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Evaluation of clinical prognostic variables on short-term outcome for colorectal cancer surgery: An overview and minimum dataset

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ABSTRACT

Introduction: Surgery for colorectal cancer is associated with post-operative morbidity and mortality. Multiple systematic reviews have reported on individual factors affecting short-term outcome following surgical resection. This umbrella review aims to synthesize the available evidence on host and other factors associated with short-term post-operative complications.

Methods: A comprehensive search identified systematic reviews reporting on short-term outcomes following colorectal cancer surgery using PubMed, Cochrane Database of Systematic Reviews and Web of Science from inception to 8th September 2020. All reported clinicopathological variables were extracted from published systematic reviews.

Results: The present overview identified multiple validated factors affecting short-term outcomes in patients undergoing colorectal cancer resection. In particular, factors consistently associated with post-operative outcome differed with the type of complication; infective, non-infective or mortality. A minimum dataset was identified for future studies and included pre-operative age, sex, diabetes status, body mass index, body composition (sarcopenia, visceral obesity) and functional status (ASA, frailty). A recommended dataset included antibiotic prophylaxis, iron therapy, blood transfusion, erythropoietin, steroid use, enhance recovery programme and finally potential dataset included measures of the systemic inflammatory response

Conclusion: A minimum dataset of mandatory, recommended, and potential baseline variables to be included in studies of patients undergoing colorectal cancer resection is proposed. This will maximise the benefit of such study datasets.

Introduction

Colorectal cancer is the second leading cause of cancer death worldwide, with an estimate of 1.8 million new cases diagnosed and almost 900 000 deaths in 2018. Despite a trend for reduction in the rate of colorectal cancer mortality, the incidence has increased over the last four decades. The World Health Organisation International Agency for Research on Cancer estimates a global incidence of colorectal cancer of 30 million by 2040[1]. In the United Kingdom, 42 081 new cases were diagnosed in 2017[2]. This represents 11% of all new cancer cases reported in 2017, making it the fourth most common cancer.

Surgical resection remains, for most of the population the primary curative mode of treatment however carries with it potential morbidity and mortality. The overall mortality rate following colorectal cancer resection ranges between 3% and 16%[3] while morbidity rates has been reported up to 35%[4]. Extensive research efforts have been focused to identify factors contributing to post-operative complications. These efforts are necessary to address the significant post-operative morbidity in this population as well as the emerging emphasis on standardised outcome measures to compare surgical quality across hospitals.

Post-operative complications can be defined as " any variation from the normal post-operative course" and classified by severity such as those described in the Clavien - Dindo classification[5, 6] or by type (infective versus non-infective). The classification of complications plays an important role in clinical and research practice as it allows the ability to directly compare, compile outcomes such as those in meta-analysis and demonstrate linkage between risk factors and specific

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post-operative complications.

Risk predictive tools such as P-POSSUM[7], SORT[8], NELA[9] and the speciality specific CR-POSSUM[10] provides an estimate of the 30-day morbidity and mortality risk to allow better informed decision making before surgery. Nevertheless, most surgical risk assessment tools utilise only some of the information available about the patient's health and the proposed surgery to provide estimates of risk and may not serve as an individual patient specific estimate. There may be other patient-specific or surgical factors that influence the risk of death significantly which are not accounted for.

Previous studies have reported that host factors (age, gender), tumour factors (cancer stage) and surgical factors (technical approach) play a role in affecting the short-term outcomes in surgery[11]. Surgery stimulates the release of pro-inflammatory cytokine that triggers a systemic inflammatory response[12]. Recent studies have demonstrated an association between post-operative systemic inflammatory response, post-operative complications, and long-term survival [13, 14]. Studies have also reported that the presence of preoperative systemic inflammatory response predisposes to post-operative complication for patients undergoing colorectal cancer surgery[15] which in turn have an effect on the long term survival outcome [16–19].

The systemic inflammatory response can be measured using acute phase proteins such as the modified Glasgow Prognostic Score (mGPS) [20] or haematological makers such as the neutrophil to lymphocyte ratio (NLR)[21]. In patients who have undergone curative colorectal cancer resection, the presence of an enhance inflammation response as measured by an elevated NLR or mPGS is associated with poorer outcomes[22].

In order to reduce post-operative complications and therefore improve both short-term and long-term outcomes, it is important to identify which factors are associated with post-operative complications. The aim of the present review was to identify prognostic host and other preoperative variables that are associated with post-operative complications. This will enable a minimum data set of prognostic variables to facilitate comparison of clinical management of colorectal cancer.

Methods

On an initial search of available literature, a large number of studies ($n > 14{,}000$) were identified. It was clear that several variables were already examined on multiple occasions and included in systematic reviews. Therefore, the approach taken was to examine systematic reviews of all validated variables rather than the individual publications. This overview of systematic reviews was conducted to assess the relationship between the host and other factors, and short- term post-operative complications.

The literature search was carried out in PubMed, Cochrane Database of Systematic Reviews (CDSR) and Web of Science (WoS) databases from inception to 8 September 2020. The following search term was used in free text and medical subject heading (MeSH) "(colon or colorectal) AND (cancer or neoplasm) AND (surgery or resection or operation) AND (complication or morbidity) AND (outcome)".

The title and abstracts of all systematic reviews returned by the search was examined for relevance. Only systematic reviews were included. Reviews not available in English and reviews published in abstract form only were excluded. Where there were multiple reviews from the same group only the most recent paper was included.

The full text of each systematic review deemed potentially relevant was obtained. Systematic reviews which included studies with non-cancer patients were also eligible if they made up less than 50% of the study population. Reviews were excluded if characteristics of individual studies were not reported. Once further exclusions outlined below were carried out, bibliography of relevant reviews was hand searched to include additional systematic reviews.

To be included, a systematic review had to examine the relationship between short-term outcomes and colorectal cancer surgery in terms of either 30-day mortality, infective complications, non-infective complications, or severity of complications defined by the Clavien- Dindo classification. Reviews on surgical factors were excluded to focus on host and preoperative factors. Any uncertainties were resolved with discussion with senior author (DM).

This umbrella review has been performed in accordance with PRISMA guidelines (Fig. 1). The data extraction in the form of a table was used to summarise study results. The following information from eligible systematic reviews were extracted: author, review aims, databases searched, years included, study design, number of studies included, total study population, outcomes measures (30-day mortality, infective complication, non-infective complications or Clavien-Dindo classification) and outcome of risk of bias assessments. The systematic reviews were grouped according to host or preoperative factors. A narrative review was performed to synthesise existing systematic reviews.

Results

Literature search

The initial search strategy identified 698 systematic reviews whose titles and abstracts were reviewed. Four further reviews were identified from searching the bibliography of included reviews and duplicates were removed ($n = 3$). At screening 513 reviews were excluded, of which were not in English ($n = 9$), were not relevant to topic or included pathologies other than colorectal cancer ($n = 504$). This led to a review of 186 full publications, of these excluded reviews included reviews that did not assess short-term outcomes ($n = 16$), reviews of operative factors ($n = 94$), reviews which included more than 50% benign colorectal disease ($n = 29$), and reviews which did not specify study population ($n = 14$). A total of 47 articles were included in this overview.

Age

Four reviews examined the relationship between age and short-term outcomes (Table 1). One review[23] included mostly open colorectal resection as open surgery was the norm during the period of study[23], one review included only laparoscopic resections[24], one review included two randomised control trials with sub-analysis on age comparing outcomes of laparoscopic versus open surgery[25] and one review examined the risk factor for anastomotic leak[26].

Nine short-term outcomes were reported across all systematic reviews.

Three reviews[23–25] examined the association between age and 30-day mortality, two [24, 25] of which reported no association, including the most recent of the reviews[24].

Two reviews [24, 25] examined the association between age and overall morbidity, both reviews reported an increase in overall morbidity in the elderly population. Three reviews [23, 24, 26] examined the association between age and anastomotic leak, all reviews reported no association. Two reviews [23, 24] examined the association between age and pulmonary complications, the more recent[24] of the two reported no association. One review [24] examined the association between age and wound infection, the review reported no association.

One review [23] examined the association between age and cerebrovascular complications, the review reported an increase in cerebrovascular complication in the elderly population. Two reviews [23, 24] examined the association between age and cardiac complications, the more recent of the two reported no association. One review [23] examined the association between age and venous thromboembolism, the review reported no association. One review [24] examined the association between age and post-operative ileus, the review reported no association.

Therefore, age was inconsistently associated with short-term outcomes in patients undergoing surgery for colorectal cancer.

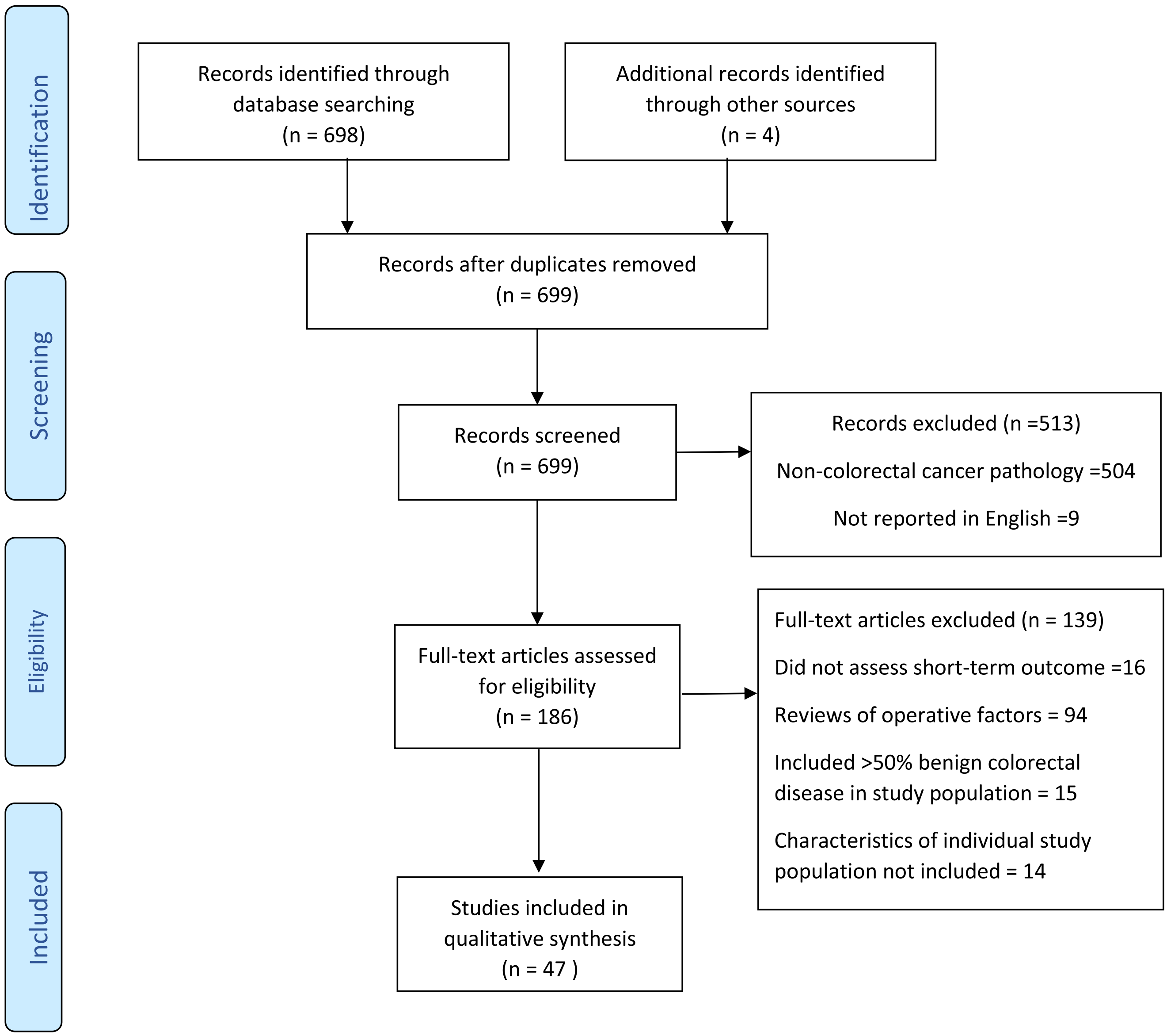

Fig. 1. PRISMA flowchart demonstrating study selection.

Sex

Two reviews examined the relationship between sex and short-term outcomes (Table 2). One review[27] examined the association with surgical site infection and one review[26] examined the association with risk factors for anastomotic leak. Two short-term outcomes were reported across all systematic reviews.

One review[27] examined the association between sex and surgical site infections, the review reported an increased risk of surgical site infections in males. One review[26] examined the association between sex and risk of anastomotic leak, the review reported increased risk of anastomotic leak in males.

None of the reviews examined the association between sex and non-infective complications.

Therefore, sex was inconsistently associated with short-term outcomes in patients undergoing surgery for colorectal cancer.

Diabetes

Two reviews examined the relationship between diabetes and short-term outcomes (Table 3).

Four short-term outcomes were reported across all systematic reviews.

One systematic review[28] examined the association between diabetes and 30-day mortality, the review reported increased 30-day mortality in diabetics.

One review[28] examined the association between diabetes and anastomotic leak, the review reported increased risk of anastomotic leak in diabetics. One review[27] examined the association between diabetes and surgical site infections, the review reported increased surgical site infections in diabetics.

One review[27] examined the association between diabetes and cardiovascular complications, the review reported increased cardiovascular complication in diabetics.

Therefore, diabetes was consistently associated with short-term outcomes in patients undergoing surgery for colorectal cancer.

Body composition and nutritional status (Body mass index, visceral obesity, and sarcopenia)

Nine reviews examined the relationship between body composition or nutritional status and short-term outcomes (Table 4). Four reviews

Table 1
Characteristics for systematic reviews on age.

Review year	Review aim	Database searched (Years included) [Type of study]	Number of studies (Number participants) [Tumour location]	Outcomes	Results (Meta-analysis) (P value)	Risk of bias assessment
Hoshino 2019 [24]	Lap for elderly versus non- elderly	PubMed, Scopus, Cochrane. (−14 October 2017) [Observational studies]	22 studies (5466) [Colorectal]	30-day mortality	No significant difference (RD 0.00, 95% CI 0.01, 0.01)(p = 0.89)	Risk of Bias in Non-Randomised Study-High risk of bias from confounding and lack of blinding of outcome assessments
				Overall morbidity	Assoc between > morbidity with elderly (RR 1.20, 95% CI 1.08, 1.34)($p < 0.01$)	
				Wound infection	No significant difference (RR 1.29, 95% CI 0.97, 1.71)(p = 0.08)	
				Anastomotic leak	No significant difference (RR 1.24, 95% CI 0.86, 1.80)(p = 0.25)	
				Pulmonary complication	No significant difference (RR 1.41, 95% CI 0.71, 2.82)(p = 0.33)	
				Post-operative Ileus	No significant difference (RR 1.47, 95% CI 0.83, 2.62)(p = 0.19)	
				Cardiac complication	No significant difference (RR 1.68, 95% CI 0.79, 3.54)(p = 0.18)	
Moug 2015 [25]	Lap versus open in elderly	Medline, Cochrane, Embase. (-December 2014) [RCT]	2 studies (1386) [Colorectal]	30-day mortality	No significant difference. (Narrative)	Jadad score -moderate quality
				Overall morbidity	Assoc between > morbidity and elderly (Narrative)	
Pommegaard 2014[26]	Risk factors for anastomotic leak and colorectal cancer surgery	Medline, CINAHL, Embase (−27 September 2012) [Observational studies]	23 studies (110,272) [Colorectal]	Anastomotic leak	No significant difference (OR 0.99, 95% CI 0.89, 1.10)(p = 0.87)	Newcastle-Ottawa Scale-high quality
Simmonds 2000[23]	Elderly vs non elderly	Medline, Embase, CancerLit, Cochrane, CINAHL, Healthstar, Science citation index, Edina Biosis, NHS Economic Evaluation database, Index to scientific and technical proceeding and Pascal. (-July 1998) [Observational studies]	28 studies (34,194) [Colorectal]	30-day mortality	Assoc between > mortality and elderly. (Narrative review)	Downs and Black checklist-not reported
				Anastomotic leak	No significant difference (p = 0.2607)	
				Pulmonary complication	Assoc between > pulmonary complication and elderly ($p < 0.0001$)	
				Cardiac complication	Assoc between > cardiac complication and elderly ($p < 0.001$)	
				Stroke	Assoc between > stroke and elderly ($p < 0.0001$)	
				DVT/PE	No significant difference (p = 0.0004)	

Assoc=association, CI=Confidence interval, CINAHL=Cumulative Index to Nursing and Allied Health Literature, DVT=deep vein thrombosis, Lap=laparoscopic, MD=Mean difference, OR=odds ratio, PE=pulmonary embolism, RCT=Randomised control trial, RD=Risk difference, RR=Relative risk, VS=versus, WOS=Web of Science.

examined the association with body mass index [26, 27, 29, 30], two reviews examined the association with visceral obesity [31, 32], one review examined the association with sarcopenia[33], one review examined the association with both sarcopenia and visceral obesity[34] and one review examined the association with a preoperative prognostic nutritional index[35]. Seven short term outcomes were reported across all systematic reviews.

Two reviews [33, 34] examined the association between sarcopenia and 30-day mortality, the reviews reported increased 30-day mortality with sarcopenia.

One review[30] examined the association between body mass index and overall morbidity, the review reported increased overall morbidity with high body mass index. Three reviews [31, 32, 34] examined the association between visceral obesity and overall morbidity, all reviews reported increased overall morbidity with visceral obesity. Two reviews [33, 34] examined the association between sarcopenia and overall morbidity, both reviews reported increased overall morbidity with sarcopenia. One review[35] examined the association between prognostic nutritional index and overall morbidity, the review reported increased overall morbidity with low prognostic nutritional index. Two reviews

Table 2
Characteristics for systematic reviews on sex.

Review year	Review aim	Database searched (Years included) [Type of study]	Number of studies (Number participants) [Tumour location]	Outcomes	Results (Meta-analysis) (P value)	Risk of bias assessment
Xu 2020[27]	Surgical site infection in colorectal cancer surgery	PubMed, Cochrane, Embase (−18 March 2020) [Comparative studies]	15 studies (60,229) [Colorectal]	Surgical site infections	Assoc between >SSI and male (OR 1.24, 95% CI 1.14, 1.34) ($p < 0.0001$)	Newcastle Ottawa Scale-moderate to high quality
Pommegaard 2014[26]	Risk factors for anastomotic leak and colorectal cancer surgery	Medline, CINAHL, Embase (−27 September 2012) [Observational studies]	23 studies (110,272) [Colorectal]	Anastomotic leak	Assoc between > anastomotic leak and male gender (OR 1.48, 95% CI 1.37, 1.60) ($p < 0.00001$)	Newcastle-Ottawa Scale-high quality

Assoc=Association, CI=Confidence interval, CINAHL=Cumulative Index to Nursing and Allied Health Literature, OR=odds ratio, WOS=web of science, SSI=surgical site infection.

Table 3
Characteristic for systematic reviews on diabetes.

Review year	Review aim	Database searched (Years included) [Type of study]	Number of studies (Number participants) [Tumour location]	Outcomes	Results (Meta-analysis) (P value)	Risk of bias
Xu 2020 [27]	Surgical site infection in colorectal surgery	PubMed, Cochrane, Embase (−18 March 2020) [Observational studies]	15 studies (60,229) [Colorectal]	Surgical site infections	Association between > SSI and diabetes (OR 1.34, 95% CI 1.1,1.64) ($p = 0.004$)	Newcastle Ottawa Scale-moderate to high quality
Stein 2010 [28]	Diabetes and colorectal cancer	Medline, Embase (- October 2008) [Observational studies]	4 studies (33,518) [Colorectal]	30-day mortality	Association between > mortality and diabetes (Narrative)	Not assessed
				Anastomotic leak	Association with > anastomotic leak and diabetes (Narrative)	
				Cardiovascular complication	Association with > cardiovascular complication (Narrative)	

CI=Confidence interval, OR=odds ratio, SSI=surgical site infection.

[27, 30, 36] examined the association between body mass index and wound infections, both reviews reported increased wound infection with high body mass index. Two reviews [32, 34] examined the association between visceral obesity and wound infections, one review[32] reported increased wound infection with visceral obesity while the other review [34] was inconclusive. One review[33] examined the association between sarcopenia and wound infection, the review reported no association. One review[27] examined the relationship between body mass index and surgical site infections, the review reported increased surgical site infection with higher body mass index. Two reviews [26, 30] examined the association between body mass index and anastomotic leak, one review[30] reported increased anastomotic leaks with higher body mass index. Two reviews [32, 34] examined the association between visceral obesity and anastomotic leak, one review reported increased anastomotic leaks with visceral obesity[32] while the other review was inconclusive[34]. One review[33] examined the association between sarcopenia and anastomotic leak, the review reported no association. One review examined the relationship between body mass index and intraabdominal collection, the review reported increased intraabdominal collections with higher body mass index[29]. One review examined the relationship between preoperative prognostic nutritional index and severe complications, the review reported an increased risk of serious complications with a low prognostic nutritional index[35].

None of the reviews examined the association between body composition and non-infective complications.

Therefore, body composition was consistently associated with short-term outcomes in patients undergoing surgery for colorectal cancer.

Functional status (ASA, functional capacity, frailty)

Four systematic reviews examined the relationship between functional status and short-term outcomes (Table 5). Two reviews [26, 27] examined the relationship with the American Society of Anaesthesiology physical status classification system (ASA), one review[37] examined the relationship with frailty and one review[38] examined the relationship with functional capacity testing. Eight short-term outcomes were reported across all reviews.

One review[38] examined the association between functional capacity and 30-day mortality, the review reported no association. One review[37] examined the association between frailty and 30-day mortality, the review reported no association.

One review[38] examined the association between functional capacity and overall morbidity, the review reported reduced overall morbidity with good functional capacity. One review[37] examined the association between frailty and overall morbidity, the review reported increased overall morbidity with frailty. One review[27] examined the association between ASA and surgical site infection, the review reported increased surgical site infections with higher ASA status. One review [38] examined the association between functional capacity and infective complications, the review reported reduced infective complications with good functional capacity. One review[37] examined the association between frailty and postoperative sepsis, the review reported an increased postoperative sepsis with frailty. One review[26] examined the association between ASA and anastomotic leak, the review reported reduction in anastomotic leak with lower ASA status. One review[38] examined the association between functional capacity and pulmonary complications, the review reported reduced pulmonary complication with good functional capacity.

One review[38] examined the association between functional capacity and wound dehiscence, the review reported reduced wound dehiscence with good functional capacity. One review[37] examined the association between frailty and readmissions, the review reported increased readmissions with frailty.

Therefore, ASA status, frailty and functional capacity was inconsistently associated with short-term outcomes in patients undergoing surgery for colorectal cancer.

Table 4
Characteristics for systematic reviews on body composition.

Review year	Review aim	Database searched (Years included) [Type of study]	Number of studies (Number participants) [Tumour location]	Outcomes	Results (Meta-analysis) (P value)	Risk of bias
Xu 2020 [27]	Surgical site infection in colorectal surgery	PubMed, Cochrane, Embase (−18 March 2020) [Comparative studies]	15 studies (60,229) [Colorectal]	Surgical site infection	Assoc between > SSI and obesity (BMI) (OR 1.59, 95% CI 1.4,1.81) ($p < 0.00001$)	Newcastle Ottawa Scale-moderate to high quality
Almasaudi 2018[29]	BMI and Postoperative surgical site infection	Medline, PubMed, Embase, Web of Science (- August 2016) [All studies]	16 observational (9535) [Colorectal]	Wound infection	Assoc between > wound infection with >BMI (BMI >25 OR 1.63, 95% CI 1.29, 2.06) ($p < 0.001$) (BMI >30 OR 2.13, 95% CI 1.66, 2.72) ($p < 0.001$)	Not assessed
				Intraabdominal collection	Assoc between > intraabdominal collection with > BMI (OR 1.5, 95% CI 1.08, 2.07) ($p = 0.01$)	
Fung 2017[30]	BMI and lap surgery	Embase, CINAHL, Global Health, BIOSIS, Web of Science, Scopus, Cochrane, DARE(- Oct 2014) [All studies]	13 observational studies (4550) [Colorectal]	Overall morbidity	Assoc between > morbidity and > BMI (OR 1.54, 95% CI 1.21, 1.97) ($p = 0.0005$)	MINORS criteria-moderate to high quality
				Wound infection	Assoc between > infection and > BMI (OR 2.43, 95% CI 1.46, 4.03) ($p = 0.0006$)	
				Anastomotic leak	Assoc between > anastomotic leak and > BMI (OR 1.65, 95% CI 1.01, 2.71) ($p = 0.05$)	
Pommegaard 2014[26]	Risk factors for anastomotic leak (BMI) and colorectal surgery	Medline, CINAHL, Embase (−27 September 2012) [Observational studies]	23 studies (110,272) [Colorectal]	Anastomotic leak	No significant difference (OR 1, 95% CI 0.93, 1.07) ($p = 0.95$)	Newcastle-Ottawa Scale - high quality
Malietzis 2014 [34]	Computerised tomography body composition (sarcopenia or visceral obesity) and colorectal surgery	Medline, Embase, Google scholar, Cochrane database (Jan 199–March 2014) [All studies]	16 observational studies (2672) [Colorectal]	30-day mortality	Assoc between > 30-day mortality and sarcopenia (Narrative)	Modified SIGN guideline-moderate quality
				Overall morbidity	Assoc between > overall morbidity and sarcopenia. Assoc between > overall morbidity and visceral obesity in colon cancer (Narrative)	
				Wound infection	3 studies association between > wound infection and visceral obesity.2 studies reported no difference (Narrative)	
				Anastomotic leak	3 out of 4 studies reported no difference between anastomotic leak and visceral obesity (Narrative)	
Cakir 2015 [31]	Visceral obesity and colorectal surgery	Medline, Embase, Cochrane (- 4 April 2014) [All studies]	7 studies (1230) [Colorectal]	Overall morbidity	Assoc between < morbidity and non-viscerally obese (RD 0.15, 95%CI 0.1, 0.21) ($p < 0.00001$)	Cochrane Collaboration tool-low quality
Yang 2015 [32]	Visceral obesity and lap surgery	PubMed, EMBASE, Cochrane Library (2000–2014) [All Studies]	4 Observational studies (659) [Colorectal]	Overall morbidity	Assoc between > morbidity and visceral obesity (OR 2.33, 95% CI 1.56, 3.48) ($p < 0.0001$)	Not assessed
				Wound infection	Assoc between > infection and visceral obesity (OR 3.22, 95% CI 1.95,5.32) ($p < 0.00001$)	
				Anastomotic leak	No significant difference (OR 2.4,95% CI 1.06,5.44) ($p = 0.04$)	
Sun 2018 [33]	Sarcopenia and colorectal cancer	PubMed, Embase, Web of Science (- 4 April 2018) [All studies]	12 observational studies (5337) [Colorectal]	30-day mortality	Assoc between > mortality and sarcopenia (OR 3.45, 95%CI 1.96.7.02) ($p < 0.01$)	Newcastle Ottawa Scale – moderate quality
				Overall morbidity	Assoc between> morbidity with sarcopenia (OR 1.7, 95% CI 1.07, 2.7) ($p < 0.01$)	
				Wound infection	No significant difference (OR 2.21, 95% CI 1.5, 3.25) ($p = 0.9444$)	
				Anastomotic leak	No significant difference (OR 0.73,95% CI 0.51,1.05)($p = 0.417$)	
Sun 2019[35]	Preoperative prognostic nutritional index and colorectal surgery	PubMed, Embase, WOS (- Oct 2018) [Comparative studies]	10 studies (6372) [Colorectal]	Overall morbidity	Assoc between > morbidity and low prognostic nutritional index	Newcastle Ottawa Scale –high quality
				Severe complications	Assoc between > serious complication and low prognostic nutritional index	

Assoc=Association, BMI=Body mass index, CINAHL=Cumulative Index to Nursing and Allied Health Literature CI=Confidence interval, Lap=Laparoscopic, OR=Odds ratio, RD=Risk difference, SSI=Surgical site infection, WMD=weighted mean difference, UTI=Urinary tract infection.

Table 5
Characteristics for systematic reviews on functional status.

Review year	Review aim	Database searched (Years included) [Type of study]	Number of studies (Number participants)[Tumour location]	Outcomes	Results (Meta-analysis) (P value)	Risk of bias
Xu 2020[27]	Surgical site infection in colorectal surgery	PubMed, Cochrane, Embase (−18 March 2020) [Comparative studies]	15 studies (60,229) [Colorectal]	Surgical site infection	Assoc between > SSI and > ASA (OR 1.22, 95% CI 1.12, 1.43) ($p < 0.00001$)	Newcastle Ottawa Scale-moderate to high quality
Lee 2018[38]	Functional capacity testing and colorectal cancer surgery	Medline, PubMed, Embase, CINAHL, and PEDro (-November 2017) [Cohort studies]	7 studies (1418) [Colorectal]	30-day mortality	No significant difference. (Narrative)	Newcastle-Ottawa scale and Jadad score- good quality
				Overall morbidity	Assoc between < morbidity and good functional capacity (OR 0.76, 95% CI 0.66, 0.85) ($p < 0.0001$)	
				Infective complication	Assoc between < infective complication and good functional capacity ($p < 0.01$)	
				Wound dehiscence	Assoc between < wound dehiscence and good functional capacity ($p<0.01$)	
				Pulmonary complication	Assoc between < pulmonary complication and good functional capacity ($p < 0.01$)	
Fagard 2016 [37]	Frailty and colorectal cancer surgery	Medline (2000–29 October 2015) [Cohort studies]	4 studies (486) [Colorectal]	30-day mortality	No significant difference (Narrative)	MINORS- good quality
				Overall morbidity	Assoc between > overall morbidity and frailty (Narrative)	
				Postoperative sepsis	Assoc between > postoperative sepsis and frailty (Narrative)	
				Readmission	Assoc between > readmission and frailty (Narrative)	
Pommegaard 2014[26]	Risk factors for anastomotic leak and colorectal surgery	Medline, CINAHL, Embase (−27 September 2012) [Observational studies]	23 studies (110,272) [Colorectal]	Anastomotic leak	Association between < anastomotic leak and low ASA (OR 1.71, 95% CI 1.09, 2.67) ($p = 0.02$)	Newcastle-Ottawa Scale- high quality

ASA=American society of Anaesthesiologist, CINAHL=Cumulative Index to Nursing and Allied Health Literature, CI=confidence interval, OR=odd ratio, SSI=surgical site infection.

Mechanical bowel preparation

Eight systematic reviews[39–46] examined the relationship between mechanical bowel preparation and short-term outcomes (Supplemental Material Table 1). All these reviews compared mechanical bowel preparation versus no preparation. Five short-term outcomes were reported across all reviews.

Five reviews [40–42, 44, 45] examined the association between 30-day mortality and mechanical bowel preparation, all reviews reported no association.

One review[45] examined the association between overall morbidity and mechanical bowel preparation, the review reported no association. Seven reviews[40–46] examined the association between wound infections and mechanical bowel preparations, six of the reviews[40–45] reported no association between wound infections and mechanical bowel preparation. Eight reviews[39–46] examined the association between anastomotic leak and mechanical bowel preparation, seven reviews [39–44, 46] reported no association. Five reviews [40, 42–45] examined the association between intraabdominal collection and mechanical bowel preparation, all reviews reported no association. Three reviews [40, 41, 44, 47–49] examined the association between reoperation and mechanical bowel preparation, all these reviews reported no association.

None of the reviews examined the association between mechanical bowel preparation and non -infective complications.

Therefore, mechanical bowel preparation was inconsistently associated with short-term outcomes in patients undergoing surgery for colorectal cancer.

Antibiotic prophylaxis

Two reviews examined the relationship between antibiotic prophylaxis and short-term outcomes (Supplemental Material Table 2). One review[50] examined the relationship between antibiotic prophylaxis in colorectal surgery and one review[51] examined the relationship between oral antibiotics and short term outcomes in the presence of mechanical bowel preparation and systemic antibiotics. Three short term outcomes were reported across all studies.

None of the reviews examined the association between antibiotic prophylaxis and 30-day mortality.

One review[50] examined the association between antibiotic prophylaxis and wound infection, the review reported reduced wound infection with antibiotic prophylaxis. One review[51] examined the association between oral antibiotic prophylaxis and wound infection in the presence of mechanical bowel preparation and systemic antibiotics, the review reported reduction in wound infections with oral antibiotics. One review examined the association between oral antibiotic prophylaxis and intraabdominal collection along with surgical site infections in the presence of mechanical bowel preparation and systemic antibiotics, the review

None of the reviews examined the association between antibiotic prophylaxis and non-infective complications.

Therefore, antibiotic prophylaxis was inconsistently associated with short-term outcomes in patients undergoing surgery for colorectal cancer.

Anaemia (Blood transfusion, iron and erythropoietin)

Five systematic reviews examined the association between management of anaemia and short-term outcomes (Supplemental Material 3). Three reviews [52, 53] examined the association between blood transfusion and short-term outcomes. Two reviews [54, 55] examined the association between iron therapy and blood transfusion requirement. One review[56] examined the association between erythropoietin and short-term outcomes. Nine short-term outcomes were reported across all studies.

One review[56] examined the association between 30-day mortality and erythropoietin, no association was reported.

One review[52] examined the association between overall morbidity and blood transfusions, the review reported increased overall morbidity with blood transfusion. Two reviews [52, 53] examined the association between infective complications and blood transfusion, both reviews reported an association between increased infective complications and blood transfusion. One review[52] examined the association between anastomotic leak and pulmonary complication with blood transfusion, the review reported increase in both anastomotic leak and pulmonary complication with blood transfusion. Two reviews [52, 53] examined the association between reoperation and blood transfusion, both reviews reported increased reoperation with blood transfusions.

Two reviews [54, 55] examined the association between iron therapy and blood transfusion requirement, the more recent[54] of the two reported an association between a reduction in blood transfusion requirement and iron therapy. One review[52] examined the association between blood transfusion and cardiac complications, the review reported an increase in cardiac complication with blood transfusion. One review[56] examined the association between erythropoietin and thrombotic complications, the review reported no association.

Therefore, blood transfusion, iron and erythropoietin were inconsistently associated with short-term outcomes in patients undergoing colorectal cancer surgery.

Enhance recovery programmes

Seventeen reviews examined the relationship between enhance recovery programmes and short-term outcomes (Supplemental Material Table 4). Five reviews[57–61] examined the association of enhanced recovery programmes versus conventional care, two review [62, 63] examined the association with physical prehabilitation, three reviews [64–66] examined the association with probiotic use, two reviews [67, 68] examined the association with chewing gum use, two reviews [69, 70] examined the association with nutritional prehabilitation, two review [71, 72] examined the combined effect of physical and nutritional prehabilitation and one review[73] examined the association with immunonutrition. Eleven short term outcomes were reported across all studies.

Four reviews [57–59, 61] examined the association between enhance recovery programme and 30-day mortality, all reviews reported no association. One review[69] examined the association between nutritional intervention and 30-day mortality, the review reported no association. One review[67] examined the association between gum chewing and 30-day mortality, the review reported no association.

Five reviews[57–61] examined the association between enhance recovery programme and overall morbidity, four reviews [57, 58, 60, 61] reported reduced overall morbidity with enhance recovery programmes. Two reviews [62, 63] examined the association between physical prehabilitation and overall morbidity, both reviews reported no association. Two reviews [69, 70] examined the association between nutritional prehabilitation and overall morbidity, both reviews reported reduced overall morbidity with nutritional prehabilitation. Two reviews [71, 72] examined the association between combined prehabilitation (physical and nutritional)with overall morbidity, one review[71] showed reduced overall morbidity with combined prehabilitation. One review[68] examined the association between gum chewing and overall morbidity, the review reported no association.

Three reviews[64–66] examined the association between probiotic use and infective complications, all three reviews reported reduction in infective complication with probiotic use. One review[73] examined the association between immunonutrition and infective complications, the review reported reduced infective complication with immunonutrition. Two reviews [57, 60] examined the association between enhance recovery programmes and wound infections, both reviews reported no association. Three reviews[64–66] examined the association between probiotic use and wound infections, two [64, 66] of the reviews reported no association. Two reviews [57, 60] examined the association between enhance recovery programmes and anastomotic leaks, both reviews reported no association. Two reviews [65, 66] examined the association between probiotic use and anastomotic leak, both reviews reported no association. One review[70] examined the association between nutritional prehabilitation and anastomotic leak, the review reported no association. Two reviews [65, 66] examined the association between probiotic use and pulmonary complications, both reviews reported reduction in pulmonary complications. One review[65] examined the association between probiotic use and urinary tract infection, the review reported no association. One review[57] examined the association between enhance recovery programmes and reoperation, the review reported no association. One review[68] examined the association between gum chewing and reoperation, the review reported no association.

Four reviews[58–61] examined the association between enhance recovery programmes and readmission, all reviews reported no association. One review[68] examined the association between gum chewing and readmission, the review reported no association. One review[69] examined the association between nutritional prehabilitation and readmission, the review reported no association. One review[57] examined the association between enhance recovery programme and post-operative ileus, the review reported reduction in post-operative ileus with enhance recovery programme. One review[67] examined the association between gum chewing and post-operative ileus, the review reported no association.

Therefore, enhance recovery programmes were inconsistently associated with short-term outcomes in patients undergoing colorectal cancer surgery.

Steroid use

One review examined the relationship between steroid use and short-term outcomes (Supplemental Material Table 5). The review[26] examined the association with anastomotic leak. One short-term outcome was reported in the review.

No review examined the association between steroid use and 30-day mortality. One review[26] reported increased anastomotic leak with steroid use. No review examined the association between steroid use and non-infective complications.

Therefore, steroid use is inconsistently associated with short-term outcomes in patients undergoing colorectal cancer resection.

Discussion

The present overview has identified several factors that are associated with the risk of developing infective complications including male sex, diabetes, high body mass index, visceral obesity, poor functional status, use of blood transfusion and steroids. While the presence of antibiotic prophylaxis, probiotic and immunonutrition use in enhance recovery programme was associated with reduction in infective complications. With reference to non-infective complications, the present overview identified that diabetes, poor functional status, and blood transfusions were associated with the risk of developing non-infective complications. Finally, the overview has identified factors that are consistently associated with 30-day mortality following colorectal cancer surgery including diabetes and sarcopenia. Therefore, these factors (in particular, those associated with 30-day mortality) should be included in a minimum dataset for future studies of post-operative outcomes in patients undergoing surgery for colorectal cancer.

In contrast, the present overview identified several factors that, on systematic review, were not consistently associated with post-operative outcomes including mechanical bowel preparation. Certain factors reported mixed outcomes associated with either 30-day mortality, infective or non-infective outcomes such as functional status, blood transfusions and enhance recovery programmes. These factors may be considered in addition to the minimum set of factors.

The presence of diabetes has commonly been associated with higher incidences of post-operative complications in cancer and non-cancer patients [74, 75]. The findings of the present overview is in keeping with a recent meta-analysis by [76] which have shown a higher rate of surgical site infection (OR 1.98; 95% CI 1.64–2.39; $p < 0.001$) and anastomotic leak (OR 2.41; 95% CI 1.84–3.16; $p < 0.001$) in diabetic compared to non-diabetic patients following surgery for both malignant and benign colorectal disease. The inflated risk of short term complications in diabetic patients may relate in part, to associated comorbidities such as hypertension, coronary heart disease, renal disease and metabolic effects of hyperglycaemia[77]. Nevertheless, the diagnosis of diabetes is a nexus to a cluster of comorbidities associated with poor post-operative outcomes. The prevalence of diabetes and impaired glucose tolerance has been steadily increasing over the decades[78] and is readily treated prior to surgery. Given in patients with colorectal cancer, identification of diabetes is of considerable importance, understanding the relationship between hyperglycaemia and colorectal cancer resection could aid in risk reduction of short-term outcomes especially in patients who have untreated or undiagnosed diabetes. Frisch et al.[79] reported that the risk of 30-day mortality increased with hyperglycaemia greater in non-diabetic patients compared to known diabetics for general and non-cardiac surgery patients while an observational study by [80], reported a higher risk of adverse event in non-diabetic patients compared to diabetic patents following surgery in the presence of hyperglycaemia (OR 1.63, 95% CI 1.27–2.10 for blood glucose > 180 mg/dL).

The National Institute of Health and Care Excellence (NICE) recommends the use of a suitable validated risk stratification tool to supplement clinical assessment preoperatively[81]. Nevertheless, diabetes is not universally taken into consideration by all risk assessment tools such as the P-POSSUM. The current recommendation by the World Health Organisation for the diagnosis of diabetes is either one of the four options including a random venous plasma glucose concentration (≥ 11.1 mmol/l), a fasting plasma glucose concentration (≥ 7.0 mmol/l), a two hour plasma glucose concentration (≥ 11.1 mmol/l) after an oral glucose tolerance test[82] or haemoglobin A1C (≥48 mmol/l or 6.5%)[83]. Several guidelines such as those from the National Institute Health and Care Excellence[84] as well as the Joint Association of British Clinical Diabetologists[85] recommends preoperative HbA1C levels within three months of surgery to identify diabetics who would benefit from optimisation but the National Confidential Enquiry into Patient Outcome and Death reports that only 64.6% of diabetics had levels check within 3 months of attending the pre-operative assessment clinic and of those 16% had HbA1c levels above the range recommended for surgery (HbA1C > 69 mmol/mol or >8.5%)[86]. Conversely, the guidelines do not recommend routine checks of HbA1C in patients not known to be diabetics[84]. The International Federation Diabetes estimates that 49.7% of people living with diabetes worldwide are undiagnosed in 2017[78] while the prevalence of diabetes in the surgical population is estimated at 15%. Kwon et al[87] found that general surgery patients with perioperative hyperglycaemia was associated with a nearly two-fold increase in the rate of surgical site infection and mortality in both diabetic and non-diabetic patients. This therefore raises the question of the proportion of patients which may benefit from management of hyperglycaemic prior to surgery.

In the present overview, various measurements of body composition have been identified as a prognostic variable for different short-term outcomes. Sarcopenia has been associated with reduced 30-day mortality and overall morbidity. While body mass index and visceral obesity has been associated with wound infection. These associations are likely a result of complex interaction between the host factors, metabolic and endocrine changes in the presence of cancer including systemic inflammation, insulin resistance and alterations in hormones. In the presence of increasing obesity prevalence in the global population[88], body mass index is likely to no longer represent the best indicator of cancer cachexia[89]. Computerised tomography assessment of body composition to characterise sarcopenia or visceral obesity are ideally required to offer a better measure [90, 91]. Cachexia is an important measurement of the physiologic reserve in cancer patients. The mechanism behind cancer cachexia is poorly understood but the effect is magnified by the subsequent surgical insult and therefore a potentially measurable and targetable prognostic area.

The present umbrella review synthesised the available evidence on factors associated with post-operative complications and allows for the application in the era of precision medicine. We have identified from the body of literature available that most validated factors have varying effects on short-term post-operative complications which we have broadly classified by type; infective, non-infective and 30-day mortality. The present review has identified those factors which have good evidence in terms of post-operative complications enabling careful patient selection using a minimum set of validated risk factors. We have chosen to focus on the preoperative risk factors and on this basis offer surgeons the pre-operative knowledge to decide on the potential impact of operative and treatment strategies.

There are several limitations in the current overview. Inevitably, a degree of heterogeneity exists between systematic reviews which limits qualitative comparison of the outcomes. A meta-analysis of systematic reviews was not performed due to significant heterogeneity of the study methodology and variation in outcome of systematic reviews. We found multiple reviews assessing similar prognostic variables however differences in reported outcomes have been detected across reviews. These differences are reflected by the interpretation of inclusion criteria and analysis. Synthesis of multiple reviews that include overlapping studies conversely contribute to potential overestimation of the strength of the findings therefore it is crucial to be mindful of the extent of evidence available on which the conclusion is based for a specific factor. All available systematic reviews were included in this overview irrespective of the quality, but most systematic reviews have performed either a risk of bias assessment or reported on the quality of studies included therefore the effect of this is expected to be minimal.

The present study included only systematic reviews therefore it likely that there are other modifiable factors not included as these have yet to be summarised in a systematic review. An area of interest with paucity on data relating to short term outcome is cancer associated systemic inflammatory response. It has been well recognised that inflammation related biomarkers play a prognostic role in predicting long term survival[92–94] however the effect on short term outcomes have yet to be quantified. Despite these limitations, the present overview has not imposed a restriction on period of included studies which allows for a stronger body of evidence on certain prognostic variables such as diabetes and body composition which have reported consistent association with short term outcomes over a wide timeline. Importantly, it forms a consistent basis for the introduction of a minimum and supplementary baseline variables to be collected prior to surgery for colorectal cancer (Table 6). This creates an opportunity for future work to improve on short-term outcomes following colorectal cancer surgery by modifying the variables in the three main prognostic areas identified: host, nutritional and functional aspects. It will also provide an opportunity for individualised tailored therapy by taking the patients' specific prognostic factors into consideration. Finally, it might prove beneficial to evaluate the interaction between those individual prognostic variables such as the influence of diabetes on body composition. The possibility of a similar inflammatory process driving both factors may have causative or synergic roles in affecting short term outcomes in colorectal resection.

Disclosure statement

The authors have no related conflicts of interest to declare.

Table 6
Minimum, recommended, and potential pre-operative baseline variables for collection in patients undergoing colorectal cancer resection.

Minimum pre-operative variables
- Age
- Sex
- Diabetes status
- Body mass index
- Body composition (sarcopenia/ visceral obesity)
- Functional status (ASA/ Frailty)
Recommended pre-operative variables
- Antibiotic prophylaxis
- Iron therapy
- Blood transfusion
- Erythropoietin
- Steroid use
- Enhance recovery programme
Potential pre-operative variables
- Systemic inflammatory response

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Chee Mei Cheong: Writing – original draft, Methodology, Investigation. **Allan M. Golder:** Methodology, Writing – review & editing. **Paul G. Horgan:** Resources. **Donald C. McMillan:** Supervision, Conceptualization, Writing – review & editing. **Campbell S.D. Roxburgh:** Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ctarc.2022.100544.

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