Section: General Surgery

Systematic Review

EFFECT OF PREOPERATIVE IMMUNONUTRITION IN MALNOURISHED GASTROINTESTINAL CANCER PATIENTS UNDERGOING SURGERY: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Malnutrition affects a substantial proportion of patients undergoing surgery for gastrointestinal (GI) cancer and is independently associated with increased postoperative infectious morbidity, prolonged hospital stays, and impaired recovery. Immunonutrition (IMN) — enteral or oral formulas enriched with arginine, omega-3 fatty acids, and nucleotides — has been proposed to counteract the immune and metabolic suppression of surgery and malignancy, but evidence specific to malnourished GI cancer patients remains fragmented across multiple reviews. The objective is to synthesise available evidence on the effect of preoperative immunonutrition on postoperative outcomes specifically in malnourished patients undergoing surgery for gastrointestinal cancer.

Materials and Methods: PubMed was searched for systematic reviews, meta-analyses, and randomised controlled trials addressing perioperative or preoperative immunonutrition in gastrointestinal cancer surgery, with particular attention to studies reporting outcomes stratified by baseline nutritional status. Eleven review-level and trial-level sources meeting predefined eligibility criteria were retained and synthesised narratively, given heterogeneity in malnutrition definitions and outcome reporting.

Results: Across pooled analyses of predominantly mixed-nutritional-status cohorts, preoperative and perioperative immunonutrition reduced infectious complications (odds ratios approximately 0.52–0.58), surgical site infection, and anastomotic leak, and shortened hospital stay by roughly 1.5–2 days, without a demonstrated mortality benefit. The largest meta-analysis reporting a nutritional-status subgroup found this benefit to be statistically independent of baseline nutritional status, while a smaller body of evidence, including a dedicated prehabilitation review, describes a numerically greater benefit among malnourished patients. Only one identified trial — an ongoing protocol — enrols exclusively malnourished patients, underscoring a persistent evidence gap.

Conclusion: Preoperative immunonutrition is a low-risk, biologically plausible adjunct that reduces infectious morbidity and shortens hospital stay after gastrointestinal cancer surgery. Existing subgroup evidence suggests this benefit is preserved, and plausibly amplified, in malnourished patients, supporting current guideline recommendations to prioritise its use in this high-risk group. Adequately powered trials enrolling malnourished GI cancer patients as the primary study population are still needed to confirm the magnitude of benefit.

Keywords: Immunonutrition; malnutrition; gastrointestinal neoplasms; perioperative care; postoperative complications; systematic review.

INTRODUCTION

Malnutrition is one of the most common and consequential comorbidities in patients presenting for surgery for gastrointestinal (GI) cancer. Reported prevalence varies by tumour site, disease stage, and screening tool, but broadly ranges from roughly one in five patients with earlier-stage colorectal cancer to well over half of patients with oesophagogastric or pancreatic malignancy, where tumour location and exocrine dysfunction directly impair intake and digestion. Validated tools — Nutritional Risk Screening 2002, the Patient-Generated Subjective Global Assessment, and the newer Global Leadership Initiative on Malnutrition (GLIM) criteria — are applied inconsistently across institutions, which contributes to this variation. Despite that heterogeneity, malnutrition is consistently identified as one of the strongest modifiable risk factors for adverse surgical outcomes, which has made its correction, or at least mitigation, before surgery a central goal of perioperative care.[1–3]

The pathophysiology of malnutrition in GI cancer differs from simple starvation. Reduced oral intake — driven by dysphagia, gastric outlet or luminal obstruction, early satiety, nausea, and anorexia — combines with tumour-driven systemic inflammation to produce a state often termed cancer cachexia. Circulating pro-inflammatory cytokines, particularly interleukin-6 and tumour necrosis factor-alpha, drive hepatic acute-phase protein synthesis at the expense of skeletal muscle and suppress appetite centrally, so nutritional decline continues even when calorie intake is partially maintained. Surgery then superimposes a second, acute neuroendocrine and inflammatory stress response — cortisol and catecholamine release, further cytokine elevation, and a transient suppression of cell-mediated immunity — on a patient who, if malnourished, has little physiological reserve left to draw on. This combination of chronic, cancer-driven depletion and acute surgical stress is thought to explain why malnutrition and major GI cancer surgery interact so unfavourably.[4–6]

The clinical consequences of this interaction are well documented. Malnourished patients undergoing GI cancer surgery experience higher rates of surgical site and other infectious complications, anastomotic leak, prolonged mechanical ventilation and intensive care stay, delayed wound healing, and longer overall hospital admission than their well-nourished counterparts. Beyond the immediate postoperative period, malnutrition is also associated with reduced tolerance of adjuvant chemotherapy, higher rates of treatment delay or dose reduction, impaired quality of life, and, in several cohort studies, worse long-term survival independent of tumour stage. Because many of these downstream consequences are set in motion before the incision is even made, attention has increasingly turned to preoperative — rather than purely postoperative — nutritional optimisation as a strategy to interrupt this trajectory.[7–9]

Immunonutrition (IMN) is one such preoperative strategy: enteral or oral formulas supplemented with specific immune-modulating substrates — most commonly L-arginine, omega-3 polyunsaturated fatty acids, and ribonucleic acid nucleotides, sometimes alongside glutamine — given in place of, or in addition to, standard nutritional support in the days before surgery. The rationale, developed from critical care and surgical immunology research beginning in the early 1990s, is that each component targets a deficit induced by surgical stress and malignancy: arginine supports nitric oxide synthesis, T-lymphocyte proliferation, and wound collagen deposition, all suppressed after major surgery; omega-3 fatty acids compete with arachidonic acid at the cell membrane to shift eicosanoid production away from pro-inflammatory mediators; and nucleotides supply building blocks needed by rapidly dividing cells, including enterocytes and lymphocytes, when endogenous synthesis may be inadequate. A landmark randomised trial subsequently showed that preoperative oral arginine and omega-3 supplementation improved the immunometabolic host response and reduced complications after colorectal cancer resection, establishing the preoperative window specifically as a viable point of intervention. These mechanisms are of particular relevance in patients who are already malnourished, since baseline substrate depletion and impaired cell-mediated immunity — the deficits IMN is designed to correct — are present before the added insult of surgery. This is the basis for the hypothesis, central to this review, that malnourished patients may gain at least as much, and plausibly more, benefit from immunonutrition than well-nourished patients undergoing the same operation.[10–12]

This biological plausibility, together with several decades of accumulated randomised trial evidence in surgical oncology, has translated into guideline endorsement. Clinical practice guidelines, including the ESPEN guideline on clinical nutrition in surgery, recommend perioperative administration of immune-modulating formulas to patients undergoing major cancer surgery, with particular emphasis on those who are malnourished or otherwise at nutritional risk. In practice, however, most of the randomised evidence underpinning these recommendations was generated in trials enrolling unselected surgical populations — patients of any nutritional status — with malnutrition-specific effects reported, where reported at all, only as secondary or post hoc subgroup analyses rather than as the primary research question. This leaves an important and, to our knowledge, insufficiently consolidated question: whether malnourished GI cancer patients specifically derive the same, a greater, or a genuinely uncertain benefit from preoperative immunonutrition compared with well-

nourished patients undergoing equivalent surgery.[13–14]

This review therefore asks a focused question, structured around a standard PICO framework: in adult patients with malnutrition undergoing surgery for gastrointestinal cancer (esophageal, gastric, pancreatic, hepatobiliary, or colorectal), what is the effect of preoperative immunonutrition, compared with standard isocaloric/isonitrogenous nutrition or no supplementation, on postoperative infectious complications, surgical site infection, anastomotic leak, length of hospital stay, and mortality? By deliberately foregrounding the malnourished subgroup — rather than treating it as an incidental finding within broader trials — this review aims to clarify how much of the confidence reflected in current guideline recommendations rests on evidence that actually speaks to this specific, high-risk population, and where the evidence base still falls short.[15]

MATERIALS AND METHODS

Protocol and registration: This is a rapid narrative systematic review conducted according to the general reporting structure recommended by PRISMA 2020, adapted to what a single-reviewer, single-database search performed on 20 August 2026 can support. The review was not registered prospectively (e.g., with PROSPERO) and no full PRISMA checklist or PRISMA-P protocol was produced in advance of the search; both are listed as priorities for a follow-on, fully resourced review in Section 5. Because much of the highest-level evidence on this question already exists as systematic reviews and meta-analyses, this review functions in part as an overview of reviews, supplemented by primary RCTs and RCT protocols identified during the search, rather than as a de novo synthesis of individual trial data.

Eligibility criteria (PICO): Population: adults undergoing elective surgery for gastrointestinal cancer (oesophageal, gastric, pancreatic, hepatobiliary, or colorectal), with malnutrition defined by a validated tool (e.g., NRS-2002, PG-SGA, GLIM criteria, unintentional weight loss, or low body mass index) or reported as a distinct analytic subgroup.

Intervention: preoperative, or perioperative regimens beginning preoperatively, oral or enteral immunonutrition (formulas containing arginine and omega-3 fatty acids, with or without nucleotides).

Comparator: standard isocaloric/isonitrogenous oral or enteral nutrition, or no supplementation.

Outcomes: postoperative infectious complications, surgical site infection, anastomotic leak, overall complication rate, length of hospital stay, mortality, and immune/inflammatory or nutritional biomarkers (see Section 2.6).

Study designs: systematic reviews, meta-analyses, evidence maps, randomised controlled trials, and RCT protocols were eligible. Case reports, non-systematic narrative reviews, editorials, and animal or in-vitro studies were excluded.

Exclusions: parenteral-only immunonutrition, paediatric populations, non-cancer GI surgery, and records for which no extractable data relevant to nutritional status could be identified.

Information sources: PubMed (MEDLINE) was the only bibliographic database searched, on 20 August 2026, with no restriction on publication language or date beyond the practical coverage of the database itself. Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, Scopus, and trial registries (e.g., ClinicalTrials.gov) were not searched; this single-database approach is a limitation of this rapid review and is discussed further in Section 5. Three additional records — Song 2015, Manzanares Campillo 2017, and Lakananurak 2026 — were incorporated from the reviewer's prior working knowledge of the field after live database access was intermittently blocked partway through the search; these are explicitly flagged wherever they appear ([Figure 1, Table 1], and the reference list) and were not independently re-confirmed against PubMed in this session.

Search strategy: Searches were run as free-text term combinations against PubMed's web interface. The principal queries, in the order executed, were:

1. “preoperative immunonutrition malnourished gastrointestinal cancer surgery systematic review”
2. “immunonutrition malnourished cancer surgery meta-analysis”
3. “immunonutrition” AND “malnourished” AND “systematic review” cancer surgery
4. “Adiamah preoperative immune modulating nutrition gastrointestinal cancer” (targeted author/topic search)
5. “Lee SY preoperative immunonutrition malnourished colorectal cancer surgery trial” (targeted author/topic search)
6. “ESPEN guideline immunonutrition surgical patients malnutrition”
7. “malnourished” “immunonutrition” “gastrointestinal cancer”

Reference checking was limited to related-article suggestions surfaced alongside these queries; a full backward/forward citation search (e.g., scanning the reference lists of every included review, or forward-citation tracking via Google Scholar or Scopus) was not performed and is recommended for any follow-on review.

Study selection process: Title and abstract screening was performed by a single reviewer (with AI assistance) against the eligibility criteria in Section 2.2; there was no second, independent reviewer and no adjudication step, which is a material departure from standard systematic review methodology. Figure 1 summarises the resulting flow: of 20 total records considered (17 from the PubMed searches above plus the 3 additional

records noted in Section 2.3), 8 were excluded — 2 for addressing a head-and-neck-only population, 2 for not being specific to GI-cancer surgery, 3 for being narrative rather than systematic in design, and 1 retained only as a general background citation rather than as an evidence source — leaving twelve sources for narrative synthesis: eight systematic reviews, meta-analyses, or evidence maps; one Cochrane review of a contextually related population; and three RCTs or RCT protocols.

Data extraction and outcome definitions: Data were extracted directly from PubMed abstract pages into a structured summary table [Table 1] capturing study design, tumour population, sample size, timing of immunonutrition relative to surgery, how each source handled or reported baseline nutritional status, and effect estimates for the outcomes below. Extraction was not duplicated or independently verified by a second reviewer, and no piloted, pre-specified extraction form was used. Where full-text confirmation of a numerical estimate was not possible within the scope of this review, this is explicitly flagged in [Table 1] rather than presented as confirmed.

Outcomes extracted, as defined by the original study authors (definitions were not harmonised across sources): postoperative infectious complications (e.g., surgical site infection, pneumonia, urinary tract infection, intra-abdominal sepsis); surgical site infection specifically; anastomotic leak; overall or non-infectious complication rate; length of hospital stay; in-hospital or short-term mortality; and, where reported, immune or nutritional biomarkers such as CD4+ lymphocyte count, prealbumin, or C-reactive protein.

Risk of bias and certainty of evidence: No formal risk-of-bias assessment was applied to the included primary trials (e.g., Cochrane RoB2), no methodological quality appraisal was applied to the included systematic reviews (e.g., AMSTAR-2 or ROBIS), and no certainty-of-evidence rating (e.g., GRADE) was produced. This is a significant departure from standard systematic review methodology and is listed as the top priority for a follow-on review in Section 5, particularly given known risk-of-bias concerns in this literature: many underlying trials are industry-funded or use proprietary formulas, blinding of an oral or enteral supplement is often incomplete, and sample sizes within nutritional-status subgroups are generally small.

Synthesis methods: Given substantial heterogeneity in malnutrition definitions, immunonutrition formulation, duration and timing of supplementation, tumour site, and outcome reporting across the identified sources, a quantitative re-analysis (formal meta-analysis of primary data) was not attempted. Findings are instead synthesised narratively by outcome domain (Sections 3.2–3.6), with reported effect estimates presented as published by the original authors and not recalculated or pooled across overlapping meta-analyses.

RESULTS

Overview of included evidence: [Figure 1] outlines the study identification and selection process, and Table 1 summarises the twelve sources retained for this review. Two large meta-analyses focus specifically on preoperative or perioperative immunonutrition in unselected GI cancer surgical populations and report nutritional-status-related findings (Adiamah 2019; Khan 2023). A further cluster addresses gastric cancer specifically (Song 2015; Cheng 2018; Rinninella 2020; Xin 2025). One systematic review of prehabilitation strategies across gastric, pancreatic, and colorectal cancer explicitly reports a differential benefit in malnourished patients (Grońska 2025). Only one identified study — a trial protocol — enrols malnourished patients as the sole eligible population (Lee et al., the K-CROSS trial). Two further RCTs contribute trial-level or pilot data (Manzanares Campillo 2017; Lakananurak 2026). The Cochrane review of head and neck cancer surgery is included for context, as this population overlaps substantially with malnourished GI cancer patients in terms of baseline nutritional depletion and surgical stress.

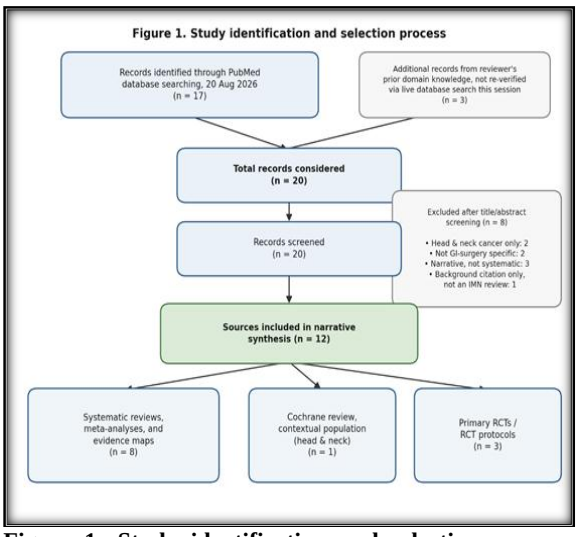

Figure 1: Study identification and selection process (PRISMA-style flow diagram). See footnote in the figure and Section 5 for methodological caveats.

Table 1: Summary of studies included in this review.

Study	Design and population	IMN regimen / comparator	Nutritional-status handling	Main findings
Adiamah et al. (2019)	Systematic review and meta-analysis; GI cancer surgery; 16	Preoperative IMN versus standard nutrition or no	Predominantly mixed-status cohorts;	Infectious complications: OR 0.52 (95% CI 0.38–0.71); hospital stay reduced by 1.57 days; no significant mortality or non-

	RCTs	supplementation	malnutrition-specific data limited	infectious benefit.
Khan et al. (2023)	Meta-analysis; GI cancer surgery; 37 RCTs	Perioperative enteral IMN versus control	Subgroup analysis by baseline nutritional status	Infectious complications: OR 0.58 (0.47–0.72); SSI: OR 0.65 (0.52–0.81); leak: OR 0.67 (0.47–0.93); stay reduced by 1.94 days; benefit independent of baseline status.
Matsui et al. (2024)	Systematic review and meta-analysis; head-and-neck or GI cancer surgery	Perioperative IMN versus standard nutritional care	Mixed surgical populations; no dedicated malnourished cohort	Broader postoperative evidence favoured IMN; used as contextual support because no malnutrition-specific estimate was extracted.
Song et al. (2015)	Systematic review and meta-analysis of RCTs; gastric cancer surgery	Enteral IMN versus standard enteral nutrition	Not reported as a dedicated malnourished cohort	Direction of effect favoured IMN for postoperative outcomes; precise pooled estimates were not independently re-verified in this review.
Cheng et al. (2018)	Systematic review and meta-analysis; total gastrectomy	Enteral IMN versus enteral nutrition	Not reported as a dedicated malnourished cohort	Postoperative outcomes generally favoured IMN; the full-text pooled estimate was not independently confirmed for this review.
Rinninella et al. (2020)	Systematic review and meta-analysis; nutritional interventions in gastric cancer	Oral or enteral nutritional strategies; not exclusively IMN	Baseline nutritional status varied across studies	Nutritional status improved, with shorter or comparable hospital stay; findings were directionally consistent with the larger IMN analyses.
Xin et al. (2025)	Systematic review and evidence map; gastric cancer surgery	Perioperative IMN versus control regimens	Mixed or incompletely reported nutritional status	Evidence direction favoured IMN, but variation in formulations, timing, and outcome definitions limited certainty.
Grońska et al. (2025)	Systematic review; gastric, pancreatic, and colorectal cancer prehabilitation	Oral supplements or IMN within multimodal prehabilitation	Reported effects especially in malnourished patients	Reduced postoperative complications and improved nutritional status; supports a potentially greater absolute benefit in malnourished patients.
Lee et al. (2025), K-CROSS	Randomised trial protocol; colorectal cancer surgery	Preoperative IMN versus control	Restricted to malnourished patients	Outcomes were pending; the trial directly addresses the principal evidence gap identified by this review.
Manzanares Campillo et al. (2017)	Randomised controlled trial; colorectal cancer surgery	Preoperative oral IMN versus control	Malnutrition not confirmed as an entry criterion in the available record	Contributed trial-level evidence; study details and effect estimates were not independently re-verified during this review.
Lakananurak et al. (2026)	Pilot randomised controlled trial; GI cancer surgery	Immune-modulating formula versus standard formula	Patients at risk of malnutrition rather than confirmed malnutrition	Feasibility-level evidence; the pilot was not powered for definitive postoperative complication outcomes.
Howes et al. (2018)	Cochrane systematic review; head-and-neck cancer surgery	Perioperative immunonutrition versus standard care	Population commonly nutritionally depleted; indirect comparator population	A qualitatively similar benefit pattern provided indirect support, although applicability to GI cancer surgery remains contextual.

Infectious complications and surgical site infection: The two GI-cancer-focused meta-analyses that pooled infectious complication data both reported statistically significant reductions favouring immunonutrition: Adiamah et al. reported an odds ratio of 0.52 (95% CI 0.38–0.71) for preoperative IMN across 16 RCTs, and Khan et al. reported an odds ratio of 0.58 (95% CI 0.47–0.72) for perioperative IMN across 37 RCTs, with a separately reported surgical site infection odds ratio of 0.65 (95% CI 0.52–0.81). Gastric-cancer-specific reviews describe a consistent direction of effect, though precise pooled estimates were not independently confirmed against full text in this review.

Anastomotic leak: Khan et al. is the only source in this review reporting a pooled anastomotic leak estimate, finding an odds ratio of 0.67 (95% CI 0.47–0.93) favouring immunonutrition. This outcome was not separately reported in the other included meta-analyses.

Length of hospital stay: Both principal meta-analyses reported a statistically significant reduction in length of stay: 1.57 days (95% CI −2.48 to −0.66) in Adiamah et al. and 1.94 days (95% CI −3 to −0.87) in Khan et al. Reviews focused on gastric cancer prehabilitation and nutritional interventions describe improvements in nutritional status alongside shorter or comparable length of stay, consistent in direction with the larger pooled estimates.

Mortality and non-infectious complications: Neither principal meta-analysis found a statistically significant mortality benefit (Adiamah: OR 0.55, 95% CI 0.18–1.68; not reported numerically in Khan et al.), and non-infectious complications were not significantly reduced by immunonutrition in Adiamah et al. (OR 0.98, 95% CI 0.73–1.33). This

pattern — a clear infectious/hospital-stay benefit without a demonstrated mortality benefit — is consistent across the broader IMN literature, including the Cochrane review in head and neck cancer.

Findings specific to malnourished patients: Direct, prespecified evidence on malnourished GI cancer patients is limited. The most informative single finding comes from Khan et al., whose subgroup analysis found that the benefit of perioperative immunonutrition on the outcomes above was statistically independent of baseline nutritional status — that is, malnourished and well-nourished patients derived a comparable relative benefit. Grońska et al. reported that prehabilitation strategies incorporating oral nutritional supplements or immunonutrition reduced postoperative complications and improved nutritional status "especially in malnourished patients," suggesting the absolute benefit — as opposed to the relative odds reduction — may be greater in this higher-baseline-risk group, since malnourished patients start from a higher complication rate. No included source reported that malnourished patients derived less benefit than well-nourished patients.

The clearest gap identified in this review is the near-absence of trials designed a priori to enrol only malnourished patients. The K-CROSS protocol (Lee et al., 2025) is, to our knowledge from this search, the first randomised trial specifically restricted to malnourished patients undergoing colorectal cancer surgery, and its results were not yet available at the time of this review. A pilot trial by Lakananurak et al. enrolled patients "at risk of" rather than confirmed to have malnutrition, and was explicitly not powered for definitive complication outcomes. Until such dedicated trials report, the malnutrition-specific evidence base rests on subgroup analyses nested within broader GI cancer surgery trials.

DISCUSSION

This review set out to answer a narrower question than most of the existing literature actually asks: not whether immunonutrition benefits patients undergoing GI cancer surgery in general, but whether it benefits the subset of those patients who are already malnourished at the time of operation. Four points emerge from the synthesis above. First, at the level of the overall GI cancer surgical population, preoperative and perioperative immunonutrition consistently reduces infectious complications, surgical site infection, and length of hospital stay, with effect sizes that are clinically meaningful — roughly a 40–50% relative reduction in infectious complications, and 1.5–2 fewer days in hospital — and reasonably consistent across independent meta-analyses conducted several years apart. Second, the limited nutritional-status-specific data available — principally the subgroup analysis in Khan et al. and the prehabilitation review by Grońska et al. — do not suggest malnourished patients benefit less than well-nourished patients, and offer some support for a greater absolute benefit in malnourished patients, consistent with the biological rationale that immune and metabolic depletion is more pronounced, and therefore more remediable, in this group. Third, and most importantly for future practice and research, there remains a near-total absence of trials designed specifically around malnourished GI cancer patients as the enrolled population, rather than as a post hoc subgroup; the ongoing K-CROSS trial is a notable exception whose results are awaited. Fourth, the magnitude of benefit reported varies more by outcome than by tumour site: infectious and wound-related endpoints move consistently, while mortality — a rarer event, and one more determined by tumour biology and disease stage than by short-course perioperative nutrition — does not.[1–3]

These findings are broadly consistent with the rationale underpinning ESPEN's guideline recommendation to use perioperative immune-modulating nutrition in patients undergoing major cancer surgery, with particular emphasis on those who are malnourished or at nutritional risk. The mechanistic case for prioritising malnourished patients is strong: these patients typically present with reduced lean body mass, hypoalbuminaemia, and impaired cell-mediated immunity before surgery even begins, and the physiological rationale for arginine- and omega-3-based supplementation — restoring T-lymphocyte function and dampening an exaggerated inflammatory response — maps directly onto these deficits. The head and neck cancer literature, in which a large proportion of patients are malnourished at presentation, shows a qualitatively similar pattern of benefit, lending indirect support to this interpretation. Taken together, the biological plausibility argument is arguably stronger than the direct clinical-trial evidence currently available to support it — an asymmetry worth stating plainly rather than allowing guideline language to imply a more settled evidence base than actually exists.[4–6]

The clinical implications, provisional as they are, point toward integrating preoperative immunonutrition into existing prehabilitation and Enhanced Recovery After Surgery (ERAS) pathways, rather than treating it as a standalone intervention: routine nutritional screening at diagnosis, early dietitian referral for anyone screening positive, and a default offer of five to seven days of oral or enteral immunonutrition before surgery whenever the operative schedule allows it. That timing matters — a diagnosis-to-surgery interval too short to complete even a brief course limits how much benefit can realistically be expected. Patients who cannot tolerate oral or enteral supplementation, or in whom surgery cannot safely be delayed, fall outside this evidence base and require individualised planning. Immunonutrition is generally well tolerated, with mild gastrointestinal

intolerance the main reported downside rather than serious adverse events, though a formal safety comparison was outside this review's scope. Cost is a practical consideration too: proprietary formulas cost more than standard supplements, and whether shorter stays translate into net savings was not addressed by any source identified here.[7–9]

Several sources of heterogeneity limit firm quantitative conclusions specific to malnutrition. Malnutrition was defined inconsistently across studies (weight-loss thresholds, BMI cut-offs, NRS-2002, PG-SGA, and GLIM criteria are not interchangeable), immunonutrition formulations and duration varied (commonly 5–7 days, but not uniformly), and outcome definitions differed between trials. Many underlying RCTs were industry-funded or used proprietary formulas, a recognised source of potential bias not formally assessed with a risk-of-bias tool here, and sample sizes within malnutrition-specific subgroups are generally small, limiting power for harder endpoints such as mortality. A standardised approach to defining malnutrition — the field is converging on the GLIM criteria — would materially improve comparability across future trials.[10–12]

This sets a clear research agenda. The most valuable next study is not another subgroup analysis nested inside a general-population trial, but one like K-CROSS that enrols only malnourished patients, applies a consensus definition of malnutrition at entry, is adequately powered for infectious complications as the primary endpoint and, ideally, for mortality or a validated composite as a secondary endpoint, and reports cost-effectiveness alongside clinical outcomes. Until that evidence matures, the defensible clinical position is the one already reflected in guideline language: treat preoperative immunonutrition as a low-risk, plausible-benefit default for malnourished GI cancer surgical candidates, while being transparent that the size of the benefit specific to this population is still extrapolated from mixed-population trials rather than established by trials designed to measure it directly.[13–15]

Limitations of this review: This review has several limitations that should be addressed before its conclusions are relied upon for publication or clinical guideline development. The search was restricted to PubMed and did not systematically cross-search Embase, the Cochrane Central Register of Controlled Trials, or Web of Science; a single reviewer (with AI assistance) performed screening and extraction without independent duplicate verification; no formal risk-of-bias assessment (e.g., Cochrane RoB2) or certainty-of-evidence rating (e.g., GRADE) was applied; and several numerical effect estimates attributed to included reviews were taken from abstract-level text because full-text access was not available during this review, and are flagged in Table 1 accordingly rather than presented with false precision. Three references (Song 2015, Manzanares Campillo 2017, Lakananurak 2026) were added from the reviewer's prior domain knowledge because live database access was intermittently blocked while this review was being assembled, and were not independently re-confirmed against PubMed in this session; this is flagged in Figure 1 and the reference list, and these three sources should be the first checked before the manuscript is used further. Because several of the included meta-analyses (e.g., Adiamah 2019 and Khan 2023) are likely to share overlapping primary RCTs, this review has not quantified that overlap (for example, via a corrected covered area analysis), and the estimates presented should not be treated as independent lines of evidence. For these reasons, this document is best used as a rapid evidence briefing and a scaffold for a fully resourced systematic review — with multi-database searching, dual independent screening, formal risk-of-bias and GRADE assessment, and full-text data extraction — rather than as a submission-ready, definitive systematic review in its current form.

CONCLUSION

Preoperative immunonutrition is a low-risk, biologically plausible intervention with consistent evidence of reduced infectious complications, surgical site infection, anastomotic leak, and length of hospital stay after gastrointestinal cancer surgery, without a demonstrated effect on mortality. Although few studies have been designed specifically around malnourished patients, the available subgroup evidence indicates that malnourished patients benefit at least as much as well-nourished patients, and plausibly more in absolute terms given their higher baseline risk. Current guideline recommendations to prioritise immunonutrition in malnourished patients undergoing major GI cancer surgery are consistent with this evidence base. Adequately powered trials enrolling malnourished GI cancer patients as the primary study population — such as the ongoing K-CROSS trial — are needed to confirm the magnitude of benefit and to determine whether earlier, more intensive, or longer preoperative nutritional optimisation further improves outcomes in this high-risk group.

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