Medicine®

SYSTEMATIC REVIEW AND META-ANALYSIS

OPEN

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

Guo-Min Song, RN, BSc, Xu Tian, RN, BSc, Lei Zhang, RN, BSc, Yang-Xiang Ou, RN, BSc, Li-Juan Yi, RN, BSc, Ting Shuai, RN, BSc, Jian-Guo Zhou, MM, Zi Zeng, RN, BSc, and Hong-Ling Yang, MM

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 Moreover, we manually checked reference lists of eligible trials and review and retrieval unpublished literature.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.

(*Medicine* 94(29):e1225)

Abbreviations: ω-3-FA = omega-3-fatty acids, Arg = arginine, EIN = enteral immunonutrition, EN = enteral nutrition, GI = gastrointestinal, Glu = glutamine, MCMC = Markov chain Monte Carlo, MeSH = medical subject heading, NMA = network meta-analysis, RCTs = randomized controlled trials, RNA = ribonucleic acid, SCURA = surface under the cumulative ranking curve, SR = systematic review.

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.[1] Hitherto, surgical resection is still the mainstay of curative treatment for patients with GI cancer in spite of effective alternatives have been developed.[2] 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.)[3–5] 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.[8–11]

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

Editor: Pamela von Reisswitz.
Received: April 23, 2015; revised: June 30, 2015; accepted: July 1, 2015.
Form the Department of Nursing (G-MS), Tianjin Hospital, Tianjin; Graduate College (XT, LZ, Y-XO, L-JY, TS, ZZ), Tianjin University of Traditional Chinese Medicine, Tianjin; Department of Oncology (J-GZ), Affiliated Hospital of Zunyi Medical University, Zunyi; and Acupuncture & Moxibustion Department (H-LY), First Teaching Hospital affiliated Tianjin University of Traditional Chinese Medicine, Tianjin, China.
Correspondence: Xu Tian, Graduate College, Tianjin University of Traditional Chinese Medicine, No. 319 Anshanxi Road, Nankai District, Tianjin 300193, China (e-mail: yxtx880919@hotmail.com).
G-MS, XT, LZ, and Y-XO have contributed equally to this work as first author.
G-MS, XT, LZ, and Y-XO conceived the study. G-MS, XT, TS, and ZZ collected the data. G-MS, XT, LZ, and Y-XO performed statistical analyses. L-JY, J-GZ, and H-LY assessed the quality of eligible studies. G-MS, XT, and LZ drafted the manuscript. XT and Y-XO improved the language. All authors read and approved the final manuscript.
The authors have no funding and conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000001225

shorten the length of postoperative hospitalization.[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.[5,18–23] Several systematic reviews (SRs) and meta-analyses comparing EIN related to standard (conventional) EN or different immunonutrition support routes in the patients who underwent the selective surgery for GI cancer have also been completed.[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 $\geq$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)[27] and the Cochrane Handbook for Systematic Reviews of Interventions[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).[29]

Searching Strategy

Databases which included PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) were electronically searched by independent investigators (G-MS 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,'' ''Colonic Neoplasms,'' ''Rectal Neoplasms,'' ''Pancreatic Neoplasms,'' ''Digestive System Neoplasms,'' ''Gastrointestinal 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 (L-JY 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[28] 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 χ^2 test,[30] and proportion of the overall variation that is attributable to between-study heterogeneity was also estimated by using I^2 statistic.[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 studies[4,5,10–23,35–44] 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.[28] 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 EIN group and standard EN group, respectively. All trials were considered to be homogenous ($\chi^2 = 8.12$, $P = 0.23$, $I^2 = 26\%$), 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 EIN 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 studies,[5,12–16,23,35–41,44] 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 ($\chi^2 = 15.68$, $P = 0.33$, $I^2 = 11\%$). 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 trials,[10,17,18,21,22,42] 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 ($\chi^2 = 0.94$, $P = 0.97$, $I^2 = 0\%$). 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 ($\chi^2 = 1.28$, $P = 0.53$, $I^2 = 0\%$), 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 Type	Sample Size	Age of Participants	No. of Malnourished Patients	Interventions		Reported Outcomes
						Study Group Regimes	Control Group Regimes	
Braga et al 1999[17]	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[10]	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.	Isonitrogenous feed 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
Sakurai et al 2007[18]	Japan	Esophagectomy	16/14	63 ± 4/63 ± 5	Unclear	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.	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[12]	America	Upper gastrointestinal malignancies operation	41/44	Unclear	Unclear	EN with supplemental Arg, RNA, and ω-3-FA in patients after operation	SEN after surgery	LPS, PIC
Daly et al 1995[13]	America	Esophagogastrectomy, gastrectomy, and pancreatectomy	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 docosahexenoic 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.	Patients received enteral alimentation with the supplemented diet via jejunostomy beginning on the first postoperative day. Jejunostomy infusion supplemented with 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

Study ID	Country	Operation Type	Sample Size	Age of Participants	No. of Malnourished Patients	Interventions		Reported Outcomes
						Study Group Regimes	Control Group Regimes	
Braga et al 1996[14]	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.	An isonitrogenous amount of glycine (2.15 g/100 mL), and ω-6-FA 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[15]	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.	Same amount of calories and nitrogen standard enteral formula 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, patients 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[16]	Germany	Upper GI tract surgery for cancers of esophageal, gastric, and pancreaticoduodenum	77/77	65.1 ± 1.5/ 66.3 ± 1.8	Unclear	The enteral feeding supplemented with L-Arg, L-serin, glycin, L-alanin, L-rrolin, 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.	The enteral feeding supplemented with 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[35]	Italy	Major abdominal surgery for cancers of stomach and pancreas	55/55	60.9 ± 10.9/ 63.5 ± 8.8	Unclear	EN which enriched with Arg, RNA, and ω-3-FA was started within 12 h following surgery. The infusion rate was progressively increased to reach the nutritional goal (25 kcal/kg/d) on postoperative day 4.	Isocaloric and isonitrogenous SEN was started within 12 h following surgery. The infusion rate was progressively increased to reach the nutritional goal (25 kcal/kg/d) on postoperative day 4.	LPS, PIC, PNIC

Study ID	Country	Operation Type	Sample Size	Age of Participants	No. of Malnourished Patients	Interventions		Reported Outcomes
						Study Group Regimes	Control Group Regimes	
Di Carlo et al 1999[36]	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 within12 h after the end of operation at a 10 mL/h. 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.	The infusion of the isoenergetic and isonitrogenous EN was stated within12 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[37]	Spain	Surgery for gastric cancer	30/30	66.7 ± 8.3/ 69.2 ± 13.8	5/8	IN 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.	SEN 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[38]	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 hat 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.	Isocaloric and isonitrogenous SEN was commenced 6 h at 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[23]	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 m/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.	Postoperative SEN was commenced 6 h after operation with 5% glucose solution at the rate of 20 mL/h for the first 12 h	LPS, PIC
Liu et al 2011[39]	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.	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 standard enteral nutrition.	LPS, PIC
Liu et al 2011[40]	China	Total gastrectomy	21/21	61.1 ± 7.50/ 61.6 ± 7.20	Unclear	Postoperative EIN diets which enriched with Arg, Glu, and ω-3-FA were infused via nasojejunum tube or jejunostic tube.	Standard postoperative EN which enriched with fiber were infused via nasojejunum tube or jejunostic tube	PIC
Liu et al 2012[41]	China	Total gastrectomy	28/28	57.3 ± 7.1/ 58.4 ± 6.3	Unclear	Postoperative IN 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.	Postoperative SEN diets 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		Reported Outcomes
						Study Group Regimes	Control Group Regimes	
Marano et al 2013[5]	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[42]	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[22]	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[21]	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	Country	Operation Type	Sample Size	Age of Participants	No. of Malnourished Patients	Interventions		Reported Outcomes
						Study Group Regimes	Control Group Regimes	
Giger et al 2007[4]	Switzerland	Major abdominal surgery for the caners of stomach, pancreas, or periampullary	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 administrated 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 administrated 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[43]	America	Surgery for cancer of esophagus, stomach, or pancreas	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	Supplemental diets supplemented with 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	PIC
Xu et al 2006[20]	China	Radical gastrectomy, radical colectomy, or radical proctocolectomy	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/kg/d, respectively, the kilojoule-to-milliliter ratio was 1:1.	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/kg/d, respectively, the kilojoule-to-milliliter ratio was 1:1.	LPS, PIC
Gunerhan et al 2009[19]	Turkey	Surgery for GI tumors	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[11]	Switzerland	Surgery for cancer of esophagus, stomach, pancreas, liver, colon, or rectum	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 isocaloric and isonitrogenous SEN placebo for 3 consecutive days before surgery	LPS, PIC, PNIC
Liu et al 2011[44]	China	Surgery for cancer of stomach, colon, or rectum	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, EN = 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.

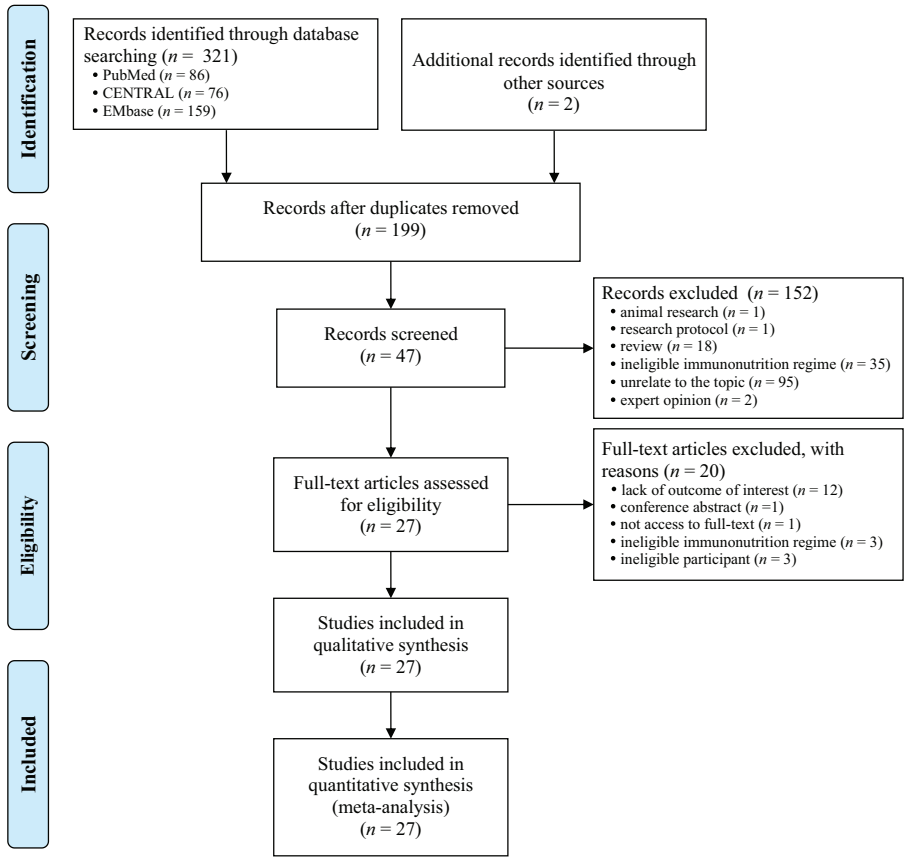

FIGURE 1. Flow diagram of retrieval and selection of literature.

Only one[4] 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, 0.76; 95% CI, 0.43–1.26) (Table 2).

Furthermore, we estimated the SCURA probabilities of different treatments for the postoperative infectious complications. The corresponding values were 72.50%, 39.57%, 87.93%, and 0.001% for preoperative, postoperative, perioperative EIN, and standard EN, respectively. The ranking of 4 treatments in terms of probability of postoperative infectious complications was shown in Figure 7A.

Postoperative Noninfectious Complications

Seven eligible studies,[11,19–22,42,43] 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,[13,16,35–37] 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 meta-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[10,17,18,21,22,42] involving 758 participants evaluated the effects of direct comparison of perioperative EIN related 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

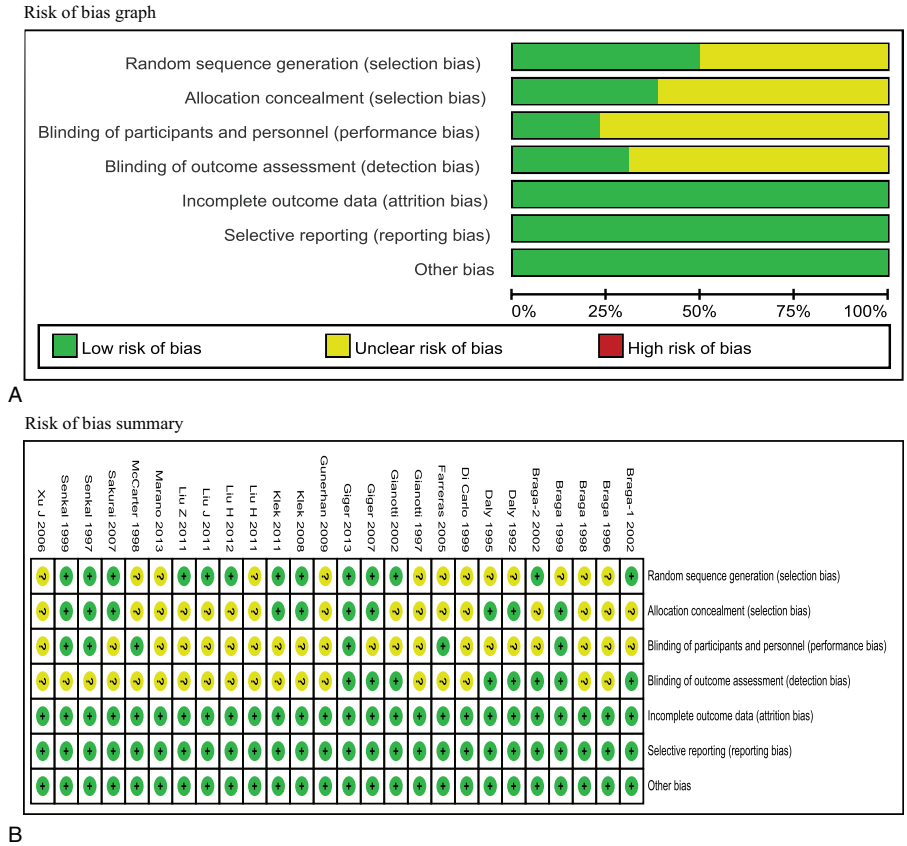

FIGURE 2. Assessment of risk of bias: (A) risk of bias graph; (B) risk of bias summary.

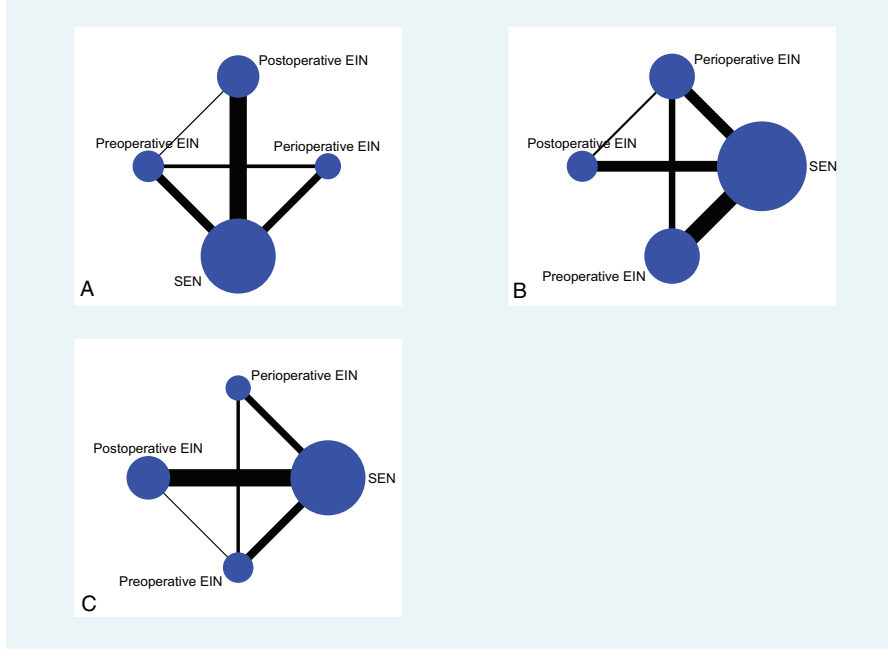

FIGURE 3. Evidence networks: (A) network for postoperative infectious complications; (B) network for postoperative noninfectious complications; (C) network for length of postoperative hospitalization. EIN = enteral immunonutrition, SEN = standard enteral nutrition.

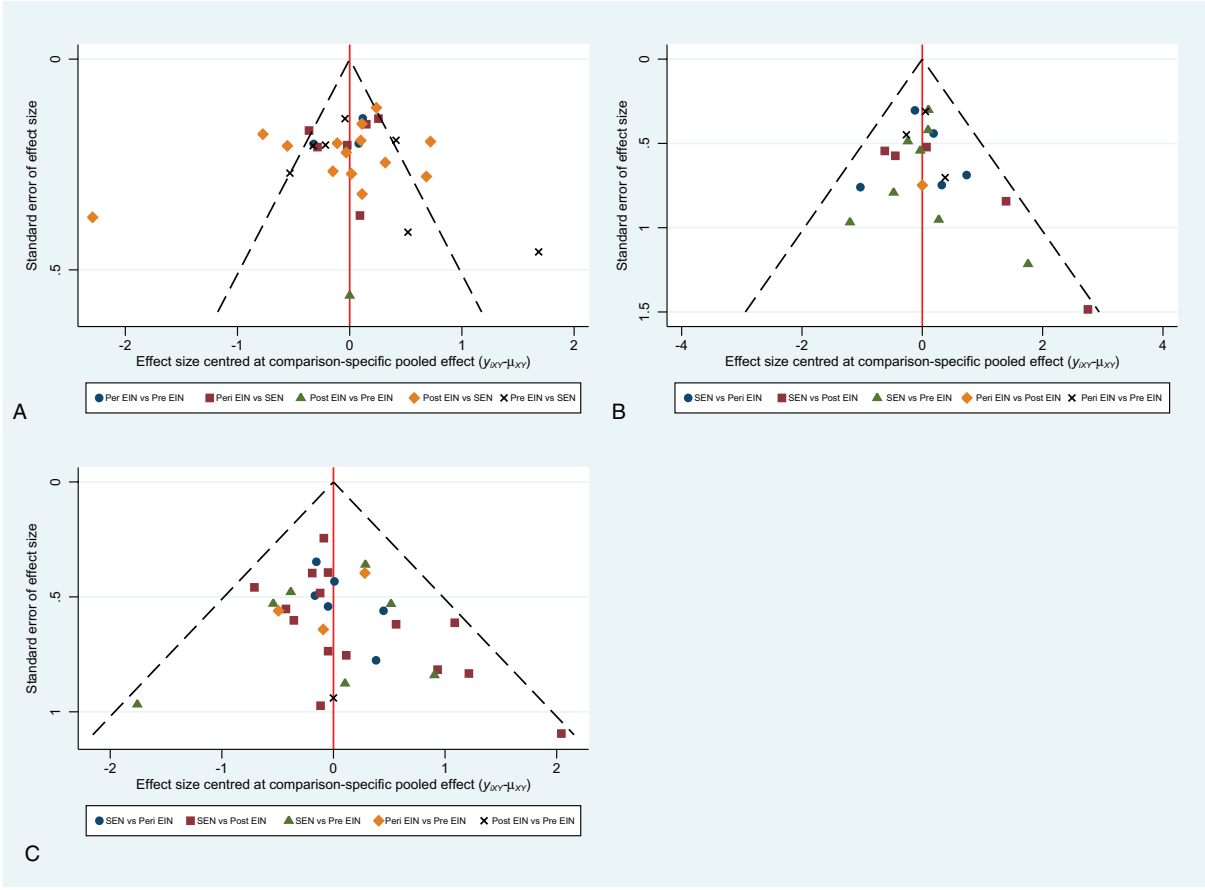

FIGURE 4. Comparison-adjusted funnel plots: (A) funnel plot for postoperative complication; (B) funnel plot for postoperative noninfectious complications; (C) funnel plot for length of postoperative hospitalization. Pre = preoperative, Post = postoperative, Peri = perioperative, EIN = enteral immunonutrition, 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, three[21,22,42] and one[4] reported the results of preoperative EIN versus perioperative and postoperative EIN relative to perioperative EIN method in terms of postoperative 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 2.33) (Figure 9A). Meanwhile, we performed a Bayesian NMA to estimate corresponding pooled result, and it generated similar result when compared standard EN with preoperative EIN (MD, 0.29; 95% CI, −0.32 to 0.89) (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)

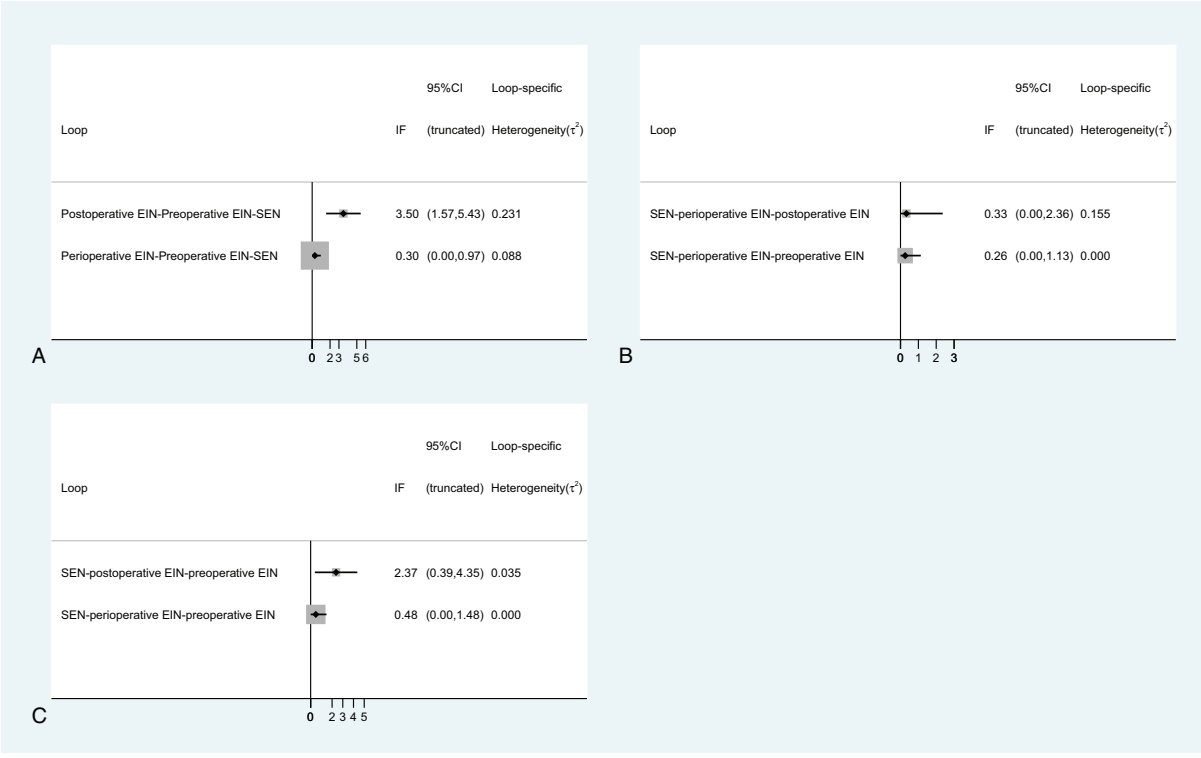

FIGURE 5. Inconsistency plot: (A) inconsistency plot for postoperative infectious complications; (B) inconsistency plot for postoperative noninfectious complications; (C) inconsistency plot for length of postoperative hospitalization. EIN = enteral immunonutrition, SEN = standard enteral nutrition.

(Figure 9B). 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[10,17,18,21,22,42] 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 postoperative 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 significance (MD, 0.84; 95% CI, 0.25–1.45) (Table 2).

In addition, three[21,22,42] and one[4] reported the results of preoperative EIN versus perioperative and postoperative EIN relative to perioperative immunonutrition method in terms of length of postoperative hospital stay, respectively. For preoperative versus perioperative comparison, no statistical heterogeneity 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 difference (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 comparison, one suggested that perioperative immunonutrition method effectively shortened the length of postoperative hospital 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 postoperative EIN approach. Hence, a Bayesian NMA was performed 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 difference (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, perioperative 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.[45] 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 immunonutrition versus standard EN,[10,12–17] and these results consistently 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

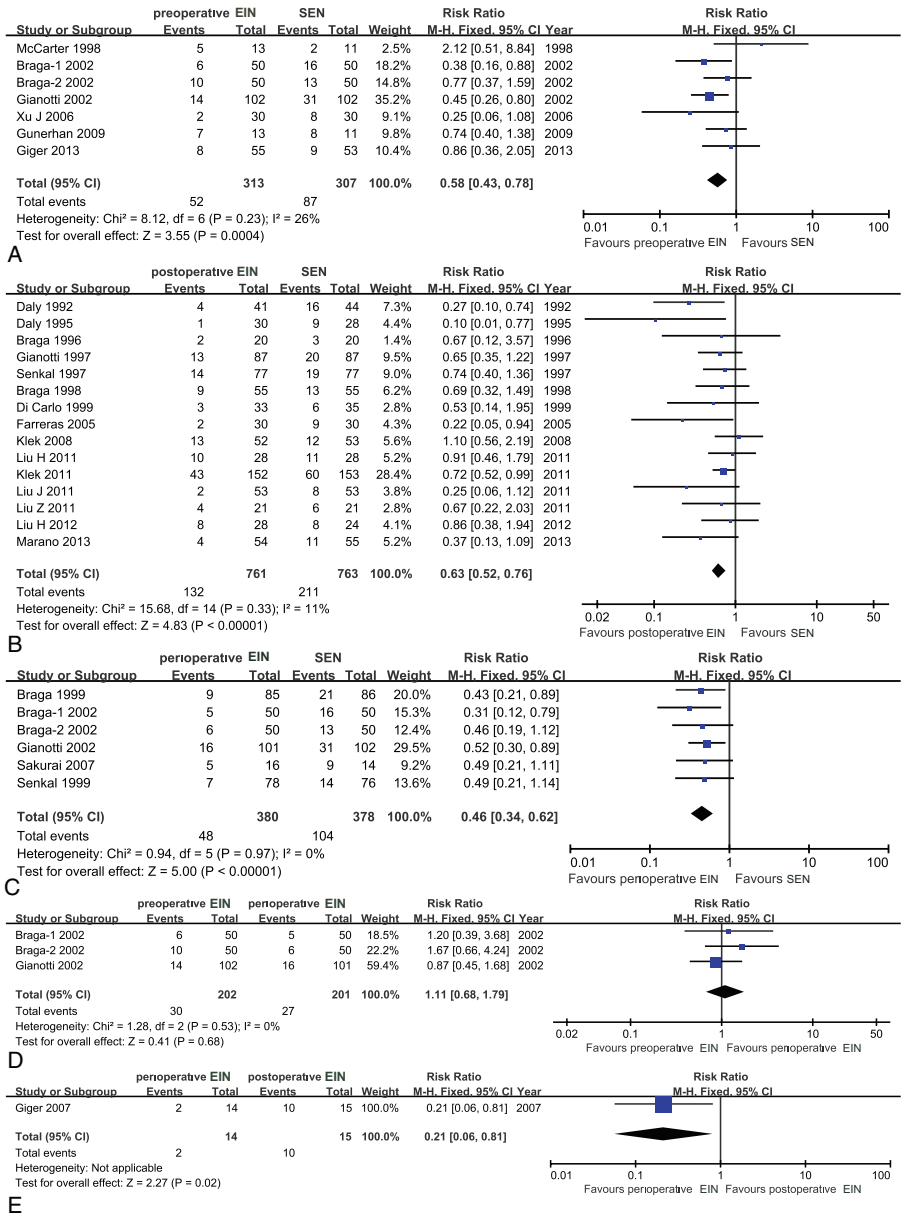

FIGURE 6. Traditional pair-wise meta-analysis on postoperative infectious complications: (A) preoperative EIN versus SEN; (B) postoperative EIN versus SEN; (C) perioperative EIN versus SEN; (D) preoperative EIN versus perioperative EIN; (E) perioperative EIN versus postoperative EIN. EIN = enteral immunonutrition.

SRs and meta-analyses which evaluated the comparative effects of EIN versus standard EN have been published.[8,25,26,46–48] In addition, of these six SRs, two systematically assessed the direct evidences between preoperative or postoperative versus perioperative EIN methods.[8,26] However, it is noted that these SRs and meta-analyses were performed by using traditional pair-wise meta-analysis method which cannot compare >2 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[21,22,42] directly compared preoperative with perioperative EIN methods, as well as only one[4] directly compared postoperative with perioperative EIN methods. However, no study,

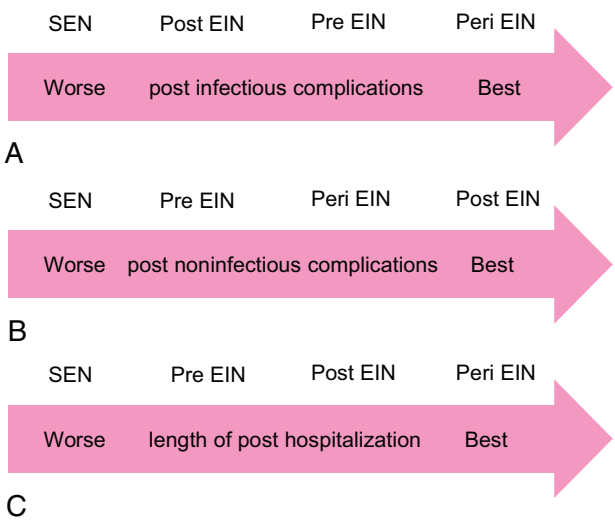

FIGURE 7. Ranking of treatments: (A) ranking of treatments in terms of postoperative infectious complications; (B) ranking of treatments in terms of postoperative noninfectious complications; (C) ranking of treatments in terms of length of postoperative hospitalization. Pre- = preoperative, Post = postoperative,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

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, interlukin-6, and tumor necrosis factor-α.[13–15,49,50] When compared with

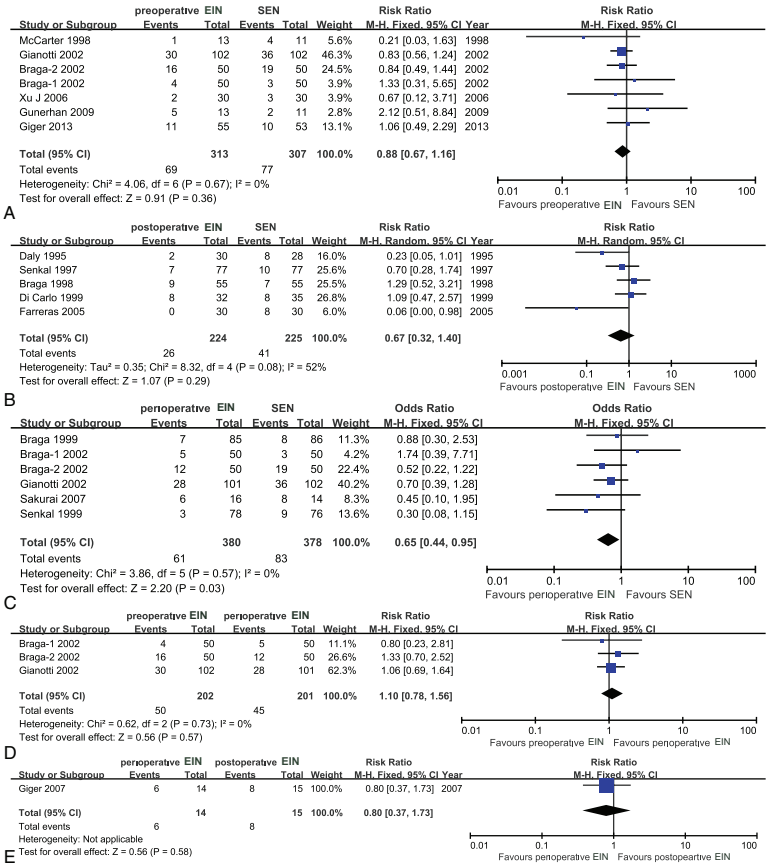

FIGURE 8. Traditional pair-wise meta-analysis on postoperative noninfectious complications: (A) preoperative EIN versus SEN; (B) postoperative EIN versus SEN; (C) perioperative EIN versus SEN; (D) preoperative EIN versus perioperative EIN; (E) perioperative EIN versus postoperative EIN. EIN = enteral immunonutrition.

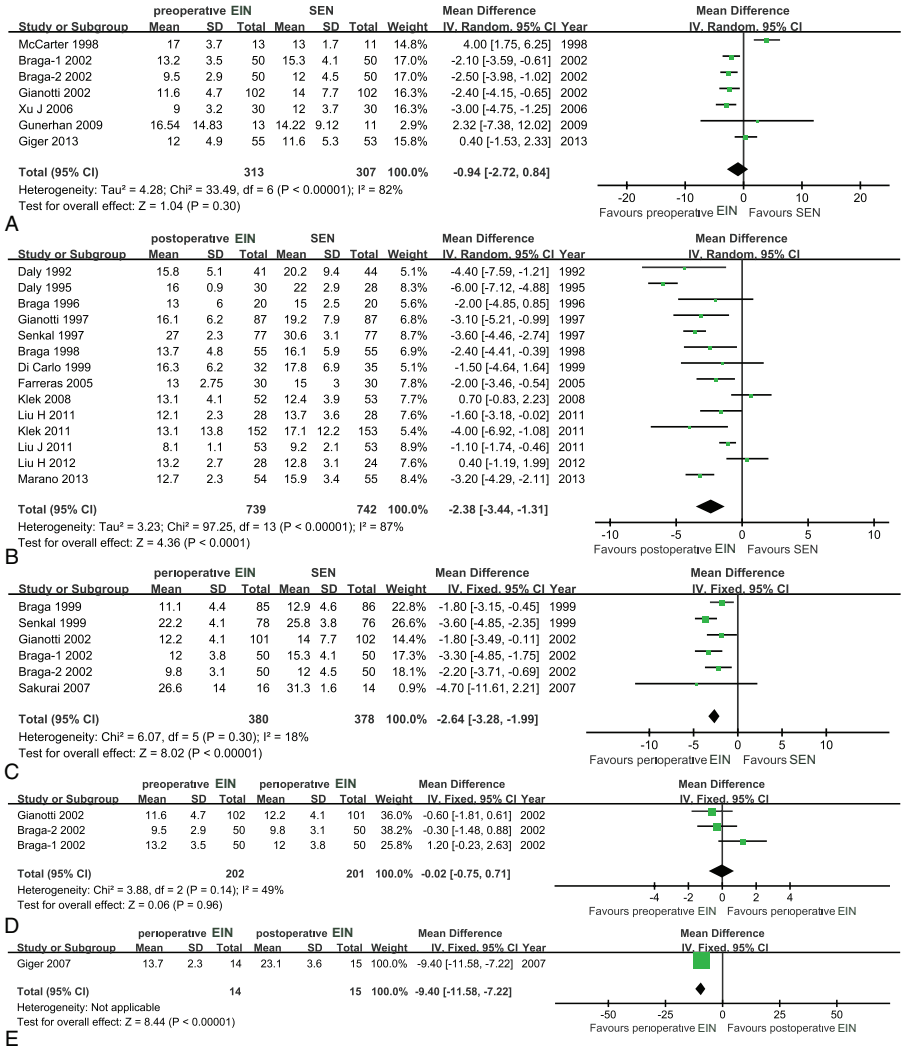

FIGURE 9. Traditional pair-wise meta-analysis on length of postoperative hospitalization: (A) preoperative EIN versus SEN; (b) postoperative EIN versus SEN; (C) perioperative EIN versus SEN; (D) preoperative EIN versus perioperative EIN; (E) perioperative EIN versus postoperative EIN. EIN = enteral immunonutrition.

postoperative EIN method, preoperative EIN regime significantly increased the level of transferring.[20]

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, postoperative was superior to perioperative and preoperative regimes (Figure 7B). In terms of length of postoperative hospital stay, perioperative was better than postoperative and preoperative immunonutrition regimes (Figure 7C). And thus,

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)					
	Pre EIN vs SEN	Post EIN vs SEN	Peri EIN vs SEN	Peri EIN vs Post EIN	Pre EIN vs Post EIN	Peri EIN vs Pre EIN
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 (0.43–1.26)	0.89 (0.50–1.49)
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 (0.33–1.59)	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)

EIN = enteral immunonutrition, GI = gastrointestinal, Peri = perioperative, Post = postoperative, Pre = preoperative, SEN = standard enteral nutrition.

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 postoperative 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.

ACKNOWLEDGMENTS

The authors appreciate the work of editors and anonymous reviewers.

REFERENCES

1. Ardizzoni A, Tiseo M, Boni L. Validation of standard definition of sensitive versus refractory relapsed small cell lung cancer: a pooled analysis of topotecan second-line trials. *Eur J Cancer.* 2014;50:2211–2218.
2. Fujitani K, Tsujinaka T, Fujita J, et al. Prospective randomized trial of preoperative enteral immunonutrition followed by elective total gastrectomy for gastric cancer. *Br J Surg.* 2012;99:621–629.
3. Ates E, Yilmaz S, Erkasap S, et al. Perioperative immunonutrition ameliorates the postoperative immune depression in patients with gastrointestinal system cancer (prospective clinical study in 42 patients). *Acta Gastroenterolo Belg.* 2004;67:250–254.
4. Giger U, Buchler M, Farhadi J, et al. Preoperative immunonutrition suppresses perioperative inflammatory response in patients with major abdominal surgery—a randomized controlled pilot study. *Ann Surg Oncol.* 2007;14:2798–2806.
5. Marano L, Porfidia R, Pezzella M, et al. Clinical and immunological impact of early postoperative enteral immunonutrition after total gastrectomy in gastric cancer patients: a prospective randomized study. *Ann Surg Oncol.* 2013;20:3912–3918.
6. Tang R, Chen HH, Wang YL, et al. Risk factors for surgical site infection after elective resection of the colon and rectum: a single-center prospective study of 2,809 consecutive patients. *Ann Surg.* 2001;234:181–189.
7. Tartter PI, Martinelli G, Steinberg B, et al. Changes in peripheral T-cell subsets and natural-killer cytotoxicity in relation to colorectal cancer surgery. *Cancer Detect Prev.* 1986;9:359–364.
8. Zheng Y, Li F, Qi B, et al. Application of perioperative immunonutrition for gastrointestinal surgery: a meta-analysis of randomized controlled trials. *Asia Pac J Clin Nutr.* 2007;16 (suppl 1):253–257.
9. Rosa F, Bossola M, Pacelli F, et al. Malnutrition and postoperative complications in abdominal surgery. *Ann Surg.* 2011;254:666–667.
10. Senkal M, Zumtobel V, Bauer KH, et al. Outcome and cost-effectiveness of perioperative enteral immunonutrition in patients undergoing elective upper gastrointestinal tract surgery: a prospective randomized study. *Arch Surg.* 1999;134:1309–1316.
11. Giger-Pabst U, Lange J, Maurer C, et al. Short-term preoperative supplementation of an immunoenriched diet does not improve clinical outcome in well-nourished patients undergoing abdominal cancer surgery. *Nutrition.* 2013;29:724–729.
12. Daly JM, Lieberman MD, Goldfine J, et al. Enteral nutrition with supplemental arginine, RNA, and omega-3 fatty acids in patients after operation: immunologic, metabolic, and clinical outcome awaiting upper gastrointestinal malignancies. *Surgery.* 1992;112: 56–67.
13. Daly JM, Weintraub FN, Shou J, et al. Enteral nutrition during multimodality therapy in upper gastrointestinal cancer patients recieve or not enteral jejunostomy feedings. *Ann Surg.* 1995;221:327–338.
14. Braga M, Vignali A, Gianotti L, et al. Immune and nutritional effects of early enteral nutrition after major abdominal operations. *Eur J Surg.* 1996;162:105–112.
15. Gianotti L, Braga M, Vignali A, et al. Effect of route of delivery and formulation of postoperative nutritional support in patients undergoing major operations for malignant neoplasms. *Arch Surg.* 1997;132:1222–1229.
16. Senkal M, Mumme A, Eickhoff U, et al. Early postoperative enteral immunonutrition: clinical outcome and cost- comparison analysis in surgical patients. *Crit Care Med.* 1997;25:1489–1496.
17. Braga M, Gianotti L, Radaelli G, et al. Perioperative immunonutrition in patients undergoing cancer surgery: results of a randomized double-blind phase 3 trial. *Arch Surg.* 1999;134:428–433.
18. Sakurai Y, Masui T, Yoshida I, et al. Randomized clinical trial of the effects of perioperative use of immune-enhancing enteral formula on metabolic and immunological status in patients undergoing esophagectomy. *World J Surg.* 2007;31:2150–2157.
19. Gunerhan Y, Koksal N, Sahin UY, et al. Effect of preoperative immunonutrition and other nutrition models on cellular immune parameters. *World J Gastroenterol.* 2009;15:467–472.
20. Xu J, Zhong Y, Jing D, et al. Preoperative enteral immunonutrition improves postoperative outcome in patients with gastrointestinal cancer. *World J Surg.* 2006;30:1284–1289.
21. Gianotti L, Braga M, Nespoli L, et al. A randomized controlled trial of preoperative oral supplementation with a specialized diet in patients with gastrointestinal cancer. *Gastroenterology.* 2002;122:1763–1770.
22. Braga M, Gianotti L, Vignali A, et al. Preoperative oral arginine and n-3 fatty acid supplementation improves the immunometabolic host response and outcome after colorectal resection for cancer. *Surgery.* 2002;132:805–814.
23. Klek S, Sierzega M, Szybinski P, et al. The immunomodulating enteral nutrition in malnourished surgical patients—a prospective, randomized, double-blind clinical trial. *Clin Nutr.* 2011;30:282–288.
24. Pradelli L, Mayer K, Muscaritoli M, et al. N-3 fatty acid-enriched parenteral nutrition regimens in elective surgical and ICU patients: a meta-analysis. *Crit Care.* 2012;16:R184.
25. Cao W, Zhang CL. Enteral immunonutrition for malignant gastrointestinal tumor during perioperative period: A meta-analysis. *Chin J Evid-based Med.* 2013;13:992–1000.
26. Zhang Y, Gu Y, Guo T, et al. Perioperative immunonutrition for gastrointestinal cancer: a systematic review of randomized controlled trials. *Surg Oncol.* 2012;21:e87–e95.
27. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev.* 2015;4:1.

28. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Vol. 5.Wiley Online Library; 2008.
29. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg*. 2010;8:336–341.
30. Bowden J, Tierney JF, Copas AJ, et al. Quantifying, displaying and accounting for heterogeneity in the meta-analysis of RCTs using standard and generalised Q statistics. *BMC Med Res Methodol.* 2011;11:41.
31. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med.* 2002;21:1539–1558.
32. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med.* 2004;23:3105–3124.
33. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol.* 2011;64:163–171.
34. Chaimani A, Higgins JP, Mavridis D, et al. Graphical tools for network meta-analysis in STATA. *PLoS One.* 2013;8:e76654.
35. Braga M, Gianotti L, Vignali A, et al. Artificial nutrition after major abdominal surgery: impact of route of administration and composition of the diet. *Crit Care Med.* 1998;26:24–30.
36. Di Carlo V, Gianotti L, Balzano G, et al. Complications of pancreatic surgery and the role of perioperative nutrition. *Dig Surg.* 1999;16:320–326.
37. Farreras N, Artigas V, Cardona D, et al. Effect of early postoperative enteral immunonutrition on wound healing in patients undergoing surgery for gastric cancer. *Clin Nutr.* 2005;24:55–65.
38. Klek S, Kulig J, Sierzega M, et al. The impact of immunostimulating nutrition on infectious complications after upper gastrointestinal surgery: a prospective, randomized, clinical trial. *Ann Surg.* 2008;248:212–220.
39. Liu H, Ling W, Cao H. Effects of immune-enhanced enteral nutrition and parenteral nutrition on immune and nutritional function in elderly patients with gastric cancer after total gastrectomy. *Journal of Shanghai Jiaotong University (Medical Science).* 2011;31:1000–1004.
40. Liu Z, Yu J. Effect of immune enhanced enteral nutrition on postoperative immune function and inflammatory responses in gastric cancer patients with radical gastrectomy. *Chinese J Cancer Prev Treat.* 2011;18:66-67+69.
41. Liu H, Ling W, Shen ZY, et al. Clinical application of immune-enhanced enteral nutrition in patients with advanced gastric cancer after total gastrectomy. *J Dig Dis.* 2012;13:401–406.
42. Braga M, Gianotti L, Nespoli L, et al. Nutritional approach in malnourished surgical patients. A prospective randomized study. *Arch Surg.* 2002;137:174–180.
43. McCarter MD, Gentilini OD, Gomez ME, et al. Preoperative oral supplement with immunonutrients in cancer patients. *JPEN J Parenter Enteral Nutr.* 1998;22:206–211.
44. Liu JZ, Lan T, Zhang JS, et al. Use of postoperative enteral immunonutrition in malnutrition patients with gastrointestinal malignant tumor. *Zhonghua Wei Chang Wai Ke Za Zhi.* 2011;14:799–802.
45. Walker WA. Current opinion in gastroenterology. *Curr Opin Gastroenterol.* 2012;28:547–550.
46. Javed MS, Taylor I. A review of recent randomized trials in colorectal disease. *Colorectal Dis.* 2002;4:90–96.
47. Mabvuure NT, Roman A, Khan OA. Enteral immunonutrition versus standard enteral nutrition for patients undergoing oesophagogastric resection for cancer. *Int J Surg.* 2013;11:122–127.
48. Osland E, Hossain MB, Khan S, et al. Effect of timing of pharmaconutrition (immunonutrition) administration on outcomes of elective surgery for gastrointestinal malignancies: a systematic review and meta-analysis. *JPEN J Parenter Enteral Nutr.* 2014;38:53–69.
49. Wu GH, Zhang YW, Wu ZH. Modulation of postoperative immune and inflammatory response by immune-enhancing enteral diet in gastrointestinal cancer patients. *World J Gastroenterol.* 2001;7:357–362.
50. Chen DW, Fei ZW, Zhang YC, et al. Role of enteral immunonutrition in patients with gastric carcinoma undergoing major surgery. *Asian J Surg.* 2005;28:121–124.