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PERIOPERATIVE NUTRITIONAL STRATEGIES IN COLORECTAL CANCER SURGERY: A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS

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ABSTRACT

Introduction and purpose: Perioperative nutritional care has become an increasingly important component of colorectal cancer (CRC) surgery, particularly in patients with malnutrition, sarcopenia, frailty, or increased metabolic vulnerability. This systematic review aimed to evaluate the effectiveness and safety of perioperative nutritional interventions in CRC surgery and to determine whether their clinical benefit is uniform or mainly concentrated in high-risk patients.

Material and methods: A systematic review of randomized controlled trials was conducted in accordance with PRISMA guidelines. PubMed/MEDLINE, Cochrane Library, and Scopus were searched through March 12, 2026. Eligible studies included adult patients undergoing elective CRC surgery and evaluated carbohydrate loading, early oral feeding, oral nutritional supplementation, immunonutrition, or multimodal prehabilitation including a nutritional component. Primary outcomes were postoperative complications and length of hospital stay; secondary outcomes included infectious complications, anastomotic leakage, recovery parameters, metabolic response, patient-reported outcomes, and safety.

Results: Twenty-one randomized controlled trials were included. Early oral feeding and carbohydrate loading were mainly associated with improved postoperative recovery, gastrointestinal function, and patient-reported well-being, whereas their effects on major clinical endpoints were less consistent. Oral nutritional supplementation and targeted nutritional support appeared most beneficial in malnourished or nutritionally at-risk patients. Immunonutrition showed the clearest signal for reduced infectious morbidity and attenuation of perioperative inflammatory response. Multimodal prehabilitation improved functional recovery and appeared particularly relevant in frail or high-risk patients. Across intervention types, safety profiles were generally acceptable.

Conclusions: Perioperative nutritional interventions may provide clinically meaningful benefits in CRC surgery, but their effects are not uniform across all patients. Current evidence supports a risk-stratified approach, with the greatest benefit observed in patients with increased nutritional or physiological vulnerability.

KEYWORDS

Colorectal Cancer, Colon Cancer, Rectal Cancer, Colorectal Surgery, Colorectal Resection, Perioperative Nutrition, Nutritional Support, Oral Nutritional Supplementation, Oral Nutritional Supplements, Immunonutrition, Early Oral Feeding, Early Enteral Nutrition, Carbohydrate Loading, Prehabilitation, Randomized Controlled Trial, Randomized And Randomised

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1. Introduction

1.1 Clinical problem

Colorectal cancer (CRC) remains one of the most common malignancies worldwide and a major cause of cancer-related morbidity and mortality. Surgical resection is still the cornerstone of curative treatment for most patients with localized disease [6]. Despite advances in surgery, anesthesia, and perioperative care, postoperative complications remain common, with infectious complications accounting for a substantial proportion of adverse outcomes [6] [8].

Malnutrition is frequent but often underrecognized in patients with CRC. Cancer-related metabolic changes, reduced dietary intake, systemic inflammation, and loss of skeletal muscle mass may all contribute to preoperative nutritional deterioration [4] [5]. Current surgical nutrition guidelines emphasize that nutritional risk assessment should not rely on body mass index (BMI) alone, as sarcopenia may also occur in patients with normal or high BMI and is associated with worse postoperative outcomes [1]. In oncological gastrointestinal surgery, low muscle mass and impaired nutritional status have been linked to increased postoperative morbidity, impaired wound healing, and higher rates of infectious complications [1] [33] [34]. In this context, the GLIM criteria may provide a more clinically informative framework than BMI alone for identifying patients at increased surgical risk [33].

The 2025 ESPEN guideline further emphasizes that perioperative nutritional optimization should be considered an essential part of surgical care, particularly in patients undergoing major oncological procedures [1]. Thus, in contemporary colorectal surgery, nutritional assessment is not only important but increasingly mandatory within evidence-based perioperative management [1] [3].

1.2 Why this matters in daily practice

Postoperative complications after colorectal surgery are associated with prolonged hospital stay, higher costs, increased readmission, and delayed adjuvant treatment, which may adversely affect long-term oncological outcomes [6] [36]. Therefore, reducing perioperative morbidity is of clear clinical importance.

ERAS protocols are widely used in colorectal surgery to improve recovery and reduce complications [6] [7]. Nutritional care is a core ERAS component and includes preoperative assessment, avoidance of prolonged fasting, carbohydrate loading, and early postoperative oral feeding [1] [6] [8]. Current guidelines also support early oral or enteral feeding and individualized nutritional support in surgical oncology patients [1] [2] [3] [4].

Perioperative nutritional strategies studied in colorectal cancer surgery include carbohydrate loading [14] [16] [17] [41] [42] [43] [44], early oral feeding [9] [10] [11] [12] [13], oral nutritional supplementation [22] [23] [24] [25], immunonutrition [18] [19] [20] [21], and multimodal prehabilitation [26] [27] [28]. Carbohydrate loading aims to reduce perioperative insulin resistance [14] [16] [17], while early oral feeding may accelerate recovery without increasing major surgical complications [9] [10] [11] [12] [13]. Prehabilitation may further improve perioperative resilience, especially in high-risk patients [26] [27] [28].

However, the evidence remains heterogeneous due to differences in patient selection, nutritional risk, timing of intervention, formula composition, and outcome definitions [29] [30] [31] [32]. An important unresolved issue is whether these interventions benefit all CRC patients equally or mainly those at high nutritional risk, such as patients with marked nutritional impairment, NRS-2002 ≥ 5, or malnutrition defined by GLIM criteria [1] [24] [33].

1.3 Aim

Therefore, the aim of this systematic review was to evaluate both the effectiveness and safety of perioperative nutritional interventions in patients undergoing colorectal cancer surgery, based exclusively on evidence derived from randomized controlled trials. Particular attention was paid to whether the clinical benefit of these interventions is consistent across all patients or is primarily observed in those at increased nutritional risk.

2. Methods

2.1 Study design

This study was designed as a systematic review of randomized controlled trials evaluating perioperative nutritional interventions in adult patients undergoing colorectal cancer surgery. The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [45].

2.2 Eligibility criteria

Eligibility criteria were defined according to the PICOS framework and are presented in Table 1. Studies were eligible if they included adult patients undergoing elective colorectal cancer surgery and evaluated perioperative nutritional interventions, including carbohydrate loading, early oral feeding, oral nutritional supplementation, immunonutrition, or multimodal prehabilitation including a nutritional component.

Comparator groups included standard perioperative care, placebo, fasting protocols, delayed feeding, conventional nutritional support, or alternative nutritional strategies. The primary outcomes were postoperative complications and length of hospital stay. Secondary outcomes included infectious complications, anastomotic leakage, postoperative recovery, metabolic response, readmission, mortality, safety-related outcomes, patient-reported outcome measures (PROMs), and changes in body composition, including muscle mass or sarcopenia-related parameters [1] [33] [41].

Only randomized controlled trials were included. Observational studies, retrospective analyses, reviews, meta-analyses, case reports, animal studies, conference abstracts without sufficient data, and studies not specifically focused on perioperative nutritional management in colorectal cancer surgery were excluded. Studies involving mixed gastrointestinal surgical populations were included only if colorectal cancer data could be extracted separately.

Because diabetes mellitus and obesity may influence the metabolic response to perioperative nutritional interventions, particularly preoperative carbohydrate loading, these characteristics were considered clinically relevant effect modifiers and were specifically recorded when reported [1] [41] [44].

2.3 Information sources and search strategy

A systematic literature search was performed in PubMed/MEDLINE, Cochrane Library, and Scopus. The final search was conducted on March 12, 2026. The search strategy combined terms related to colorectal cancer, surgery, perioperative nutrition, and randomized trials. Full search terms and database-specific search strings are provided in the Supplementary Material.

Reference lists of relevant reviews and current clinical guidelines were also screened manually to identify additional eligible studies. Only articles published in English were considered.

2.4 Study selection and data extraction

Titles and abstracts were screened for relevance, followed by full-text assessment of potentially eligible studies according to the predefined inclusion and exclusion criteria. Data were extracted using a standardized form, including author, year, country, sample size, patient population, nutritional risk status, comorbidities such as diabetes and obesity, type of surgery, type and timing of nutritional intervention, comparator, outcomes, and main findings.

Special attention was paid to variables with potential clinical impact on treatment effect, including baseline nutritional status, body composition or muscle-related measures, and subgroup characteristics when reported. For studies assessing anastomotic leakage, the definition used by the authors was extracted in order to account for between-study variability in outcome reporting. For PROMs, extracted outcomes included measures such as subjective well-being, thirst, hunger, nausea, fatigue, and quality of life when available [41].

2.5 Risk of bias assessment

The methodological quality of the included randomized controlled trials was assessed using the revised Cochrane Risk of Bias tool for randomized trials (RoB 2) [46].

2.6 Data synthesis

A qualitative narrative synthesis was performed. Due to expected heterogeneity in study populations, nutritional risk, intervention protocols, timing, and reported outcomes, results were grouped according to intervention type: carbohydrate loading, early oral feeding, oral nutritional supplementation, immunonutrition, and multimodal prehabilitation including a nutritional component.

The synthesis focused on both effectiveness and safety, with particular emphasis on clinically relevant outcomes such as postoperative morbidity, infectious complications, anastomotic leakage, length of hospital stay, recovery profile, PROMs, and changes in body composition [1] [6] [33] [41].

Where data allowed, findings were interpreted according to baseline nutritional risk, with particular interest in whether treatment effects differed between malnourished or high-risk patients and well-nourished patients, in order to avoid dilution of clinically relevant effects in unselected populations. Where reported, the potential modifying role of diabetes mellitus and obesity was also considered, especially in studies of carbohydrate loading [1] [41] [44].

Table 1. PICOS framework used to define the eligibility criteria for study inclusion.

Component	Description
P (Population)	Adult patients undergoing elective surgery for colorectal cancer
I (Intervention)	Perioperative nutritional interventions, including carbohydrate loading, early oral feeding, oral nutritional supplementation, immunonutrition, and multimodal prehabilitation including a nutritional component
C (Comparison)	Standard perioperative care, placebo, fasting protocols, delayed feeding, conventional nutritional support, or alternative nutritional strategies
O (Outcomes)	Primary outcomes: postoperative complications and length of hospital stay. Secondary outcomes: infectious complications, anastomotic leakage, postoperative recovery, metabolic response, readmission, mortality, safety/tolerance of the intervention, PROMs, and changes in body composition including muscle mass-related parameters
S (Study design)	Randomized controlled trials only

Results

3.1 Study selection

A total of 98 records were identified through database searching, including 53 from PubMed/MEDLINE, 28 from Cochrane Library, and 17 from Scopus. After removal of 15 duplicates, 83 records remained for title and abstract screening. Of these, 35 were excluded based on title and abstract. The full texts of 48 articles were assessed for eligibility.

After full-text review, 27 studies were excluded for predefined reasons. Ultimately, 21 randomized controlled trials were included in the qualitative synthesis. The study selection process is presented in Figure 1.

3.2 Characteristics of included studies

The 21 randomized controlled trials included in the qualitative synthesis evaluated five main categories of perioperative nutritional interventions in colorectal surgery: carbohydrate loading, early oral feeding, oral nutritional supplementation or targeted nutritional support, immunonutrition, and multimodal prehabilitation including a nutritional component [9] [10] [11] [12] [13] [14] [18] [19] [20] [21] [22] [23] [24] [25] [26] [27] [28] [41] [42] [43] [44]. Most studies involved patients undergoing elective colorectal resection, although operative approach, perioperative pathways, and timing of intervention varied across trials.

The interventions were heterogeneous in both design and duration. Carbohydrate loading trials assessed preoperative carbohydrate drinks [14] [41] [42] [43] [44], early oral feeding studies compared immediate versus delayed postoperative intake [9] [10] [11] [12] [13], ONS trials evaluated preoperative or perioperative nutritional support [22] [23] [24] [25], immunonutrition studies used formulas enriched with arginine, omega-3 fatty acids, and nucleotides [18] [19] [20] [21], and prehabilitation trials combined nutrition with exercise-based conditioning [26] [27] [28].

Baseline nutritional status was reported inconsistently. Some studies specifically enrolled malnourished or nutritionally at-risk patients [24] [25], whereas others included broader colorectal surgical populations [9] [10] [11] [12] [13] [14] [21] [27] [28] [41] [42] [43]. Older trials relied mainly on weight loss or subjective nutritional assessment rather than contemporary definitions of malnutrition [18] [19], while newer frameworks such as GLIM were not consistently represented [33]. Surgical technique also varied and included both open and laparoscopic approaches [10] [11] [13] [21], which is clinically relevant because it may affect postoperative ileus and tolerance of early feeding.

The most commonly reported outcomes were postoperative complications, length of hospital stay, gastrointestinal recovery, and treatment tolerance [9] [10] [12] [14] [22] [24] [25] [41] [42]. Some studies also assessed metabolic and inflammatory responses, and more recent trials reported patient-reported outcomes such as well-being, thirst, anxiety, and quality of life [21] [41]. A detailed summary of the included studies is presented in Table 2.

3.3 Risk of bias assessment

The methodological quality of the included randomized controlled trials was assessed using the RoB 2 tool [46]. Overall, the included studies were of moderate methodological quality, with the most frequent concerns related to insufficient reporting of the randomization process, lack of blinding, and selective or incomplete outcome reporting.

Additional uncertainty arose from heterogeneity in outcome definitions, particularly for clinically relevant endpoints such as anastomotic leakage, postoperative complications, and selected patient-reported outcomes. Nevertheless, the included trials provided sufficient data to allow qualitative synthesis, although these methodological limitations should be taken into account when interpreting the findings.

3.4 Effects of perioperative nutritional interventions

3.4.1 Carbohydrate loading

Randomized controlled trials evaluating preoperative carbohydrate loading in colorectal surgery assessed its effects on metabolic response, postoperative recovery, length of hospital stay, return of bowel function, and patient-reported outcomes [14] [41] [42] [43] [44]. Carbohydrate-containing drinks were typically administered during the preoperative fasting period and compared with conventional fasting regimens or standard perioperative care [14] [41] [42] [43] [44]. The physiological rationale is that this intervention shifts the patient from a fasting, catabolic state toward a fed, more anabolic state before surgical injury, thereby attenuating perioperative insulin resistance and reducing the metabolic stress response [1] [47].

Overall, the findings were more consistent for metabolic, inflammatory, gastrointestinal, and patient-centered outcomes than for major postoperative clinical endpoints. Several trials suggested improved perioperative well-being, including reduced thirst, anxiety, and better overall quality of life [14] [41] [42]. Preoperative carbohydrate loading was also associated with faster return of bowel function, including earlier passage of flatus and defecation in more recent colorectal studies [41] [42]. In addition, these trials reported favorable effects on inflammatory markers, including lower postoperative IL-6 and CRP, suggesting attenuation of the inflammatory response to surgery [41] [42].

Its effect on hard clinical outcomes, including length of hospital stay, remained less consistent across studies [14] [42] [43]. However, this may partly reflect differences in procedure complexity and discharge criteria, as any reduction in length of stay appears more evident in major abdominal surgery, including colorectal cancer resection [1] [48].

From a safety perspective, preoperative carbohydrate loading was generally well tolerated [14] [41] [42] [43] [44]. No clear increase in major postoperative complications or aspiration-related concerns was observed in colorectal surgical patients [14] [41] [42] [43]. Some evidence also suggests that carbohydrate loading may support better peri-induction hemodynamic stability through improved preoperative hydration [49]. Safety is particularly relevant in metabolically vulnerable patients. Current ESPEN guidance advises against routine carbohydrate drinks in patients with severe diabetes, especially when gastroparesis is anticipated [1]. At the same time, a randomized trial in diabetic patients undergoing gastrointestinal surgery showed that carbohydrate loading combined with an individualized insulin regimen was feasible, did not increase aspiration-related risk, and improved perioperative well-being, although gastrointestinal recovery was less pronounced than in non-diabetic populations [44]. Available evidence also suggests that carbohydrate loading does not increase gastric residual volume in obese patients [50].

Taken together, the available randomized evidence suggests that carbohydrate loading is a feasible and generally safe perioperative strategy in colorectal surgery, with the strongest support for improved metabolic recovery, attenuation of inflammatory stress, faster gastrointestinal recovery, and better patient-reported well-being, whereas evidence for a consistent effect on major clinical outcomes remains less conclusive [14] [41] [42] [43] [44] [48].

3.4.2 Early oral feeding

Randomized controlled trials evaluating early oral feeding after colorectal surgery consistently examined its feasibility, tolerance, and impact on postoperative recovery [9] [10] [11] [12] [13]. Across the included studies, early oral feeding was generally initiated within the first postoperative day and compared with more traditional postoperative regimens based on delayed oral intake [9] [10] [11] [12] [13]. The physiological rationale for this approach is based on the observation that the traditional "nil by mouth" strategy was founded on the assumption of prolonged postoperative ileus, whereas small bowel function is known to recover relatively early after surgery; early enteral stimulation may also help limit fasting-related mucosal atrophy and support restoration of gut function [1] [8].

Overall, early oral feeding appeared to be feasible and clinically acceptable in patients undergoing colorectal resection [9] [10] [11] [12] [13]. The included trials suggested that this strategy did not adversely affect postoperative recovery and, in several studies, was associated with faster return of bowel function and earlier tolerance of oral intake [9] [10] [12]. Its effect on length of hospital stay, however, was less consistent across studies. Dag et al. reported a marked reduction in hospital stay in the early feeding group [10], whereas Fujii et al. did not observe a difference in length of stay between groups [13]. This inconsistency suggests that length of hospital stay may depend not only on physiological recovery, but also on institutional discharge criteria and non-clinical factors.

From a safety perspective, early oral feeding did not appear to increase the rate of major postoperative complications, including anastomotic leakage, when implemented in appropriately selected patients [9] [10] [11] [12] [13]. In both clinical trials and current guidelines, this generally refers to patients without conditions such as mechanical bowel obstruction, severe hemodynamic instability, or other contraindications to oral or enteral intake [1]. Reported adverse effects were mainly related to gastrointestinal tolerance, including nausea, transient feeding intolerance, and in some studies vomiting [10] [12]. Although early feeding may increase the frequency of minor gastrointestinal symptoms, these events were generally self-limited and did not translate into higher rates of serious postoperative complications in the included trials [9] [10] [11] [12] [13].

In addition to clinical feasibility, some studies suggested improved patient experience with earlier feeding, including better subjective comfort and postoperative well-being [10]. Similar improvements in patient-reported outcomes have also been described in other perioperative nutritional interventions, particularly carbohydrate loading [41]. Taken together, the available randomized evidence supports early oral feeding as a safe perioperative strategy after colorectal surgery, with benefits that appear to relate primarily to enhanced recovery and patient comfort rather than a uniform reduction in major postoperative morbidity [9] [10] [11] [12] [13]. This interpretation is consistent with the updated ESPEN 2025 guideline, which identifies early oral feeding as the preferred mode of postoperative nutritional management in surgical patients [1].

3.4.3 Oral nutritional supplementation

Randomized controlled trials evaluating oral nutritional supplementation (ONS) and targeted perioperative nutritional support in colorectal surgery assessed their effects on postoperative complications, nutritional recovery, length of hospital stay, and treatment tolerance [22] [23] [24] [25]. The interventions ranged from preoperative nutritional support in malnourished patients to perioperative or postoperative ONS combined with dietary counselling [22] [23] [24] [25].

Overall, the available evidence suggests that the benefit of targeted nutritional support was more apparent in patients with impaired baseline nutritional status than in unselected surgical populations [23] [24] [25]. According to current ESPEN guidance, patients at high nutritional risk include those with severe nutritional impairment, such as marked recent weight loss, low BMI, or high nutritional risk screening scores [1]. Trials focusing on malnourished or nutritionally at-risk patients reported more favorable effects on postoperative recovery and nutritional outcomes [24] [25].

The timing and duration of intervention also appear clinically relevant. Current recommendations indicate that preoperative nutritional support should ideally continue for 7–14 days in high-risk patients to achieve measurable benefit [1]. This may partly explain why results are less consistent when nutritional interventions are introduced late or applied for shorter periods.

The effect of ONS on major clinical outcomes, such as postoperative complications or length of hospital stay, remained less consistent across studies [22] [23] [25]. However, targeted nutritional support was generally well tolerated and may have improved postoperative nutritional recovery, especially when combined with structured dietary counselling [22] [25]. Its effectiveness also depends on patient adherence and tolerance [22] [25].

At the same time, ESPEN 2025 suggests that ONS should not be reserved only for overtly malnourished patients, but also considered in surgical patients who are unable to meet their nutritional requirements through normal food intake alone [1].

Taken together, the randomized evidence indicates that perioperative ONS and targeted nutritional support may be most useful in patients with pre-existing malnutrition or increased nutritional risk, whereas evidence for a consistent reduction in major complications in unselected colorectal surgical populations remains limited [22] [23] [24] [25]. Continuation of nutritional support into the postoperative period may also help attenuate weight loss and support functional recovery beyond the immediate postoperative phase [1] [25].

3.4.4 Immunonutrition

Randomized controlled trials evaluating perioperative immunonutrition assessed its effects on postoperative complications, infectious morbidity, length of hospital stay, and inflammatory response in patients undergoing gastrointestinal surgery, including colorectal procedures [18] [19] [20] [21]. The tested interventions generally involved formulas enriched with immunomodulating substrates, most commonly arginine, omega-3 fatty acids, and nucleotides, administered preoperatively or perioperatively [18] [19] [20] [21]. From a physiological perspective, this approach is relevant because surgical stress is associated with depletion of arginine, which may impair immune function and wound healing; in addition, arginine serves as a substrate for nitric oxide synthesis, potentially supporting microcirculation in healing tissues [1] [18] [19].

Overall, the findings suggest a clinically meaningful benefit of immunonutrition, particularly with regard to infectious complications and perioperative inflammatory response, although the magnitude of effect varied across studies [18] [19] [20] [21]. In some randomized trials, postoperative infectious complications were reduced substantially, with rates falling from approximately 30% in control groups to around 14–16% in patients receiving immunonutrition [19] [20]. In colorectal-specific evidence, preoperative immunonutrition was also associated with favorable changes in inflammatory markers, supporting its biological plausibility as a strategy aimed at modulating the surgical stress response [21]. Its effect on broader clinical endpoints, such as overall postoperative morbidity or length of hospital stay, was less uniform, but subgroup observations suggest that the greatest benefit may occur in patients with impaired nutritional status [18] [19].

Available evidence also suggests that the duration and timing of supplementation are clinically relevant. In well-nourished patients, short-term preoperative administration may be sufficient, whereas in malnourished patients perioperative administration extending into the postoperative period appears more appropriate because of greater metabolic and protein demands [1] [18]. Specific subgroup observations, including those reported in the Braga trial, suggest that the most pronounced reduction in complications may be seen when immunonutrition is continued postoperatively in malnourished patients [18].

Immunonutrition was generally well tolerated in the included trials [18] [19] [20] [21]. In the Braga trial, nutritional targets were achieved in the large majority of patients, and adverse effects such as abdominal cramps or diarrhea were infrequent and usually did not require discontinuation of the protocol [18]. Taken together, the available randomized evidence suggests that perioperative immunonutrition is a clinically relevant strategy, particularly in oncological patients undergoing major abdominal surgery and in those at increased nutritional risk. This interpretation is consistent with the ESPEN 2025 guideline, which supports immunonutrition as a recommended option in oncological patients undergoing major abdominal procedures [1].

3.4.5 Multimodal prehabilitation including a nutritional component

Randomized controlled trials evaluating multimodal prehabilitation with a nutritional component assessed its effects on postoperative recovery, functional capacity, postoperative complications, and length of hospital stay in patients undergoing major abdominal surgery, including colorectal cancer resection [26] [27] [28]. These interventions generally combined nutritional optimization with exercise-based conditioning and, in some cases, psychological or behavioral support [26] [27] [28]. The nutritional component typically included oral nutritional supplementation and dietary counselling to ensure adequate protein and energy intake [1] [26] [27] [28].

Overall, the available evidence suggests that multimodal prehabilitation may improve perioperative functional recovery and reduce postoperative morbidity, although the magnitude of benefit varied across trials [26] [27] [28]. While earlier RCTs were heterogeneous, more recent evidence syntheses indicate that prehabilitation may reduce postoperative complications and shorten hospital stay in patients undergoing major surgery [1] [51] [52]. In colorectal cancer populations, prehabilitation combining nutrition and exercise was associated with improved functional performance and more favorable perioperative recovery [27] [28] [51].

This heterogeneity likely reflects differences in program composition, duration, patient selection, and outcome assessment [26] [27] [28] [52]. Current guidance suggests that meaningful improvements in functional capacity usually require 2 to 6 weeks of prehabilitation, which may explain why shorter protocols do not always show clear benefit [1]. Clinically, prehabilitation appears particularly relevant in patients with reduced physiological reserve, including frail, elderly, and higher-risk individuals [1] [26] [51]. In the trial by Barberan-Garcia et al., personalized prehabilitation in high-risk patients, including ASA III/IV individuals, was associated with a substantial reduction in postoperative complications [26]. This is consistent with more recent syntheses suggesting that risk-adapted prehabilitation may be most beneficial in vulnerable surgical populations [51] [52].

Multimodal prehabilitation was generally well tolerated, with no consistent safety concerns reported [26] [27] [28]. Taken together, the available randomized evidence suggests that prehabilitation including a nutritional component is a clinically relevant perioperative strategy in colorectal cancer surgery, particularly for improving functional recovery and reducing postoperative complications in high-risk patients, although its benefit may depend on patient selection and intervention duration [1] [26] [27] [28] [51] [52].

3.5 Safety outcomes across interventions

Across the included randomized controlled trials, perioperative nutritional interventions were generally well tolerated and were not associated with a consistent increase in major adverse postoperative events [9] [10] [11] [12] [13] [14] [18] [19] [20] [21] [22] [23] [24] [25] [26] [27] [28] [41] [42] [43] [44]. Safety reporting varied between studies, but the available evidence did not indicate that these strategies increased the risk of major surgical complications when applied in appropriately selected patients.

For early oral feeding, the main safety concern was gastrointestinal tolerance. Although nausea, vomiting, or transient feeding intolerance were reported in some studies, these events were usually self-limited and did not appear to increase the rate of major complications, including anastomotic leakage [9] [10] [11] [12] [13]. Importantly, in the analyzed trials, anastomotic leakage was generally reported as a clinically relevant postoperative event, often requiring objective confirmation and, in severe cases, reintervention, which supports the reliability of the conclusion that early oral feeding did not increase this risk [9] [10] [11] [12] [13].

Similarly, carbohydrate loading was generally well tolerated, with no clear increase in aspiration-related complications or other serious adverse events in colorectal surgical populations [14] [41] [42] [43]. In addition to not increasing anesthetic risk, some evidence suggests that preoperative carbohydrate loading may improve peri-induction hemodynamic stability, likely through better preoperative hydration and fewer hypotensive episodes during anesthesia induction [49]. In patients with metabolic vulnerability, particularly those with diabetes, safety required more careful interpretation. Current guidance advises against routine carbohydrate drinks in patients with severe diabetes or suspected gastroparesis [1], although one randomized trial demonstrated that carbohydrate loading combined with an individualized insulin regimen could be implemented safely in diabetic patients undergoing gastrointestinal surgery [44].

For oral nutritional supplementation and targeted perioperative nutritional support, tolerance was generally acceptable, although adherence may have influenced the observed effect [22] [23] [24] [25]. In the immunonutrition trials, adverse effects such as abdominal discomfort, cramps, or diarrhea were reported infrequently and rarely required discontinuation of supplementation [18] [19] [20] [21]. Multimodal prehabilitation was also generally safe, with no consistent intervention-related harm reported in the available randomized trials [26] [27] [28].

Taken together, the available evidence suggests that perioperative nutritional interventions are generally safe when used according to clinical context, patient selection, and tolerance, with most adverse events being mild and predominantly gastrointestinal in nature [1] [9] [10] [11] [12] [13] [14] [18] [22] [26] [41] [44] [49].

3.6 Findings in nutritionally at-risk and other clinically relevant subgroups

Across the included randomized controlled trials, the benefits of perioperative nutritional interventions did not appear to be uniform across all patients. Treatment effects were generally more pronounced in patients with impaired nutritional status, reduced physiological reserve, or increased metabolic vulnerability [1] [18] [24] [25] [26] [44].

For oral nutritional supplementation and targeted nutritional support, the clearest benefits were observed in malnourished or nutritionally at-risk patients [24] [25]. According to current guidance, this high-risk group includes patients with severe recent weight loss, low BMI, or high nutritional risk screening scores (e.g. weight loss >10–15% within 6 months, BMI <18.5 kg/m², or NRS ≥ 5) [1]. Similarly, in the immunonutrition trials, greater benefit appeared to occur in patients with higher nutritional or surgical risk, particularly when supplementation was continued into the postoperative period [18] [19].

For multimodal prehabilitation, the available evidence suggests particular relevance in patients with reduced physiological reserve, including frail individuals and those at higher perioperative risk [1] [26] [27] [28]. In contrast, subgroup-specific data were more limited for early oral feeding, where most studies supported overall feasibility and safety but did not provide robust stratified analyses [9] [10] [11] [12] [13]. For carbohydrate loading, baseline metabolic status appeared important, with diabetes mellitus and obesity emerging as potential effect modifiers, especially in relation to glycemic response, gastrointestinal recovery, and safety [1] [41] [42] [44].

Overall, these findings support a risk-stratified approach rather than uniform use of all perioperative nutritional interventions. However, subgroup-specific evidence remained limited, and most trials were not powered to detect differences across nutritional or metabolic risk categories, highlighting the need for future RCTs specifically designed for high-risk nutritional populations [18] [24] [25] [26] [44].

3.7 Summary of main findings

Taken together, the included randomized controlled trials suggest that perioperative nutritional interventions may provide clinically meaningful benefits in colorectal cancer surgery, although the strength and consistency of effects differed across intervention types. Early oral feeding and carbohydrate loading were mainly associated with improved recovery, gastrointestinal function, and patient-reported well-being, while their effects on major postoperative outcomes were less consistent [9] [10] [11] [12] [13] [14] [41] [42] [43] [44]. Oral nutritional supplementation and targeted nutritional support appeared to be most beneficial in patients with pre-existing malnutrition or increased nutritional risk [22] [23] [24] [25]. Immunonutrition showed the clearest signal for reduction of infectious morbidity and modulation of perioperative inflammatory response, particularly in higher-risk patients [18] [19] [20] [21]. Multimodal prehabilitation including a nutritional component was associated with improved functional recovery and, in selected populations, reduced postoperative complications [26] [27] [28] [51] [52].

Overall, the evidence supports a risk-stratified perioperative nutritional approach rather than uniform application of all interventions. Benefits appeared more pronounced in malnourished, frail, or otherwise high-risk patients, whereas findings in unselected colorectal surgical populations were less consistent [1] [18] [24] [25] [26] [44]. Across intervention types, safety profiles were generally acceptable, with most adverse events being mild and predominantly gastrointestinal in nature [1] [9] [10] [12] [14] [18] [22] [26] [41] [44].

Identification

Records identified through database searching (n = 93)
- PubMed/MEDLINE (n = 53)
- Cochrane Library (n = 23)
- Scopus (n = 17)

↓

Duplicate records removed (n = 15)

↓

Screening

Records screened (n = 78)

↓

Records excluded (n = 35)

↓

Eligibility

Full-text articles assessed for eligibility (n = 43)

↓

Full-text articles excluded (n = 27)

↓

Included

Randomized controlled trials included in qualitative synthesis (n = 16)

Fig. 1. *PRISMA flow diagram of study identification, screening, eligibility assessment, and inclusion.*

4. Discussion

4.1 Principal findings

This systematic review of randomized controlled trials suggests that perioperative nutritional interventions may provide clinically meaningful benefits in colorectal cancer surgery, although the magnitude and consistency of effects differ across intervention types. The most consistent benefits were observed in postoperative recovery, gastrointestinal function, patient-reported well-being, and, in selected settings, reduced postoperative morbidity.

Among the evaluated strategies, early oral feeding and oral nutritional supplementation appeared to act mainly through a nutritional mechanism, by improving substrate availability and supporting recovery. By contrast, immunonutrition showed features of a more targeted immunometabolic intervention, with the clearest signal for reduction of infectious morbidity and modulation of perioperative inflammatory response, including favorable effects on markers such as IL-6 and CRP, particularly in patients undergoing major surgery or presenting with higher nutritional risk [18] [19] [20] [21]. Carbohydrate loading was mainly associated with improved metabolic recovery, gastrointestinal function, and perioperative comfort, while its effects on major postoperative outcomes were less uniform [14] [41] [42] [43] [44].

A further important finding is that the clinical value of these interventions does not appear to be uniform across the entire colorectal cancer population. Multimodal prehabilitation including a nutritional component was associated with improved functional recovery and appears to be particularly relevant in vulnerable surgical populations, especially frail patients and those with higher perioperative risk, such as ASA III/IV individuals [26] [27] [28]. Recent evidence syntheses referenced in the ESPEN 2025 guideline further suggest that the reduction in postoperative complications may be most pronounced in these higher-risk groups, with reported relative reductions in the range of approximately 36–44% in selected populations [1]. Overall, the available evidence supports a risk-stratified approach, in which the greatest benefit is observed in patients with malnutrition, frailty, reduced physiological reserve, or increased metabolic vulnerability, whereas effects on hard clinical endpoints remain less consistent in unselected populations [1] [18] [24] [25] [26] [44].

4.2 Interpretation by intervention type

The findings of this review suggest that perioperative nutritional interventions in colorectal cancer surgery should not be interpreted as a single, uniform category, as their mechanisms and clinical effects differ substantially.

Early oral feeding appears to be best understood as a recovery-oriented intervention. Its main value lies in supporting earlier return of gastrointestinal function and improving patient comfort without increasing the risk of major postoperative complications [9] [10] [11] [12] [13]. The effect on harder endpoints, such as length of hospital stay, was less consistent, likely because discharge timing is also influenced by local protocols and non-clinical factors.

Carbohydrate loading seems to exert its primary effect at the metabolic level. The available trials suggest benefits in terms of perioperative well-being, attenuation of insulin resistance, and faster gastrointestinal recovery, while evidence for a consistent reduction in major postoperative complications remains less robust [14] [41] [42] [43] [44]. This pattern supports the view that carbohydrate loading mainly improves the physiological response to surgery rather than acting as a direct complication-reducing intervention in all patients.

Oral nutritional supplementation and targeted perioperative nutritional support appear to have the greatest clinical relevance in patients with impaired baseline nutritional status [22] [23] [24] [25]. Their limited and less consistent effect in unselected populations suggests that simple supplementation alone may not be sufficient to change outcomes unless there is a demonstrable nutritional deficit or inadequate intake. This is clinically important, as it supports selective rather than routine use when the objective is complication reduction.

Immunonutrition occupies a somewhat distinct position. Unlike standard nutritional support, its effect appears to extend beyond substrate delivery and include modulation of perioperative inflammatory and immune responses [18] [19] [20] [21]. This may explain why its strongest signal was seen in infectious morbidity and inflammatory markers rather than across all postoperative endpoints. The available evidence suggests that this strategy may be particularly useful in oncological patients undergoing major surgery and in those with increased nutritional risk [1] [18] [19].

Finally, multimodal prehabilitation including a nutritional component should be interpreted as a broader perioperative optimization strategy rather than an isolated nutritional intervention [26] [27] [28] [51] [52]. Its benefit likely results from the combined effect of improved nutritional intake, enhanced physical conditioning, and greater physiological reserve before surgery. This also explains why its effects appear most pronounced in frail or otherwise high-risk patients, while results are more variable in broader surgical populations.

Taken together, these findings indicate that perioperative nutritional care in colorectal cancer surgery should be individualized. Some interventions primarily enhance recovery, others mainly improve metabolic or inflammatory responses, and some appear most effective only in selected high-risk groups. This distinction is essential for translating the evidence into rational clinical practice.

4.3 Risk-stratified clinical relevance

One of the most clinically relevant findings of this review is that perioperative nutritional interventions do not appear to provide equal benefit across the entire colorectal cancer population. Instead, the available evidence consistently suggests that their value is greatest in patients with higher nutritional, functional, or metabolic risk.

This is most apparent for oral nutritional supplementation, targeted nutritional support, and immunonutrition, where the strongest effects were observed in patients with pre-existing malnutrition, impaired nutritional status, or higher surgical stress burden [1] [18] [19] [24] [25]. In these groups, nutritional interventions are more likely to correct clinically meaningful deficits in energy intake, protein availability, immune competence, and metabolic reserve. By contrast, in well-nourished or unselected populations, the same interventions may produce smaller and less consistent effects on major postoperative outcomes.

A similar pattern can be observed in multimodal prehabilitation, where the most pronounced benefits appear to occur in patients with reduced physiological reserve, such as frail individuals, elderly patients, and those classified as ASA III/IV [1] [26] [51] [52]. In such populations, the combined impact of nutritional support, physical conditioning, and functional optimization may be especially important in improving resilience to surgical stress. This supports a more personalized perioperative strategy, rather than routine implementation of the same intervention package in all patients.

For carbohydrate loading, risk stratification appears relevant for a different reason. Here, the issue is not only potential benefit, but also metabolic appropriateness and safety. The available evidence suggests that baseline metabolic status, particularly the presence of diabetes mellitus or obesity, may modify both physiological response and tolerability [1] [41] [42] [44]. This highlights the need to individualize carbohydrate loading rather than treat it as universally applicable.

Taken together, these findings suggest that perioperative nutritional care in colorectal cancer surgery should be guided by risk profile rather than diagnosis alone. Screening tools and structured nutritional assessment are therefore essential, not only to identify patients with overt malnutrition, but also to distinguish those most likely to benefit from more intensive perioperative nutritional strategies [1] [33].

4.4 Consistency with current guidelines

The findings of this review are broadly consistent with current perioperative nutrition guidelines, particularly the updated ESPEN 2025 recommendations [1]. Overall, the available randomized evidence supports the central role of perioperative nutritional care in colorectal cancer surgery, although the strength of evidence differs between interventions and patient groups.

The strongest agreement with guideline recommendations was observed for early oral feeding and carbohydrate loading, which reflect the standard ERAS-based pathway recommended for most surgical patients [1] [9] [10] [11] [12] [13] [14] [41] [42] [43] [44]. In this sense, ESPEN 2025 may be viewed as a "Plan A" approach based on avoidance of prolonged fasting, preoperative carbohydrate loading, and early postoperative oral feeding [1]. The included trials generally support this strategy, although carbohydrate loading still requires caution in patients with severe diabetes or suspected gastroparesis [1] [14] [41] [42] [43] [44].

For oral nutritional supplementation, targeted perioperative support, and immunonutrition, the agreement with current guidance is also strong, particularly in patients at increased nutritional risk [1] [18] [19] [20] [21] [22] [23] [24] [25]. Here, ESPEN 2025 effectively introduces a "Plan B" strategy involving more intensive nutritional therapy in patients with malnutrition, major deficits, postoperative complications, or inadequate oral intake [1]. In such patients, nutritional therapy is increasingly regarded as an essential, and in practice often mandatory, component of surgical care [1].

An important update in the 2025 guidance is the stronger emphasis on sarcopenia as an independent perioperative risk factor, even in patients with normal or elevated BMI [1]. This is relevant because many earlier RCTs did not consistently assess muscle mass, whereas current recommendations support identifying risk beyond BMI alone [1] [33].

The evidence on multimodal prehabilitation also aligns with recent guideline trends, particularly for frail and high-risk surgical patients [1] [26] [27] [28] [51] [52]. At the same time, current guidelines are broader than the CRC-specific randomized evidence alone, as some recommendations are also supported by data from wider major abdominal and oncological surgical populations [1].

4.5 Limitations

This review has several limitations. First, the included randomized controlled trials were heterogeneous in terms of intervention type, timing, duration, patient selection, and outcome assessment, which limits direct comparability across studies. Second, baseline nutritional status was not reported consistently, and older trials often relied on less precise definitions of malnutrition, without systematic assessment of sarcopenia or body composition [18] [19] [33]. Third, many studies included relatively small samples and were not powered to detect subgroup-specific effects, particularly in malnourished, frail, obese, or diabetic patients [24] [25] [26] [44].

Additional limitations arise from variability in clinically important endpoint definitions, including postoperative complications, anastomotic leakage, and patient-reported outcomes. Furthermore, the inherent difficulty of blinding both patients and investigators in nutritional trials, particularly those evaluating early oral feeding or dietary counselling, introduces a potential risk of performance and detection bias. This is especially relevant in studies with subjective or recovery-related endpoints.

Methodological limitations were also evident in the assessment of metabolic outcomes. Several trials evaluating carbohydrate loading relied on surrogate indices of insulin resistance rather than gold-standard dynamic metabolic methods, which may reduce the precision of reported metabolic effects [14] [41] [42]. In addition, some interventions, particularly immunonutrition and prehabilitation, were evaluated using protocols that differed substantially in composition and duration, making interpretation less uniform [18] [19] [20] [21] [26] [27] [28].

Finally, the clinical effect of oral interventions may have been influenced by variable patient adherence to predefined nutritional targets, a factor that was not consistently or rigorously reported across studies. This is particularly relevant for oral nutritional supplementation and immunonutrition, where tolerance, satiety, and acceptability may affect the actual delivered dose. Moreover, although this review focused on colorectal cancer surgery, some recommendations discussed in relation to current guidelines are supported by evidence from broader major abdominal or oncological surgical populations, which may limit strict CRC-specific generalizability [1].

4.6 Future directions

Future research should focus on better-defined, risk-stratified colorectal cancer populations, particularly patients with malnutrition, sarcopenia, frailty, obesity, or diabetes, as these groups appear most likely to benefit from individualized perioperative nutritional strategies [1] [24] [25] [26] [33] [44]. There is also a need for trials using standardized definitions of nutritional risk and body composition, ideally incorporating contemporary frameworks such as GLIM and objective assessment of muscle mass [1] [33].

Further randomized studies should aim to standardize the timing, duration, and composition of nutritional interventions, especially for immunonutrition, oral nutritional supplementation, and multimodal prehabilitation [18] [19] [20] [21] [26] [27] [28]. More consistent reporting of clinically relevant outcomes, including anastomotic leakage, postoperative complications, patient-reported outcomes, and long-term functional recovery, would improve comparability across studies.

Future trials should also place greater emphasis on adherence to nutritional protocols, subgroup-specific analyses, and clinically meaningful endpoints rather than surrogate measures alone. This would help clarify which perioperative nutritional interventions should be applied routinely and which are most effective only in selected high-risk patients. In addition, future research should incorporate cost-effectiveness analyses and explore improved approaches to body composition assessment in order to enhance the precision and practical applicability of perioperative nutritional care.

5. Conclusions

Perioperative nutritional interventions appear to play an important role in colorectal cancer surgery, although their effects differ across intervention types and patient populations. The available randomized evidence suggests that early oral feeding and carbohydrate loading mainly support postoperative recovery and patient well-being, whereas oral nutritional supplementation, immunonutrition, and multimodal prehabilitation seem particularly relevant in patients with increased nutritional or physiological risk.

Overall, the findings of this review support a risk-stratified approach to perioperative nutritional care rather than uniform implementation of all interventions in all patients. Nutritional strategies appear most beneficial in individuals with malnutrition, frailty, sarcopenia, or other features of increased perioperative vulnerability. In patients with established malnutrition or major nutritional risk, perioperative nutritional therapy should be regarded not merely as beneficial, but as an increasingly mandatory component of surgical care.

Further high-quality randomized trials using standardized definitions, better subgroup characterization, and clinically relevant outcomes, including patient-reported outcome measures (PROMs), are needed to refine the role of perioperative nutritional care and improve its implementation in colorectal cancer surgery.

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