Review Article

Impact of preoperative immunonutrition on postoperative outcomes in gastrointestinal cancer surgery: a systematic review and meta-analysis

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ABSTRACT

Gastrointestinal cancer patients are at a significant risk of malnutrition, which negatively impacts their postoperative recovery and increases complications such as infections and prolonged hospital stays. This systematic review and meta-analysis of 19 studies highlight immunonutrition as an effective strategy to reduce these risks by improving immune responses in malnourished patients. Further randomized trials are recommended to optimize immunonutrition protocols in multimodal preoperative care guidelines.

Keyword: Meta-analysis, systematic review, malnutrition, immunonutrition, gastrointestinal cancer, hospital stay.

Introduction

Cancers of the esophagus, stomach, pancreatic, and colorectal tracts are a major global health problem, often requiring surgical treatments to be cured [1]. Complications are more common among patients who undergo surgical operations to remove tumors from the gastrointestinal (GI) tract, despite advancements in surgical techniques [2]. The metabolic effects of tumors and systemic inflammation can exacerbate malnutrition and sarcopenia, which are among the most serious consequences. [3, 4]. Up to 60% of gastrointestinal cancer patients exhibit nutritional deficiencies at diagnosis, which significantly reduces their immune condition and increases the challenges posed by surgery. [5, 6]. As a specific nutritional intervention, immunonutrition (IM) aims to modify the immune system and minimize the postoperative inflammatory response [7]. Immunomodulatory nutrition (IM) preparations differ from other types of nutritional support in that they include substrates that affect the immune system, such as nucleotides, omega-3 fatty acids (n-3 PUFAs), and L-arginine [8].

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Essential for T cell activity and wound healing, L-arginine is utilized in the synthesis of nitric oxide and polyamines. Systemic inflammation can be reduced by the modulation of arachidonic acid metabolism by omega-3 polyunsaturated fatty acids (n-3 PUFAs) [9, 10]. This process reduces the production of potent pro-inflammatory cytokines, with nucleotides being crucial for the rapid proliferation of immune system cells under metabolic stress. [11]. A large amount of clinical research has focused on preoperative immunonutrition. An updated assessment of preoperative immunonutrition's effectiveness has been offered by recent meta-analyses and RCT studies. Citations [12, 13]. Matsui et al.'s 2024 meta-analysis provides compelling evidence that preoperative immunonutrition therapy considerably reduced the risk of overall postoperative complications (RR = 0.78) and infectious complications (RR = 0.72) in patients with gastrointestinal malignancies who underwent surgical procedures [2]. Similarly, immunonutrition formulae including n-3 PUFAs are the subject of a 2025 meta-analysis that finds a 30% reduction in the relative risk for surgical site infections (SSIs) [15,16]. The function of preoperative immunonutrition in the ERAS pathway has also been the subject of research. Investigations have revealed a synergistic effect that shortens patients' hospital stays and speeds up their recoveries [17]. However, the application of IM is still controversial. Recent high-quality studies, including the 2026 study by Sakhri et al., have failed to demonstrate the clinical benefit of perioperative IM in well-nourished patients, thereby raising the question of the cost-effectiveness of IM and the target groups that are likely to benefit from the application of IM [11]. Heterogeneity in the results of the studies is often due to the formula used in the IM, the duration of application, and the nutritional status of the patients [11]. Though the application of IM in malnourished patients or in patients with major abdominal surgery is recommended by the revised 2025 ERAS protocol, no consensus exists with respect to the preoperative duration and the dosage of immunomodulators [20].

An overview of nutritional oncology highlights advancements in immunonutrition before gastrointestinal surgery in cancer patients. This meta-analysis reviews literature on its effects on inflammatory response, postoperative infections, and hospital stay duration, aiming to clarify its importance in cancer treatment through data analysis up to 2026.

Methods

Study Design: This review follows PRISMA guidelines and was registered in the PROSPERO database (Registration ID: CRD42024598122) before commencement.

Eligibility Criteria: Eligible studies focused on adults (≥18 years) undergoing elective gastrointestinal cancer surgery and receiving perioperative immunonutrition support, encompassing supplements like arginine, omega-3 fatty acids, and glutamine preoperatively. Control groups received standard preoperative nutrition or no supplements. Key outcomes included postoperative complications, hospital stay, and immune function parameters. All study designs were included, such as RCTs, non-RCTs, cohort, case-control, and observational studies, with only peer-reviewed articles and clinical trials involving human subjects published in English considered. Information Sources and Search Strategy: A comprehensive literature search of the following online databases was undertaken: MEDLINE, EMBASE via Ovid, Google Scholar, Clinical Trials.gov, and Cochrane Central Register of Controlled Trials (CENTRAL). No date restrictions were used. The search strategy used MeSH terms and free text words, including: (("immunonutrition" [MeSH Terms] OR "immunonutrition" [Title/Abstract] OR "immune-enhancing nutrition" [Title/Abstract]) AND ("gastrointestinal neoplasms" [MeSH Terms] OR "gastrointestinal cancer" [Title/Abstract]) AND ("surgical procedures, operative" [MeSH Terms] OR "surgery" [Title/Abstract])) AND ("postoperative complications" [MeSH Terms] OR "postoperative outcomes" [Title/Abstract] OR "length of stay" [MeSH Terms] OR "hospitalstay" [Title/Abstract] OR "immune function" [Title/Abstract]) AND ("preoperative care" [MeSHTerms] OR "preoperative" [Title/Abstract]) AND ("randomized controlled trial" [Publication Type] OR "controlled clinical trial" [Publication Type]) NOT ("pediatric" [Title/Abstract] OR "children" [Title/Abstract]) NOT ("case reports" [Publication Type] OR "review" [PublicationType]) AND (English[lang]). Study Selection: All citations were imported into a reference management tool, with duplicates excluded, and titles and abstracts were reviewed by two reviewers. Inclusion and exclusion criteria were applied to full texts, resolved by a third reviewer if discrepancies arose, as documented in the PRISMA flow chart. Data Extraction: The review team established a standardized data extraction process, focusing on key areas: study identification details, patient demographics, interventions related to immunonutrition, and outcomes including complications and hospital stay duration. Additional information was obtained by reaching out to original study authors when necessary. Quality Assessment:

The studies' methodological quality was evaluated by two reviewers, with RCTs assessed using the Cochrane Risk of Bias Tool (RoB 2) and observational studies using the Newcastle-Ottawa Scale (NOS).

Data analysis

Data analysis utilized both qualitative and quantitative methods, including a meta-analysis with STATA software (version 17) using a random-effects model to derive pooled effect estimates. Treatment effects for dichotomous outcomes, such as postoperative infections and overall complications, were reported as pooled odds ratios (OR) with 95% confidence intervals (CI). Continuous outcomes like hospital stays were measured as standardized mean differences (Hedges' *g*) with 95% CI. Statistical heterogeneity was evaluated via the I^2 statistic and Cochran's Q statistic, with subgroup analyses identifying effect size differences by variable type, supported by forest plots. A two-tailed p value of <0.05 indicated significance.

Results

The PRISMA flow diagram outlines the selection process for a systematic review, beginning with 1,271 records and eliminating 284 duplicates. After screening 987 titles/abstracts, 892 were excluded for not meeting initial criteria. From 95 full-text articles assessed, 76 were discarded due to unsuitable outcomes or insufficient data, culminating in 19 high-quality studies included in the review (Figure 1). Characteristics of Included Studies: The systematic review evaluated 19 studies from 2002 to 2024 regarding the effects of preoperative immunonutrition on gastrointestinal cancer surgeries. Most studies (78.9%) were interventional, primarily random controlled trials (RCTs), covering various surgical procedures: gastric (5), esophageal (5), colorectal (2), pancreatic (1), and major abdominal surgeries (6) (Table 1). Participant Characteristics: A total of 2,536 participants from 19 studies were analyzed. Sample sizes varied from a small pilot study to large multicenter trials. The mean age of participants was within the 60s. The age ranges reported in studies such as Giger et al. (2007) [28], Sultan et al. (2012),[32] and Fujitani et al. (2012) [24], confirmed the inclusion of adults from their 20s into their 90s, though the typical cohort centered on patients in their sixth and seventh decades. A reported male predominance was evident across all cohorts, indicating the higher epidemiological incidence of gastrointestinal cancers in males. For example, male participants constituted 86% of the cohort in Kanekiyo et al. (2018) [39], and approximately 75% in Fujitani et al. (2012) [24]. This gender distribution was consistent even in studies with smaller sample sizes.

The study focused on patients with histologically confirmed resectable gastrointestinal cancers who were scheduled for elective curative surgery, primarily involving older male adults, some of whom were malnourished or had cachexia. Follow-Up Duration: Variability in follow-up durations among studies is primarily dictated by the outcomes assessed. Most research uses a 30-day follow-up for short-term postoperative outcomes, monitoring complications and hospital stay length. Some studies extend follow-up until hospital discharge, while others focus on long-term survival and oncological outcomes, with specific laboratory assessments up to postoperative day 7. This illustrates the difference between immediate postoperative morbidity evaluations and longer-term efficacy investigations. Intervention, Timing, and Surgical Procedures: Intervention Composition IM intervention utilized oral or enteral formulas enhanced with immunomodulating substrates, primarily L-arginine, omega-3 fatty acids (eicosapentaenoic and docosahexaenoic acids), and RNA nucleotides. Common commercial products included Impact® and its variants, while control groups were typically given standard diets, enteral formulas, or standard intravenous nutrition, often implemented in a double-blind manner with matched placebo formulas (Table 1). Timing of Administration:The timing of immunonutrition administration varied, with preoperative-only supplementation being the most common, lasting 5 to 7 days before surgery. Some studies utilized shorter durations, while a perioperative approach combined preoperative and postoperative supplementation for similar time frames. Direct comparisons between preoperative-only and perioperative regimens against control were conducted in a few studies (Table 1). Surgical Procedures: The surgical interventions were exclusively major oncological resections for gastrointestinal malignancies. Gastric Cancer: Radical gastrectomy (total or partial), performed via open, laparoscopic, or robot-assisted approaches. Esophageal Cancer: Esophagectomy or oesophagogastrectomy, including transthoracic and transhiatal techniques. Colorectal Cancer: Elective laparoscopic or open resection for colon cancer. Pancreatic Cancer: Pancreatoduodenectomy (Whipple procedure). Mixed/Abdominal Procedures: Several studies included heterogeneous cohorts undergoing major elective surgery for cancers of the upper and lower GI tract, including hepatic and pancreatic resections. This confirms that immunonutrition is evaluated mainly in high-stress surgical oncology procedures, with variations in the timing and duration of nutritional interventions. Effects of Preoperative Immunonutrition on Postoperative Results. The analysis indicated a mixed but generally positive influence of preoperative immunotherapy (IM) on clinical, immune, and biochemical outcomes in patients undergoing gastrointestinal cancer surgery, based on 19 studies.

1. Postoperative Complications and Infectious Morbidity: The effect of IM on overall and infectious complication rates was heterogeneous. Several studies reported statistically significant reductions in key morbidity metrics. For example, A study found that IM significantly lowered both infectious (21.4% vs. 37.5%, p=0.040) and overall complication rates (28.6% vs. 44.6%, p=0.049) in gastric cancer patients with cachexia] 22[. Similarly, another study reported a marked reduction in postoperative infections (17.5% vs. 34.9%, p<0.05), and a third observed significantly fewer infections in the IM group following gastrectomy (7% vs. 28%, p=0.039) [34,31]. In malnourished cohorts, perioperative IM significantly reduced infection rates and length of hospital stay compared to standard care [34,35]. On the other hand, other high-quality trials in colon, gastric, and esophageal cancer found no significant benefit [21,24,27]. In the oesophagogastric surgery study reported no statistically significant differences in overall or infectious complications were reported between IM and control groups [32]. One study found no benefit of a short 3-day IM regimen in well-nourished patients[33].

2. Immune Function and Inflammatory Response: A more consistent beneficial effect was observed on modulating the postoperative immune and inflammatory response, multiple studies revealed that IN helped improve postoperative immune depression, this was evidenced by better preservation or faster recovery of immune cell counts (e.g., higher lymphocyte counts and CD4/CD8 ratios) and immunoglobulin levels (e.g., IgA, IgG) in the IM groups [22,26,29,31]. Furthermore, IM was also associated with attenuation of the postoperative systemic inflammatory response, as evidenced by reductions in key inflammatory markers like IL-6 and CRP in IM groups compared to controls [28,29,35]. This contrasts with mixed results in terms of clinical complications.

3. Nutritional and Recovery Parameters: IM showed a positive impact on nutritional status and recovery metrics. One study reported significantly better weight recovery one month after surgery in the IM group compared to ongoing weight loss in controls (p=0.002) [21]. Improvements in rapid-turnover proteins like prealbumin and transferrin were also observed in many studies [26,25,39]. While the length of hospital stay was significantly reduced in some studies, this was not a universal finding [28,34].

4. Long-Term and Exploratory Outcomes: Evidence for long-term oncological benefits was limited. One study found no significant difference in 2-year overall or progression-free survival [23]. Exploratory analyses of the tumor microenvironment in another study revealed IM might promote a more immunologically favorable profile, though clinical correlations remain unestablished [36].

Preoperative immunonutrition has a modulating effect on postoperative immune and inflammatory responses, with its influence on clinical complications being variable. This effect seems to be more significant in specific subpopulations, such as malnourished patients or those with gastric cancer cachexia, compared to well-nourished patients undergoing major resections (Table 1). Meta-Analysis results: The random-effects meta-analysis indicates a significant protective effect of preoperative immunonutrition against postoperative complications in gastrointestinal cancer surgery (Pooled OR = 0.57, p = 0.001). It particularly reduces infectious complications by about 50% (Pooled OR = 0.48, p = 0.00), with low heterogeneity (I^2 = 5.24%). However, no significant effect was found on overall complications (Pooled OR = 0.78, p = 0.54), which exhibited high heterogeneity (I^2 = 64.82%). The data suggest that immunonutrition effectively lowers infectious morbidity, aligning with its role in immune modulation, while the overall complication rates may be influenced by non-infectious events. Subgroup differences showed no significance (p = 0.28), reinforcing the robust effect on infectious outcomes. (Figure 2). The random effects of meta-analysis evaluating preoperative immunonutrition's impact on postoperative length of hospital stay (LOS) revealed no statistically significant effect (pooled Hedges' g 0.37, 95% CI -0.59 to 1.34, p = 0.45). A trend toward a longer stay in the immunonutrition group was noted, with extreme heterogeneity (I^2 = 97.61%, τ^2 = 2.35) indicating real differences among studies rather than sampling error. Individual study results were

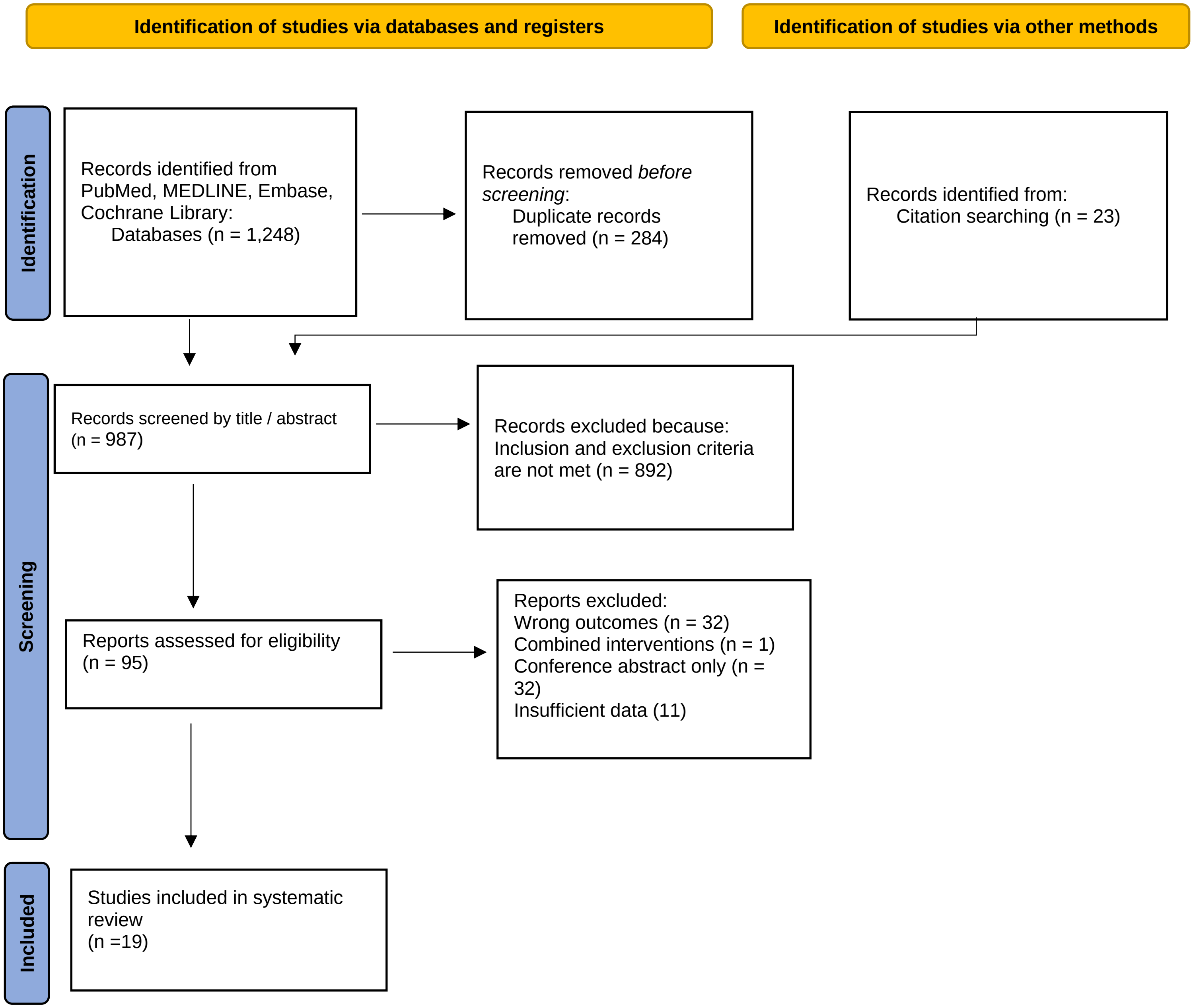

Figure 1: PRISMA 2020 Flow Diagram for Systematic Review.

Table 1: Summary of Included Studies Investigating Preoperative Immunonutrition in Gastrointestinal Cancer Surgery.

Study ID (Author, Year)	**Country**	**Study Design**	**Population (Cancer Type)**	**Sample size**	**Intervention (IM Group)**	**Control Group**	**Primary Outcome (s) Assessed**	**Key Findings on Postoperative Outcomes**
Lee et al., 2021 [21]	South Korea	RCT	Colon Cancer	161	Oral IM (7 days pre-op)	Normal diet	Complications, Nutritional status	No difference in complications. Better weight recovery at 1 month in IM group.
Yu et al., 2024 [22]	China	RCT	Gastric Cancer (Cachexia)	112	Enteral IM (7 days pre-op)	Isocaloric standard EN	Infectious/Overall complications, Immune function	Significant Reduction in infectious & overall complications. Improved lymphocyte count & IgA.
Li et al., 2021 [23]	China	RCT	Esophageal Cancer	103	Enteral IM (7 days pre-op)	Isocaloric, non-IM EN	Complications, Immune function, 2-year survival	Lower infectious complications (NS). Improved CD4/CD8

								ratio. No difference in 2-year survival.
Fujitani et al., 2012 [24]	Japan	RCT	Gastric Cancer	244	Oral Impact® (5 days pre-op)	Regular diet	Postoperative complications, CRP	No significant difference in complications or CRP levels.
Gunerhan et al., 2009 [25]	Turkey	RCT	GI Tumors (Mixed)	42	Specialized IM formula (7 days pre-op)	Normal diet / Standard EN	Immune parameters, LOS	Increased prealbumin in IM group. No difference in infection rate or LOS.
Xu et al., 2006 [26]	China	RCT	Colorectal/Gastric Cancer	60	Enteral IMPACT (7 days pre-op)	Isocaloric standard EN	Complications, Immune/Biochemical markers	Significant reduction in complications (6.7% vs 26.7%). Improved IgG, CD4/CD8, prealbumin.
Mudge et al., 2018 [27]	Australia	RCT	Esophageal Cancer	276	IN (7 days pre/post-op)	Standard nutrition	Infectious complications	No significant difference in infection rates (37-51%

								across groups).
Giger et al., 2013 [28]	Switzerland	RCT	GI Cancer (Mixed)	46	IN (5- or 2-days pre-op)	No pre-op IN	Inflammatory response, LOS	Reduced IL-6 & CRP. Shorter LOS in IN groups. No difference in infections.
Ateş et al., 2004 [29]	Turkey	RCT	Gastric/Colorectal Cancer	42	EEN (Impact) peri-op	TPN	Immune parameters	Improved CD4+ count, reduced CRP & cortisol in EEN group.
Braga et al., 2002 [30]	Italy	RCT	GI Cancer (Mixed)	160	IMPACT (5d pre + 7d post-op)	Standard formula	Infectious complications	Significant reduction in infections (17.5% vs 34.9%).
Okamoto et al., 2009 [31]	Japan	RCT	Gastric Cancer	60	Immune-enhanced formula (7d pre-op)	Isoenergetic standard formula	Infectious complications, Immune response	Significant reduction in infections (7% vs 28%). Better preservation of CD4+ cells.
Sultan et al., 2012 [32]	Australia	RCT	Esophagogastric Cancer	195	Omega-3 EN (7d	Standard EN / Post-op only	Morbidity, Mortality, Immune function	No significant difference

					pre/post-op)			in morbidity, mortality, LOS, or immune markers.
Giger-Pabst et al., 2013 [33]	Switzerland	RCT	GI Cancer (Mixed, Well-nourished)	108	Impact RTD (3 days pre-op)	Isocaloric/isonitrogenous placebo	Complications, Immune function	No significant difference in complications or immune outcomes.
Braga et al., 2002 [34]	Italy	RCT	GI Cancer (Mixed, Malnourished)	150	IM (7d pre and/or post-op)	Standard post-op diet	Infections, LOS	Significant reduction in infections and shorter LOS with perioperative IM.
Gianotti et al., 2002 [35]	Italy	RCT	GI Cancer (Mixed)	305	Specialized diet (5d pre and/or post-op)	Conventional IV	Complications, Immune/Inflammatory response	Pre/peri-op IM reduced infections, improved immune markers (CD4/CD8, IL-2), reduced CRP/IL-6.
D'Ignazio et al., 2020 [36]	Italy	Prospective Observational	GI Cancer (Mixed)	24	Impact Oral (7 days pre-op)	Regular diet	Tumor microenvironment	IM associated with favorable immune cell profile in tumor tissue.

Tumas et al., 2020 [37]	Lithuania	Clinical Trial	Pancreatic/Periampullary	70	Oral IM (5 days pre-op)	Control	Severe complications, Inflammatory markers	Fewer severe complications in IM group. No significant difference in inflammatory markers.
Martin et al., 2018 [38]	Switzerland	Retrospective	Esophageal Cancer	76	Enteral IM (7 days pre-op)	No IM	Complications (CCI, leaks, infections)	Mixed results: Higher major complications & leaks in IM group, but similar median CCI.
Kanekiyo et al., 2018 [39]	Japan	Prospective Randomized	Esophageal Cancer	40	IM (7d pre + 7d post-op)	Control	Complications, Nutritional markers	Fewer infectious complications & antibiotic use in IM group. Higher prealbumin levels

IM: Immunonutrition; RCT: Randomized Controlled Trial; EN: Enteral Nutrition; EEN: Enteral Immunonutrition; TPN: Total Parenteral Nutrition; LOS: Length of Hospital Stay; CRP: C-reactive protein; IL-6: Interleukin-6; CCI: Comprehensive Complication Index; GI: Gastrointestinal.

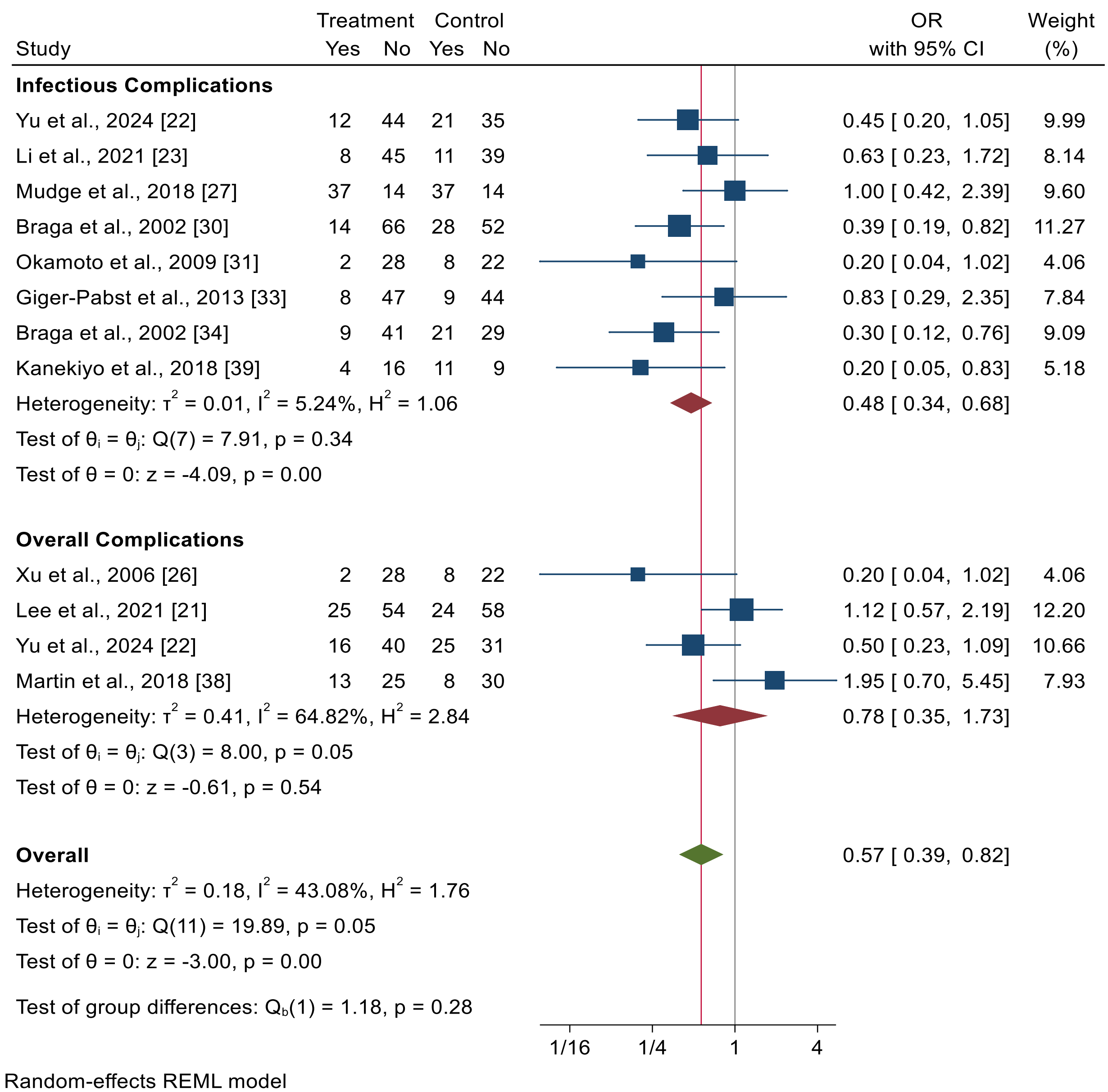

Figure 2: Forest Plot Illustrating the Impact of Preoperative Immunonutrition on Postoperative Complications in GI Cancer Surgery.

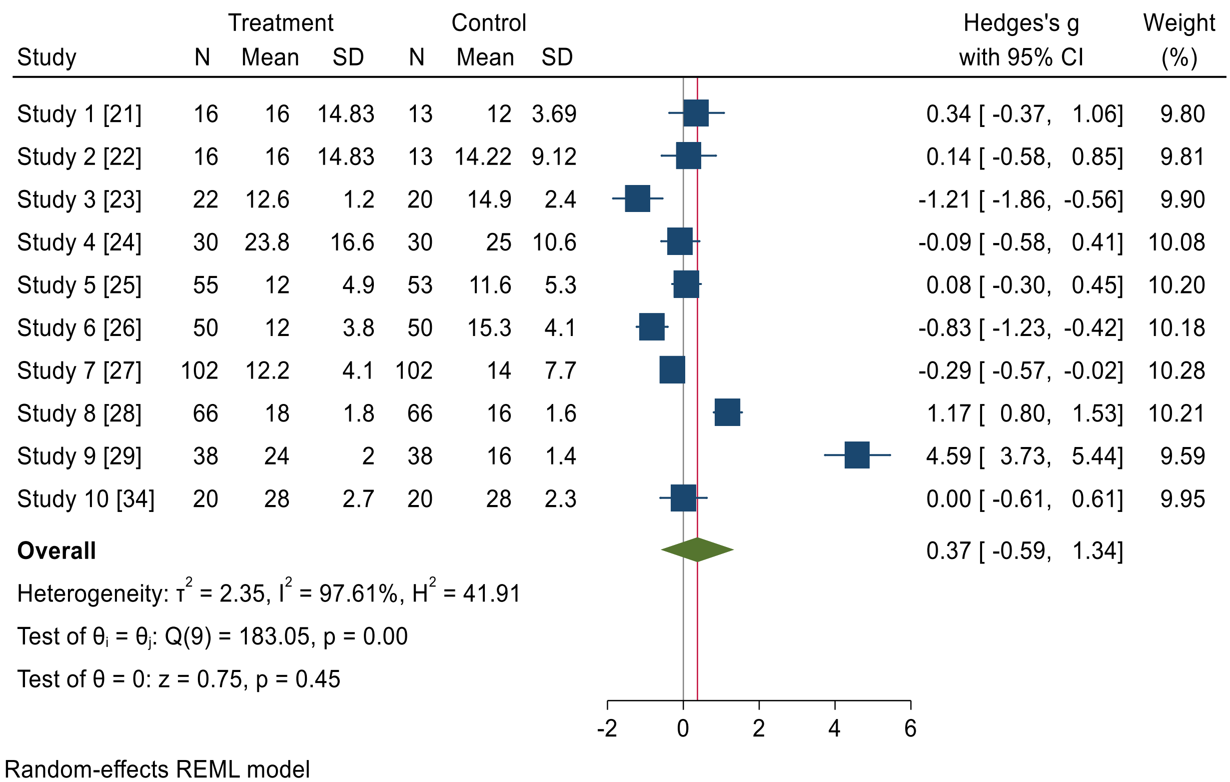

Figure 3: Forest Plot of the Effect of Preoperative Immunonutrition on Postoperative Length of Hospital Stay in GI Cancer Surgery.

Figure 4:Risk of Bias assessment by ROB II tool.

Table 2: Risk of Bias assessment by NOS tool.

Study ID	Newcastle-Ottawa scale for cohort								
	Selection				Comparability	Outcome			Score (Out of 9)
	Representativeness of the exposed cohort (*)	Selection of the non-exposed cohort (*)	Ascertainment of exposure (*)	Demonstration that outcome of interest was not present at start of study (*)	Comparability of cohorts based on the design or analysis (* *)	Assessment of outcome (*)	Was follow-up long enough for outcomes to occur (*)	Adequacy of follow up of cohorts (*)	
D'Ignazio, 2020 [36]	-	*	*	*	-	*	*	*	6
Martin, 2018 [38]	-	*	*	*	-	*	*	*	6

inconsistent; three showed significant reductions in LOS favoring immunonutrition, while two indicated significant increases. Overall, the meta-analysis does not provide conclusive support that preoperative immunonutrition affects LOS in gastrointestinal cancer surgery, with the variability potentially linked to unmeasured factors such as patient nutritional status and surgical type (Figure 3). Risk of Bias assessment: ROB II tool for RCTs and NOS for non-RCTs were utilized to assess risk of bias in the studies (Figure 4). Most RCTs displayed some concerns, while Lee 2021 [21] indicated a low risk. Non-RCTs also presented concerns, with Martin and D'Ignazio both scoring 6 out of 9 [38,36] (Table 2).

Discussion

The systematic review and meta-analysis of 19 studies show that preoperative immune modulation (IM) significantly impacts the immune and inflammatory response in patients undergoing GI cancer surgery, particularly reducing postoperative infectious complications. The pooled odds ratio of 0.57 suggests a nearly 50% lower risk of infections, such as surgical site infections and pneumonia. This is backed by the understanding that surgical stress leads to immunosuppression, increasing infection susceptibility, which IM components like arginine and omega-3 fatty acids may mitigate. Despite improvements in immune parameters correlating with reduced infections, the overall complication rates showed no significant pooled effect, likely due to the composite nature of this endpoint encompassing various unrelated events. This indicates that future research should focus on more precise outcomes relevant to immune modulation mechanisms. The impact on length of stay (LOS) was also inconclusive, with high heterogeneity (I^2 = 97.61%). LOS is multifactorial, influenced by institutional protocols, social factors, and discharge practices that vary across healthcare systems [43]. Some studies like Braga et al. [34] and Ateş et al [29]. reported shorter stays with IM, likely due to fewer infections, while others, including Martin et al. [38], suggested longer stays, possibly due to confounding by indication. This highlights a key limitation: LOS is a weak primary endpoint for nutritional trials unless care pathways are standardized.

A critical factor influencing immunonutrition (IM) efficacy is baseline nutritional status, with malnourished patients or those with cancer cachexia showing greater benefits compared to well-nourished groups. Well-nourished patients may handle surgical stress without extra support, while those with nutrient depletion benefit more, indicating a "therapeutic window" for IM. Future guidelines should focus on patient stratification like NRS 2002. Recent studies, including a pilot by D'Ignazio et al. [36], investigate IM's potential to alter the tumor microenvironment and improve responses to therapy, despite not showing survival advantages. Limitations include uncertain optimal dosing and duration, with studies indicating a 3–7-day regimen, and variations in IM products affecting results. Additionally, the impact of evolving Enhanced Recovery After Surgery (ERAS) protocols remains unaddressed in previous research.

Conclusion

Preoperative immunonutrition reduces infectious complications in gastrointestinal cancer surgery patients and enhances postoperative inflammatory and immunological responses, especially in malnourished patients. Further investigation into pathophysiological pathways and multimodal perioperative care is necessary, along with recent RCTs to establish optimal timing, formulations, and patient selection for high-risk malnourished individuals.

Conflict of Interest

None

Funding

None

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