Enteral nutrition versus parenteral nutrition after major abdominal surgery in patients with gastrointestinal cancer: a systematic review and meta-analysis

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▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/jim-2016-000083).

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Accepted 1 April 2016
Published Online First 25 April 2016

ABSTRACT

To clarify the benefits of enteral nutrition (EN) versus total parenteral nutrition (TPN) in patients with gastrointestinal cancer who underwent major abdominal surgery. Medline, Cochrane, EMBASE, and Google Scholar were searched for studies published until July 10, 2015, reporting outcomes between the two types of postoperative nutritional support. Only randomized controlled trials (RCTs) were included. A χ^2-based test of homogeneity was performed using Cochran's Q statistic and I^2. A total of 2540 patients (1268 who received EN and 1272 who received TPN; average age range: 58.3–67.7 years) from 18 RCTs were included for assessment. Patients who received EN had shorter lengths of hospital stay (pooled difference in mean=−1.74, 95% CI −2.41 to −1.07, p<0.001, shorter time to flatus (pooled difference in mean=−1.27, 95% CI −1.69 to −0.85, p<0.001), and significantly greater increases in albumin levels (pooled difference in mean=−1.33, 95% CI −2.18 to −0.47, p=0.002) compared with those who received TPN after major abdominal surgery, based on a random-effects model of analysis. EN after major abdominal surgery provided better outcomes compared with TPN in patients with gastrointestinal cancer.

Significance of this study

What is already known about this subject?

- Nutritional supplements have been shown to improve the clinical outcomes of patients after many types of surgery by diminishing the incidence of postoperative complications.
- Enteral or parenteral nutrition are two major routes of supplement administration.
- Enteral nutrition is traditionally favored due to its low cost, easier administration and better absorbance, but its practical use remains debatable due to gastrointestinal intolerance, especially in patients with high-risk cancer.
- The optimal route of substrate distribution remains unclear in patients with high-risk cancer undergoing major abdominal surgery.

What are the new findings?

- Patients who received enteral nutritional supplement had a shorter length of hospital stay, shorter time to flatus, and a greater increase in albumin levels than patients receiving parenteral nutrition.
- No significant difference in postoperative complication, such as anastomotic leakage, fistula, intra-abdominal infection or mortality rates between two groups.
- Enteral nutrition seems to be a more cost-effective supplement with at least comparable efficacy and safety as parenteral nutrition for patients after major abdominal surgery.

INTRODUCTION

One of the most significant therapeutic advances of the past century occurred when Dudrick *et al*[1 2] demonstrated a practical method of providing total nutrition intravenously. They perceived that postoperative patients who were fasted for extended periods of time had increased morbidity and mortality due to undernutrition.[2] Total intravenous nutrition, also known as total parenteral nutrition (TPN), is a liquid mixture containing amino acids, glucose, electrolytes, lipid emulsion, and multivitamins (MV) that is delivered intravenously via a central line.[3] In contrast, peripheral parenteral nutrition is delivered via a peripheral line and usually does not contain MV or LE.[3] Enteral nutrition (EN) is an oral nutritional supplement which can also be administered via a gastrostomy tube (G-tube) or other type of feeding tube.

Over the past 60 years, the indications, constituents and methods of administration of both TPN and EN have evolved. Both types of nutritional supplements have been shown to improve the clinical outcomes of patients after many types of surgery by diminishing the incidence of postoperative complications.[4] In addition, postoperative nutritional support has

To cite: Zhao X-F, Wu N, Zhao G-Q, *et al*. *J Investig Med* 2016;**64**: 1061–1074.

Significance of this study

How might these results change the focus of research or clinical practice?

- The results suggest that enteral nutrition provided better outcomes over parenteral nutrition and should be considered a priority for patients with GI cancer undergoing major abdominal surgery.
- Enteral nutrition should be encouraged as early as possible and as much as tolerated during the postoperative period.
- To make the nutritional goal, patients in enteral nutrition may still receive partial parenteral nutrition at early stages (postoperative days 1–4). Hence, the benefit of combining enteral and parenteral nutrition to optimize postoperative care should be further evaluated.
- On the basis of patient tolerance and availability of sufficient primary care, physicians need to evaluate individual patients for the optimal choice of management.

been shown to improve wound healing and maintain immunocompetence.[5–8] There is also an emerging consensus that early postoperative nutritional support reduces septic morbidity in the high-risk surgical patient.[5] The optimal route of substrate delivery (enteral vs parenteral), however, continues to be debated, especially in malnourished patients with GI cancer during the perioperative period[9 10]

Safety, convenience, and cost have been traditional arguments favoring the enteral route;[10] however, fear of gastrointestinal (GI) intolerance has discouraged its use in the postoperative stressed patient.[5 11] However, basic and clinical research offers compelling physiological benefits from enteral feeding. Substrates delivered by the enteral route are better utilised by the gut than those administered parenterally[5 12 13] Additionally, total enteral nutrition (TEN), when compared with current TPN solutions, prevents GI mucosal atrophy, attenuates the injury stress response, and preserves normal gut flora.[5 14–18]

Despite these considerations, there are few prospective randomized controlled trials (RCTs) comparing TEN with TPN in high-risk surgical patients, and the available studies lack the sample size necessary to document whether TEN, by maintaining gut function, improves clinical outcome.[5]

Some RCTs have concluded that EN is better than TPN for patients with GI cancer who undergo resection[4] and that early enteral nutrition (EEN) significantly reduces the complication rates and duration of postoperative stays compared with parenteral nutrition.[19] However, other studies have reported no differences in immune function, nutritional state, or inflammatory response between patients supported with TPN and those supported with EN.[20]

In order to clarify the benefits of EN versus TPN in postoperative patients who underwent major abdominal surgery for GI cancer, a meta-analysis was performed to evaluate nutritional support based on primary outcomes such as rate of anastomotic leakage/fistula formation, intra-abdominal infection, and mortality. Secondary outcomes included length of hospital stay, time to flatus and changes in albumin levels.

MATERIALS AND METHODS

Selection criteria

Only RCTs of patients with GI cancer (eg, gastric cancer, pancreatic cancer, hepatocellular carcinoma or colorectal cancer) undergoing major abdominal surgery (eg, total gastrectomy, pancreaticoduodenectomy or colonic resection) who received EN or TPN were included in this meta-analysis. Patients were assigned to either the EN group or TPN group postoperatively.

Cohort studies, letters, comments, editorials, case reports, proceedings, personal communications or articles that included cancers other than GI cancer or hepatitis and chronic liver disease, traumatic injury, or acute pancreatitis were excluded. In addition, any article that did not contain a quantitative primary outcome was also excluded.

Search strategy

Searched databases included Medline, Cochrane, EMBASE and Google Scholar until July 10, 2015. The reference lists of relevant studies were hand-searched. Keywords used for the search included parenteral nutrition, EN, total, surgery, postoperative, postsurgical, complication, length of stay.

Study selection and data extraction

Studies were identified by two independent reviewers using the search strategy. When there was uncertainty regarding eligibility, a third reviewer was consulted and a consensus was reached. The following data were extracted from studies that met the inclusion criteria: the name of the first author, year of publication, study design, number of participants in each group, participants' age and gender, and the major outcomes.

Quality assessment

The Cochrane Collaboration's tool[21] was used to assess the quality of all included studies.

Outcome measures

The primary outcomes were the rate of anastomotic leakage/fistula formation, intra-abdominal infection/abscess, and mortality among patients with GI cancer who received EN group versus TPN group after major abdominal surgery. Secondary outcomes included length of hospital stay, time to flatus and changes in albumin levels.

Statistical analysis

ORs with 95% CIs were calculated for dichotomous outcome (rates of anastomotic leakage/fistula formation, intra-abdominal infection/abscess, and mortality) between patients with GI cancer who received EN group versus TPN group after major abdominal surgery for each individual study and for all the studies combined. The difference in means with 95% CI between two groups was calculated for continuous outcome (length of hospital stay, time to flatus, and change in albumin levels before and after surgery). Median, range, and the size of a sample were used to estimate the mean and variance if data lacked a

mean and SD.[22] A χ^2-based test of homogeneity was performed and the inconsistency index (I^2) and Q statistics were determined. If the I^2 statistic was >50%, a random-effects model was used. Otherwise, a fixed-effect model was employed. Pooled effects were calculated and a two-sided p value <0.05 was considered statistically significant.

Sensitivity analysis was carried out using the leave-one-out approach. Moreover, publication bias was assessed by constructing funnel plots using Egger's test. The absence of publication bias was indicated if the data points formed a symmetric funnel-shaped distribution and one-tailed significance level p>0.05 (Egger's test). However, a funnel plot was only included if the meta-analysis included more than 10 studies.[23] All analyses were performed using Comprehensive Meta-Analysis statistical software, V.2.0 (Biostat, Englewood, New Jersey, USA).

RESULTS

Literature search

From the initial 362 records identified through the database search, 27 studies were assessed for eligibility. Once the full text of each of the 27 studies was reviewed, nine studies were excluded for the following reasons: their full text was unavailable (n=2), one study was a meta-analysis, they had no outcome of interest (n=3), they had a different objective (n=1), or they involved a different intervention (n=2). A flow chart outlining our study selection is shown in figure 1.

The 18 remaining studies evaluated in this meta-analysis[4 19 24–39] enrolled a total of 2540 patients, including 1268 patients who received EN support (EN group) and 1272 patients who received TPN support (TPN group). The characteristics of the studies and details of nutritional support are summarized in table 1. Patients' ages ranged from 58.3 to 67.7 years and the proportion of patients who were male ranged from 39% to 84%.

Rate of anastomotic fistula/leakage between EN versus TPN groups

The forest plot illustrating the results of the meta-analysis for the rate of anastomotic leakage/fistula formation between patients in the EN versus TPN group is shown in figure 2A. Eight studies[24 28 29 32 33 37–39] were excluded from this analysis because they did not report rates of anastomotic leakage/fistula formation. There was no significant heterogeneity when data from the remaining 10 studies

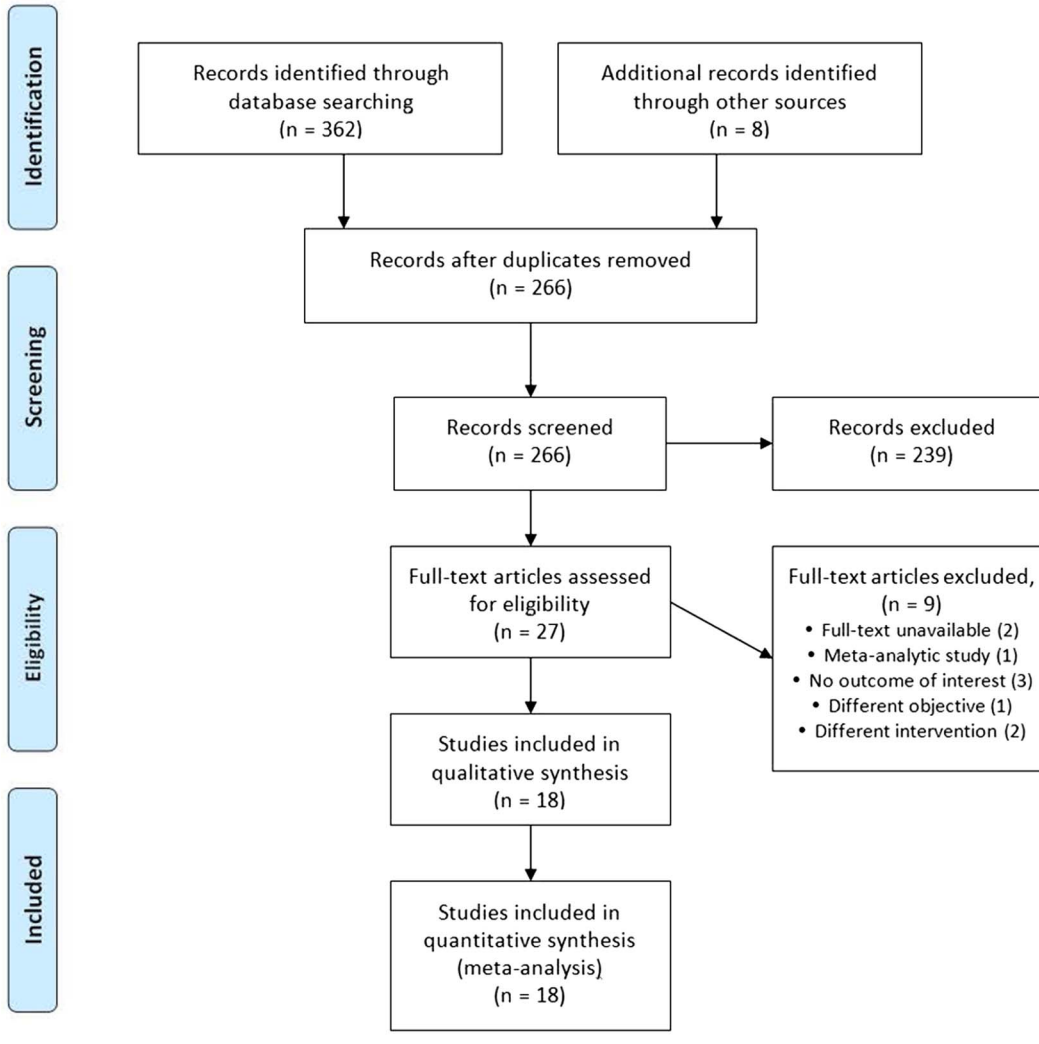


Figure 1 PRISMA flow diagram.

Table 1 Summary of basic characteristics of selected studies for meta-analysis

Ref #	First author (year)	Comparison groups	Number of patients	Age (year)	Male (%)	Type of abdominal malignancy	Nutritional goal	Nutritional goal and duration
24	Li (2015)	EEN group PN group	136 136	67.7	66%	Gastric cancer	30 kcal/kg/day	With gradual increase 3–5 days after anal exhaust
25	Boelens (2014)	EEN group EPN group	61 62	64 65	67% 69%	Primary or recurrent rectal carcinoma	5187.5 calories/5 days 6814.1 calories/5 days	With gradual increase from 500 mL from 2 L/day
26	Liu (2013)	TEN group TPN group	40 40	65.8 64.6	70% 60%	Gastric cancer	25 kcal/kg/day 1920 mL nutritional fluid per day;	3–4 days usually 7–10 days before proceeding to a semi-liquid diet
27	Park (2012)	EEN group PN group	18 20	62.7 61.3	39% 60%	Pancreatic carcinoma, Periampullary cancer	25 kcal/kg/day;	EN or TPN infusion continued until oral intake reached 800 kcal/day
28	Kim (2011)	EEN group	17	60	71%	NA	Total daily calories: 25 kcal/kg/day Total daily protein: 1.5 g/kg/day	Total of 5 days (EN+partial parenteral nutrition given for the first 3 days)
		TPN group	16	64.5	81%			TPN was initiated on the first postoperative day, and discontinued until POD 5
4	Liu (2011)	EN group TPN group	28 30	59.7 60.5	57% 57%	NA	Calories: 27 kcal/kg/day; Nitrogen: 0.2 g/kg/day	50% daily value at POD1, full volume from POD2 to POD6
29	Dong (2010)	EN group PN group	19 19	61.7 60.2	84% 84%	Gastric cancer	20–25 kcal/kg/day	Continued until POD 7
30	Klek (2008)	SEN group IMEN group	53 52	61.4 61.2	74% 65%	Gastrointestinal cancer	Starting at 25 mL/h (1.25 kcal/mL), with 25 mL increase daily until 100 mL/h	Continued until POD 7
		SPN group IMPN group	49 51	60 61.4	71% 71%		Protein: 0.15 g N/kg Energy: 150 kcal/day Supplements PRN	Continued until POD 7
31	Wu (2007)	EN group PN group	215 215	61.7 62.3	55% 57%	Gastrointestinal cancer	28 kcal/kg/day 30 kcal/kg/day	Continued until POD 7; gradual transition to normal diet
32	Alivizatos (2005)	EIN group Glu-TPN group	15 14			Gastric, pancreatic, hepatocellular, or colon carcinoma	25 kcal/kg/day	Continued at least 5 days or until normal diet possible (oral diet ≧1000 kcal/day)
33	Ates (2004)	EEN group TPN group	22 20	58.3 60.1	82% 80%	Gastric cancer, colorectal cancer	*Non-protein calorie*: 35 kcal/kg/day; *Nitrogen*: 0.26 g/kg/day; *Carbohydrate/lipid ratio*: 5	Initiated 5 days prior to surgery and continued until POD 7. EEN group received partial parenteral nutrition from POD 1–4 (after reaching nutritional goal: 2 mL/kg/h).
19	Bozzetti (2001)	EN group PN group	159 158	64.8 64.1	59% 58%	Stomach/esophagus cancer, hepatobiliary cancer	Total calorie: 26.75 kcal/kg/day; Nitrogen: 1.4 g amino acid/kg/day	Gradual increase of infusion rate to full regimen from POD1–4, continued until end of treatment (oral intake of 3350 kJ/day)
34	Braga (2001)	EEN group TPN group	126 131	64.1 62.9	54% 54%	Gastric cancer, pancreatic cancer, esophageal cancer	25 kcal/kg/day	Gradual increase to full regimen on POD4, then continue until oral intake of 800 kcal/day
35	Pacelli (2001)	EN group	119	61.5	61%	Gastric, colorectal, pancreatic, and cholangiocarcinoma, other GI cancers	Nonprotein: 25 kcal/kg/day Nitrogen: 0.2 g/kg/day	EN+TPN for POD 1–3; EN continued until oral intake of ≧1000 mL fluids/day
		TPN group	122	61.6	59%			continued until oral intake of ≧1000 mL fluids/day
36	Braga (1998)	Enriched group	55	60.9	NA	NA	NA	NA
		TPN group	56	61.7	NA			
37	Gianotti (1997)	EN group	87	64.5	55%	Pancreatic and gastric cancer	25 kcal/kg per day	EN+TPN for POD 1–3 to reach nutritional goal; EN only until POD 7; Oral intake begins POD8
		PN group	86	63.8	54%			NA

Continued

Table 1 Continued

Ref #	First author (year)	Comparison groups	Number of patients	Age (year)	Male (%)	Type of abdominal malignancy	Nutritional goal	Nutritional goal and duration
38	Braga (1996)	EEN group	20	59	60%	Gastric cancer, pancreatic cancer	Calorie: 25 kcal/kg/day Protein: 0.25 g N/kg/day	EN+TPN for POD 1–4; EN continued until POD 8
		TPN group	20	60				NA
39	Braga (1995)	Enriched group	26	59.3	NA	Gastric cancer, pancreatic cancer	25 kcal/kg/day 0.25 g of N/kg/day	EN+TPN for POD 1–4; EN continued until POD 8
		Parenteral group	27	59.8	NA			

EEN, early enteral nutrition; EN; enteral nutrition; EPN, early parenteral nutrition; IMEN, immunostimulating enteral nutrition; IMPN, immunostimulating parenteral nutrition; N, nitrogen; NA, not applicable; PN, parenteral nutrition; POD, postoperative day; PRN, pro re nata (as needed); SEN standard enteral nutrition; SPN, standard parenteral nutrition; TEN, total; enteral nutrition; TPN, total parenteral nutrition.

were pooled (heterogeneity test: Q=8.353, I^2=0%); therefore, a fixed-effect model of analysis was used. The overall analysis revealed no significant difference in the rate of anastomotic leakage/fistula formation between patients in the EN versus TPN groups (pooled OR=0.77, 95% CI 0.54 to 1.10, p=0.147).

Rate of intra-abdominal infection between the EN versus TPN groups

Eight studies[24 27–29 32 33 38 39] were excluded from this analysis because of lack of intra-abdominal infection data (figure 2B). There was no significant heterogeneity when data from the remaining 10 studies were pooled (heterogeneity test: Q=3.141, I^2=0%); therefore, a fixed-effect model of analysis was used. The overall analysis revealed no significant difference in the rate of intra-abdominal infection between patients in the EN versus TPN groups (pooled OR=0.78, 95% CI 0.51 to 1.17, p=0.228).

Mortality rates between patients in the EN versus TPN groups

The forest plot showing the results of the meta-analysis for mortality rate is illustrated in figure 2C. Only seven studies[19 30–32 34 35 37] provided mortality data and were included in the analysis. A fixed-effect model of analysis was used because no significant heterogeneity among the seven studies was found (heterogeneity test: Q=3.030, I^2=0%). The overall analysis revealed no significant difference in mortality between patients in the EN versus TPN groups (pooled OR=1.00, 95% CI 0.52 to 1.92, p=0.999).

Length of hospital stay between the EN versus TPN groups

The forest plot illustrating the result of the meta-analysis for the length of hospital stay between patients in the EN versus TPN groups is shown in figure 3A. Two studies[26 32] were excluded from this analysis because they did not report the length of hospital stay. There was significant heterogeneity when data from the remaining 16 studies were pooled (heterogeneity test: Q=63.432, I^2=74.74%); therefore, a random-effects model of analysis was used. The overall analysis revealed that patients who received EN had shorter lengths of hospital stay than those who received TPN after major abdominal surgery (pooled difference in mean=−1.74, 95% CI −2.41 to −1.07, p<0.001).

Time to flatus between the EN versus TPN groups

Only five studies[24 25 31 34 37] provided time to flatus information and were included in the analysis (figure 3B). There was significant heterogeneity among the five studies (heterogeneity test: Q=66.475, I^2=93.99%); therefore, a random-effects model of analysis was used. The overall analysis revealed that patients in the EN group had a shorter time to flatus compared with those in the TPN group (pooled difference in mean=−1.27, 95% CI −1.69 to −0.85, p<0.001).

Mean change in albumin before and after surgery between EN versus TPN groups

The forest plot illustrating the results of the meta-analysis regarding the mean change in albumin before and after surgery between patients in the EN and TPN groups is shown in figure 3C. A total of nine studies[24 26–30 34 38 39] provided the mean change in albumin before and after surgery and were included in the analysis. There was significant heterogeneity among the nine studies (heterogeneity test: Q=19.044, I^2=52.74%); therefore, a random-effects model of analysis was used. The overall analysis revealed that patients in the EN group had significantly increased albumin levels compared with those in the TPN group (pooled difference in mean=−1.33, 95% CI −2.18 to −0.47, p=0.002).

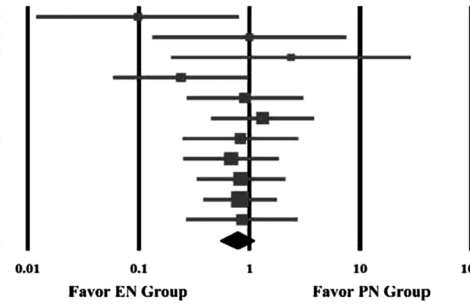
Sensitivity analysis and publication bias

Sensitivity analyses were performed using the leave-one-out approach in which the meta-analysis was performed with each study removed in turn (table 2). The direction and magnitude of combined estimates did not vary markedly with the removal of the studies, indicating that the meta-analysis was robust and the data were not overly influenced by each study.

In addition, there was no significant evidence of publication bias for the rate of anastomotic leakage/fistula formation, intra-abdominal infection rate, length of hospital stay, or mean change in albumin, as assessed using Egger's test (all p>0.05; figure 4). However, regarding mortality and time to flatus, the power of the tests for publication bias was too low to distinguish chance from real asymmetry because of the small number of studies for those two outcomes.

A

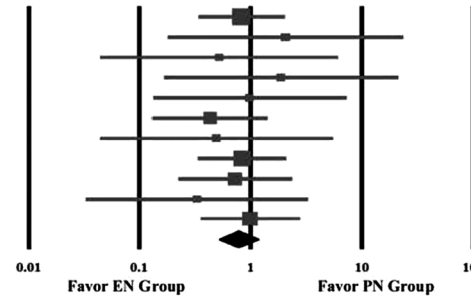
First author (year)	Anastomotic fistula/ leakage		Statistics for each study					Odds ratio with 95% CI	Relative weight
	EN group	PN group	Odds ratio	Lower limit	Upper limit	Z-Value	P-Value		
Boelens (2014)	1 / 61	9 / 62	0.10	0.01	0.80	-2.17	0.030		2.812
Liu (2013)	2 / 40	2 / 40	1.00	0.13	7.47	0.00	1.000		3.063
Park (2012)	2 / 18	1 / 20	2.38	0.20	28.67	0.68	0.496		1.996
Liu (2011)	3 / 28	10 / 30	0.24	0.06	0.99	-1.97	0.049		6.161
Klek (2008)_standard	6 / 53	6 / 49	0.91	0.27	3.05	-0.14	0.885		8.533
Klek (2008)_immunomodulating	9 / 52	7 / 51	1.32	0.45	3.85	0.50	0.616		10.749
Wu (2007)	5 / 215	6 / 215	0.83	0.25	2.76	-0.31	0.760		8.570
Bozzetti (2001)	7 / 159	10 / 158	0.68	0.25	1.84	-0.76	0.449		12.585
Braga (2001)	9 / 126	11 / 131	0.84	0.34	2.10	-0.37	0.708		14.730
Pacelli (2001)	14 / 119	17 / 122	0.82	0.39	1.76	-0.50	0.615		21.596
Braga (1998)	6 / 55	7 / 56	0.86	0.27	2.73	-0.26	0.795		9.203
Pooled effect			0.77	0.54	1.10	-1.45	0.147		



Heterogeneity test:Q =8.353, df = 10, P = 0.594, I-square = 0.00%

B

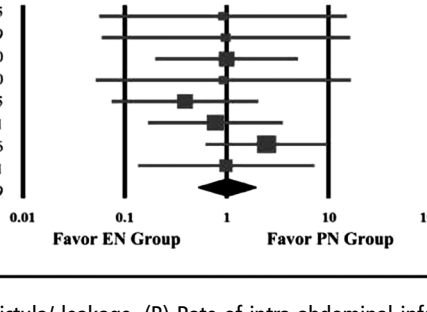
First author (year)	Intra-abdominal infection / abscess		Statistics for each study					Odds ratio with 95% CI	Relative weight
	EN group	PN group	Odds ratio	Lower limit	Upper limit	Z-Value	P-Value		
Boelens (2014)	11 / 61	13 / 62	0.83	0.34	2.03	-0.41	0.682		21.104
Liu (2013)	2 / 40	1 / 40	2.05	0.18	23.59	0.58	0.564		2.832
Liu (2011)	1 / 28	2 / 30	0.52	0.04	6.06	-0.52	0.600		2.794
Klek (2008)_standard	2 / 53	1 / 49	1.88	0.17	21.44	0.51	0.610		2.853
Klek (2008)_immunomodulating	2 / 52	2 / 51	0.98	0.13	7.24	-0.02	0.984		4.224
Wu (2007)	4 / 215	9 / 215	0.43	0.13	1.43	-1.37	0.170		11.855
Bozzetti (2001)	1 / 159	2 / 158	0.49	0.04	5.50	-0.57	0.566		2.905
Braga (2001)	9 / 126	11 / 131	0.84	0.34	2.10	-0.37	0.708		20.076
Pacelli (2001)	5 / 119	7 / 122	0.72	0.22	2.34	-0.55	0.585		12.197
Braga (1998)	1 / 55	3 / 56	0.33	0.03	3.25	-0.95	0.340		3.206
Gianotti (1997)	8 / 87	8 / 86	0.99	0.35	2.76	-0.02	0.981		15.953
Pooled effect			0.78	0.51	1.17	-1.21	0.228		



Heterogeneity test:Q =3.141, df = 10, P = 0.978, I-square = 0.00%

C

First author (year)	Mortality		Statistics for each study					Odds ratio with 95% CI	Relative weight
	EN group	PN group	Odds ratio	Lower limit	Upper limit	Z-Value	P-Value		
Klek (2008)_standard	1 / 53	1 / 49	0.92	0.06	15.17	-0.06	0.955		5.447
Klek (2008)_immunomodulating	1 / 52	1 / 51	0.98	0.06	16.11	-0.01	0.989		5.448
Wu (2007)	3 / 215	3 / 215	1.00	0.20	5.01	0.00	1.000		16.435
Alivizatos (2005)	1 / 15	1 / 14	0.93	0.05	16.42	-0.05	0.960		5.172
Bozzetti (2001)	2 / 159	5 / 158	0.39	0.07	2.04	-1.12	0.265		15.587
Braga (2001)	3 / 126	4 / 131	0.77	0.17	3.53	-0.33	0.741		18.540
Pacelli (2001)	7 / 119	3 / 122	2.48	0.63	9.82	1.29	0.196		22.515
Gianotti (1997)	2 / 87	2 / 86	0.99	0.14	7.18	-0.01	0.991		10.855
Pooled effect			1.00	0.52	1.92	0.00	0.999		



Heterogeneity test:Q =3.030, df = 7, P = 0.882, I-square = 0.00%

Figure 2 Meta-analysis for dichotomous outcomes. (A) Rate of anastomotic fistula/ leakage. (B) Rate of intra-abdominal infection/ abscess. (C) Mortality rate.

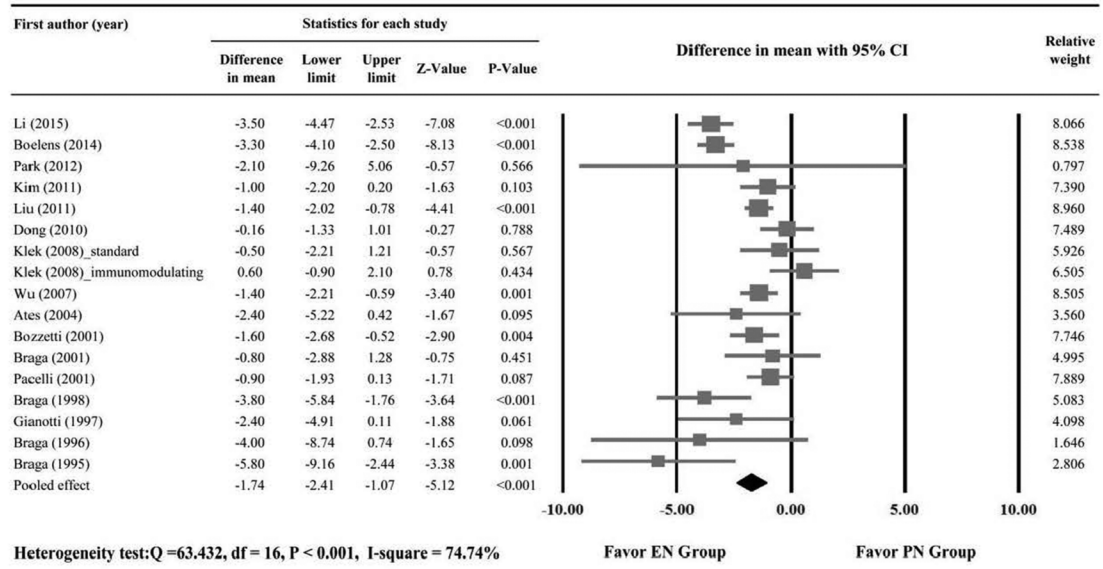
Quality assessment

Figure 5 shows the assessed outcomes for the 18 included studies. The assessment showed adequate quality and fair application concerns in terms of random sequence generation, attrition bias, and reporting bias (figure 5A). However, the assessment was unclear as to the high risk of performance and detection bias for all studies in general. One study in particular, conducted by Liu *et al*,[26] had a high risk of selection bias. It was difficult to avoid the risk of performance and detection bias in clinical interventions (such as those mentioned in the 18 studies) as patients and care providers were well aware of the different routes of nutritional administration.[5]

DISCUSSION

The purpose of this meta-analysis was to examine the most recent clinical outcomes using EN versus TPN in patients with GI cancer after major abdominal surgery. The pooled data suggested that there were no differences between TPN or EN use with respect to anastomotic leakage/fistula

A



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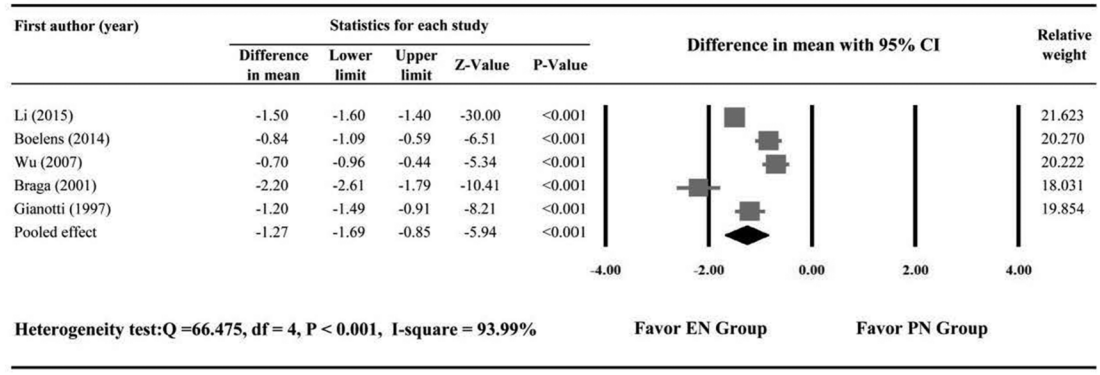

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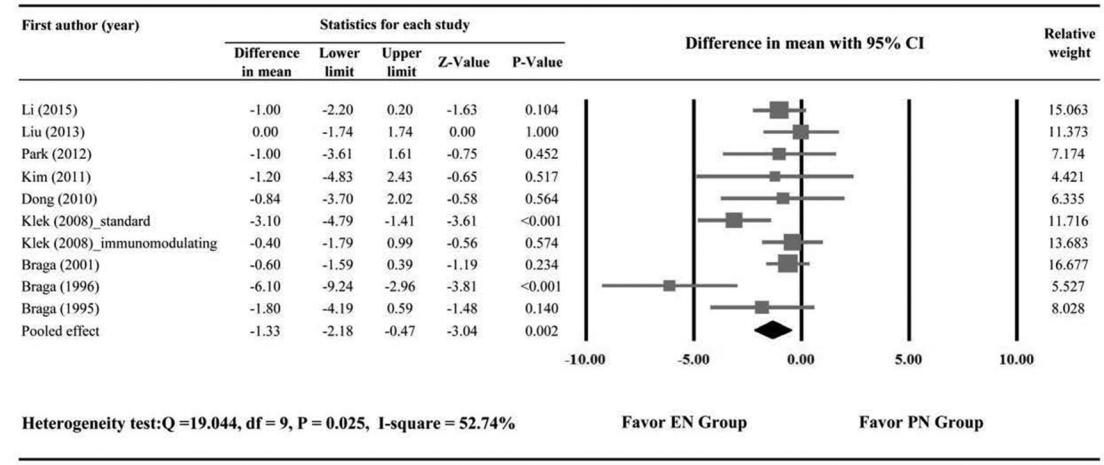

Figure 3 Meta-analysis for continuous outcomes. (A) Length of hospital stay. (B) Time to flatus. (C) Change in albumin.

formation, intra-abdominal infection, or mortality, but there was significant correlation between clinical recovery and use of EN in patients with all types of GI cancer. The EN group had shorter lengths of hospital stay, shorter times to flatus, and greater increases in albumin levels compared with the TPN group.

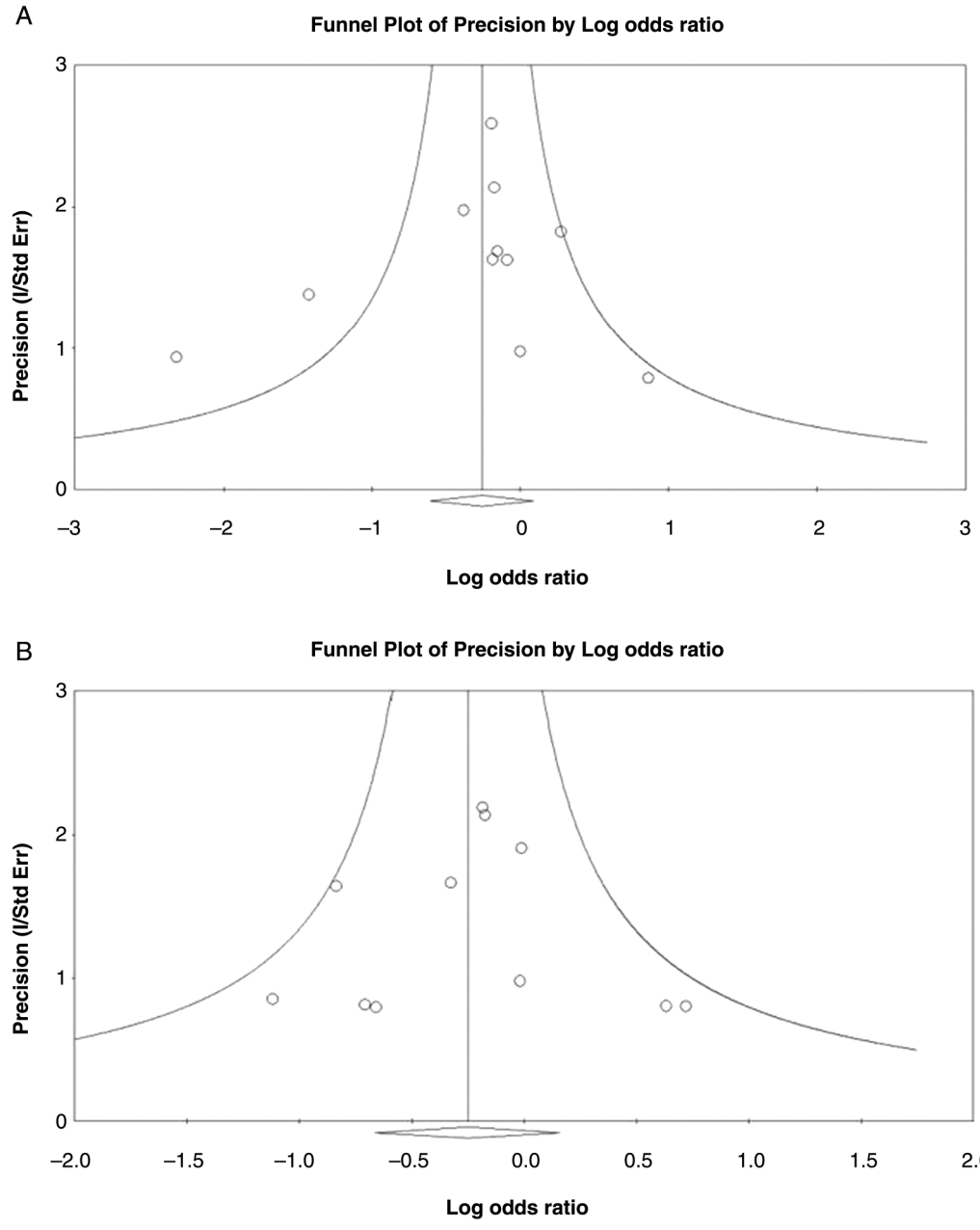

Figure 4 Funnel plots showing the distribution of published study outcomes. (A). Rate of anastomotic fistula/ leakage. (B) Rate of Intra-abdominal infection/abscess. (C) Length of Hospital Stay. (D) Change in Albumin.

Our current results are in agreement with the previous meta-analyses,[5 40–42] where they found a lower risk of infection, reduced septic morbidity rate, and a shorter hospital stay in patients supported by EN. In a meta-analysis of 27 studies comprising 1828 patients, Braunschweig *et al*[41] observed a significantly lower relative risk of infection with tube feeding (0.64; 95% CI 0.54 to 0.76) and standard care (0.77; 95% CI 0.65 to 0.91) than parenteral nutrition. However, in malnourished populations, there was a significantly higher risk of mortality (3.0; 95% CI 10.9 to 8.56) and a trend toward a higher risk of infection with standard care than with parenteral nutrition (1.17; 95% CI 0.88 to 1.56). Early feeding has been shown to reduce the risk of any type of infection (relative risk 0.72, 95% CI 0.54 to 0.98, p=0.036) and the mean length of stay in hospital (number of days reduced by 0.84, 95% CI 0.36 to 1.33, p=0.001) in a meta-analysis by Lewis *et al*.[42] Similarly, Peng *et al*[40] have shown that early postoperative EN support could decrease pulmonary complications (RR=0.37, 95% CI 0.22 to 0.62, p=0.00) and anastomotic leakage (RR=0.46, 95% CI 0.22 to 0.96, p=0.04) as compared with PN in patients with esophageal cancer following esophagectomy, while maintaining a better nutritional status than parenteral nutrition support. Although similar conclusions were drawn that EN is better than TPN, our meta-analysis revealed no difference in terms of anastomotic leakage in patients with GI cancer after any major abdominal surgery.

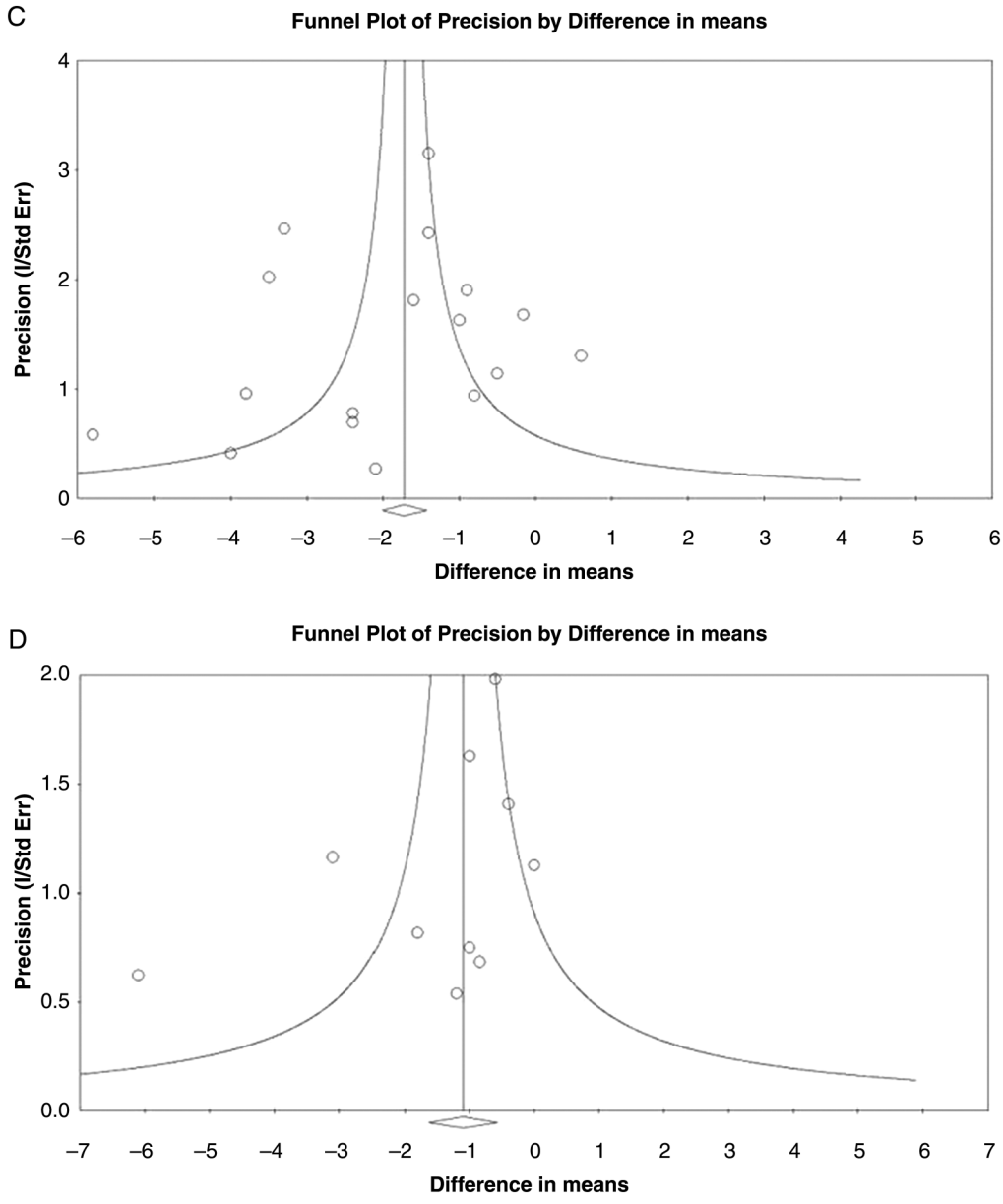

Figure 4 Continued.

In a two-part meta-analysis combining data from eight prospective randomized trials, Moore *et al*[5] found that postoperative enteral feeding is feasible in high-risk surgical patients and may reduce the septic morbidity rates. Significantly fewer septic complications were observed in TEN patients as compared to the TPN group (TEN, 18%; TPN, 35%; p=0.01). In addition, the albumin levels were also slightly higher in the EN patients, although the difference did not reach significance.[5] In contrast, in an animal model of abdominal wall wounds and colonic anastomoses in protein-malnourished rats, Law and Ellis[7 8] found a positive correlation of serum albumin levels with colonic anastomotic healing in rats given postoperative parenteral nutrition. However, the current results revealed a beneficial effect of nutritional support on postoperative albumin levels in the EN group, as compared with those in the TPN group.

Significant supportive data from our study also showed a shorter time to flatus, which is a strong indicator of the return of GI functionality after surgery. Similar to the findings from the current meta-analysis, Nomura *et al*[8] also showed earlier first day of defecation and higher postoperative meal intake in the early enteral feeding (EEF) group compared with the non-EEF group. The restoration of gut function by EEN was also accompanied by a reduction in the translocation of intestinal bacteria, suggesting an important role in protecting the intestinal mucosa.[24 43–45] On the basis of results from animal models, factors that govern the phenomenon of intestinal bacterial translocation include a variety of insults (shock, burns, endotoxin) that can compromise gut mucosal integrity, allowing the egress of bacteria into the mesenteric lymph nodes of the experimental animals with eventual spread of the bacteria into the blood.[5 15 46 47]

Table 2 Sensitivity analysis

	Statistics with study removed				
First author (year)	**Points**	**Lower limit**	**Upper limit**	**Z-value**	**p Value**
Anastomotic fistula/leakage					
Boelens (2014)	0.82	0.57	1.17	−1.10	0.271
Liu (2013)	0.76	0.53	1.09	−1.47	0.141
Park (2012)	0.75	0.53	1.08	−1.56	0.118
Liu (2011)	0.83	0.58	1.20	−0.99	0.322
Klek (2008)_standard	0.76	0.53	1.10	−1.47	0.141
Klek (2008)_immunomodulating	0.72	0.50	1.05	−1.71	0.088
Wu (2007)	0.77	0.53	1.11	−1.42	0.155
Bozzetti (2001)	0.78	0.54	1.14	−1.26	0.207
Braga (2001)	0.76	0.52	1.11	−1.41	0.157
Pacelli (2001)	0.76	0.51	1.13	−1.37	0.170
Braga (1998)	0.76	0.53	1.10	−1.44	0.150
Intra-abdominal infection/abscess					
Boelens (2014)	0.76	0.48	1.21	−1.15	0.252
Liu (2013)	0.75	0.50	1.15	−1.32	0.186
Liu (2011)	0.79	0.52	1.19	−1.13	0.257
Klek (2008)_standard	0.76	0.50	1.15	−1.31	0.190
Klek (2008)_immunomodulating	0.77	0.51	1.17	−1.23	0.219
Wu (2007)	0.84	0.54	1.30	−0.78	0.434
Bozzetti (2001)	0.79	0.52	1.19	−1.12	0.261
Braga (2001)	0.76	0.48	1.21	−1.16	0.246
Pacelli (2001)	0.78	0.51	1.22	−1.08	0.279
Braga (1998)	0.80	0.53	1.21	−1.05	0.293
Gianotti (1997)	0.74	0.47	1.16	−1.30	0.192
Mortality					
Klek (2008)_standard	1.00	0.51	1.97	0.01	0.990
Klek (2008)_immunomodulating	1.00	0.51	1.96	0.00	0.998
Wu (2007)	1.00	0.49	2.04	0.00	0.999
Alivizatos (2005)	1.00	0.51	1.96	0.01	0.992
Bozzetti (2001)	1.19	0.58	2.42	0.48	0.632
Braga (2001)	1.06	0.51	2.18	0.16	0.876
Pacelli (2001)	0.77	0.37	1.61	−0.70	0.485
Gianotti (1997)	1.00	0.50	2.00	0.00	0.998
Postoperative hospital stay					
Li (2015)	−1.57	−2.21	−0.92	−4.75	<0.001
Boelens (2014)	−1.57	−2.21	−0.93	−4.82	<0.001
Park (2012)	−1.74	−2.42	−1.07	−5.05	<0.001
Kim (2011)	−1.81	−2.52	−1.10	−4.99	<0.001
Liu (2011)	−1.79	−2.55	−1.03	−4.62	<0.001
Dong (2010)	−1.87	−2.54	−1.19	−5.39	<0.001
Klek (2008)_standard	−1.82	−2.51	−1.13	−5.16	<0.001
Klek (2008)_immunomodulating	−1.89	−2.55	−1.24	−5.67	<0.001
Wu (2007)	−1.79	−2.53	−1.05	−4.74	<0.001
Ates (2004)	−1.72	−2.41	−1.03	−4.91	<0.001
Bozzetti (2001)	−1.76	−2.49	−1.04	−4.78	<0.001
Braga (2001)	−1.79	−2.49	−1.10	−5.08	<0.001
Pacelli (2001)	−1.82	−2.53	−1.11	−5.01	<0.001
Braga (1998)	−1.63	−2.30	−0.95	−4.73	<0.001
Gianotti (1997)	−1.72	−2.41	−1.03	−4.88	<0.001
Braga (1996)	−1.70	−2.38	−1.03	−4.95	<0.001
Braga (1995)	−1.62	−2.28	−0.97	−4.86	<0.001
Time to flatus					
Li (2015)	−1.21	−1.75	−0.68	−4.43	<0.001
Boelens (2014)	−1.38	−1.86	−0.91	−5.70	<0.001
Wu (2007)	−1.41	−1.83	−0.99	−6.55	<0.001

Continued

Table 2 Continued

First author (year)	Statistics with study removed				
	Points	Lower limit	Upper limit	Z-value	p Value
Braga (2001)	−1.07	−1.50	−0.64	−4.89	<0.001
Gianotti (1997)	−1.29	−1.82	−0.77	−4.81	<0.001
Change in albumin					
Li (2015)	−1.43	−2.45	−0.41	−2.74	0.006
Liu (2013)	−1.51	−2.43	−0.58	−3.19	0.001
Park (2012)	−1.37	−2.30	−0.44	−2.90	0.004
Kim (2011)	−1.35	−2.26	−0.44	−2.91	0.004
Dong (2010)	−1.38	−2.30	−0.46	−2.94	0.003
Klek (2008)_standard	−1.03	−1.82	−0.23	−2.53	0.011
Klek (2008)_immunomodulating	−1.50	−2.47	−0.53	−3.03	0.002
Braga (2001)	−1.50	−2.52	−0.49	−2.90	0.004
Braga (1996)	−0.97	−1.57	−0.38	−3.22	0.001
Braga (1995)	−1.30	−2.23	−0.38	−2.75	0.006

Rates of complications such as anastomotic leakage/fistula formation, infection, or mortality did not show any significant differences between the two groups in the current study, suggesting that these factors may be more closely associated with the severity of the disease, extent of resection, physician skills or operative time. Postoperative nutrition was important but had no significant effect on complications or mortality as a whole. These findings were in contradistinction to an earlier meta-analysis performed by Moore *et al*,[5] which showed an advantage of early postoperative TEN in high-risk surgical patients, that is, those patients given TEN had reduced septic morbidity rates compared with those administered TPN.[5] However, a more recent meta-analysis by Bozzetti *et al*[48] showed nutritional support, in general, that included IEEN, EN, and TPN, yielded a clinical benefit by reducing infectious complications in high-risk or malnourished patients. Marano *et al*[49] have attempted to explain the discrepancies in findings regarding EN versus TPN in such studies based on the differences in patient groups studied. According to their analysis, those studies that reported no clinical effect of nutritional intervention were usually performed on well-nourished patients, whereas the findings of beneficial effects (reduction in complications) from nutritional support included moderately to severely malnourished patients[8 49]

TEN is cheaper[24] and safer, but TPN is easier to administer.[6] In a study by Moore *et al*,[5] nitrogen balance data consistently favored the TPN group which received the conventional therapy of that time, that is, no nutritional support for 5 days and then, if intolerant to oral intake, high-nitrogen TPN (non-protein calorie to nitrogen ratio=133:1). The EN group received a high-nitrogen elemental diet, delivered early after operation, by needle catheter jejunostomy. In contrast, this study included articles that provided similar nutritional goals, 25–30 kcal/kg/day (although administered via different routes), including supplemental nutrition to control total daily protein to between 0.15 and 1.5 g of nitrogen per kg per day, although some of the studies did not report the type of supplements used.

This study found that the duration of treatment, in general, continued from POD1 until POD7 (with only a few exceptions, ie, TEN was only studied for 3–5 days in three studies[24 26 28]). Our results suggested that EN use is preferable to TPN use for patients after major abdominal surgery. The efficacy of EEN has also been gradually accepted by clinicians[24 50 51] and the enteral route is currently recommended as the treatment of choice in patients requiring nutritional support.[30 41 42 52 53] Patients should also be educated on its clinical benefit regarding faster recovery times. Early introduction of oral intake, as tolerated, should be encouraged as part of a standardized protocol.

This study provided a pooled data analysis of predominantly RCTs conducted within the past two decades involving a large number of patients (2540 patients) and herein lies the contribution of this study to the literature. In addition, the sensitivity analysis using the leave-one-out approach showed that the data were robust.

This meta-analysis also had several limitations including significant heterogeneity among studies, that is, the studies evaluated lacked a standardized type, amount, and duration of EN or TPN administered. Different hospitals had different treatment protocols; therefore, there was no standardized procedure in terms of postsurgical intervention. Future studies that use a 'universal standard' are encouraged for better analysis.

This study included patients with abdominal malignancy, but some studies did not specify which type of abdominal malignancy, severity, or if concurrent chemo/radiotherapies were used. Hence, this information may have affected the clinical outcome of individual patients. In addition, studies that reported the type of abdominal surgery performed (as shown in Supplemental Table) differed fundamentally regarding operative time and severity and could have contributed a potential bias to the pooled analysis.

Studies that used EN and TEN were grouped together for pooled analysis. However, there were actual differences among the patients who only received EN versus those who received parenteral nutrition in the first few days, which was then replaced with EN. This may be a difficult

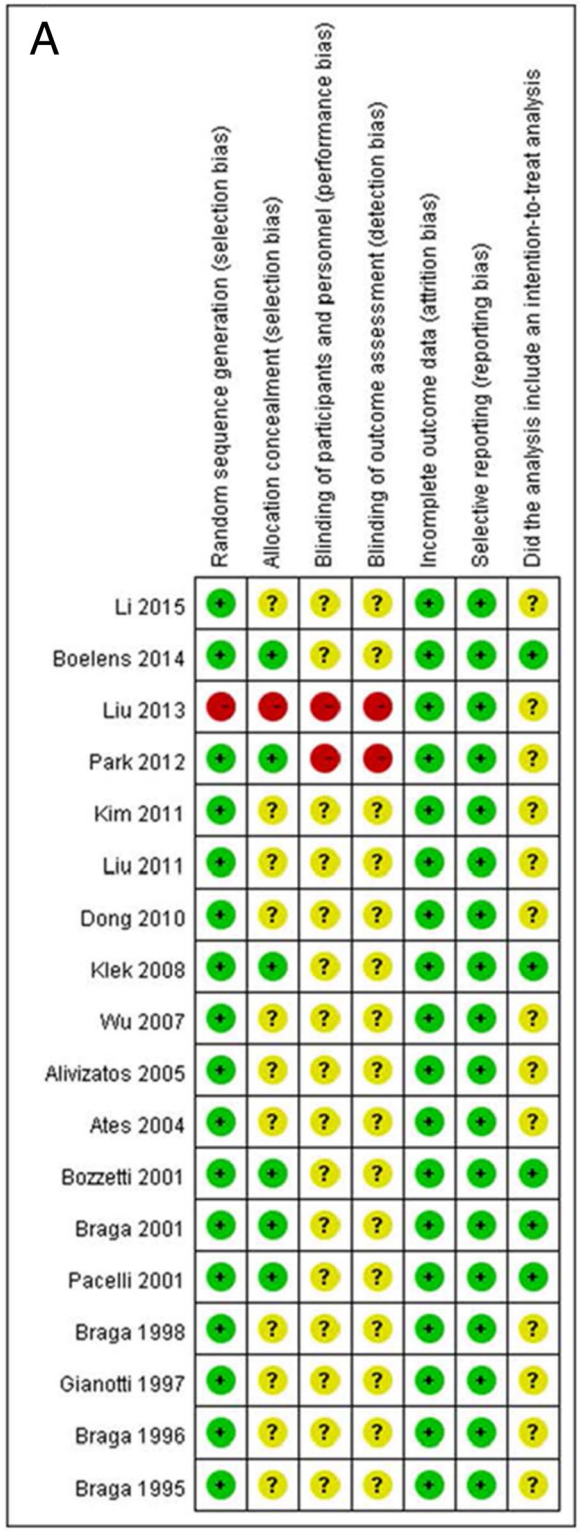

Figure 5 Quality assessment of (A) the individual study, and (B) the overall risk of biases.

confounder to adjust for, since some patients may prefer one route of administration over another, based on their tolerance and possible complications.

We included four studies from Braga *et al*[34] in our analysis, performed in 2001, 1998,[36] 1996[38] and 1995.[39] We were unable to fully exclude the chance that the study populations may have overlapped as attempts to contact the author met with no success. Thus, the possibility of duplicates exists and may have caused an overestimation of the results of our meta-analysis. Besides, the correlation of the selected outcomes to the severity of the disease or the duration of surgery was not assessed by the included studies. The severity of the disease is associated with longer operation time and complications such as increased blood loss, recovery time, and basic health status, which in turn may influence the nutritional status. It is possible that some patients with less severe disease would have had a much faster recovery with shorter hospital stay and may have benefited from EN, whereas more severe disease patients received TPN and had a longer recovery time. Further studies evaluating the effect of EN versus TPN in patients with different stages of GI cancer or the duration of operation should be performed.

In conclusion, EN was associated with shorter length of hospital stay, shorter time to flatus, and improved albumin levels in patients with GI malignancy after major abdominal surgery. The significance of the two different routes of nutritional support on the incidence of anastomotic leakage/fistula formation, intra-abdominal infection/abscess or mortality is less clear. The current results support the use of EN after major abdominal surgery in patients with GI cancer; however, we propose that the nutritional support should be tailored to match the baseline health status of an individual.

Contributors X-FZ was involved in the conception and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, final approval of the manuscript, guarantor of integrity of the entire study, statistical analysis, definition of intellectual content, literature research and clinical studies. NW was involved in the conception and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, final approval of the manuscript, statistical analysis, literature research and clinical studies. G-QZ was involved in the conception and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, final approval of the manuscript, statistical analysis, literature research and clinical studies. J-FL was involved in the conception and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, final approval of the manuscript, statistical analysis, literature research and clinical studies; Y-FD was involved in the conception and design, acquisition of data, analysis and interpretation of data, critical revision of the manuscript, final approval of the manuscript, obtaining funding, administrative, technical or material support, Supervision. All authors read and approved the study.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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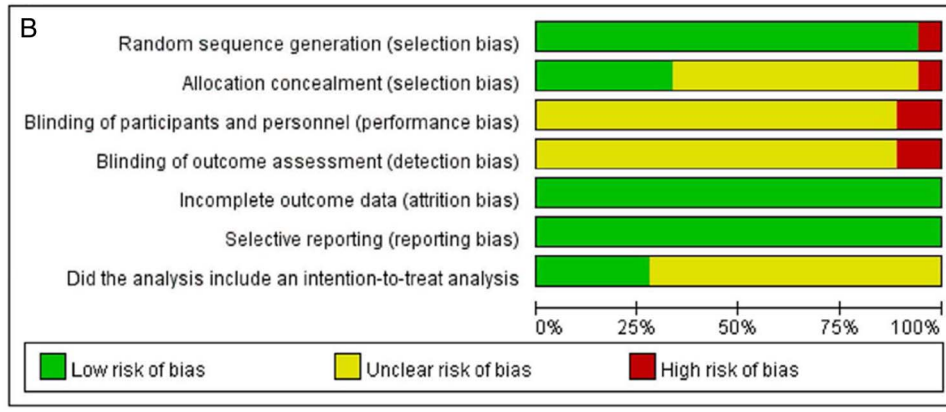

Figure 5 Continued.

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