraisal

Also shown in Table 4A, 4B and 4C is the quality assessment of the studies. The risk for bias can be subdivided into selection bias (participant selection and sample attrition), information bias (predictor and outcome assessment concerns) and analysis concerns.

3.4.1. Selection Bias

The risk of selection bias for the prediction models studied was rated moderate to high; eight studies rated 'high' for risk of selection bias. In two studies, participant selection was unclear [19,27]. For these studies and five others that did not report loss of follow up, there were high attrition concerns [14,16,17,20,31]. In only four prediction model studies, there was no loss of follow-up [13,20,21,29].

3.4.2. Information Bias

In the majority of the studies, the risk of information bias related to the outcome was considered low. Three studies [15,19,27] did not use data-driven predictor selection, but predictor selection was based on a meta-analysis or Delphi Round. In the studies that did not have mortality as an outcome, the risk was higher due to the unclear measurement of the outcome, lack of blinding or non-standardised timing of the outcome.

3.4.3. Analysis Bias

Lastly, for the risk related to the analysis, all studies were rated 'moderate' to 'high'. In the majority of the studies, the number of missing values was not reported, and predictors were included not independent of the *p*-value. Other concerns were related to the small sample sizes for estimation of the predictor effect; the event/predictor ratio being less than ten events per predictor in seven studies [19,22,23,27,30,34].

Table 4A
Model performance and risk of bias for "mortality" prediction models.

Author	Development			Validation				Presen-tation	Risk of bias				
	Events (n)	Predictors (n)	Discr. AUC	Type	Ref.	Discr. AUC	Calibr.		Participant Selection	Outcome	Predictor	Attrition	Analysis
Tekkis et al. [10]	387	18	0.90	External	[39–42]	0.78 0.74 0.74 0.65	O:E 0.75 O:E 1.25 H-L $p < .01$ O:E 1.11	FOR-MULA	M	L	L	M	M
Fazio et al. [11]	116	6	0.80	External	[43]	0.81	H-L $p = .03$	CHART	M	M	L	M	M
Slim et al. [12]	48	4	0.82	External	[44]	0.89	H-L $p = .37$	CHART	L	L	L	M	M
Cohen et al. [13]	1126 7014 3290	15 15 15	0.91 0.68 0.72	Internal	–	0.91 0.68 0.73	NR	ONLINE [2]	M	L	L	L	M
Farooq et al. [14]	50 80	5 5	0.81 0.70	External	[41]	0.56	O:E 1.0	FOR-MULA	M	L	L	H	M
Richards et al. [16]	153	5	0.73	External	[45]	0.83	H-L p < .01	FOR-MULA	L	L	L	M	M
Kiran et al. [18]	817	7	NR	Internal	-	0.89	Plot	NOMO-GRAM	M	L	L	M	M
Van der Sluis et al. [20]	146	5	0.83	External[1]	[42]	0.83 0.74	H-L $p = .51$ H-L p < .01	FOR-MULA	M	L	L	L	M
Kong et al. [23]	24	4	0.81	External[1]	–	0.85	H-L $p = .2$	FOR-MULA	L	L	L	H	M
Murray et al. [26]	1080	8	0.82	Internal	–	0.83	H-L $p = .63$ Plot	CHART	L	L	L	M	M

Calibr, Calibration; Discr. Discrimination; H-L: Hosmer-Lemeshow Chi-square X^2 (p-value); O:E expected/observed ratio, NR, not reported. AUC Area Under the Curve with (95% CI) 95% Confidence Interval; NR, not reported 1;External validation published together with internal validation. Mode of presentation [2]: ONLINE, online calculator; Risk of bias: L, low risk; M, moderate; H, high risk.

Table 4B
Model performance and risk of bias for "Anastomotic leakage" prediction models.

Author	Development			Validation				Presen-tation	Risk of bias				
	Events (n)	Predictors (n)	Discr. AUC	Type	Ref	Discr. AUC	Calibr.		Participant Selection	Outcome	Predictor	Attrition	Analysis
Dekker et al. [15]	10	11	0.95	External	[27] [46]	0.65 0.80	NR	CHART	L	M	M	H	M
Pasic et al. [19]	14	4	NR	External[1]		1.0	NR	CHART	M	M	M	H	H
Frasson et al. [21]	277	6	0.63	External	[46]	0.73	NR	NOMO-GRAM[2]	L	L	L	M	M
Hu et al. [22]	63	4	NR	None	–			CHART	L	L	L	H	M
Rojas-Machando et al. [27]	31	23	0.82	None	–			CHART	M	M	M	L	M
Rencuzogullari et al. [29]	332	9	0.65	External[1]	[46]	NR 0.58	O:E 1.1 NR	NOMO-GRAM	M	L	L	L	M
Hoshino et al. [33]	149	5	0.72	Internal		0.72	Plot	NOMO-GRAM	L	L	L	M	M

Calibr, Calibration; Discr. Discrimination; H-L: Hosmer-Lemeshow Chi-square X^2 (p-value); O:E expected/observed ratio. NA, not applicable; NR, not reported; CI, 95% Confidence Interval; NR, not reported[1];External validation published together with internal validation; Mode of presentation[2]: Including an online calculator.

Table 4C
Model performance and risk of bias for "Other Outcomes" prediction models.

Author	Development			Validation				Presen-tation	Risk of bias				
	Events	Predictor	Discr. AUC	Type	Ref.	Discr. AUC	Calibr.		Participant Selection	Outcome	Predictor	Attrition	Analysis
Gervaz et al [17].	387	4	0.70	External	[60]	0.64 0.60	"poor"	CHART	L	L	H	H	M
Vather et al. [24]	116	6	0.68	None	–	–	NR	CHART	L	L	L	M	M
Watanabe et al. [25]	48	4	0.83	None	-	–		CHART	L	L	L	M	M
Bailey et al. [28]	1126 7014 3290	7	0.73	Internal	–	0.83	NR ("well")	CHART	M	L	L	M	M
Zhang et al. [30]	56	9	0.92	None	–	–	plot	NOMO-GRAM	L	M	M	M	M
Battersby et al. [31]	NA	6	0.62	External[1]	–	0.63	plot	CHART[2]	L	M	M	M	M
Fieber et al. [32]	1143	4	0.64	External[1]	–	0.63	O:E 1.0	CHART	M	L	L	H	M
Shen et al. [34](SCSECC)	118	5	NR	Internal	–	0.74	H-L p = .81	FOR-MULA	M	L	M	H	M
Shen et al. [34](SSISEC)	72	10	0.80	Internal	–	0.82	H-L p = .93	NOMO-GRAM	M	L	M	H	M

Discr. Discrimination; Calibr. Calibration. H-L: Hosmer-Lemeshow, O:E expected/observed ratio. Chi-square X^2 (p-value); NR, not reported; CI, 95% Confidence Interval; NR, not reported[1]; External validation published together with internal validation.
Mode of presentation[2]: Including an online calculator; Risk of bias: L, low risk; M, moderate risk; H, high risk.

In 6 out of the 25 studies, internal or external validation was not performed or reported [14,15,22,24,25,27]. Therefore assessment of potential overfitting and optimism could not be assessed.

4. Discussion

We identified 26 prediction models out of 25 studies for postoperative outcomes of colorectal surgery; ten models studied mortality as an outcome and seven anastomotic leakages. Other outcomes were surgical complications, gastrointestinal problems (including prolonged ileus), perioperative cardiac events, readmissions, and discharge not to home. The average age of included patients ranged from 61 to 76 years. Two models were exclusively developed for patients 65 years and older. We found no models with quality of life or functional dependency as an outcome. Age, gender and ASA score were common predictors. Twelve studies included intraoperative predictors, such as surgical extent, the distance of the anastomosis, duration of surgery, and intraoperative complications, including both models for older patients, which limits their use for preoperative decision making [29,34].

There were methodological concerns relating to sample in size (28%), missing external validation (42%) and not reporting on calibration (28%). Information bias and analysis bias was considered moderate to high in 22 studies (88%).

In external validation studies, discrimination and calibration were more likely to be worse compared to the original study. Based on the applicability and methodological concerns, no useful model for older patients was identified that could be used for preoperative shared decision making.

For older patients risks and benefits of treatment should be weighted at an individual level. Identification of high-risk patients enables the initiation of geriatric interventions such as prehabilitation [47] that could reduce the risk of surgery. Geriatric Assessment (GA) has been shown to reveal previously unknown medical issues in older (surgical-) oncology patients, that are associated with poor outcomes of treatment [48–50]. Predictors of surgical outcomes in older patients are comorbidity, functional dependency [13,18,26], falls and cognitive impairment [51]. Introduction of such predictors in existing prediction tools may improve a prediction model's performance for older patients.

Methodological concerns affect clinical applicability and generalizability of prediction models. Especially in small datasets, the effect of included predictors may be overestimated [15,19,23,34]. Hence, alternative methods are available for the selection process of candidate predictors to reduce this risk of overestimation. These include selecting candidate predictors based on meta-analysis or literature [15,27], or more modern techniques such as least absolute shrinkage and selection operator (LASSO) [31,52]. These methods still need a sufficient sample size to provide reliable estimations.

Concerns in generalisability exist, when data-driven models are not internally or externally validated [22,24,25,27,30]. Furthermore, a split-sample validation does not assess the external validity of a model in the development study [10,11,18,26,32,34].

For more recently published models, it was more easy to judge bias and applicability, because these were more often reported in line with the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) [53]. That does not disqualify the validity of the earlier developed models, however it hampers the formal assessment of the quality and performance and applicability for older patients as used by the CHARMS checklist.

This review summarised the information available on the included predictors and performance of the different models. By selecting 25 studies out of almost 1900 publications, it is unlikely that we missed any unknown prediction models, which adds to the strength of this review. The assessment of the risk of bias aids in the critical appraisal of a prediction model for clinical practice. Albeit, the various prediction models did not prove to be specifically useful for older patients with CRC.

There are some limitations to our review. Firstly, we focused on clinical prediction models, excluding studies only describing logistic models without further analysis of their model performance. Secondly, with 25 studies included in this review, we decided not to assess the individual predictors on their association with the outcomes. Therefore, no information is provided on the weight of predictors, although the CHARMS checklist suggests providing these details [7]. For these details as well as for the definition of outcomes such as anastomotic leakage and severe morbidity were refer to the individual studies.

5. Recommendations for Future Research

For prediction model development and validation studies, sample size should be sufficient to reliably estimate a model's performance. Furthermore, for prognostic research, calibration measures (reliability of the prediction for the different risk groups) within external validation studies have more importance than discrimination (who is at risk and who is not) [54] because only reliable individual risks predictions can be used to make treatment decisions.

Also, a model may require periodic updating because of changes in the population of interest [55]. Outcomes of CRC surgery have improved due to care innovations such as auditing, ERAS (including laparoscopic surgery) [56], neoadjuvant treatment and wait-and-see policies for rectal cancer and liberal use of defunctioning colostomy [57]. Furthermore, a decrease in 30-day and one-year mortality after CRC surgery occurred in the past decades [58,59].

Lastly, transparent reporting of future prediction model studies can improve by systematically using the TRIPOD guidelines [53].

6. Conclusion

Many prediction models are available that address mortality and surgical complications after CRC surgery, but not for prediction of quality of life or functional decline. Most of these models were not developed for older patients and include only a limited number of risk factors specific to older patients. Half of the included prediction models included intraoperative predictors, which limit their use for preoperative decision making. Future research should address geriatric characteristics to improve prediction models for preoperative decision making with older patients.

Authorship Contributions

Contribution: Name(s) of author(s)
Study concepts: E.T.D. Souwer
Study design: E.T.D. Souwer, E. Bastiaannet, J.E.A. Portielje, F. van den Bos
Data acquisition: E.T.D. Souwer, E. Bastiaannet
Quality control of data and algorithms: E.T.D. Souwer, E. Bastiaannet
Data analysis and interpretation: E.T.D. Souwer, E. Bastiaannet
Statistical analysis: not applicable
Manuscript preparation: E.T.D. Souwer
Manuscript editing: E.T.D. Souwer
Manuscript review: All authors

Declaration of Competing Interest

All authors declare that there is no conflict of interest.

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Appendix A. Full Search Pubmed and Embase

Pubmed

("Colon"[majr] OR "Colon"[ti] OR "colonic"[ti] OR "colorectal"[ti] OR "Rectum"[majr] OR "Rectum"[ti] OR "rectal"[ti] OR "large bowel"[ti] OR lower gastro*[ti]) AND ("Colorectal Surgery"[majr] OR "General Surgery"[majr] OR "surgery"[ti] OR "surgical"[ti] OR "Colectomy"[majr] OR "Colectomy"[ti] OR "Colectomies"[ti] OR resect*[ti] OR dissect*[ti] OR "Anastomosis, Surgical"[Majr:NoExp] OR "anastomosis"[ti] OR "anastomoses"[ti] OR "anastomotic"[ti] OR "Surgical Stomas"[majr] OR "stoma"[ti] OR "stomas"[ti] OR "Ostomy"[Majr:NoExp] OR "Ostomy"[ti] OR "ostomies"[ti] OR "Enterostomy"[majr] OR "Enterostomy"[ti] OR "Enterostomies"[ti] OR "Colostomy"[ti] OR "Colostomies"[ti] OR "Ileostomy"[ti] OR "Ileostomies"[ti]) AND ("Decision Support Techniques"[Mesh] OR "Nomograms"[Mesh] OR nomogram*[tw] OR ((model*[tw] OR calculat*[tw]) AND (predict*[tw] OR "Risk"[Mesh] OR "risk"[tw] OR "risks"[tw]))) NOT ("animals"[mesh] NOT "humans"[mesh])

Embase

(exp *colon/ OR "Colon".ti. OR "colonic".ti. OR "colorectal".ti. OR exp. *rectum/ OR "Rectum".ti. OR "rectal".ti. OR "large bowel".ti. OR lower gastro*.ti.) AND (exp *colorectal surgery/ OR *general surgery/ OR "surgery".ti. OR "surgical".ti. OR exp. *colon resection/ OR "Colectomy".ti. OR "Colectomies".ti. OR resect*.ti. OR dissect*.ti. OR exp. *anastomosis/ OR "anastomosis".ti. OR "anastomoses".ti. OR "anastomotic".ti. OR *stoma/ OR *colon stoma/ OR *ileostoma/ OR "stoma".ti. OR "stomas".ti. OR *ostomy/ or *enterostomy/ OR "Ostomy".ti. OR "ostomies".ti. OR "Enterostomy".ti. OR "Enterostomies".ti. OR "Colostomy".ti. OR "Colostomies".ti. OR "Ileostomy".ti. OR "Ileostomies".ti.) AND (exp decision support system/ OR nomogram/ OR nomogram*.ti,ab. OR ((model*.ti,ab. OR calculat*.ti,ab.) AND (predict*.ti,ab. OR risk/ OR mortality risk/ OR patient risk/ OR risk factor/ OR "risk".ti,ab. OR "risks".ti,ab.))) NOT conference abstract.pt. NOT (animal/ NOT human/)

Appendix B. Criteria for Scoring of Risk of Bias Based on the CHARMS Checklist

Potential bias	Risk of bias		Items to be considered for potential bias
Participant selection	L	Low risk if	- selection bias was unlikely, - study avoided inappropriate inclusions or exclusions, - in- and exclusion criteria were adequately described - participants were enrolled at a similar presentation of their

(continued on next page)

(*continued*)

Potential bias	Risk of bias	Items to be considered for potential bias
		disease - differences were accounted for by including appropriate predictors in the analysis
Selective inclusion	M Moderate risk if	- not satisfying one of the above or - no adequate description of the recruitment of the study sample - no adequate description of the sample for key predictors
	H High risk if	if both items were not adequately described
Predictor assessment	Risk of bias	
	L Low risk if	- predictor definitions were the same for all participants - predictor measurement was blinded to outcome data - all predictors were available at the time the model is intended to be used - predictors were measured with valid and reproducible methods such that misclassification was limited and if - predictors were assessed in a similar way for all study participants
Treatment predictors; do the modify outcome and were they handled appropriately	M Moderate risk if	if one of the criteria was not satisfied
	H High risk if	if method for assessment of outcome was not adequately described
Outcome assessment	Risk of bias	
	L Low risk if	- the outcome was pre-specified and - measured with sufficient validity and reproducibility and - measured in a similar way for all study participants and - if the outcome was assessed independently from the assessment of predictors Note: for easy to obtain predictors such as gender, it is not possible to assess outcome independent of predictor information
	M Moderate risk if	- if one of the criteria was not satisfied
	H High risk if	- if the assessment of outcome was not adequately described
Attrition	Risk of bias	
	L Low risk if	- there was no loss-to-follow-up - there were no important differences on key characteristics between included participants and those who were lost-to-follow-up or missing
	M Moderate risk if	- loss-to-follow-up was lower than 20% and - there were no important differences on key characteristics between included participants and those who were lost-to-follow-up or missing OR: - loss-to-follow-up was higher than 20% but missing data and loss-to-follow-up were imputed adequately or there were no important differences on key characteristics between included participants and those who were lost-to-follow-up or missing
	H High risk if	- loss-to-follow-up was higher than 20% and/or - there were important differences on key characteristics between included participants and those who were lost-to-follow-up or missing or -loss-to-follow-up was not described
Analysis (including? time interval between predictor and outcome was reasonable, part of eligibility)	Risk of bias	
	L Low risk if	- relevant aspects of analysis were described allowing to judge the quality of the analysis to be adequate - # outcome events per candidate predictor reasonable - missing data handled appropriately or no differences - predictors included independent of *p*-value - overfitting and optimism accounted for - weights assigned according to the regression coefficient - calibration and discrimination assessed - recalibrated or described that it was not needed
	M Moderate risk if	- relevant aspects of analysis were described allowing to judge the quality of the analysis to be adequate and part or none of the model evaluation items were reported
	H High risk if	- not satisfying any of the aspects under low risk of bias

Applicability	Applicability concern	Items to be considered for applicability concern
Participant selection	L Low if	Truly representative of an average elderly patient with colorectal cancer And > 30% older patients (65) were included
	M Moderate if	Somewhat representative of the average older patient with colorectal cancer
	H High if	- Not representative of the average older patient with colorectal cancer OR - no clear definition
Predictor	Applicability concern	
	L Low if	- Predictors are available for older patients with colorectal cancer and - All Predictors are *preoperatively* assessed
	M Moderate if	- One of the above criteria was not met
	H High if	- Both criteria were not met
Outcome	Applicability concern	
	L Low if	- Outcome applicable to older patients with colorectal cancer - Outcomes discussed could change a treatment decision
	M Moderate if	- If one of the above criteria was not met
	H High if	- None of the criteria was met

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