Immunonutrition Support for Patients Undergoing Surgery for Gastrointestinal Malignancy: Preoperative, Postoperative, or Perioperative? A Bayesian Network Meta-Analysis of Randomized Controlled Trials

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Abstract: Enteral immunonutrition (EIN) has been established to be as a significantly important modality to prevent the postoperative infectious and noninfectious complications, enhance the immunity of host, and eventually improve the prognosis of gastrointestinal (GI) cancer patients undergoing surgery. However, different support routes, which are the optimum option, remain unclear. To evaluate the effects of different EIN support regimes for patients who underwent selective surgery for resectable GI malignancy, a Bayesian network meta-analysis (NMA) of randomized controlled trials (RCTs) was conducted.

A search of PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) was electronically searched until the end of December 2014. Moreover, we manually checked reference lists of eligible trials and review and retrieval unpublished literature. RCTs which investigated the comparative effects of EIN versus standard enteral nutrition (EN) or different EIN regimes were included if the clinical outcomes information can be extracted from it.

A total of 27 RCTs were incorporated into this study. Pair-wise meta-analyses suggested that preoperative (relative risk [RR], 0.58; 95% confidence interval [CI], 0.43–0.78), postoperative (RR, 0.63; 95% CI, 0.52–0.76), and perioperative EIN methods (RR, 0.46; 95% CI, 0.34–0.62) reduced incidence of postoperative infectious complications compared with standard EN. Moreover, perioperative EIN (RR, 0.65; 95% CI, 0.44–0.95) reduced the incidence of postoperative noninfectious complications, and the postoperative (mean difference [MD], –2.38; 95% CI, –3.4 to –1.31) and perioperative EIN (MD, –2.64; 95% CI, –3.28 to –1.99) also shortened the length of postoperative hospitalization compared with standard EN. NMA found that EIN support effectively improved the clinical outcomes of patients who underwent selective surgery for GI cancer compared with standard EN.

Our results suggest EIN support is promising alternative for operation management in comparison with standard EN, and perioperative EIN regime is the optimum option for managing clinical status of patients who underwent selective surgery for GI cancer.

INTRODUCTION

Gastrointestinal (GI) malignancy has been the leading cause of cancer death worldwide, and it cannot be radically treated resulting from the complexity of pathomechanism and mutations of drug-resistant.6 Hitherto, surgical resection is still the mainstay of curative treatment for patients with GI cancer in spite of effective alternatives have been developed.7 However, it is noted that patients who underwent the selective surgery for GI cancer are at high risk of developing postoperative adverse events (eg, postoperative infectious or noninfectious complications, immune depression, longer length of hospitalization, etc.)1–3 because of several factors such as malnourished status, absolute diet, neoplasm-induced host immunity defection, and surgery-associated stress.6–8 The postoperative clinical outcomes will be modulated by multiple factors which included anti-inflammatory agent, immunoenhancer, nutrition status, etc; however, nutrition support is the most important alternative which was used to decrease the incidence of postoperative infectious and noninfectious complications, enhance the host immunity, and eventually shorten the length of postoperative hospitalization and greatly decrease the medical expenditure, as well as improve the prognosis of the given patients.5–11

Published evidences suggested that enteral immunonutrition (EIN) diet which enriched with at least 2 of arginine (Arg), omega-3-fatty acids (ω-3-FA), glutamine (Glu), or ribonucleic acid (RNA) has the potential to decrease the infection risk and...
shorten the length of postoperative hospitalization.\textsuperscript{10,12–17} Multiple randomized controlled trials (RCTs) have been performed to investigate the comparative effects of EIN versus standard enteral nutrition (EN) or different deliver routes of immunonutrition.\textsuperscript{5,18–23} Several systematic reviews (SRs) and meta-analyses comparing EIN related to conventional EN or different immunonutrition support routes in the patients who underwent the selective surgery for GI cancer have also been completed.\textsuperscript{8,24–26} No study was published to evaluate which is the optimum EIN support regime. Traditional head-to-head meta-analyses can directly analyze the comparative effects of 2 individual interventions; however, it was not applicable to this case in which one expected to compare >3 treatments. Bayesian network meta-analysis (NMA), which was an expansion of traditional direct comparison meta-analysis, can cover the shortage by combining direct and indirect evidences simultaneously.

So, we undertook a Bayesian NMA of RCTs regarding different deliver routes of EIN compared with standard EN in order to establish the optimum immunonutrition support regime.

**MATERIAL AND METHODS**

The Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P)\textsuperscript{27} and the Cochrane Handbook for Systematic Reviews of Interventions\textsuperscript{28} were used to guide this study. We performed all analyses based on the published studies previously, and thus no ethical approval and informed consent were required. In addition, we critically appraised the quality of reporting of this study by using the PRISMA 2009 checklist (Table S1, http://links.lww.com/MD/A345).

**Searching Strategy**

Databases which included PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) were electronically searched by independent investigators (GM and XT) to collect any RCTs which investigated the comparative effects of EIN versus standard EN or different deliver routes of EIN support until the end of December 2014. We used following search terms to perform procedures by using combination of medical subject heading and free word embedded in specific files involving title, keywords, and abstract: "Esophageal Neoplasms," "Stomach Neoplasms," "Liver Neoplasms," "Colon Neoplasms," "Rectal Neoplasms," "Pancreatic Neoplasms," "Digestive System Neoplasms," "Breast Neoplasms," "Other Digestive System Neoplasms," "Colorectal Neoplasms," "Bile Duct Neoplasms," "Gallbladder Neoplasms," "Arginine," "Fatty Acids, Omega 3," "Glutamine," "RNA," "Nutritional Support," "Parenteral Nutrition," "Enteral Nutrition," "Postoperative Period," and "General Surgery." This search strings were constructed by using Boolean operator. We also manually checked the reference of lists of eligible studies and corresponding review to include any potential study to guarantee the precision and recall ratio. No other restrictions were imposed. The search terms and strings were presented in Supplement 1, http://links.lww.com/MD/A345.

**Identification of Study**

The following inclusion criteria were identified according to the PICOS acronym (participant, intervention, comparison, outcomes of interest, and study design): Population (P): all the patients who were scheduled to selective surgery for GI cancer were included in this study. Intervention (I) and Comparison (C): the trials evaluated the comparative effects of EIN diet which enriched with at least 2 of Arg, Glu, ω-3-FA, and RNA versus standard EN. EIN diet administration was performed at preoperation, postoperation, or perioperation period. Outcomes of interest (O): we assessed the following outcome measures: postoperative infectious or noninfectious complications and length of postoperative hospitalization. Study design (S): only RCTs with or without blind method were considered.

We would like to exclude the following studies: patients have unresectable GI malignancy, underlying cardiovascular pathology, active preoperative infection, administration of corticosteroids or immunosuppressive agents, and renal or hepatic function impairment; experimental data; lack of essential information and cannot acquire primary data from authors; the article with the most strict methodology and most complete data was chosen to be analyzed in terms of duplicate literature; and nonoriginal research such as review, letter and specialist comments, and non-RCTs.

**Data Extraction**

Two independent investigators (LZ and Y-XO) extracted the following basic information and essential continuous and binary data for expected outcome of interest from each included study by using the predesigned standard data extraction form (Tables S2, http://links.lww.com/MD/A345): study ID which included first author and publication year, country, surgery type, age of participants, sample size, nutrition status, interventions, and reported outcome of interest. The author would be contacted to acquire the complete data when necessary. Any divergences between authors concerning the eligibility of a study were resolved by consensus or consulting a third author (XT).

**Assessing Quality of Methodology**

Two independent investigators (LJY and J-GZ) were assigned to critically appraise the methodology quality of all eligible studies in accordance with the Cochrane Handbook of Systematic Review of Interventions\textsuperscript{29} to pool reliable and robust estimated effect sizes which were used to improve clinical practice. Seven indexes were independently appraised accordingly, and the following evaluation results were cross-checked: randomization sequence generation, allocation concealment, blinding of participants and study personnel, blinding of outcome assessors, incomplete outcome data, selective reporting, and other biases. The risk of each incorporated study was rated as “high bias risk,” “unclear bias risk,” or “low bias risk” according to the adequate level of information extracted. A third investigator (Hong-Lin Yang) was assigned to disagreement between assessors.

**Traditional Pair-Wise Meta-Analysis**

We performed initially the traditional pair-wise meta-analysis to evaluate the comparative effects of 2 individual treatments which can be directly compared. The estimates of dichotomous and continuous data were expressed as relative risk (RR) and mean difference (MD), respectively. The heterogeneity between studies was tested by using $\chi^2$ test,\textsuperscript{30} and proportion of the overall variation that is attributable to between-study heterogeneity was also estimated by using $I^2$ statistic.\textsuperscript{31} Substantial heterogeneity was considered unless the value of $I^2$ statistic was <50%. We adopted fixed- or random-effect model to calculate the summary statistic according to the
Clinical diversity and methodological variation, as well as the homogeneity test.

**Bayesian Network Meta-analysis**

Bayesian NMA is a generalization of pair-wise meta-analysis. It is an alternative to pool direct and indirect or different indirect evidences simultaneously. A Bayesian random-effects NMA, which was based on the Markov chain Monte Carlo (MCMC) simulation from the posterior distribution, was adopted to calculate the estimates of relative effects and all model parameters.32 To gain convergence, we performed each MCMC chain with 40,000 iterations and 10,000 burn-in. We have drawn the comparison-adjusted funnel plot to assess the small study effects. The results were also presented by using the surface under the cumulative ranking curve (SUCRA) and the higher SUCRA value was correspond to better results for respective treatment.33 A Bayesian NMA can be carried out based on a key assumption which shows the consistency of results between direct and indirect comparisons. We calculate the inconsistency factor by using the loop-specific method to assess the inconsistency.34

All analyses were carried out by using the RevMan 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2013), Stata 12 (StataCorp, TX), and WinBUGS 1.4 (Imperial College School of Medicine at St Mary’s, London).

**RESULTS**

**Search Results and Characteristics of Trials**

We captured 321 potential citations based on these given search terms and strings at the initial search stage. One hundred and twenty-five duplications were excluded by using EndNote 7.2 (Thomson Reuters, MI). One hundred and fifty-two citations were excluded after screening the title and abstract. We accessed the remaining full-text to further assess the eligibility. After screening the full-text, 20 ineligible trials were excluded resulting from several reasons such as lack of outcomes of interest, ineligible intervention regimes, and ineligible participants. All procedures were performed independently by 2 investigators. And eventually, 27 eligible studies3,4,9--25,35--44 were incorporated into this SR and meta-analysis. The basic characteristics of included studies were shown in Table 1. The flow chart of retrieval and selection of literature was shown in Figure 1.

**Assessment of Methodological Quality**

We critically appraised the methodological quality of included studies in accordance with the Cochrane Collaboration’s Risk of Bias Tool.35 The proportion of appropriate description of randomization, allocation concealment, and blinding is the 48% (13/27), 37% (10/27), and 44%, respectively. All included trials were rated as low bias risk in incomplete outcome data because the authors stated the drop-out reasons in detail and used the intent-to-treat method to analyze the data. The quality of all eligible studies was graded as low bias risk because expected outcomes of interest were all reported in terms of selective reporting index. Other bias sources were not identified. The graphical result of methodological quality was shown in Figure 2.

**Evidence Network**

In this SR and meta-analysis, we investigated the comparative effects of EIN which included 3 support routes involving preoperative, postoperative, and perioperative periods related to standard EN. We have drawn the evidence network plot in terms of postoperative infectious complications, postoperative noninfectious complications, and length of postoperative hospitalization. Twenty-four are two-arm studies and the remaining are three-arm trials. The evidence network plot was shown in Figure 3.

**Inconsistency Test**

We performed the comparison-adjusted funnel plot to test the small study effect. The funnel plots indicated asymmetrical graph, and suggested that the pooled results may be negatively affected by small study effects (Figure 4). We also tested the inconsistency of results between direct and indirect comparisons. The inconsistency plots suggested that the statistical inconsistency was generally low for weight control as the corresponding confidence intervals (CIs) included zero (Figure 5).

**Postoperative Infectious Complications**

We identified 7 eligible trials,11,19--22,42,43 which directly evaluated the comparative effects of preoperative EIN diet versus standard EN, and all were incorporated into this traditional pair-wise meta-analysis. A total of 313 and 307 patients were randomly divided into preoperative EN group and standard EN group, respectively. All trials were considered to be homogenous (χ² = 8.12, P = 0.23, I² = 26%), and thus a fixed-effect model based on Mantel–Haenszel (M-H) method was used to estimate the pooled result. The meta-analysis indicated that the preoperative EN effectively decreased the incidence of postoperative infectious complications compared with standard EN (RR, 0.58; 95% CI, 0.43–0.78) (Figure 6A). The Bayesian NMA obtained similar results (RR, 0.41; 95% CI, 0.26–0.63) (Table 2).

Fifteen eligible studies5,12--16,23,35--41,44 which included 1524 participants, directly compared the effects of postoperative EIN related to standard EN in terms of postoperative infectious complications. The homogenous test did not identify the statistical heterogeneity (χ² = 15.68, P = 0.33, I² = 11%). So, we selected a fixed-effect model based on M-H framework to calculate the estimate. The meta-analysis indicated a significant difference, and the postoperative EIN was better than standard EN (RR, 0.63; 95% CI, 0.52–0.76) (Figure 6B). Bayesian NMA also indicated significant difference (RR, 0.55; 95% CI, 0.40–0.74) (Table 2).

Six trials10,17,18,21,22,42 which included 380 and 378 patients, between perioperative EIN and standard EN groups reported the incidence of postoperative infectious complications. No statistical heterogeneity was detected by using homogeneous test (χ² = 0.94, P = 0.97, I² = 0%). Then a fixed-effect model was adopted to perform the meta-analysis. The pooled result suggested that perioperative EIN was superior to standard EN concerning effects of decreased incidence of postoperative infectious complications (RR, 0.46; 95% CI, 0.34–0.62) (Figure 6C). The result was maintained by the Bayesian NMA (RR, 0.36; 95% CI, −0.23 to 0.55) (Table 2).

The incidence of postoperative infectious complications was presented in 3 eligible studies,21,22,42 which assessed the comparative effects of preoperative versus perioperative EIN. In total, 202 and 201 patients were randomly received preoperative and perioperative EIN diet, respectively. No statistical heterogeneity was identified (χ² = 1.28, P = 0.53, I² = 0%), so a fixed-effect model was used to carry out the pair-wise meta-analysis. The meta-analysis indicated no significant difference (RR, 1.11; 95% CI, 0.68–1.79) (Figure 6D), and the Bayesian NMA confirmed the result (Table 2).
### TABLE 1. Basic Characteristics of Included Studies Comparing Enteral Immunonutrition Regimes Which Included Preoperative, Postoperative, and Perioperative Versus Standard Enteral Nutrition

| Study ID | Country | Operation | Operation Type | Sample Size | Age of Participants | No. of Malnourished Patients | Interventions | Control Group Regimes | Reported Outcomes |
|----------|---------|-----------|----------------|-------------|---------------------|----------------------------|---------------|----------------------|---------------------|
| Braga et al 1999<sup>17</sup> | Italy | Surgery | for GI cancer involving neoplasm of colorectum, stomach, or pancreas | 85/86 | 60.9 ± 11.9/60.8 ± 9.7 | 22/18 | Perioperative nutrition diets which enriched with 12.5 g of Arg, 3.3 g of ω-3-FA, and 1.2 g of RNA drink 1 L/d for 7 consecutive days before surgery. 6 h after surgery with a jejunal infusion rate of 10 mL/h, which was progressively increased up to a volume of 1500 mL/d, oral food intake was allowed on postoperative day 7. | Isonitrogenous, isoenergetic perioperative liquid diet drink 1 L/d for 7 consecutive days before surgery. Six hours after surgery with a jejunal infusion rate of 10 mL/h, which was progressively increased up to a volume of 1500 mL/d, oral food intake was allowed on postoperative day 7. | LPS, PIC, PNIC |
| Senkal et al 1999<sup>10</sup> | Germany | Elective upper GI tract surgery | for cancers of esophageal, gastric, and pancreaticoduodenum | 78/76 | 64 ± 11/67 ± 9 | Unclear | Perioperative EIN supplemented with Arg, RNA, and ω-3-FA feed 1000 mL/d for at least 5 d before surgery, in 250-mL portions in addition to the usual hospital diet. 12 h after surgery with a jejunal infusion rate of 20 mL/h, which was progressively increased up to an 80 mL/h by the fifth postoperative day. | Drink 1000 kcal/d of EN which enriched with Arg, Glu, ω-3-FA, and RNA as oral supplement, in addition to consume regular diet for 3 consecutive days before surgery. Postoperative enteral nutrition was also administered within 24 h after surgery via a jejunostomy catheter. The enteral nutrition was started postoperatively from 250 kcal/d and was progressively increased daily. The postoperative enteral nutrition via jejunostomy was continued even after oral intake was started until approximately 14 d after surgery to reach 1.2 times the basal energy expenditure calculated by Harris-Benedict equation. | LPS, PIC |
| Sakurai et al 2007<sup>18</sup> | Japan | Esophagectomy | | 16/14 | 63 ± 4/63 ± 5 | Unclear | Perioperative nutrition diets which enriched with 12.5 g of Arg, 3.3 g of ω-3-FA, and 1.2 g of RNA drink 1 L/d for 7 consecutive days before surgery. 6 h after surgery with a jejunal infusion rate of 10 mL/h, which was progressively increased up to a volume of 1500 mL/d, oral food intake was allowed on postoperative day 7. | Drink 1000 kcal/d of perioperative regular polymeric enteral formula as oral supplement, in addition to consume regular diet for 3 consecutive days before surgery. Postoperative enteral nutrition was also administered within 24 h after surgery via a jejunostomy catheter. The enteral nutrition was started postoperatively from 250 kcal/d and was progressively increased daily. The postoperative enteral nutrition via jejunostomy was continued even after oral intake was started until approximately 14 d after surgery to reach 1.2 times the basal energy expenditure calculated by Harris-Benedict equation. | LPS, PIC, PNIC |
| Daly et al 1992<sup>12</sup> | America | Upper gastrointestinal malignancies operation | | 41/44 | Unclear | Unclear | PERI with supplemental Arg, RNA, and ω-3-FA in patients after operation | | | |
| Daly et al 1995<sup>13</sup> | America | Esophagectomy, gastrectomy, and pancreatocystectomy | | 30/30 | 61 ± 12/61 ± 10 | 12/10 | Patients received enteral alimentation with the supplemented diet via jejunostomy beginning on the first postoperative day. Jejunostomy infusion supplemented with free L-Arg, linoleic acid, eicosapentaenoic acid and docosahexaenoic acid, RNA, intact protein, medium chain triglycerides, and carbohydrates was initiated with full-strength feedings at 25 mL/h and then increased to the optimal goal (75–100 mL/h) by the third postoperative day. Patients were continued on their enteral supplements via jejunostomy tube at these rates until they were able to take fluids and food by mouth. | | LPS, PIC, PNIC |

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| Study ID | Country     | Operation Type                          | Sample Size | Age of Participants | No. of Malnourished Patients | Interventions                                                                 | Reported Outcomes |
|---------|-------------|-----------------------------------------|-------------|---------------------|-----------------------------|-------------------------------------------------------------------------------|------------------|
| Braga et al 1996 | Italy | Surgery for cancers of stomach and pancreas | 20/20       | 59 ± 9/61 ± 7        | 12/9                        | Postoperative EIN which enriched with Arg (1.25 g/100 mL), RNA (0.12 g/100 mL), and ω-3-FA (n-3/n-6 = 1:4) was given through a jejunostomy or a nasojejunal tube and started 6 h after the end of operation (10 mL/h). The infusion rate was increased progressively until the nutritional goal was reached on postoperative day 4. On postoperative days 1, 2, and 3 the amount of energy taken by the enteral route were 480, 720, and 1200 kcal, respectively. Until day 4 enteral feeding was integrated with a parenteral nutrition to reach the nutritional goal. | LPS, PIC |
| Gianotti et al 1997 | Italy | Major operations for malignancies which included cancer of stomach and pancreatoduodenal | 87/87       | 62.7 ± 14.3/64.5 ± 13.4 | Unclear | The infusion of the IM which enriched with Arg, RNA, and ω-3-FA was started 6 h after the operation at a rate of 10 mL/h. The velocity was progressively increased by 20 mL/d until reaching the full nutritional goal (105 kJ/kg/d). During the first 3 postoperative days, patient also received calories and nitrogen by parenteral route to achieve the nutritional goal. Enteral feeding was continued for 7 postoperative days. Regular food was allowed on postoperative day 8. | LPS, PIC |
| Senkal et al 1997 | Germany | Upper GI tract surgery for cancers of esophageal, gastric, and pancreatoduodenal | 77/77       | 65.1 ± 1.5/66.3 ± 1.8 | Unclear | The enteral feeding supplemented with L-Arg, L-serin, glycine, L-alanine, L-ornithin, RNA, caseinprotein, fat, energy, minerals, vitamins, and trace elements was started 12 h after surgery via an intraoperatively placed needle-catheter jejunostomy using continuous infusion. Enteral feeding started with 20 mL/h on the first postoperative day and progressed to the optimal goal (80 mL/h) by the fifth postoperative day. The oral intake was allowed when clinically indicated between the fifth and seventh postoperative day and started with clear liquids. All patients received intravenous fluids and other electrolytes as clinically indicated. | LPS, PIC, PNIC |
| Braga et al 1998 | Italy | Major abdominal surgery for cancers of stomach and pancreas | 55/55       | 60.9 ± 10.9/63.5 ± 8.8 | Unclear | The enteral feeding supplemented with caseinprotein, fat, energy, minerals, vitamins, and trace elements was started 12 h after surgery via an intravenously placed needle-catheter jejunostomy using continuous infusion. Enteral feeding started with 20 mL/h on the first postoperative day and progressed to the optimal goal (80 mL/h) by the fifth postoperative day. The oral intake was allowed when clinically indicated between the fifth and seventh postoperative day and started with clear liquids. All patients received intravenous fluids and other electrolytes as clinically indicated. | LPS, PIC, PNIC |

**Table Notes:**
- **LPS, PIC:** Lipid Palmitic, Intravenous}
- **PNIC:** Parenteral Nutrition, Intravenous
| Study ID | Country  | Operation Type | Sample Size | Age of Participants | No. of Malnourished Patients | Interventions | Control Group Regimes | Reported Outcomes |
|----------|----------|----------------|-------------|---------------------|-----------------------------|---------------|----------------------|-------------------|
| Di Carlo et al 1999 | Italy | Pancreatic surgery | 33/35 | 63.1 ± 13.1/61.7 ± 12.0 | 13/14 | The infusion of the EIN diets supplemented with Arg, RNA, and ω-3-FA was stated within 12 h after the end of operation at a 10 mL/h rate. The velocity was progressively increased by 20 mL/d until reaching the full nutritional goal (25 kcal/kg). It was continued until the patient’s oral intake was approximately 800 kcal/d. | LPS, PIC, PNIC |
| Farreras et al 2005 | Spain | Surgery for gastric cancer | 30/30 | 66.7 ± 8.3/69.2 ± 13.8 | 5/8 | The infusion of the EIN diets supplemented with Arg, ω-3-FA, and RNA was stated 12 to 18 h after the end of operation at a 20 mL/h rate. The velocity was progressively increased by 50 mL/d in third day with reaching the full nutritional goal (1200 kcal/d). From day 4, the amount of nutritional support was adjusted every day according to the caloric requirements but the mean flow was 65 mL/h. The length of the treatment was 7 d and during this period the patients were only fed the treatment formulas, water or infusions. After 7 d, when possible, the diet was replaced with oral feeding. | LPS, PIC, PNIC |
| Klek et al 2008 | Poland | Upper GI surgery | 52/53 | 61.2 ± 11.7/61.4 ± 11.9 | 8/9 | EN supplemented with Glu 2.0 mL/kg/d and ω-3-unsaturated FA 1.0 mL/kg/d was commenced 6 h after a rate of 20 mL/h during the first 12 h. Administered with an infusion pump over 20 to 22 h/d at the following rates: day 1—25 mL/h, day 2—50 mL/h, day 3—75 mL/h, and 100 mL/h thereafter until the seventh postoperative day. | LPS, PIC |
| Klek et al 2011 | Poland | Resection for pancreatic or gastric cancer | 152/153 | 61.5 ± 11.8/60.2 ± 12.4 | Malnourished patients | Postoperative EIN which enriched with Arg and Glu was commenced 6 h after operation with 5% glucose solution at the rate of 20 mL/h on day 1, 50 mL/h on day 2, 75 mL/h on day 3 and 100 mL/h thereafter until the seventh day. | LPS, PIC |
| Liu et al 2011 | China | Total gastrectomy | 28/28 | 71.5 ± 6.1/74.1 ± 9.3 | Unclear | The intravenous drip of NS with 250 to 500 mL was performed via tube of stomach and duodenum or jejunostomy at the first day after surgery. Tolerance patients were supported by using intravenous drip of IN which enriched with Arg of 9.0 g/L and Glu of 12.5 g/L. | LPS, PIC |
| Liu et al 2011 | China | Total gastrectomy | 21/21 | 61.1 ± 7.5/61.6 ± 7.2 | Unclear | Postoperative EIN diets which enriched with Arg, Glu, and ω-3-FA were infused via nasojejunum tube or jejunostopic tube. | LPS, PIC |
| Liu et al 2012 | China | Total gastrectomy | 28/28 | 57.3 ± 7.1/58.4 ± 6.3 | Unclear | Postoperative EIN supplemented with Arg and Glu were supported after the operation for 7 d with the energy intake of 25 to 30 kcal/kg/d, nitrogen of 0.2 g/kg/d, ratio of nonprotein energy to nitrogen of 150:1 and necessary minerals, vitamins, and trace elements. | LPS, PIC |
| Study ID | Country   | Operation Type                     | Sample Size | Age of Participants | No. of Malnourished Patients | Interventions                                                                                      | Study Group Regimes                                                                 | Control Group Regimes                                                                 | Reported Outcomes |
|---------|-----------|-------------------------------------|-------------|---------------------|-----------------------------|-------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Marano et al 2013 | Italy | Total gastrectomy in gastric cancer patients | 54/55       | 55–78/49–83         | 33/30                       | Nutrition supplemented with Arg, ω-3-FA, and RNA through jejunostomy was introduced in both groups 6 h after the surgery until the seventh postoperative day, beginning with an infusion of 10 mL/h with an increasing rate of 10 mL/h every 12 h, until the maximum feed target rate of 80 mL/h was achieved corresponding to target individual of 35 kcal/kg/d. | Isocaloric and isonitrogenous SEN through jejunostomy was introduced in both groups 6 h after the surgery until the seventh postoperative day, beginning with an infusion of 10 mL/h with an increasing rate of 10 mL/h every 12 h, until the maximum feed target rate of 80 mL/h was achieved corresponding to target individual of 35 kcal/kg/d. | LPS, PIC |
| Braga et al 2002 | Italy | Resection for pancreatic, gastric, colorectal, or esophageal cancer | 50/50       | 65.9 ± 12.6/64.1 ± 12.8 | Malnourished patients       | Before surgery, drank 1 L of a supplemented liquid diet per day for 7 consecutive days. After surgery, patients were given a standard enteral formula. Postoperative nutrition was administered within 12 h of surgery via a feeding catheter jejunostomy or a nasojejunal feeding tube. The initial rate of 10 mL/h was progressively increased 20 mL/h/d until reaching the full nutritional goal (28 kcal/kg/d). Enteral infusion was continued until patients resumed adequate oral food intake (approximately 50% of the basal energy requirement). | Before surgery, drank 1 L of a supplemented liquid diet per day for 7 consecutive days. After surgery, patients continued to be fed enterally with the same supplemented formula. Postoperative nutrition was administered within 12 h of surgery via a feeding catheter jejunostomy or a nasojejunal feeding tube. The initial rate of 10 mL/h was progressively increased 20 mL/h/d until reaching the full nutritional goal (28 kcal/kg/d). Enteral infusion was continued until patients resumed adequate oral food intake (approximately 50% of the basal energy requirement). | LPS, PIC, PNIC |
| Braga et al 2002 | Italy | Colorectal resection for cancer | 50/50       | 63.0 ± 8.1/60.5 ± 11.5 | 6/5                         | Patients were asked to drink 1 L/d of a liquid diet supplemented with Arg (12.5 g/L) and ω-3-FA (3.3 g/L), for 5 d before operation. Enteral feeding was started 6 h after operation with an infusion rate of 10 mL/h, and further increased to reach the volume of 1500 mL/d on day 4. | Patients were asked to drink 1 L/d of a liquid diet supplemented with Arg (12.5 g/L) and ω-3-FA (3.3 g/L), for 5 d before operation. The administration was prolonged in the postoperative course by jejunal infusion through a naso-enteric tube. Enteral feeding was started 6 h after operation with an infusion rate of 10 mL/h, and further increased to reach the volume of 1500 mL/d on day 4. | LPS, PIC, PNIC |
| Gianotti et al 2002 | Italy | Resection for gastroesophageal, pancreatic, or colorectal cancer | 101/102     | 62.3 ± 12.3/65.6 ± 11.5 | Unclear                    | Before surgery, patients were asked to drink 1 L/d for 5 consecutive days of a supplemented liquid diet. In the postoperative course, the patients were given an intravenous solution of 5% glucose and electrolytes until the day of recovery of oral food. | Before surgery, patients were asked to drink 1 L/d for 5 consecutive days of a supplemented liquid diet. In the postoperative period, these patients were given jejunal feeding with the same enriched formula starting within 12 h after surgery. The enteral diet was administered via a feeding jejunostomy or a nasojejunal tube with a flow controlled by a peristaltic infusion pump. The postoperative regimen was continued until patients resumed oral food. | LPS, PIC, PNIC |
| Study ID   | Operation Type                          | Country       | Sample Size | Age of Participants | No. of Malnourished Patients | Study Group Regimes                                                                 | Control Group Regimes                                                                 | Reported Outcomes |
|-----------|----------------------------------------|---------------|-------------|---------------------|-------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-------------------|
| Giger et al 2007<sup>7</sup> | Major abdominal surgery for the canals of stomach, pancreas, or periampullary | Switzerland   | 14/15        | 30–84/47–79         | 9/9                           | Drink preoperatively 1 L of an immunoenriched formula for 5 d. The same product as the patient received preoperatively was given to both groups for 7 d postoperatively. Enteral feeding was initiated 6 h after surgery was completed. Immunonutrition was administered continuously over 24 h in the 3 groups by an infusion pump. The initial application rate was 20 mL/h and it was progressively increased up to 60 or 80 mL/h at postoperative day | Patients only received Impact for 7 d postoperatively; there was no preoperative treatment. Enteral feeding was initiated 6 hours after surgery was completed. Immunonutrition was administered continuously over 24 hours in the 3 groups by an infusion pump. The initial application rate was 20 mL/h and it was progressively increased up to 60 or 80 mL/h at postoperative day | LPS, PIC, PNIC |
| McCarter et al 1998<sup>3</sup> | Surgery for cancer of esophagus, stomach, or pancreas | America       | 13/11        | 62.0 ± 2.3/66.0 ± 4.4 | 3/2                          | Supplemental diets which enriched with Arg, ω-3-FA, protein, fat, carbohydrate, nitrogen, dietary fiber to be taken each day for 7 d before surgery. Patients were instructed to consume 750 mL of the supplement each day, in addition to their normal meals, for at least 7 d before surgery | Patients received SEN (25 kcal/kg/d), administered by nasal feeding catheter for 7 consecutive days until operation. After surgery, patients continued to be fed enterally with the same enteral formula. Total dietary calories and nitrogen given was 25 kcal/kg/d and 0.9 lg/kg/d, respectively, the kilojoule-to-milliliter ratio was 1:1. | PIC |
| Xu et al 2006<sup>20</sup> | Radical gastrectomy, radical colectomy, or radical proctocolectomy | China         | 30/30        | 60.1 ± 10.1/57.7 ± 11.5 | Unclear                     | Patients received EIN which enriched with Arg, ω-3-FA (25 kcal/kg/d), administered by nasal feeding catheter for 7 consecutive days until operation. After surgery, patients continued to be fed enterally with the standard enteral formula. Total dietary calories and nitrogen given was 25 kcal/kg/d and 0.9 lg/kg/d, respectively, the kilojoule-to-milliliter ratio was 1:1. | Patients received SEN (25 kcal/kg/d), administered by nasal feeding cathether for 7 consecutive days until operation. After surgery, patients continued to be fed enterally with the same enteral formula. Total dietary calories and nitrogen given was 25 kcal/kg/d and 0.9 kg/d, respectively, the kilojoule-to-milliliter ratio was 1:1. | LPS, PIC |
| Gunerhan et al 2009<sup>29</sup> | Surgery for GI tumors | Turkey        | 16/13        | 64.6 ± 16.2/61.3 ± 12.1 | Malnourished patients        | Patients received a combination of Arg, ω-3-FA, and RNA. Nutrition protocols were administered for 7 d before the operation. |Patients received a SEN. Nutrition protocols were administered for 7 d before the operation. | LPS, PIC, PNIC |
| Giger et al 2013<sup>11</sup> | Surgery for cancer of esophagus, stomach, pancreas, liver, colon, or rectum | Switzerland   | 55/53        | 64.9 ± 13.6/63.2 ± 11.8 | Unclear                     | Patients received a total of 750 mL of Impact RTD which enriched with 16.72 g of Arg, 3.3 g of ω-3-FA, and 1.32 g of RNA for 3 consecutive days before surgery | Patients received a total of 750 mL of an isonitrogenous and isocaloric SEN placebo for 3 consecutive days before surgery | LPS, PIC, PNIC |
| Liu et al 2011<sup>94</sup> | Surgery for cancer of stomach, colon, or rectum | China         | 53/53        | 57.6 ± 9.7/55.4 ± 11.0 | Malnourished patients        | Patients received postoperative EIN diets which enriched with ω-3-FA and RNA for at least 7 d after surgery. | Patients received postoperative SEN diets for at least 7 d after surgery. | LPS, PIC, PNIC |

ω-3-FA = omega-3 fatty acids, ω-6-FA = omega-6 fatty acids, Arg = arginine, EIN = enteral immunonutrition, IN = enteral nutrition, GI = gastrointestinal, Gln = glutamine, IN = immunonutrition, LPS = length of postoperative stay, NS = normal saline, PIC = postoperative infectious complications, PNIC = postoperative noninfectious complications, RNA = ribonucleic acid, SEN = standard enteral nutrition.
Only one study involving 29 patients investigated the comparative effects of postoperative EIN compared with perioperative EIN, and the result indicated that perioperative period decreased the incidence of postoperative infectious complications compared with postoperative period method (RR, 0.21; 95% CI, 0.06–0.81) (Figure 6E). However, the result from Bayesian NMA did not indicate significant difference when the perioperative EIN compared with postoperative EIN (RR, 0.65; 95% CI, 0.39–1.12) (Table 2).

No study which directly compared the effects in decreasing postoperative infectious complications between preoperative and postoperative method was identified. However, we adopted a Bayesian NMA to evaluate the comparative effects of preoperative compared with postoperative EIN in terms of given outcome. The indirect evidence indicated no significant difference (RR, 0.67; 95% CI, 0.32–1.40) (Figure 8B). The reliability and robust of this result was enhanced by Bayesian analysis, where the difference between the postoperative EIN compared with perioperative EIN method was identified. However, we adopted a Bayesian NMA to evaluate the comparative effects of preoperative compared with postoperative EIN in terms of given outcome. The indirect evidence indicated no significant difference (RR, 0.67; 95% CI, 0.32–1.40) (Figure 8B). The reliability and robust of this result was enhanced by Bayesian analysis, where the difference between the

**Postoperative Noninfectious Complications**

Seven eligible studies, which included 620 patients, reported the direct effects which EIN for the decreased the incidence of postoperative noninfectious complications relative to standard EN. All studies were considered to be homogenous ($\chi^2 = 4.06, P = 0.67, I^2 = 0\%$). Then, we used a fixed-effect model to calculate the estimate. The meta-analysis did not indicate significant difference (RR, 0.88; 95% CI, 0.67–1.16) (Figure 8A). Meanwhile, we performed a Bayesian NMA to estimate corresponding pooled result, and it generated similar results (RR, 0.80; 95% CI, 0.48–1.33) (Table 2).

We identified 5 eligible trials, which included 449 patients, to investigate the comparative effects of decreased postoperative noninfectious complications of postoperative EIN versus standard EN. The homogeneous test detected substantial statistical heterogeneity ($\chi^2 = 8.32, P = 0.08, I^2 = 52\%$), so a random-effect model based on inverse variance was used to calculate the estimate. The summary analysis indicated no significant difference (RR, 0.67; 95% CI, 0.32–1.40) (Figure 8B). The reliability and robust of this result was enhanced by Bayesian NMA (RR, 0.59; 95% CI, 0.31–1.07) (Table 2).

Six eligible trials involving 758 participants evaluated the effects of direct comparison of perioperative EIN relative to standard EN. No statistical heterogeneity was tested ($\chi^2 = 3.86, P = 0.57, I^2 = 0\%$), and then a fixed-effect model was used to perform this meta-analysis. The pair-wise meta-analysis revealed that perioperative immunonutrition method was better than the standard EN in decreasing incidence of postoperative noninfectious complications (RR, 0.65; 95% CI, 0.44–0.95) (Figure 8C). A similar trend was obtained by Bayesian analysis, where the difference between the
FIGURE 2. Assessment of risk of bias: (A) risk of bias graph; (B) risk of bias summary.

FIGURE 3. Evidence networks: (A) network for postoperative infectious complications; (B) network for postoperative noninfectious complications; (C) network for length of postoperative hospitalization. EIN = enteral immunonutrition, SEN = standard enteral nutrition.
perioperative immunonutrition method and standard EN groups almost reached significance (RR, 0.62; 95% CI, 0.37–1.00) (Table 2).

In addition, three21,22,42 and one4 reported the results of preoperative EIN versus perioperative and postoperative EIN relative to perioperative noninfectious complications, respectively. All pooled results did not reach significance (Figure 8D and E). The similar summary results were generated from corresponding Bayesian NMA (Table 2).

Study which directly established the comparative effects of preoperative versus postoperative EIN in terms of the incidence of postoperative noninfectious complications was not identified. However, we adopted a Bayesian NMA to evaluate the comparative effects of postoperative EIN compared with preoperative EIN in terms of given outcome. The indirect evidence indicated no significant difference (RR, 0.75; 95% CI, 0.33–1.59) (Table 2).

To determine the best treatment method, we calculated SUCRA probability of 4 interventions for the incidence of postoperative noninfectious complications. The SUCRA probabilities were 40.06%, 76.96%, 74.33%, and 8.09% for the preoperative, postoperative, perioperative EIN, and standard EN, respectively. The ranking of the 4 treatments for the postoperative noninfectious complications was shown in Figure 7B.

Length of Postoperative Hospitalization

Seven eligible studies,11,19–22,42,43 which included 620 patients, reported the results of preoperative EIN directly compared with standard EN in shortening the length of postoperative hospitalization. Statistical heterogeneity was detected ($\chi^2 = 33.49$, $P < 0.00$, $I^2 = 82\%$). So, a fixed-effect model was used to calculate the estimate. The meta-analysis indicated no significant difference (MD, $-0.94$; 95% CI, $-1.53$ to $-0.32$) (Table 2).

Fifteen eligible studies,5,12–16,23,35–39,41,44 which included 1481 participants, directly compared the effects of postoperative EIN related to standard EN in terms of length of postoperative hospitalization. The homogenous test identified the substantial statistical heterogeneity ($\chi^2 = 97.25$, $P < 0.00$, $I^2 = 87\%$). Then, we used a fixed-effect model within M-H framework to calculate the estimate. The meta-analysis indicated a significant difference and the postoperative EIN was better than standard EN (MD, $-2.38$; 95% CI, $-3.44$ to $-1.31$).
related to standard EN. No statistical heterogeneity was tested.

evaluated the effects of direct comparison of perioperative EIN
length of postoperative hospital stay, respectively. For preo-
relative to perioperative immunonutrition method in terms of
preoperative EIN versus perioperative and postoperative EIN

Bayesian NMA also indicated significant difference
between standard EN and postoperative EIN in terms of
length of postoperative hospitalization (MD, 0.48; 95% CI,
0.06–0.91) (Table 2).

Six eligible trials involving 758 participants
evaluated the effects of direct comparison of perioperative EIN
related to standard EN. No statistical heterogeneity was tested
($\chi^2 = 6.07, P = 0.30, I^2 = 18\%$). Then, we used a fixed-effect
model to estimate the summary result. The pair-wise meta-
analysis revealed that perioperative immunonutrition method
was better than standard EN in shortening the length of post-
operative hospitalization (MD, −2.64; 95% CI, −3.28 to 1.99)
(Figure 9C). However, an opposite trend was obtained from
Bayesian analysis, in which the difference between the standard
EN and perioperative immunonutrition method reached significa-
cance (MD, 0.84; 95% CI, 0.25–1.45) (Table 2).

In addition, three and one reported the results of
perioperative EIN versus perioperative and postoperative EIN
relative to perioperative immunonutrition method in terms of
length of postoperative hospital stay, respectively. For perio-
operative versus perioperative comparison, no statistical hetero-
genrety was detected ($\chi^2 = 3.88, P = 0.14, I^2 = 49\%$), so a fixed-
effect model was adopted to perform this pair-wise meta-
analysis. The pooled result did not indicate significant differ-
ce (MD, −0.02; 95% CI, −0.75 to 0.71) (Figure 9D), and the
Bayesian NMA obtained similar result (MD, 0.56; 95% CI,
−0.17 to 1.30). For postoperative versus perioperative compa-
comparison, one suggested that perioperative immunonutrition
method effectively shortened the length of postoperative hos-
ital stay relative to postoperative (MD, −9.40; 95% CI,
−11.58 to −7.22) (Figure 9E). The similar summary results
were generated from corresponding Bayesian NMA (MD, 0.36;
95% CI, −0.34 to 1.07) (Table 2).

No study directly compared the effects of preoperative EIN
on postoperative length of hospitalization compared to post-
operative EIN approach. Hence, a Bayesian NMA was per-
fomed to establish the comparative effects of preoperative EIN
compared with postoperative EIN in terms of this measure of
interest. The indirect evidence indicated no significant differ-
ce (MD, 0.20; 95% CI, −0.53 to 0.93) (Table 2).

We calculated SUCRA probability of 4 interventions for
the length of postoperative hospitalization to quantitatively rank
these treatments. The SUCRA probability was 39.73%, 61.48%,
92.53%, and 6.25% for the preoperative, postoperative, perio-
perate EIN, and standard EN, respectively. The ranking of the
4 treatments for the length of postoperative hospital stay was
shown in Figure 7C.

**DISCUSSION**

EIN which enriched with some interested immunonutrients
(Arg, ω-3-FA, Glu, and RNA) has been recommended to
manage the postoperative clinical status since 1990. However,
various different EIN support methods confused the clinical
decision. The optimum option for patient who underwent
surgery for GI malignancy remains a topic of debate. Several
published RCTs investigated the comparative effects of immu-
nonutrition versus standard EN and these results consis-
tently suggested that EIN plays a key role in managing
postoperative clinical status of patients undergoing surgery
for GI cancer. The timing of EIN support method involved
preoperative, postoperative, and perioperative periods. Several
SRs and meta-analyses which evaluated the comparative effects of EIN versus standard EN have been published. In addition, of these six SRs, two systematically assessed the direct evidences between preoperative or postoperative versus perioperative EIN methods. However, it is noted that these SRs and meta-analyses were performed by using traditional pair-wise meta-analysis method which cannot compare treatments concerning certain topic simultaneously. Selecting optimum treatment to guide the clinical practice is a dynamic source, which drives the development of medical science. NMA within Bayesian framework can solve these problems, which cannot direct traditional comparison meta-analysis.

Unfortunately, no NMA, which evaluated the comparative effects of different EIN support methods and ranked these methods, was published. As far as we know, this is the first Bayesian NMA that established the relative effects of various different EIN methods for patients who underwent the surgery for GI cancer. We have incorporated 27 eligible trials into this study. To clearly present the relationship of treatments, we have plotted the evidence networks for each outcome of interest, and 3 included trials directly compared preoperative with perioperative EIN methods, as well as only one directly compared postoperative with perioperative EIN methods. However, no study,

SRs and meta-analyses which evaluated the comparative effects of EIN versus standard EN have been published. In addition, of these six SRs, two systematically assessed the direct evidences between preoperative or postoperative versus perioperative EIN methods. However, it is noted that these SRs and meta-analyses were performed by using traditional pair-wise meta-analysis method which cannot compare treatments concerning certain topic simultaneously. Selecting optimum treatment to guide the clinical practice is a dynamic source, which drives the development of medical science. NMA within Bayesian framework can solve these problems, which cannot direct traditional comparison meta-analysis.

Unfortunately, no NMA, which evaluated the comparative effects of different EIN support methods and ranked these methods, was published. As far as we know, this is the first Bayesian NMA that established the relative effects of various different EIN methods for patients who underwent the surgery for GI cancer. We have incorporated 27 eligible trials into this study. To clearly present the relationship of treatments, we have plotted the evidence networks for each outcome of interest, and 3 included trials directly compared preoperative with perioperative EIN methods, as well as only one directly compared postoperative with perioperative EIN methods. However, no study,
which directly compared preoperative with postoperative EIN methods, was captured.

Traditional pair-wise meta-analyses well demonstrated that EIN method, including preoperative, postoperative, and perioperative periods, effectively reduced the incidences of postoperative infectious. For the postoperative noninfectious complications, only perioperative EIN method effectively decreased associated incidence compared with standard EN. In terms of length of postoperative hospitalization, postoperative and perioperative EIN method are superior to standard EN. Moreover, it indicated that there was no significant difference among 3 methods of EIN support in terms of postoperative infectious and noninfectious complications and length of postoperative hospitalization. We have also performed Bayesian NMA to further assess corresponding comparative effects of different treatments. These pooled results which generated from NMA are similar to that of traditional meta-analyses.

It is noted that these results of our meta-analysis are in accordance with previous reports, in which EIN could enhance host immunity and reduce inflammatory response by modulated immune mediators, biochemical indicator, and inflammatory mediators. For example, a plenty of studies published previously revealed that early postoperative supplementation with EIN suppressed the expression of prostaglandin-2, interleukin-6, and tumor necrosis factor-α.13–15,49,50 When compared with

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**FIGURE 7.** Ranking of treatments: (A) ranking of treatments in terms of postoperative infectious complications; (B) ranking of treatments in terms of postoperative noninfectious complications; (C) ranking of treatments in terms of length of postoperative hospitalization. Pre = preoperative, Post = postoperative, Peri = perioperative, EIN = enteral immunonutrition, SEN = standard enteral nutrition.

**FIGURE 8.** Traditional pair-wise meta-analysis on postoperative noninfectious complications: (A) preoperative EIN versus SEN; (B) postoperative EIN versus SEN; (C) perioperative EIN versus SEN; (D) preoperative EIN versus perioperative EIN; (E) perioperative EIN versus postoperative EIN. EIN = enteral immunonutrition.
In order to provide clinical practitioners with the optimum treatment, we also quantitatively ranked all alternatives according to the SUCRA probabilities. The results manifested that perioperative was better than preoperative and postoperative EIN regimes in terms of postoperative infectious complications (Figure 7A). For postoperative noninfectious complications, perioperative was superior to preoperative and postoperative regimes (Figure 7B). In terms of length of postoperative hospital stay, perioperative was better than postoperative and preoperative immunonutrition regimes (Figure 7C). And thus, postoperative EIN method, preoperative EIN regime significantly increased the level of transferring.20

**TABLE 2. Network Meta-Analysis of Direct and Indirect Evidence Comparisons of EIN and SEN for GI Cancer**

| Outcome | Pooled OR (95% CI) or MD (95% CI) |
|---------|----------------------------------|
| Post infectious complications | 0.41 (0.26–0.63) | 0.55 (0.40–0.74) | 0.36 (0.23–0.55) | 0.65 (0.39–1.12) | 0.76 (0.43–1.36) | 0.89 (0.50–1.54) |
| Post noninfectious complications | 0.80 (0.48–1.33) | 0.59 (0.31–1.07) | 0.62 (0.37–1.00) | 0.95 (0.43–1.97) | 0.75 (0.33–1.69) | 0.78 (0.42–1.40) |
| Length of post hospitalization | 0.29 (0.32–0.89) | 0.48 (0.06–0.91) | 0.84 (0.25–1.45) | 0.36 (0.34–1.07) | 0.20 (0.53–0.93) | 0.56 (0.17–1.30) |

**FIGURE 9.** Traditional pair-wise meta-analysis on length of postoperative hospitalization: (A) preoperative EIN versus SEN; (B) postoperative EIN versus SEN; (C) perioperative EIN versus SEN; (D) preoperative EIN versus perioperative EIN; (E) perioperative EIN versus postoperative EIN. EIN = enteral immunonutrition.
we recommended preferentially perioperative immunonutrition regime as the nutrition support option for patients who underwent surgery for GI cancer.

We performed a comprehensive search strategy of literature so that this NMA can generate more accurate estimates of effects, whereas some limitations existed in this study which need to be acknowledged. First, the nutrition status of participants who enrolled into these eligible original trials varies from across studies. Second, conference abstract was ineligible for selection criteria of this study, and it may cause incomplete retrieval of literature. Third, the comparison-adjusted funnel plots were drawn and these graphs indicated small study effects. Last but not least, most of the results generated from NMA are in accordance with that of traditional pair-wise meta-analyses, but there were significant inconsistency existed in the loop which was consisted of standard EN, postoperative EIN, and preoperative EIN for post-operative infectious complications and one which was made of standard EN, preoperative EIN, and postoperative EIN.

CONCLUSION

We concluded that EIN support method is superior to standard EN, and the perioperative EIN regime is the optimum treatment option for patients who underwent surgery for GI cancer because of low incidence of postoperative infectious and noninfectious complications and shorter length of postoperative hospital stay.

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