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SYSTEMATIC REVIEW

The use of preoperative enteral immunonutrition in patients undergoing elective colorectal cancer surgery: A systematic review and meta-analysis

Tyler McKechnie[1,2] | Tania Kazi[1] | Ghazal Jessani[3] | Victoria Shi[3] | Niv Sne[1,3] | Aristithes Doumouras[1,2,3] | Dennis Hong[1,3] | Cagla Eskicioglu[1,3]

[1]Division of General Surgery, Department of Surgery, McMaster University, Hamilton, Ontario, Canada

[2]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada

[3]Michael G. DeGroote School of Medicine, McMaster University, Hamilton, Ontario, Canada

Correspondence
Cagla Eskicioglu, Division of General Surgery, Department of Surgery, McMaster University, St Joseph's Healthcare, 50 Charlton Avenue East Hamilton, Ontario, L8N 4A6, Canada.
Email: eskicio@mcmaster.ca

Abstract

Aim: The present systematic review and meta-analysis aims to compare adult patients receiving enteral immunonutrition prior to elective colorectal surgery with those receiving conventional preoperative nutrition.

Methods: MEDLINE, Embase and the Cochrane Central Register of Controlled Trials were searched from database inception to March 2024. Articles were included if they were randomized controlled trials or cohort studies evaluating adult patients undergoing elective colorectal surgery comparing preoperative enteral immunonutrition with conventional preoperative nutrition protocols. Main outcomes of interest included surgical site infection, anastomotic leak, overall postoperative morbidity and postoperative length of stay. An inverse variance random effects meta-analysis was performed. Risk of bias was assessed with Cochrane risk of bias assessment tools. The GRADE approach was conducted to assess quality of evidence.

Results: After reviewing 2508 relevant citations, 10 studies met inclusion criteria. Overall, 1521 patients (mean age 64.9 ± 10.0 years, 49.4% women) received preoperative immunonutrition and 1816 patients (mean age 64.1 ± 11.0 years, 52.1% women) received conventional preoperative nutrition. Across seven studies, there was a non-significant 30% relative risk reduction of surgical site infection (risk ratio 0.70, 95% CI 0.44–1.11, $P = 0.13$, $I^2 = 33\%$) and a non-significant 44% relative risk reduction of anastomotic leak (risk ratio 0.56, 95% CI 0.28–1.10, $P = 0.09$, $I^2 = 0\%$) in the immunonutrition group. Across eight studies, postoperative length of stay was 0.48 days shorter in the immunonutrition group (mean difference −0.48, 95% CI −0.84 to −0.12, $P = 0.01$, $I^2 = 53\%$). GRADE certainty of evidence was low or very low for all outcomes.

Conclusion: While point estimates suggest a likely benefit associated with preoperative enteral immunonutrition, wide corresponding 95% CIs suggest uncertainty remains. Further prospective study is warranted.

KEYWORDS
colorectal cancer, colorectal surgery, immunonutrition, preoperative nutrition, systematic review

Tyler McKechnie and Tania Kazi are co-first authors and contributed equally.

INTRODUCTION

While perioperative protocols have significantly improved over the past several decades, the risk of experiencing postoperative morbidity such as infection continues to impact patients undergoing colorectal cancer surgery [1, 2]. Incidence of postoperative surgical site infection (SSI) can be as high as 22.5%, an especially worrisome statistic given the prevalence of colorectal cancer [2, 3]. Additionally, total lifetime treatment costs of colorectal cancer in Canada can range from $187 million to as high as $333 million Canadian dollars with over 60% of the lifetime costs being associated with hospitalization, highlighting the financial burden that postoperative complications place on both patients and healthcare systems alike [4].

Enhanced recovery after surgery (ERAS) guidelines have improved postoperative outcomes in patients undergoing colorectal surgery, recommending bundled preoperative, intraoperative and postoperative care packages specifically aimed at reducing postoperative morbidity and speeding postoperative recovery [5–7]. The most recent ERAS guidelines for elective colorectal surgery strongly recommend preoperative nutritional screening and preoperative nutritional supplementation based on low and moderate certainty of evidence, respectively [5, 8]. Nonetheless, approaches to preoperative nutritional optimization are variable, with none uniformly recommended.

Immunonutrition products, composed of arginine, omega-3 fatty acids, glutamine and/or nucleotides, are often advertised as effective agents for reducing negative clinical outcomes like infection and inflammation amongst colorectal cancer patients [9–15]. Parenteral and enteral forms are available [16]. While studies have begun exploring the role of immunonutrition in preoperative care, demonstrating both safety and efficacy, immunonutrition has yet to become the standard of care for elective colorectal cancer surgery. Systematic reviews and meta-analyses have published data examining the pooled effect of preoperative immunonutrition in this population [9]. However, there have been recent randomized controlled trials (RCTs) and large observational studies since the most recent data synthesis [10, 11]. Moreover, most past systematic reviews primarily focused on both enteral and parenteral immunonutrition both prior to and following colorectal surgery [9–15, 17, 18]. Our study aims to update these and compare adult patients receiving enteral immunonutrition prior to elective colorectal surgery to those receiving conventional preoperative nutrition.

MATERIALS AND METHODS

This systematic review and meta-analysis are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA; Appendices S1 and S2) [19]. The study protocol was registered on the International Prospective Register for Systematic Reviews (PROSPERO) a priori (CRD42022379834). Local ethics review board approval was not required.

Search strategy

MEDLINE, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched from inception through March 2024. The search was designed and conducted by a medical research librarian with input from study investigators. Search terms included 'colorectal cancer', 'immunonutrition' and more (complete search strategy available in Appendices S3 and S4). References of published studies and grey literature were manually searched.

Study selection

Articles were eligible for inclusion if they were RCTs, prospective cohort studies or retrospective cohort studies evaluating adult patients (i.e., over the age of 18) undergoing elective colorectal surgery comparing preoperative enteral immunonutrition with conventional preoperative nutrition protocols/control and reporting any of the outcomes of interest. Enteral immunonutrition was defined as dietary supplementation solutions containing one or more of the following: arginine, glutamine, omega-3 fatty acids, nucleotides [20]. Articles written in any language were considered for inclusion. Conference abstracts were eligible for inclusion. Studies including patients receiving parenteral immunonutrition, paediatric patients, patients undergoing non-colorectal cancer surgeries and patients undergoing emergency surgery were excluded. Studies with a comparison group also receiving immunonutrition as well as studies evaluating immunonutrition in the context of the ERAS protocol and not reporting outcome data specific for nutrition were also excluded. Single-arm, non-comparative studies, as well as case–control studies, case series, case studies, surveys or any study not reporting primary data were excluded.

Outcomes assessed

The outcomes assessed were SSI, anastomotic leak, postoperative genitourinary (GU) complication, postoperative respiratory complication, overall postoperative morbidity, postoperative length of stay (LOS) and 30-day readmission. SSI was defined according to the Centers for Disease Control and Prevention classification of SSIs [21]. If a study did not report overall SSI, the following order of priority for infective outcomes was used to represent the event rate: (i) organ or space SSI, (ii) deep incisional SSI, (iii) superficial incisional SSI. Anastomotic leak was defined as communication between the intraluminal and extraluminal compartments of the site of surgical anastomosis resulting from defect of the intestinal wall, identified radiologically or intraoperatively [22]. For our purposes, overall postoperative morbidity was defined as any deviation from the expected postoperative course as reported by each included study. If studies did not report overall morbidity as a pooled outcome, the outcome was reported as missing. Similarly, other outcomes from the primary studies were excluded if they were deemed to be dissimilar to our pre-defined outcomes by members of

the study team. Postoperative LOS was defined as the number of days from the index procedure to the time the patient left an acute care bed. Thirty-day readmission was defined as readmission to hospital reported within 30 days of the index surgery.

Data extraction

Three reviewers (TK, GJ, VS) independently screened the systematically searched titles and abstracts using a standardized, pilot-tested form on Covidence. Discrepancies in the title and abstract screening phases were resolved by inclusion. At the full-text screening stage, discrepancies were resolved by consensus between the three reviewers. If disagreement persisted, a fourth reviewer (TM) was consulted. Three reviewers (TK, GJ, VS) independently and in duplicate conducted data extraction into a data collection form designed a priori and pilot tested on Microsoft Excel©. The extracted data included study characteristics (e.g., author, year of publication), patient demographics (e.g., age, gender, diagnosis), intervention characteristics (e.g., immunonutrition components), postoperative outcomes (e.g., SSI, anastomotic leak, overall postoperative morbidity) and healthcare cost (i.e., total inpatient healthcare cost).

Risk of bias assessment and certainty of evidence

Risk of bias was assessed using the Cochrane Risk of Bias Tool for Randomized Controlled Trials 2.0 and the Non-randomized Studies of Interventions (ROBINS-I) assessment tool for RCTs and observational studies, respectively [23, 24]. Three reviewers assessed the risk of bias and quality of these studies independently. Discrepancies were discussed until consensus was reached.

Certainty of evidence for estimates derived from meta-analyses was assessed by Grading of Recommendations, Assessment, Development and Evaluation (GRADE), scored as high, moderate, low or very low for each outcome according to six pre-specified categories (i.e., risk of bias, inconsistency of results, directness of evidence, imprecision, publication bias and other) [25]. These results were ultimately collated in a summary of findings table using the GRADEPro software [26].

Statistical analysis

Statistical analyses were performed on STATA version 15 (StataCorp, College, TX, USA) and DataParty (Hamilton, ON, Canada). The threshold for statistical significance was set a priori at $P < 0.05$. A pairwise meta-analysis was performed using an inverse variance random effects model for all comparative data stratified based on type of study (i.e., randomized study vs. non-randomized study). If an event rate was very low (i.e., < 5%) then a Mantel–Haenszel random effects model was used for comparative dichotomous data. A fixed effects model was used if a small study bias was suspected. Pooled effect estimates for binary outcomes were estimated by calculating the risk ratio (RR) along with the respective 95% CI. Pooled effect estimates for continuous outcomes were estimated with mean difference (MD) along with the respective 95% CI. Mean and SD were estimated for studies that only reported median and interquartile range using the method described by Wan et al. [27]. Missing SD data were calculated according to the prognostic method [28]. Assessment of between-study heterogeneity was done using the inconsistency (I^2) statistic. An I^2 greater than 40% was considered to represent considerable heterogeneity [29]. Bias in meta-analysed outcomes was assessed with funnel plots if over 10 studies were included in the meta-analysis [30]. A leave-one-out sensitivity analysis was performed iteratively, removing one study at a time from the inverse variance random effects model to ensure pooled effect estimates were not driven by a single study. Subgroup analysis was determined a priori and performed based on risk of bias (i.e., high vs. moderate/low). Planned subgroup analyses in the protocol that were not performed included operative approach (i.e., more than 50% minimally invasive vs. less than 50% minimally invasive), type of disease (i.e., more than 50% colorectal cancer vs. less than 50% colorectal cancer) and type of control (i.e., active vs. control/no intervention) due to a paucity of data.

RESULTS

Study characteristics

Database and registry searches identified 2572 relevant records. After excluding 16 duplicates, 2556 independent records were available for screening. Title and abstract screening excluded 2521 records. Four full texts were sought but not retrieved. After assessing 31 full texts for eligibility, two RCTs, seven cohort studies and one conference abstract were included [11–14, 31–36]. A PRISMA flow diagram of the study selection process is given in Figure 1. Excluded studies with their reason for exclusion are given in Table S1.

Study characteristics including demographics and a description of the preoperative immunonutrition regime for each included study are reported in Table 1. Included studies were conducted from 2006 to 2023. Overall, 1521 patients (mean age 64.9 ± 10.0 years, 49.4% women) received preoperative immunonutrition and 1816 patients (mean age 64.1 ± 11.0 years, 52.1% women) received conventional preoperative nutrition. Two studies specifically reported following ERAS protocols for all participants [34, 36].

Intervention details

There was significant between-study heterogeneity in type of immunonutrition formula used and preoperative regimen followed. Four studies reported using some variation of the Impact® brand

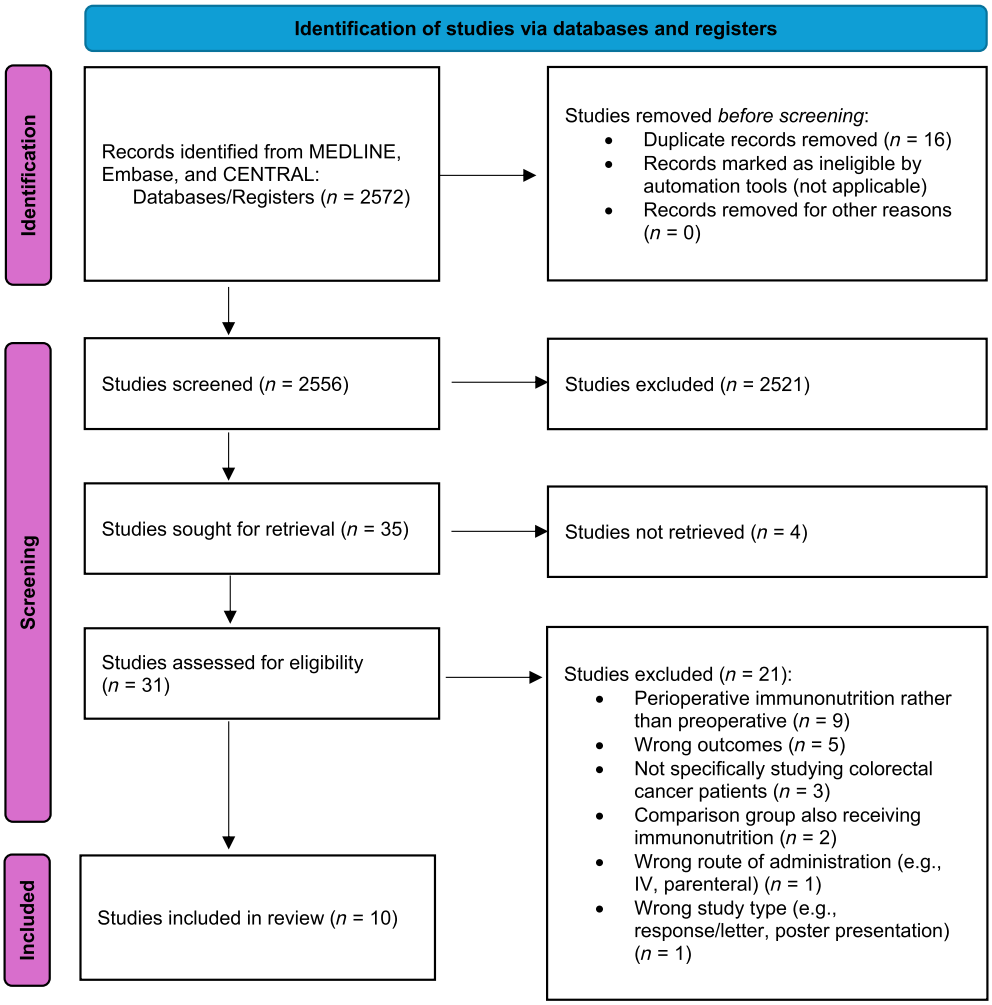

FIGURE 1 PRISMA diagram: transparent reporting of systematic reviews and meta-analysis flow diagram outlining the search strategy results from initial search to included studies.

of immunonutrition, whereas the remaining studies reported immunonutrition regimes involving some combination of arginine, omega-3 fatty acids and nucleotides. Seven studies utilized a 5-day preoperative course of immunonutrition, one study utilized a 7-day preoperative course of immunonutrition, one study utilized an 8-day preoperative course of immunonutrition and one study utilized a 10-day preoperative course of immunonutrition.

Control details

Most control groups received conventional preoperative care, following a normal preoperative diet. Tesauro et al. was the only study where the control group followed a specific preoperative diet, consisting of 3 days of high protein and low fibre, with clear fluids consisting of sugar/simple carbohydrates consumed up to 4 h before surgery [36]. Three studies specifically reported both mechanical and chemical bowel preparation for all participants [16, 17, 34].

Treatment characteristics

Treatment characteristics are reported in Table 2. The most common indication for colorectal surgery was colorectal cancer (55.0%). Most colorectal cancer surgeries were performed on Stage III tumours (37.2%). Most operations were performed laparoscopically (85.5%). There were no data reported on stoma rates across the 10 studies.

Postoperative outcomes

Postoperative outcomes for each of the individual included studies are reported in Table 3. Pooling from five studies, there was a non-significant 20% relative risk reduction in the risk of overall postoperative morbidity in the immunonutrition group (RR 0.8, 95% CI 0.57–1.12, $P = 0.20$, $I^2 = 64\%$; Figure 2). Subgroup analyses based on risk of bias could not be performed. Results were unchanged with leave-one-out sensitivity analysis.

TABLE 1 Study characteristics of included studies.

Study	Study type	*N* total	Inclusion	Description of immunonutrition	Arm	*N*	Mean age in years (SD)	*N* female (%)	Mean BMI (SD)	ASA score (%)	Preoperative serum albumin g/dL (SD)
Achilli, 2020 [31]	Single-centre retrospective analysis	130	Frail, CCI greater than or equal to 3, colorectal resection for cancer with curative intent between January 2014 and December 2017	10-day preoperative course of Impact® Oral (arginine, ω-3 fatty acids and nucleotides). Increased to 14-day preoperative course for patients identified as being at high nutritional risk (i.e., BMI less than 18.5 kg/m^2)	Immunonutrition	65	78.8 (6.0)	45 (44.6)	–	I–II: 48 (73.9) III–IV: 17 (26.2)	–
					Control	65	77.5 (6.9)	34 (46.2)	–	I–II: 48 (73.9) III–IV: 17 (26.2)	–
Banerjee, 2017 [32]	Retrospective cohort study	716	Patients 18 years of age or above who underwent elective colorectal surgery with anastomosis in a Washington hospital that participated in the S4S initiative between 2012 and 2013	5-day preoperative course of arginine-based nutrition supplement	Immunonutrition	151	58.8 (1.3)	74 (49.0)	26.0 (0.4)	–	–
					Control	565	60.2 (0.7)	331 (58.6)	28.7 (0.3)	–	–
Horie, 2006 [12]	Prospective study	67	Patients with CRC undergoing elective surgery without malnutrition, bowel obstruction, severe cardiopulmonary complications, diabetes, collagen disease or renal failure	5-day preoperative course of 750 mL/day Impact® Japanese version containing 9.6 g arginine, 2.49 g ω-3 fatty acids and 0.96 g ribonucleic acid	Immunonutrition	33	69.0 (9)	8 (24.2)	22.8 (2.9)	I: 13 (39.4); II: 20 (60.6)	4.1 (0.3)
					Control	34	63.0 (11)	16 (47.1)	22.8 (3.2)	I: 18 (52.9); II: 16 (47.1)	4.0 (0.3)
Lee, 2023 [11]	Randomized controlled trial	161	Patients 20–80 years of age with primary colon cancer who provided written informed consent to participate	7-day preoperative course of 400 mL/day of immunonutrient-enriched oral nutrition supplements with high protein levels, arginine and ω-3 fatty acids	Immunonutrition	79	65.3 (9.2)	23 (29.1)	24.4 (3.5)	–	4.4 (0.4)
					Control	82	65.3 (11.7)	32 (39.0)	24.1 (4.1)	–	4.3 (0.4)
Manzanares Campillo, 2017 [13]	Randomized controlled trial	84	Patients 18 years of age or above with CRC, scheduled and underwent intestinal resection surgery with curative intent (including resectable metastatic disease patients), signed informed consent for surgery and study	8-day preoperative course of 3 × 237 mL per day of Impact® Oral containing high proteins (L-arginine), carbohydrates, fats (ω-3 fatty acids), fibre, nucleotides, vitamins, trace elements	Immunonutrition	42	69.9 (11)	13 (31.0)	–	–	–
					Control	42	69.9 (11)	13 (31.0)	–	–	–
Ogilvie, 2023 [33]	Retrospective cohort study	826	Patients undergoing elective, major intra-abdominal colorectal surgery between January 2014 and December 2016 (control) and October 2017 and November 2019 (intervention) with a nutritional index in the 30 days prior to surgery	5-day preoperative course of 3 × 237 mL per day of Ensure Surgery, Abbott Laboratories, Abbott Park, Illinois, containing 18 g of protein and 4.2 g of arginine	Immunonutrition	514	60.6 (15.0)	282 (54.9)	28.8 (7.0)	I–II: 242 (47.3); III: 257 (50.2); IV–V: 13 (2.5)	–
					Control	312	59.9 (17.1)	174 (55.8)	27.9 (6.8)	I–II: 146 (46.8); III: 152 (48.7); IV-V: 14 (4.5)	–

(Continues)

TABLE 1 (Continued)

Study	Study type	*N* total	Inclusion	Description of immunonutrition	Arm	*N*	Mean age in years (SD)	*N* female (%)	Mean BMI (SD)	ASA score (%)	Preoperative serum albumin g/dL (SD)
Putrus, 2015 [34]	Retrospective cohort study	114	Patients seen by the colorectal clinical specialist consultant in pre-admission clinic and underwent elective colorectal surgery	5-day preoperative course of 3×237 mL per day of Impact Advanced Recovery® containing ω-3 fatty acids, nucleotides and arginine	Immunonutrition	57	–	–	–	–	–
					Control	57	–	–	–	–	–
Tang, 2023 [35]	Retrospective cohort study	106	Patients with rectal cancer who underwent neoadjuvant chemoradiotherapy and oncological resection between January 2013 and July 2022	5 or more days of preoperative glutamine supplementation (50–100 mL of 20% alanyl-glutamine once daily)	Immunonutrition	53	57.5 (11.0)	20 (37.7)	23.6 (2.7)	I: 6 (11.3); II: 29 (54.7); III: 18 (34.0)	4.1 (0.4)
					Control	53	57.2 (12.6)	19 (35.8)	22.7 (3.3)	I: 6 (11.3); II: 30 (56.6); III: 17 (32.1)	4.0 (0.5)
Tesauro, 2021 [36]	Retrospective cohort study	173	Patients 18 years of age or above, normo-nourished (MNA-SF score ≥ 12), diagnosed with primary colorectal carcinoma, underwent elective laparoscopic colorectal resection following ERAS, ASA I, II, III	5-day preoperative course of IN containing arginine and leptin, as well as a maltodextrin load a few hours before surgery	Immunonutrition	47	65.6 (12.2)	19 (40.4)	26.0 (3.5)	I: 9 (19.2); II: 27 (57.4); III: 11 (23.4)	4.0 (0.6)
					Control	126	66.3 (12.3)	49 (38.9)	25.6 (4.1)	I: 26 (20.6); II: 64 (50.8); III: 36 (28.6)	3.9 (0.5)
Thornblade, 2017 [14]	Prospective study	960	Adult patients who underwent colorectal surgery at a SCOAP hospital administering IN to at least 10 patients during the study period of 1 January 2012 to 30 June 2015	5-day preoperative course of 3×237 mL per day IN containing arginine and ω-3 fatty acids	Immunonutrition	480	58.4 (15.5)	239 (50.0)	27.7 (6.8)	I–II: 284 (59.0); III–V: 196 (41.0)	–
					Control	480	57.9 (15.7)	248 (52.0)	28.1 (6.5)	I–II: 255 (53.0); III–V: 225 (47.0)	–

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; CCI, Charlson Comorbidity Index; CRC, colorectal cancer; ERAS, enhanced recovery after surgery; IN, immunonutrition; MNA-SF, Mini Nutritional Assessment – Short Form; *N*, number of patients; S4S, strong for surgery; SCOAP, Surgical Care and Outcomes Assessment Program.

TABLE 2 Treatment characteristics of included studies.

Study	Arm	Indication for surgery (%)	Type of colorectal resection (%)	Tumour stage (%)	Laparoscopic (%)	Neoadjuvant therapy (%)
Achilli, 2020 [31]	Immunonutrition	Colorectal cancer 65 (100)	Right colectomy 37 (56.9); left colectomy 10 (15.4); rectal resection with ileostomy/colostomy 7 (10.8); rectal resection without ileostomy/colostomy 2 (3.1); Miles procedure 9 (13.9)	I: 18 (27.69); II: 20 (30.77); III: 25 (38.46); IV: 2 (3.08)	74 (83.1)	CRT 16 (21.6)
	Control	Colorectal cancer 65 (100)	Right colectomy 38 (58.5); left colectomy 14 (21.5); rectal resection with ileostomy/colostomy 5 (7.7); rectal resection without ileostomy/colostomy 4 (6.2); Miles procedure 4 (6.2)	I: 15 (23.08); II: 20 (30.77); III: 30 (46.15); IV: 0 (0)	62 (69.2)	CRT 7 (6.9)
Banerjee, 2017 [32]	Immunonutrition	–	–	–	–	–
	Control	–	–	–	–	–
Horie, 2006 [12]	Immunonutrition	Caecal cancer 3 (9.1); ascending colon cancer 5 (15.2); transverse colon cancer 1 (3.0); descending colon cancer 1 (3.0); sigmoid colon cancer 8 (24.2); rectal cancer 15 (45.4)	Ileocaecal resection 3 (9.1); right hemicolectomy 5 (15.2); transverse colectomy 1 (3.0); descending colectomy 1 (3.0); sigmoid colectomy 8 (24.2); lower anterior resection 10 (30.3); super low anterior resection 2 (6.1); abdominoperineal resection 3 (9.1)	–	–	–
	Control	Caecal cancer 2 (5.9); ascending colon cancer 7 (20.6); transverse colon cancer 1 (2.9); descending colon cancer 0 (0.0); sigmoid colon cancer 8 (23.53); rectal cancer 16 (47.1)	Ileocaecal resection 1 (2.9); right hemicolectomy 9 (26.5); transverse colectomy 0 (0); descending colectomy 0 (0); sigmoid colectomy 8 (23.5); lower anterior resection 14 (41.2); super low anterior resection 0 (0.0); abdominoperineal resection 2 (5.9)	–	–	–
Lee, 2023 [11]	Immunonutrition	Right colon cancer 31 (39.2); left colon cancer 48 (60.8)	Right hemicolectomy 26 (32.9); transverse colectomy 2 (2.5); left hemicolectomy 3 (3.8); anterior resection 48 (60.8)	I: 28 (35.4); II: 14 (17.7); III: 33 (41.8); IV: 4 (5.1)	79 (100.0)	–
	Control	Right colon cancer 30 (36.6); left colon cancer 52 (63.4)	Right hemicolectomy 27 (32.9); transverse colectomy 2 (2.4); left hemicolectomy 5 (6.1); anterior resection 48 (58.5)	I: 20 (24.4); II: 14 (17.1); III: 40 (48.8); IV: 8 (9.8)	79 (96.3)	–
Manzanares Campillo, 2017 [13]	Immunonutrition	Colon cancer 20 (47.6); rectal cancer 22 (52.4)	–	–	–	–
	Control	Colon cancer 26 (61.9); rectal cancer 16 (38.1)	–	–	–	–

(Continues)

TABLE 2 (Continued)

Study	Arm	Indication for surgery (%)	Type of colorectal resection (%)	Tumour stage (%)	Laparoscopic (%)	Neoadjuvant therapy (%)
Ogilvie, 2023 [33]	Immunonutrition	Colorectal cancer 213 (41.5); benign disease 301 (58.5)	Segmental colectomy 427 (83.1); subtotal colectomy 33 (6.4); total proctocolectomy 11 (2.1); APR 28 (5.4); small bowel resection 15 (2.9)	I–III: 188 (88.3); IV: 25 (11.7)	392 (76.3)	–
	Control	Colorectal cancer 109 (34.9); benign disease 203 (65.1)	Segmental colectomy 261 (83.7); subtotal colectomy 25 (8.0); total proctocolectomy 4 (1.3); APR 10 (3.2); small bowel resection 12 (3.9)	I–III: 77 (70.6); IV: 32 (10.3)	230 (73.7)	–
Putrus, 2015 [34]	Immunonutrition	Colorectal cancer 57 (100)	–	–	–	–
	Control	Colorectal cancer 57 (100)	–	–	–	–
Tang, 2023 [35]	Immunonutrition	Rectal cancer 53 (100)	Low anterior resection 43 (81.1); APR 10 (18.9)	I: 4 (7.5); II: 20 (37.7); III: 29 (54.7)	53 (100)	CRT 24 (45.3); RT 1 (1.9); chemotherapy 28 (52.9)
	Control	Rectal cancer 53 (100)	Low anterior resection 45 (84.9); Hartmann's procedure 1 (1.9); APR 7 (13.2)	I: 3 (5.7); II: 17 (32.1); III: 33 (62.3)	52 (98.1)	CRT 16 (30.2); RT 1 (1.9); chemotherapy 36 (67.9)
Tesauro, 2021 [36]	Immunonutrition	Colorectal cancer 47 (100)	Right hemicolectomy 16 (34.1); left hemicolectomy 26 (43.8); anterior rectal resection 4 (22.6); other 1 (4.1)	–	47 (100.0)	–
	Control	Colorectal cancer 126 (100)	Right hemicolectomy 33 (26.2); left hemicolectomy 59 (46.8); anterior rectal resection 28 (22.2); other 6 (4.8)	–	126 (100.0)	–
Thornblade, 2017 [14]	Immunonutrition	Colorectal cancer 282 (59.0); diverticulitis 72 (15.0); IBD 69 (14.0); other 57 (12.0)	Colon resection 366 (76.0); rectal resection 114 (24.0)	–	–	–
	Control	Colorectal cancer 282 (59.0); diverticulitis 64 (13.0); IBD 72 (15.0); other 62 (13.0)	Colon resection 359 (75.0); rectal resection 121 (25.0)	–	–	–

Abbreviations: APR, abdominal perineal resection; CRT, chemoradiotherapy; IBD, inflammatory bowel disease; *N*, number of patients; RT, radiotherapy.

TABLE 3 Study morbidity outcomes reported in included studies.

Study	Arm	*N* total postoperative complications (%)	*N* sSSI (%)	*N* respiratory complication (%)	*N* GU complication (%)	*N* anastomotic leak (%)	*N* ileus (%)	Mean LOS (SD)	*N* 30-day readmission (%)
Achilli, 2020 [31]	Immunonutrition	–	–	–	–	–	–	8.5 (1.7)	–
	Control	–	–	–	–	–	–	9.8 (1.9)	–
Banerjee, 2017 [32]	Immunonutrition	–	–	4 (0.7)	–	0 (0.0)	–	6.5 (0.0)	–
	Control	–	–	2 (1.6)	–	2 (1.1)	–	6.9 (0.0)	–
Horie, 2006 [12]	Immunonutrition	–	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)	12.5 (3.8)	–
	Control	–	4 (11.8)	1 (2.9)	1 (2.9)	1 (2.9)	1 (2.9)	14 (7.2)	–
Lee, 2023 [11]	Immunonutrition	25 (31.6)	8 (10.3)	1 (1.3)	3 (3.8)	0 (0.0)	5 (6.4)	7.6 (2.5)	2 (2.5)
	Control	24 (29.3)	6 (7.3)	0 (0.0)	3 (3.7)	0 (0.0)	8 (9.8)	7.4 (2.3)	5 (6.1)
Manzanares Campillo, 2017 [13]	Immunonutrition	–	10 (23.8)	–	–	5 (11.9)	–	12.7 (8.3)	–
	Control	–	17 (40.5)	–	–	7 (16.7)	–	13.1 (10.8)	–
Ogilvie, 2023 [33]	Immunonutrition	123 (23.9)	35 (6.9)	–	–	–	–	5.0 (3.0)	–
	Control	67 (21.5)	20 (6.4)	–	–	–	–	5.7 (3.2)	–
Putrus, 2015 [34]	Immunonutrition	–	9 (15.8)	4 (7.0)	9 (15.8)	1 (1.8)	–	9.2	–
	Control	–	14 (24.6)	10 (17.5)	13 (22.8)	5 (8.8)	–	12.2	–
Tang, 2023 [35]	Immunonutrition	12 (22.6)	1 (1.9)	0 (0.0)	1 (1.9)	2 (3.8)	1 (1.9)	7.7 (2.3)	–
	Control	27 (50.9)	7 (13.2)	1 (1.9)	2 (3.8)	4 (7.5)	2 (3.8)	9.5 (4.2)	–
Tesauro, 2021 [36]	Immunonutrition	7 (14.9)	1 (2.1)	0 (0.0)	–	2 (4.3)	4 (8.5)	4.9 (2.3)	2 (4.1)
	Control	32 (25.4)	10 (7.9)	3 (2.4)	–	9 (7.1)	11 (8.7)	6.1 (3.9)	3 (2.4)
Thornblade, 2017 [14]	Immunonutrition	–	–	–	–	–	–	5.9 (4.9)	–
	Control	–	–	–	–	–	–	5.8 (4.5)	–

Abbreviations: GU, genitourinary; LOS, length of stay; *N*, number of patients; sSSI, superficial surgical site infection.

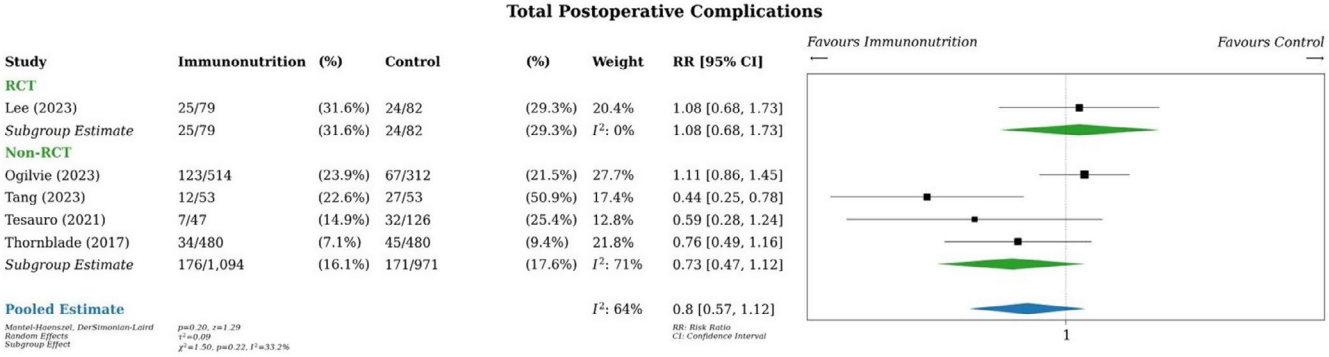

FIGURE 2 Forest plot of total postoperative complications results.

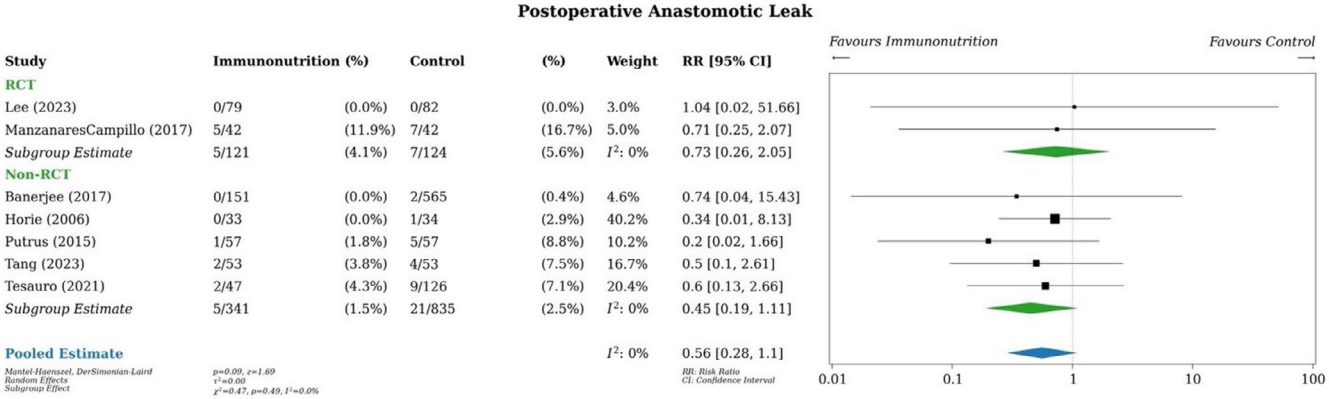

FIGURE 3 Forest plot of postoperative anastomotic leak results.

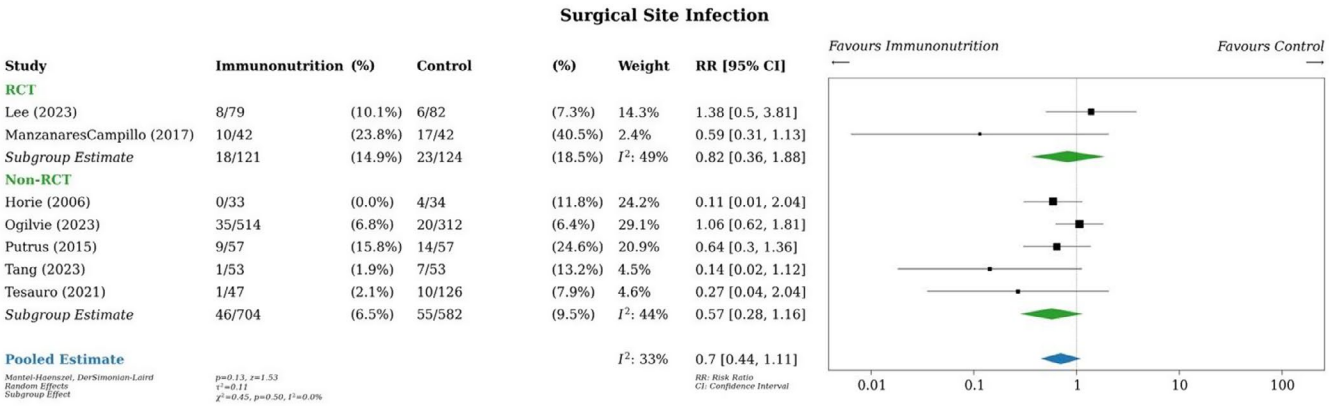

FIGURE 4 Forest plot of surgical site infection results.

Pooling data from seven studies, there was a non-significant 44% relative risk reduction in the risk of anastomotic leak in the immunonutrition group (RR 0.56, 95% CI 0.28–1.10, $P=0.09$, $I^2=0\%$; Figure 3). No subgroup interaction was observed according to risk of bias ($P=0.41$). Results were unchanged with leave-one-out and publication status sensitivity analyses.

Pooling data from seven studies, there was a non-significant 30% relative risk reduction in the risk of SSI in the immunonutrition group (RR 0.70, 95% CI 0.44–1.11, $P=0.13$, $I^2=33\%$; Figure 4). No subgroup interaction was observed according to risk of bias ($P=0.57$). Results were unchanged with leave-one-out and publication status sensitivity analyses.

Pooling data from five studies, there was a non-significant 36% relative risk reduction in the risk of postoperative GU complication in the immunonutrition group (RR 0.64, 95% CI 0.41–1.02, $P=0.06$, $I^2=0\%$; Figure 5). No subgroup interaction was observed according

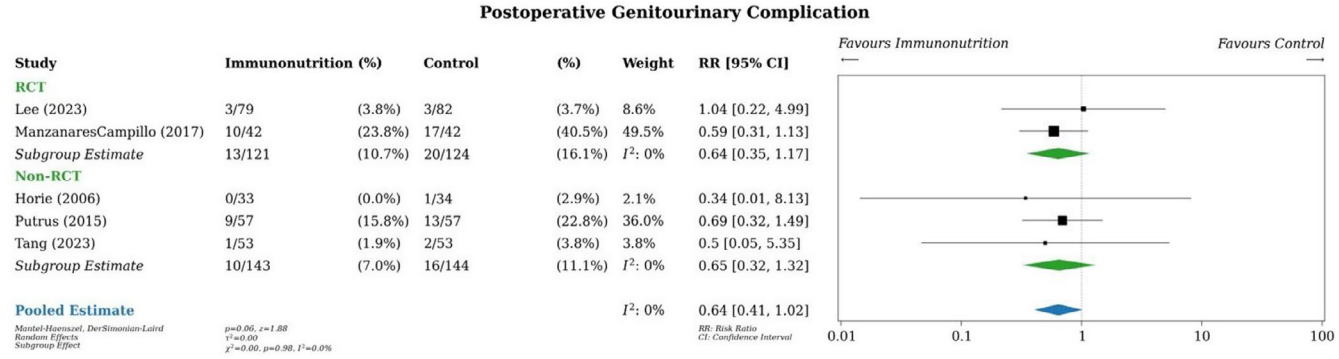

FIGURE 5 Forest plot of postoperative genitourinary complication results.

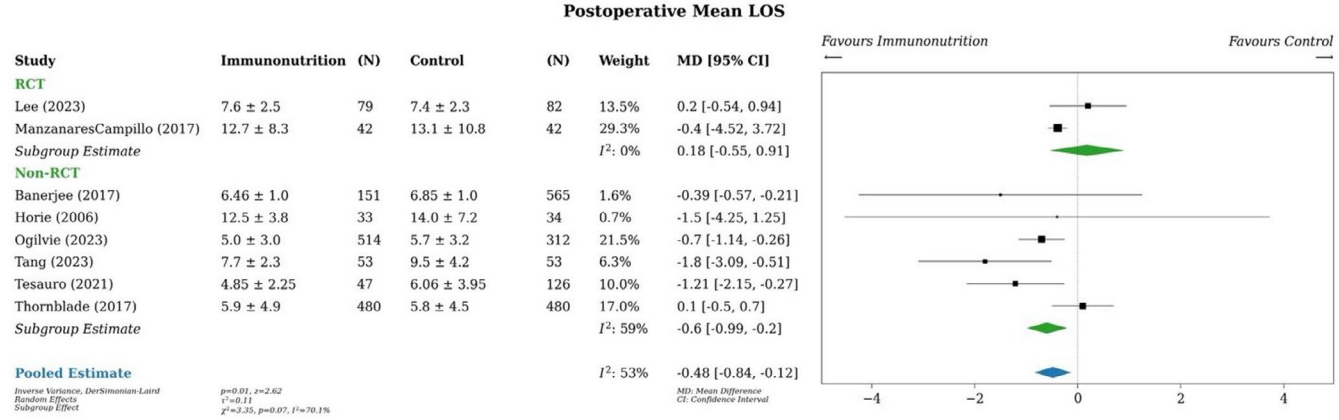

FIGURE 6 Forest plot of postoperative mean LOS results.

to risk of bias ($P=0.91$). Results were unchanged with leave-one-out and publication status sensitivity analyses.

Pooling data from six studies, there was no significant reduction in the relative risk of postoperative respiratory complication in the immunonutrition group (RR 0.95, 95% CI 0.26–3.48, $P=0.94$, $I^2=49\%$; Figure S1). No subgroup interaction was observed according to risk of bias ($P=0.14$). Results were unchanged with leave-one-out and publication status sensitivity analyses.

Pooling data from four studies, there was no significant relative risk reduction in the risk of postoperative ileus in the immunonutrition group (RR 0.81, 95% CI 0.38–1.57, $P=0.48$, $I^2=0\%$; Figure S2). Subgroup analyses based on risk of bias could not be performed. Results were unchanged with leave-one-out sensitivity analysis.

Across eight studies, postoperative LOS was 0.48 days shorter in the immunonutrition group (MD −0.48, 95% CI −0.84 to −0.12, $P=0.01$, $I^2=53\%$; Figure 6). No subgroup interaction was observed according to risk of bias ($P=0.14$). Results were unchanged with leave-one-out sensitivity analysis.

Lastly, only two studies reported 30-day readmission, and so meta-analysis was not possible (RR 0.82, 95% CI 0.20–3.46, $P=0.79$, $I^2=31\%$; Figure S3).

Risk of bias

Figure 7 presents the risk of bias analyses according to the RoB 2.0 tool for the two included randomized control trials. Figure 8 presents the risk of bias analyses according to the ROBINS-I for the seven included full-text observational cohort studies. Overall, four studies were deemed to be at serious risk of bias due to significant concerns of confounding [12, 32–34]. Five studies were deemed to have some concerns/moderate risk of bias and one study was deemed to be at low risk of bias. No included studies were at risk of bias due to missing data.

Certainty of evidence

The GRADE certainty of evidence summary table is presented in Table 4. Overall GRADE certainty of evidence was low for anastomotic leak and postoperative GU complication, and very low for the remaining outcomes. Outcomes were downgraded due to inclusion of high risk of bias studies, inconsistency, indirectness and imprecision. Variability in the patient populations across studies also contributed to serious concerns for indirectness with some studies

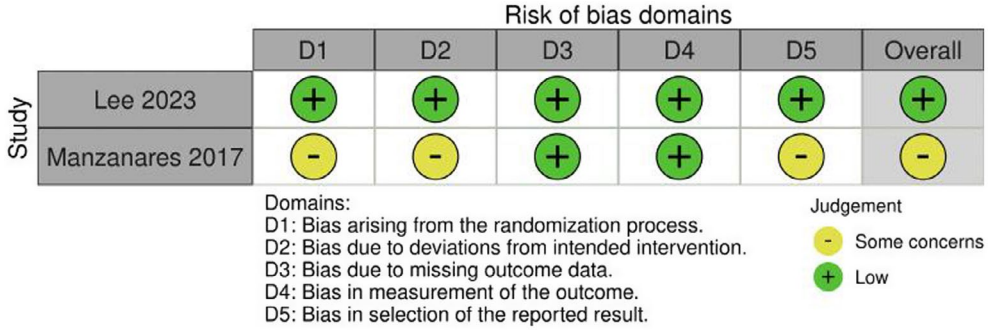

FIGURE 7 Revised Cochrane risk-of-bias tool for randomized trials (RoB 2.0) results per individual randomized controlled trial.

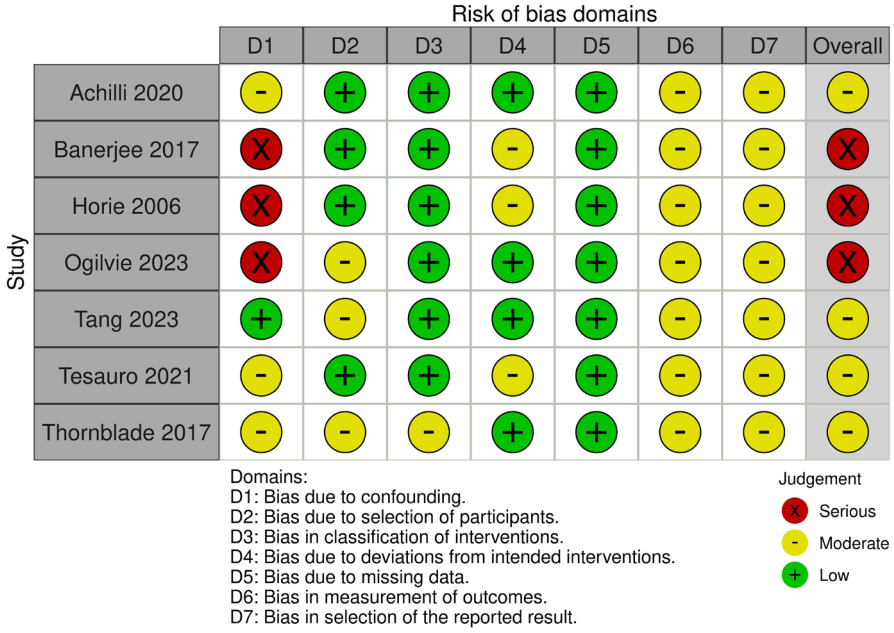

FIGURE 8 Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) assessment tool results per individual observational cohort study.

including a significant portion of patients undergoing colorectal surgery for benign disease. Small pooled sample sizes and wide 95% CIs led to serious concerns for imprecision.

DISCUSSION

The current systematic review and meta-analysis is the first to pool previously published data pertaining specifically to the use of preoperative enteral immunonutrition in patients undergoing elective colorectal surgery. The pooled data suggest a 20% non-significant decrease in relative risk of overall postoperative morbidity, 44% non-significant decrease in relative risk of anastomotic leaks, 30% non-significant decrease in relative risk of SSIs, 36% non-significant decrease in relative risk of postoperative GU complication, and a statistically significant 0.48 day shorter postoperative LOS for the enteral immunonutrition group compared to conventional nutrition. All point estimates had wide associated 95% CIs crossing the line of no effect.

The strengths of this study include novelty, rigorous methodology, thorough risk of bias analysis, and certainty of evidence evaluation with GRADE. Limitations include reliance on non-randomized data, residual confounding and between-study heterogeneity. We were only able to identify two RCTs pertaining to this research question, while the remainder of the included studies were non-randomized, heightening the risk of various biases, including residual confounding. Most included studies did not report data such as smoking status and receipt of neoadjuvant therapy, amongst other baseline demographics with the potential to impact postoperative outcomes [37, 38]. Importantly, between-study heterogeneity impacted the certainty of evidence in our meta-analysed outcomes. Specifically, differences in type of immunonutrition supplementation used, duration of use, as well as differences in types of diseases and operations, increased heterogeneity amongst our observed

TABLE 4 Summary of findings table for meta-analysed outcomes.

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With control	With immunonutrition	Relative effect (95% CI)	Risk with control	Risk difference with immunonutrition
Overall postoperative morbidity											
2065 (4 non-randomized studies)	Serious[a]	Serious[b]	Serious[c]	Serious[d]	None	⨁◯◯◯ Very low	171/971 (17.6%)	176/1094 (16.1%)	RR 0.73 (0.47–1.12)	176 per 1000	48 fewer per 1000 (from 93 fewer to 21 more)
Postoperative length of stay											
245 (2 RCTs)	Not serious	Serious[b]	Serious[c]	Serious[e]	None	⨁◯◯◯ Very low	124	121	–	The mean postoperative length of stay was **9.3** days	MD 0.2 days higher (0.6 lower to 0.9 higher)
Anastomotic leak											
245 (2 RCTs)	Not serious	Not serious	Serious[c]	Serious[d]	None	⨁⨁◯◯ Low	7/124 (5.6%)	5/121 (4.1%)	RR 0.73 (0.26–2.05)	56 per 1000	15 fewer per 1000 (from 42 fewer to 59 more)
Surgical site infection											
245 (2 RCTs)	Not serious	Serious[b]	Serious[c]	Serious[d]	None	⨁◯◯◯ Very low	23/124 (18.5%)	18/121 (14.9%)	RR 0.82 (0.36–1.88)	185 per 1000	33 fewer per 1000 (from 119 fewer to 163 more)
Postoperative respiratory complication											
1176 (5 non-randomized studies)	Serious[a]	Serious[b]	Serious[c]	Very serious[f]	None	⨁◯◯◯ Very low	17/835 (2.0%)	8/341 (2.3%)	RR 0.80 (0.19–3.45)	20 per 1000	4 fewer per 1000 (from 16 fewer to 50 more)
Postoperative genitourinary complication											
245 (2 RCTs)	Not serious	Not serious	Serious[c]	Serious[d]	None	⨁⨁◯◯ Low	20/124 (16.1%)	13/121 (10.7%)	RR 0.64 (0.35–1.17)	161 per 1000	58 fewer per 1000 (from 105 fewer to 27 more)
Prolonged postoperative ileus											
346 (3 non-randomized studies)	Serious[a]	Not serious	Serious[c]	Serious[d]	None	⨁◯◯◯ Very low	14/213 (6.6%)	6/133 (4.5%)	RR 0.88 (0.38–1.57)	66 per 1000	8 fewer per 1000 (from 41 fewer to 37 more)

Abbreviations: MD, mean difference; RCT, randomized control trial; RR, risk ratio.

[a]Downgraded one level for inclusion of studies at high risk of bias.

[b]Downgraded one level for I^2 >40%.

[c]Downgraded one level for differences in patient populations and intervention details.

[d]Downgraded one level for the 95% CIs crossing the clinical decision threshold and for the overall pooled sample size being less than the optimal information size.

[e]Downgraded one level for the 95% CIs crossing the clinical decision threshold.

[f]Downgraded two levels for the 95% CIs crossing the clinical decision threshold, for the overall pooled sample size being less than the optimal information size, and small number of pooled outcome events.

outcomes. We explored this heterogeneity with subgroups based on study type and risk of bias. Limitations in the greater body of evidence pertaining to the use of preoperative enteral nutrition prior to elective colorectal surgery include the lack of RCT data and the possibility of selection bias amongst non-randomized studies.

The molecular constituents of preoperative enteral immunonutrition often encompass omega-3 fatty acids, glutamine and/or arginine in varying amounts [39]. Omega-3 fatty acids exhibit anti-inflammatory properties, potentially mitigating surgical stress responses and reducing complications [40]. This is particularly relevant for colorectal cancer patients in whom tumour-derived cytokines drive systemic inflammation [41]. Glutamine, a critical fuel for enterocytes and immune cells, aids in preserving gut integrity and supporting immune function, crucial for optimal recovery [42]. Arginine serves as a precursor for nitric oxide synthesis, facilitating vasodilation and improving tissue perfusion, thereby contributing to wound healing [43]. For intestinal tissue in particular, arginine may significantly improve the host immune response, oxygenation and micro-perfusion at the time of surgery [44].

In surgical contexts beyond colorectal procedures, preoperative enteral immunonutrition presents a compelling avenue for enhancing patient outcomes. Studies across diverse surgical procedures, including but not limited to oesophagectomy, gastrectomy and joint arthroplasty, have suggested potential benefits associated with perioperative enteral nutrition [45–48]. Mingliang et al. meta-analysed seven RCTs comparing perioperative enteral immunonutrition to standard nutrition and found the relative risk of anastomotic leak to be reduced by 41% with associated confidence intervals crossing the line of no effect (5.4% vs. 9.4%, RR 0.59, 95% CI 0.33–1.04, $P=0.07$) [46]. Cheng et al. meta-analysed seven RCTs in patients undergoing gastrectomy for gastric cancer, assessing clinical outcomes (i.e., overall postoperative morbidity) and biochemical outcomes (i.e., CD4, CD8 and immunoglobulin levels), finding significant improvements in both with the use of perioperative enteral immunonutrition [45]. Still, further guidance on the optimal preoperative nutrition regimen for patients undergoing colorectal surgery is essential for the development of clearer ERAS guidelines. Immunonutrition may play a role in this optimal preoperative regimen and may offer clinical benefits; however, the ideal immunonutrition formula and regimen remains understudied. Current immunonutrition strategies vary widely, and individual nutritional needs often differ, complicating the identification of the optimal approach for each clinical scenario. Substantial work is necessary prior to the formal integration of immunonutrition within future colorectal ERAS protocols.

Overall, enteral immunonutrition prior to elective colorectal surgery may decrease the risk of overall postoperative morbidity, as well as specific postoperative complications such as anastomotic leak, SSI, postoperative GU complication and postoperative respiratory complication. While point estimates associated with these outcomes suggest a potential important benefit, the wide associated 95% CIs and resultant risk of type II error creates uncertainty surrounding their potential benefit in this setting. A large, high-quality RCT evaluating preoperative enteral immunonutrition in patients undergoing elective colorectal surgery is required to resolve this uncertainty.

AUTHOR CONTRIBUTIONS

Tyler McKechnie: Conceptualization; methodology; data curation; formal analysis; writing – review and editing; writing – original draft. **Tania Kazi:** Conceptualization; methodology; data curation; formal analysis; writing – original draft; writing – review and editing. **Ghazal Jessani:** Conceptualization; methodology; data curation; formal analysis; writing – review and editing; writing – original draft. **Victoria Shi:** Conceptualization; methodology; formal analysis; writing – review and editing. **Niv Sne:** Conceptualization; methodology; formal analysis; writing – review and editing. **Aristithes Doumouras:** Conceptualization; methodology; formal analysis; writing – review and editing. **Dennis Hong:** Conceptualization; methodology; formal analysis; writing – review and editing. **Cagla Eskicioglu:** Conceptualization; methodology; formal analysis; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

None of the authors have any potential conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Tyler McKechnie https://orcid.org/0000-0002-7668-4096
Tania Kazi https://orcid.org/0009-0004-2360-2159
Victoria Shi https://orcid.org/0009-0001-2102-1498
Cagla Eskicioglu https://orcid.org/0000-0003-3920-066X

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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