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REVIEW ARTICLE

Effect of Perioperative Nutritional Supplementation on Postoperative Complications—Systematic Review and Meta-Analysis

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Abstract

Background Perioperative carbohydrate loading, increased protein intake, and immunonutrition may decrease postoperative complications. Studies on the topic have led to controversial results.

Methods We searched Medline, EMBASE, and CENTRAL up to August 2018 for randomized trials comparing the effect of perioperative nutritional supplements (intervention) versus control on postoperative complications in patients undergoing gastrointestinal cancer surgery. Secondary outcomes included infectious complications and length of hospital stay (LOS). Random effects model was used to estimate the pooled risk ratio (RR) of treatment effects. Pooled mean difference (MD) was used to compare LOS. Heterogeneity was assessed using I^2. Sources of heterogeneity were explored through subgroup analysis by nutritional supplementation protocol, type of surgery, and type of nutritional supplement. Risk of bias and quality of the evidence were assessed.

Results Of 3951 articles, we identified 56 trials ($n = 6370$). Perioperative nutrition was associated with a lower risk of postoperative complications (RR 0.74, 95% confidence interval (CI) 0.69–0.80); postoperative infections (RR 0.71, 95% CI 0.64–0.79, $n = 4582$); and postoperative non-infectious complications (RR 0.79, 95% CI 0.71–0.87, $n = 4883$). There were no significant heterogeneity outcomes analyzed ($I^2 = 14\%$, 1%, and 7%, respectively). LOS was shorter for the intervention group, MD −1.58 days; 95% CI −1.83 to −1.32; $I^2 = 89\%$). Subgroup analysis did not identify sources of heterogeneity. The quality of evidence for postoperative complications was high and for LOS was moderate.

Conclusion Perioperative nutritional optimization decreases the risk of postoperative infectious and non-infectious complications. It also decreases LOS in patients undergoing gastrointestinal cancer surgery, but these findings should be taken with caution given the high heterogeneity.

Keywords Nutritional support · Postoperative complications · Digestive system surgical procedures · Gastrointestinal neoplasms

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Introduction

Despite recent advances in perioperative care, the rate of postoperative morbidity for patients undergoing major surgery of the gastrointestinal tract is between 40 and 50%.[1,2] Surgery can impair immune system function and increase the likelihood of postoperative infectious complications.[3,4] Patients with gastrointestinal cancers are at a particularly high risk of malnutrition due to decreased oral food intake, comorbid chronic diseases, and impaired absorption secondary to intestinal obstruction or surgical bowel resection.[5] The current practice of *nil* per os (NPO) preoperatively is associated with insulin resistance and high levels of inflammatory mediators, which can delay wound healing and increase infectious and non-infectious postoperative complications, and length of hospital stay.[6–8] Some studies have suggested that early postoperative enteral feeding, specifically with immunonutrition (i.e., nutritional supplements such as arginine, omega fatty acids, and RNA) and increased protein intake is associated with improved wound healing and reduced postoperative complications.[1,3,7,9]

Surgery also increases the release of cortisol and glucagon, leading to a decrease in peripheral glucose uptake, resulting in postoperative hyperglycemia and insulin resistance.[10] Therefore, several studies have shown a beneficial effect of preoperative carbohydrate supplementation to prevent postoperative insulin resistance.[10–12] Preoperative carbohydrate-rich drinks can reduce postoperative insulin resistance by up to 50% and reduce length of hospital stay.[11] Furthermore, the consumption of carbohydrates prior to surgery is strongly endorsed by the Enhanced Recovery after Surgery (ERAS) Society.[13]

Immunonutrition is thought to improve the function of the immune system, which is also known as immunomodulation.[14–16] Arginine is an amino acid that is associated with tissue repair and wound healing by acting as an essential metabolic substrate for immune cells which is necessary for proper lymphocyte function.[17] Clinical studies have suggested that perioperative supplementation of arginine can decrease postoperative infection rates. Similarly, omega fatty acids, n-6 and n-3, have been shown to attenuate the production of inflammatory compounds and reduce the cytotoxicity of inflammatory cells.[18,19]

Insufficient protein intake is a particularly relevant problem for patients with gastrointestinal cancers who often experience anorexia and malnutrition because of disease progression and side effects of medical treatment. Metabolically healthy patients lose between 40 and 80 g of nitrogen after open abdominal operations, which is equivalent to 1.2 to 2.4 kg of wet skeletal muscle.[20] Patients with insulin resistance can experience a 50% greater protein loss.[21] The loss of lean muscle can delay wound healing, impair organ function, and compromise immune function.[22] Thus, optimizing nutritional status both before and after surgery by meeting protein requirements creates an opportunity to reduce postoperative complications for these patients.[23]

To date, the literature lacks a comprehensive systematic review that examines the combined effects of perioperative immunonutrition, carbohydrate loading, and protein supplementation in patients undergoing gastrointestinal cancer surgery. Therefore, we have performed a systematic review and meta-analysis to evaluate the effect of nutritional supplementation compared to control with respect to postoperative infectious and non-infectious complications and length of hospital stay. We defined nutritional supplementation as those components known to be required for proper healing following surgery, including protein supplementation, carbohydrate loading, and immunonutrition (a solution that contains nutrients such as arginine and omega fatty acids).

Materials and Methods

The protocol was published a priori in the international prospective register of systematic reviews PROSPERO (CRD42017076266). This study was conducted following the methods of the *Cochrane Handbook for Systematic Review of Interventions*[24] and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA) statement.[25]

Search Strategy

A comprehensive literature search of Medline, EMBASE, and CENTRAL databases was conducted until August 2018, with no language restriction. The pre-tested SIGN filters (http://www.sign.ac.uk) were used to identify randomized controlled trials for the Medline and EMBASE searches. Both Medical Subject Headings (MeSH) and Emtree headings and subheadings were applied to increase sensitivity. A broad definition for perioperative nutritional supplementation was used to ensure a comprehensive search. Further details on search strategy in Appendix 1.

Inclusion and Exclusion Criteria

We included randomized controlled trials (RCTs) involving participants over 18 years of age who underwent any gastrointestinal surgery for any type of malignancy. Studies that included patients with prior surgeries or distant metastases were eligible. The intervention involved the administration of a perioperative nutritional supplementation with immunonutrition, protein solution, or carbohydrate loading. Controls were defined as standard diet or control solutions with no nutritional value. Studies were excluded if they[1] had less than 30-day follow-up,[2] included patients with chronic

pancreatitis, gastric outlet obstruction, organ failure (i.e., liver, kidney, lungs or heart),[3] included patients on investigational medicines within the last 6 months,[4] included patients on prednisone, patients with immune system disorder, septic patients, patients who cannot tolerate oral intake, patients with poorly controlled types 1 and 2 diabetes, or[5] included patients with intestinal obstruction, ongoing infection, stomach emptying disorders or documented gastric esophageal reflux diseases, emergency surgery interventions, inflammatory bowel disease, neutropenia, and pregnancy.

Study Selection and Data Extraction

Two reviewers (BZ and ZN) screened the title and abstracts of all eligible studies independently using the Distiller® platform.[26] Duplicate articles were first excluded using Endnote. Two reviewers (BZ and ZN) independently completed the full text-review using piloted forms. During the data abstraction stage, information such as study design, disease etiology, intervention characteristics, incidence of postoperative complications, and postoperative infections were collected. Discrepancies were primarily addressed through consensus discussion. Primary outcome was the weighted proportion (incidence) of postoperative complications across all comparator groups. The secondary outcome was postoperative infectious complications and length of hospital stay.

Two reviewers (BZ and ZN) performed an assessment of methodological quality using the Cochrane Risk-of-Bias tool for all RCTs,[27] which included the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting other bias. Publication bias was also assessed. The quality of evidence across outcomes was assessed by the Grading of Recommendations, Assessment, Development and Education (GRADE) approach.[28] The quality of evidence was graded as high, moderate, low, or very low, depending on study limitations, consistency, directness, precision, and publication bias of each outcome.

Statistical Analysis

Interobserver agreement for title and abstract screening and full-text screening were calculated with the Cohen unweighted κ statistic.[29] Meta-analysis was performed using a random-effects model, and the weights of the included studies were estimated using the inverse variance method with RevMan[30] (Review Manager Version 5.4; The Nordic Cochrane Centre, Copenhagen, Denmark) based on the intention-to-treat principle. Forest plots were created to visualize the effect estimates and the variance in the data. Publication bias was assessed with a funnel plot for each outcome. Heterogeneity was assessed by using the chi-square test and the I^2 statistic.[24] We considered substantial heterogeneity when I^2 statistic was above 50% or a P value ≤ 0.1 for the χ^2 test. Two a priori hypotheses were developed to explain potential sources of clinical heterogeneity including diversity of interventions and surgical indications. Subgroup analyses were conducted to explore potential sources of heterogeneity. Post-hoc subgroup analysis based on geographical location was performed to try to explain heterogeneity. Postoperative complications were estimated with risk ratios (RR), and length of hospital stay was presented as a mean difference (MD) between the intervention and control groups. All estimates of effect were reported with their respective 95% confidence intervals (CI).

Results

Search Results and Study Characteristics

The literature search generated 3951 relevant citations, containing 71 duplicates. Following duplicate removal, 3880 were eligible for title and abstract screening. Of the 236 articles eligible for full-text screening, 56 ($n = 6370$) met all of the inclusion criteria from which data was extracted (Fig. 1). Further characteristics of the type of intervention and control of the studies included in this meta-analysis can be found in Fig. 2.

Overall Complications

Fifty-four RCTs ($n = 6363$ patients) evaluated postoperative complications in patients receiving perioperative nutritional supplementation versus control. The pooled RR of experiencing a postoperative complication was lower for patients in the perioperative nutritional supplementation group compared to control (RR 0.78; 95% CI, 0.72 to 0.85) (Fig. 3). There was moderate heterogeneity, $I^2 = 34\%$ within studies. The quality of the evidence was moderate due to imprecision in the pooled estimate.

Supplementation Protocol

A subgroup analysis performed by preoperative, perioperative, and postoperative supplementation protocol found that the greatest pooled risk reduction of postoperative complications was seen with postoperative supplementation (RR 0.76; 95% CI, 0.66 to 0.88, $I^2 = 34\%$), followed by preoperative supplementation (RR 0.79; 95% CI, 0.69 to 0.92, $I^2 = 14\%$), and perioperative supplementation (RR 0.82, 95% CI 0.72 to 0.94, $I^2 = 23\%$). More specific information about the frequency and duration of nutritional supplementation can be found in Supplementary Table 1.

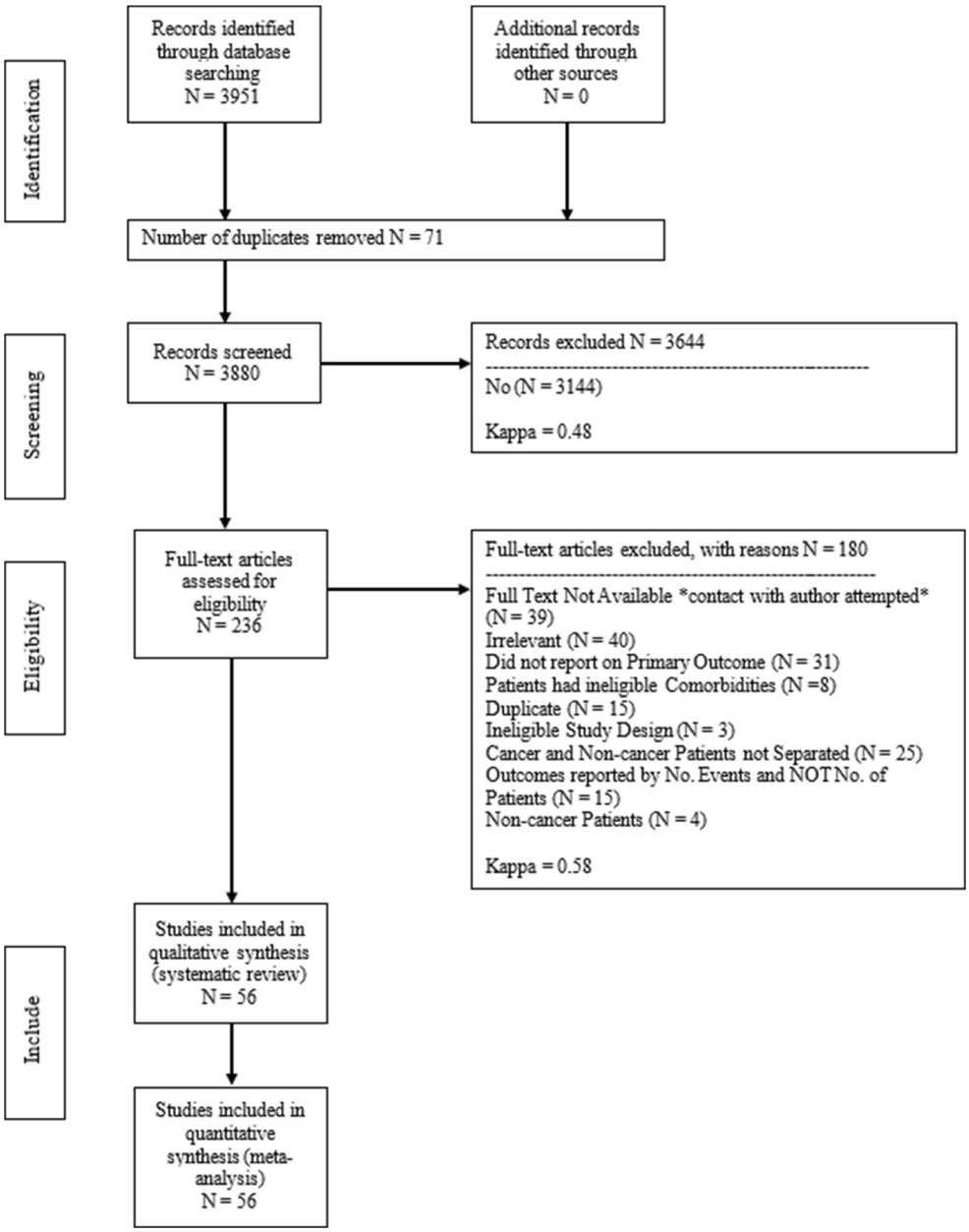

Fig. 1 PRISMA flow diagram describing the inclusion of studies

Infectious Complications

Forty studies with 4768 participants evaluated the risk of experiencing postoperative infectious complications including abdominal abscess, surgical site infection, pneumonia, urinary tract infection, or septicemia as confirmed by a microbiological analysis or elevated leukocyte levels. There was a decreased risk of experiencing postoperative infectious complications for patients in the perioperative nutritional supplementation group when compared to controls, pooled RR 0.71; 95% CI 0.64 to 0.79. There was no significant heterogeneity, $I^2 = 4\%$. The pooled incidence of infectious complications in the intervention group was 18.9% (453/2398) and 27.2% (645/2370) in the control group, with a pooled absolute risk difference of 8.3%.

Subgroup analysis was performed to investigate risk of infectious complications by type of surgery (hepatobiliary, colorectal, or foregut procedures). The greatest benefit of supplementation was found in hepatopancreatobiliary procedures (RR 0.56; 95% CI 0.41 to 0.76, $I^2 = 0\%$), followed by colorectal procedures (RR 0.70; 95% CI 0.49 to 0.99; $I^2 = 41\%$). A smaller effect, which was not statistically significant was seen among foregut surgeries (RR 0.90; 95% CI, 0.75 to 1.09; $I^2 = 0\%$).

An additional subgroup analysis was performed to examine the association between type of nutritional supplementation

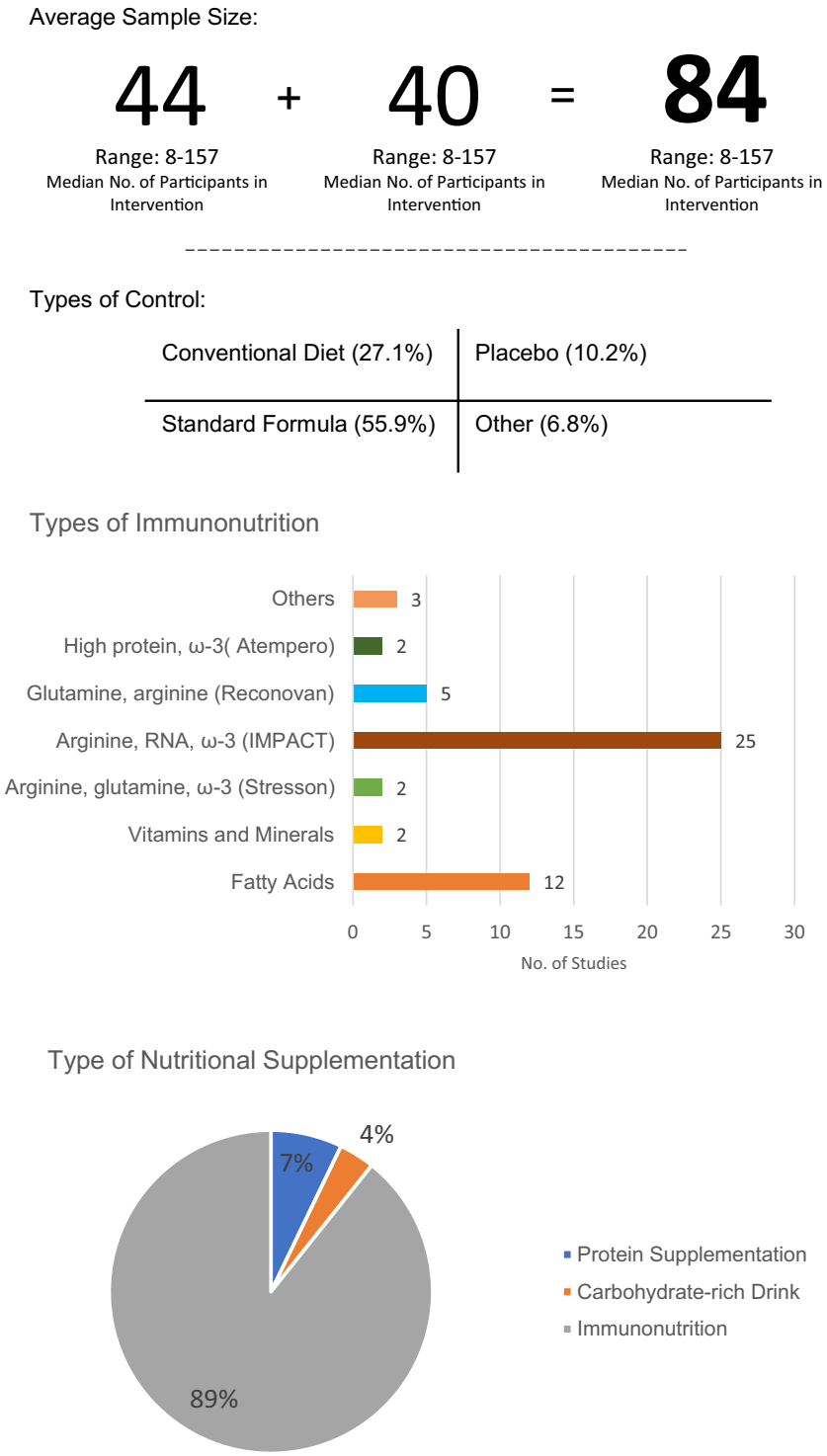

Fig. 2 Study characteristics

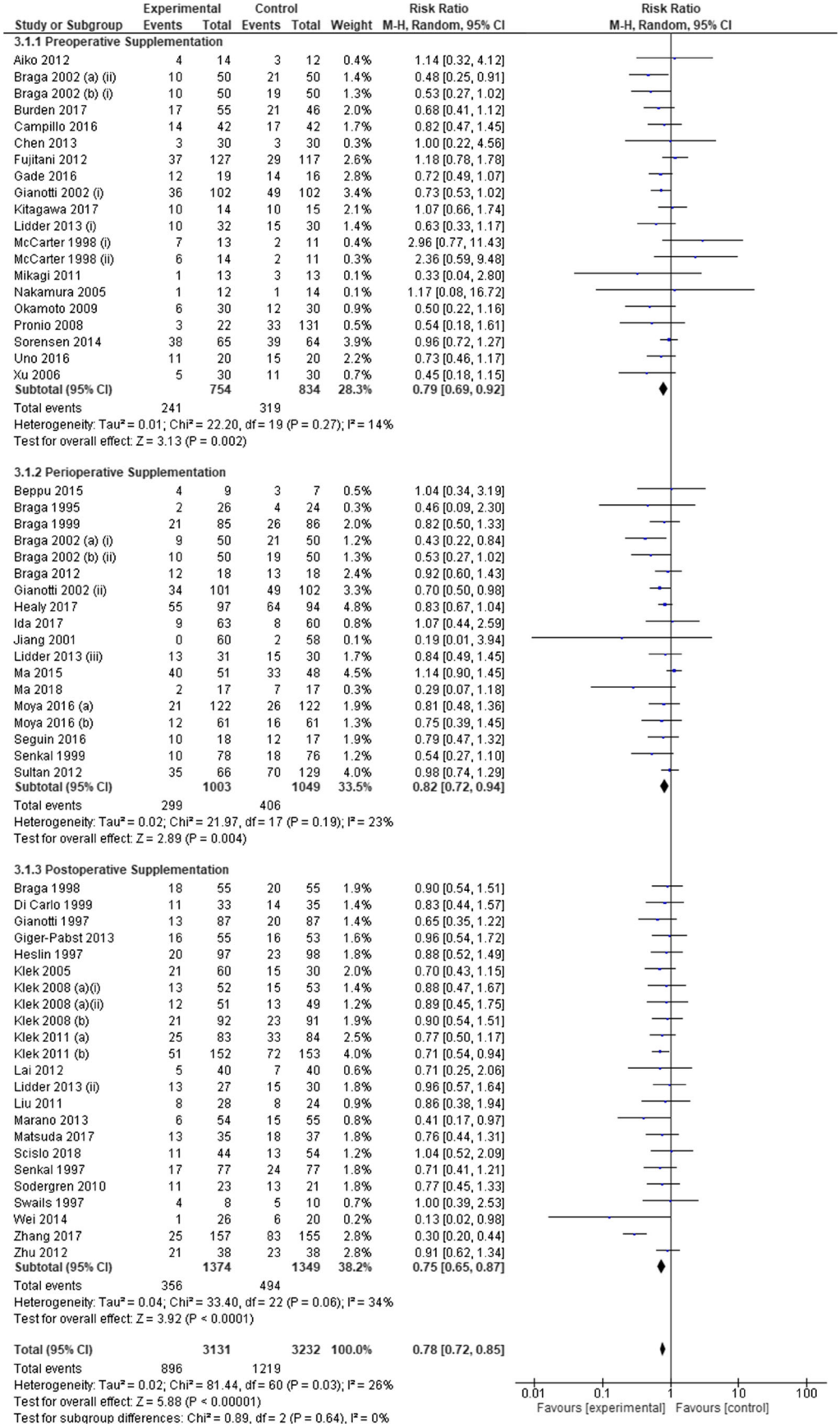

Fig. 3 Risk of overall postoperative complication in perioperative nutritional supplementation group versus control

and postoperative infectious complications. Combined supplementation of protein and fatty acids for immunonutrition had the largest protective effect (RR 0.60; 95% CI, 0.50 to 0.73; $I^2 = 0\%$) compared to fatty acids alone (RR 0.80; 95% CI 0.54 to 1.17; $I^2 = 26\%$). Both subgroup analyses explained potential sources of heterogeneity.

Noninfectious Complications

Thirty-eight studies with 4985 participants reported noninfectious postoperative complications. There was a decreased risk of postoperative noninfectious complication among participants taking nutritional supplements compared to controls RR 0.79; 95% CI 0.71 to 0.87. There was no substantial heterogeneity, $I^2 = 16\%$. The pooled incidence of noninfectious complications in the intervention group was 18.3% (455/2490) and in the control group 22.8% (568/2495), with a pooled absolute risk difference of 4.5%. The definition of noninfectious complication varied significantly between studies while gastrointestinal complications were reported across all studies;[7,31–84] some studies also classified cardiovascular and pulmonary events as complications.[35,39,42,46,48,52–54,68,80,84] The intervention group had the lowest risk ratio for the subgroup of patients undergoing hepatopancreatobiliary surgeries, (RR 0.71; 95% CI, 0.48 to 1.05; $I^2 = 43\%$), followed by foregut surgery, (RR 0.77; 95% CI, 0.65 to 0.91; $I^2 = 0\%$), and colorectal surgery, (RR 0.89; 95% CI, 0.71 to 1.11; $I^2 = 0\%$).

Length of Hospital Stay

Thirty-three studies with 4458 participants evaluated the effect of nutritional supplements on the length of hospital stay. There was a decrease in the pooled mean length of hospital stay among participants taking perioperative nutritional supplementation compared to control (pooled MD − 1.58 days; 95% CI − 1.83 to − 1.32) (Fig. 4). Common control groups included conventional diet or standard enteral nutrition (Supplementary Table 1). There was significant heterogeneity across studies $I^2 = 89\%$. To explore potential sources of heterogeneity, we performed a subgroup analysis on length of hospital stay by type of nutrition supplementation. The greatest reduction in length of hospital stay was seen in the postoperative supplementation group (MD − 1.95; 95% CI − 2.31, − 1.59, $I^2 = 77\%$), followed by perioperative supplementation (MD − 1.64; 95% CI − 2.15, − 1.12, $I^2 = 69\%$), and preoperative supplementation (MD − 0.74; 95% CI − 1.25, − 0.22, $I^2 = 95\%$).

Another subgroup analysis was performed by length of hospital stay which was significantly lower in the intervention group for hepatopancreatobiliary surgeries (pooled MD − 5.18 days; 95% CI − 10.73 to 0.37; $I^2 = 98\%$). Colorectal surgery saw less benefit (pooled MD − 1.31 days; 95% CI − 2.26 to − 0.37, $I^2 = 0\%$), followed by foregut surgeries (pooled MD − 0.88 days; 95% CI − 3.47 to 1.72, $I^2 = 90\%$). The heterogeneity was unable to be resolved by subgroups analysis of type of surgery. To further our investigation, we conducted an exploratory analysis on length of hospital stay by geographic location based on a hypothesis that the guidelines for hospital discharge after major abdominal surgery may vary greatly across healthcare systems. Studies conducted in Asia had a pooled MD of − 2.11; 95% CI − 2.51 to − 1.71, $I^2 = 96\%$, North American studies, a pooled MD of 1.79; 95% CI 0.13 to 3.46, $I^2 = 76\%$, and European studies a pooled MD of − 1.45; 95% CI − 1.85 to − 1.06, $I^2 = 95\%$. While these results seem to show different trends in effect across geographic regions, the high heterogeneity limits our interpretation of the results.

Risk of Bias

Publication bias was low as the distribution of the RR was evenly distributed across the funnel plot, with no significant outliers and mostly centered around one. (Supplementary Fig. 2). Most studies had a low risk of bias in all domains of the Cochrane Risk of Bias tool. Allocation concealment was adequate and low risk of bias in 42 studies.[7,31,33–39,42–49,53–56,61–68,70–82,84] The rest of the studies had an unclear/high risk of bias. Forty-three studies had adequate sequence generation. Two studies were at high risk of bias.[64] Blinding of participants and personnel was performed in 29 studies, which were identified at low risk of bias.[7,33,34,36,37,42,46,47,53–56,61–63,66–68,71–75,77–79,81,82] Thirty-nine studies reported all planned outcomes and were at a low risk for selective reporting.[7,31,33–36,42–49,52–56,61–68,70–72,74,76–82,84] There was low risk of bias from incomplete outcome data in 42 studies.[7,31,33–35,37–39,42–49,53–56,61–63,65–68,71–82,84] (Supplementary Fig. 3).

Quality of the Evidence

For the primary outcome evaluating postoperative complications in participants taking nutritional supplement compared to control, the quality of evidence was high (Supplementary Fig. 1a). All included studies were RCTs with a low risk of bias and low risk for inconsistency, indirectness, and imprecision. We are therefore highly confident that the true effect is likely to be close to the estimate of the effect in our meta-analysis. Pertaining to the secondary outcome evaluating length of hospital stay in both groups, the quality of evidence was low. We downgraded two levels due to a very serious risk for inconsistency (Supplementary Fig. 1a). This was due to the high heterogeneity that could not be explained by either of the a priori or post-hoc hypothesis. The point estimates for length of hospital stay also vary widely across studies. Therefore, our confidence

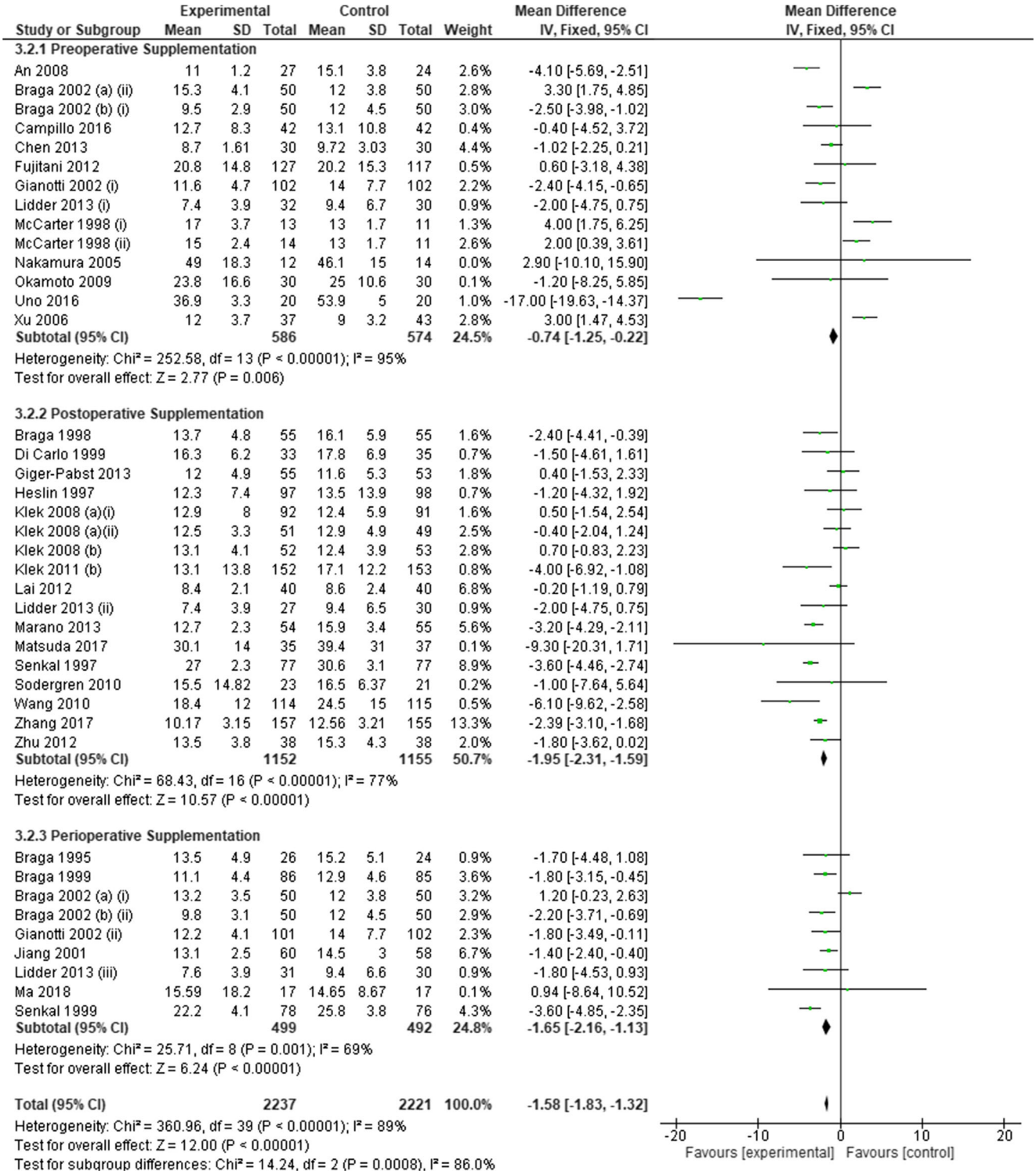

Fig. 4 Length of hospital stay in perioperative nutritional supplementation group versus control

in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Additionally, the relevance of the outcome to patients led us to classify the overall quality of evidence as low.

Discussion

This meta-analysis showed that perioperative nutritional supplementation improves nutritional balance and reduces postoperative complications, mortality, and length

of hospital stay in the setting of gastrointestinal cancer surgeries. We established via subgroup analysis that the greatest reduction of postoperative complications and length of hospital stay was seen among patients receiving postoperative supplementation, with the greatest benefit seen among patients undergoing hepatobiliary procedures. We also demonstrated that combined supplementation of protein and fatty acids had the greatest risk reduction of infectious complications. Our findings are consistent with previously published data from Probst et al.[85] who found that immunonutrition reduces the risk of postoperative complications. However, the high heterogeneity reported by the author [85] was not seen in our meta-analysis, perhaps due to a more homogenous sample of patients undergoing gastrointestinal cancer surgery in our study.[86,87]

Since Dr. Dudrick first pioneered the concept that all nutritional needs can be concentrated in solution and delivered intravenously, there have been many proposed theories about how to maximize the therapeutic effect of nutritional supplementation to improve postoperative outcomes through duration, timing of administration (pre-, post-, or perioperative), type of supplementation used, and method of administration (enteral or parenteral).[88] Some authors believe that postoperative supplementation within 24–48 h after surgery is not early enough to prevent the immunosuppression induced by surgery and advocates for the superiority of a perioperative supplementation.[89] We consider that the greatest benefit seen among patients receiving postoperative nutritional supplementation may be attributable to the diversity of the type of supplementation seen in the other groups, which often included a blend of carbohydrate and immunonutrition feeds. However, there was substantial variability of the duration of the postoperative supplementation, varying from 3 to 30 days and little information was provided about compliance. It is noteworthy to consider that one of the studies utilizing postoperative nutritional supplementation was an outlier, displaying a substantially higher risk reduction compared to other studies.[79]

Our conclusions regarding the effect of nutritional supplementation on length of hospital stay should be taken with caution as we found significant heterogeneity across the studies, which limits our confidence in the results. This heterogeneity is in line with findings from Smith et al.[90] and Probst et al.[85]; neither identified a specific source of heterogeneity. Smith et al.[90] from the Cochrane group suggested that the high heterogeneity may be due to inherent clinical heterogeneity in length of hospital stay as seen in clinical practice after abdominal cancer surgery. For instance, hospitals from different geographical areas may have different length of hospital stay for each procedure. Although our subgroup analysis based on geographic location demonstrated a difference in length of hospital stay across geographical regions, it was unable to completely explain heterogeneity. Notably, we found four outliers from Japan that had a mean length of hospital stay of over 20 days. In-depth analysis of these studies found that they had either unusually large confidence intervals or treatment effects.[43,62,67,76]

We based our review in the methods recommended by the Cochrane Handbook for Systematic Reviews of Interventions, PRISMA guidelines for reporting, and GRADE assessments for quality of the evidence. Furthermore, we used a set of strict patient selection criteria and formed conclusions from RCTs to ensure that our results are based on the highest quality of evidence using a rigorous meta-analysis methodology. We planned our outcomes a priori and published the protocol in advance to be transparent. However, our meta-analysis is not exempt of limitations; there is a lack of inclusion of studies specifically investigating the effects of carbohydrate loading, despite its regular use in the ERAS pathway for colorectal surgery, which may have restricted our ability to compare the three main types of nutritional supplements and may have reduced the scope of our review.[22] Moreover, the diversity of interventions made it difficult to common on a specific guideline for the administration of perioperative nutritional supplements.

In conclusion, this review confirmed that nutritional supplements reduce postoperative complications in patients undergoing surgery for gastrointestinal cancer. Further research may be justified to focus on defining the optimal duration of administration, route of administration, and type of nutrients in the formulations as well as to identify the specific subgroup of patients that will benefit from the treatment. The results of this systematic review should inform the design of future feasibility studies and RCTs that look at combining all three forms of nutritional supplements. These trials should use consistent definitions for postoperative complications and continue to inform the limited body of literature on length of hospital stay.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Contributions All authors provided substantial contributions to the conception and design of the work, drafting the work, and revising it critically for important intellectual content and gave final approval of the version to be published. The authors agree to be accountable for all aspects of the work.

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