The Optimal Time of Applying Enteral Immunonutrition in Esophageal Cancer Patients Receiving Esophagectomy: A Network Meta-Analysis of Randomized Clinical Trials

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Abstract

Background: Enteral immunonutrition (EIN) has been extensively applied in cancer patients, however its role in esophageal cancer (EC) patients receiving esophagectomy remains unclear. We performed this network meta-analysis to investigate the impact of EIN on patients undergoing surgery for EC and further determine the optimal time of applying EIN.

Methods: We searched PubMed, EMBASE, Cochrane library, and China National Knowledgement Infrastructure (CNKI) to identify eligible studies. Categorical data was expressed as the odds ratio with 95% confidence interval (CI), and continuous data was expressed as mean difference (MD) with 95% CI. Pair-wise and network meta-analysis was performed to evaluate the impact of EIN on clinical outcomes using RevMan 5.3 and ADDIS V.1.16.8 softwares. The surface under the cumulative ranking curve (SUCRA) was calculated to rank all nutritional regimes.

Results: Total 14 studies involving 1071 patients were included. Pair-wise meta-analysis indicated no difference between EIN regardless of the application time and standard EN (SEN), however subgroup analyses found that postoperative EIN was associated with decreased incidence of total infectious complications (OR=0.47; 95%CI=0.26 to 0.84; p=0.01) and pneumonia (OR=0.47; 95%CI=0.25 to 0.90; p=0.02) and shortened LOH (MD=-1.01; 95%CI=-1.44 to -0.57; p<0.001) compared to SEN, which were all supported by network meta-analyses. Ranking probability analysis further indicated that postoperative EIN has the highest probability of being the optimal option in terms of these three outcomes.

Conclusions: Postoperative EIN should be preferentially utilized in EC patients undergoing esophagectomy because it has optimal potential of decreasing the risk of total infectious complications and pneumonia and shortening LOH.

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Background

Esophageal cancer (EC) is one of the most common gastrointestinal malignancy worldwide(1, 2). Issued data estimated that EC accounts for 3.1% new cancer cases and 5.5% cancer-related deaths in 2020(3). The survival rate of patients with EC remains poor although the rapid improvements of surgical techniques(4). Esophagectomy still play a critical role in treating patients with resectable EC to date(5). It must be pointed out that, however, patients will experience various complications after undergoing esophagectomy(6), which has negative impact on the recovery and healthcare costs(7).

Nutrition supplementation has been regarded as a vital therapeutic option for the treatment of patients receiving tumor resection(8). Previous studies suggested that enteral nutrition (EN) can effectively decrease the risk of postoperative complications and enhance the recovery among patients undergoing gastrointestinal surgery compared to parenteral nutrition (PN)(9–11). However, standard EN do not contain immune-enhancing ingredients of improving host immunity and relieving inflammatory response(12), and thus additional immune-modulating substances such as arginine and omega-3 polyunsaturated fatty acids has been added to standard EN, which is defined as enteral immunonutrition (EIN)(13, 14).

To date, several meta-analyses have determined the effectiveness of EIN in patients undergoing gastrointestinal surgery(8, 10, 15, 16). Meanwhile, there are two meta-analyses also investigated the role of EIN in treating EC patients receiving esophagectomy(17, 18) and do not obtain a definitive conclusion. However, conclusions from previous two meta-analyses must be cautiously interpreted because several limitations can not be ignored, such as incomplete inclusion of eligible studies(17) and incorrect inclusion of an study(18). Moreover, several factors such as the time of applying EIN(10) and formula of containing different substances(11) were directly associated with the effectiveness of EIN. We therefore performed this network meta-analysis to further determine the effectiveness of EIN compared to standard EN and investigate the optimal time of applying EIN among EC patients receiving esophagectomy.

Methods

Design and registration

This network meta-analysis was conducted based on the methodological framework developed by the Cochrane Comparing Multiple Interventions Methods Group(19, 20). Meanwhile, we reported all statistical results according to the criteria recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement(21), the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions(22) and the International Society for Pharmacoeconomics and Outcomes Research Task Force on Indirect Treatment Comparisons Good Research Practices(23). The protocol of this network meta-analysis has been registered in Open Science Framework (OSF) with a registration DOI of 10.17605/OSF.IO/KJ9UY (accessable at: https://osf.io/kj9uy).

Sources of identification

A systematic search was conducted by two independent reviewers in PubMed, EMBASE, Cochrane Library, and China National Knowledgement Infrastructure (CNKI) in order to identify potentially eligible studies from their inception util to December 30, 2020.
Medical subject heading (MeSH) and text words were simultaneously used to develop the search strategy according to the specified criteria of each database. We summarized search strategies of all databases in Table S1. Additionally, we also manually checked the references of all included studies and two topic-related meta-analyses to identify any eligible studies which were missed at the electronic search stage. Moreover, we updated our search weekly, and the latest update was performed on January 23, 2021. Any divergence about identification of sources was resolved based on the consensus principle.

Selection of studies

Two independent reviewers conducted the selection of studies according to the following developed criteria: (a) adult patients undergoing esophagectomy for EC; (b) patients were instructed to intake EIN or standard EN; (c) study reported at least one of the following clinical outcomes including total infectious complications, pneumonia, wound infection, sepsis, urinary tract infection, anastomotic leakage, and length of hospitalization (LOH); (d) only randomized controlled trial was eligible for our inclusion criteria; (e) language was limited to English and Chinese; and (f) study reported in Chinese must be published in core journal. We excluded a study when it covered at least one of the following criteria: (a) experimental and animal studies;

(b) studies without insufficient information; and (c) duplicate study with poor quality or insufficient data. Any divergence about the selection of studies was resolved based on the consensus principle.

Information extraction

We designed information extraction sheet in advance, and two independent reviewers were assigned to extract the following information with our sheet: (a) characteristics of eligible study including name of the first author, country, and year of publication; (b) characteristics of statistical design including sample size and outcomes; (c) characteristics of participants including age and gender; (d) details of nutritional regimes; and (e) information of risk of bias.
Any divergence about data extraction was resolved based on the consensus principle.

In this network meta-analysis, we only considered clinical outcomes because other outcomes such as biochemical parameters and immune parameters are the surrogate variable for developing clinical decision. Therefore, we defined total infectious complications, anastomotic leakage, and LOH as the primary outcomes. Remaining outcomes including pneumonia, wound infection, sepsis, and urinary tract infection were defined as the secondary outcomes. If an outcome was reported as median and range or interquartile range, we estimated the mean and standard difference (SD) using the method proposed by Hozo and colleagues after extracting data(24).

Assessment of risk of bias

The risk of bias of individual study was assessed by two independent reviewers with the Cochrane Risk of Bias assessment tool(25) from the following six domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other bias. A study was labeled with low, unclear, or high risk of bias according to the matching degree between actual information and assessment criteria. Any divergence about the assessment of risk of bias was resolved based on the consensus principle.

Statistical analysis

For traditional pair-wise meta-analysis, we used Review Manager 5.3 (Cochrane Collaboration, Copenhagen, Denmark) to conduct all statistical analyses(26). In our study, only LOH was continuous data, and it therefore was expressed as the mean difference (MD) with 95% confidence interval (CI). Remaining outcomes were categorical data, and all were expressed as odds ratio (OR) with 95% CI. We firstly qualitatively evaluated the heterogeneity across studies with Cochrane Q test(27), and then quantitatively estimated the level of heterogeneity with I2 statistic(28). We adopted random-effects model to perform meta-analysis because variations across studies in the real world can not be ignored. We designed subgroup analysis basing on the time of applying EIN in order to specifically investigate the pure effectiveness of each EIN regime compared to standard EN. Moreover, we draw funnel plots of primary outcomes to qualitatively inspect the possibility of existence of publication bias when accumulated number of eligible studies was more than 10(29).

In order to determine the optimal time of applying EIN, we further conducted a Bayesian network analysis with the Aggregate Data Drug Information System (ADDIS V.1.16.8, Drugis, Groningen, NL), which was developed based on Markov Chain Monte Carlo (MCMC) method(30, 31). The following parameters were set for

achieving good convergence: 4 chains for simulation, 50,000 simulation iterations, 2.5 variance scaling factor, 10 thinning interval, and 20000 tuning iterations. With ADDIS software, Brooks-Gelman-Rubin method was automatically performed to evaluate the convergence degree through calculating the potential scale reduction factor (PSRF)(32), and a PSRF indicated a better convergence when it was greatly closed to 1(32). We firstly estimated the effect size based on consistency and inconsistency assumptions respectively when two types of comparisons were simultaneously available(31), and then we used node-splitting method to test whether effect sizes from two assumptions were inconsistent(33). The assumption of consistency between direct and indirect comparisons was right when a P of more than 0.05 was generated(33). For network meta-analysis, LOH was expressed as MD with 95% credible interval (CrI), and categorical data was expressed as OR with 95% CrI. Finally, we estimated the surface under the cumulative ranking curve values in order to determine the possibility of considering a regime as the best option. Based on the results calculated from ADDIS software, a regime was considered to be worse if the corresponding possibility of ranking was greatly closed to 100% (34). We utilized league figures to document the results of network meta-analysis. Moreover, we also used STATA software 14.0 (Stata Corp LP, College Station, Texas, USA) to create evidence structure of primary outcomes(35).

Results

Identification and selection of study

We identified 714 records after initially searching PubMed, EMBASE, Cochrane library, and CNKI databases. After removing 71 duplicate records, we continue to remove 612 ineligible records through checking the title and abstract. Then, 15 studies were excluded after checking eligibility based on full-text due to following reasons: lack of outcome (n = 1), ineligible nutritional regimes (n = 6), Chinese study with poor quality (n = 1), ineligible study design (n = 1), and abstract (n = 1). Moreover, we also identified additional two studies from meta-analysis published in China. Finally, 14 studies(13, 14, 36−47) met our inclusion criteria. The process of identification and selection of studies was delineated in Fig. 1.

Characteristics of eligible studies

Most of the 14 eligible studies were conducted in Japan(13, 14, 36, 39, 41, 42, 44) and China(38, 45−47). The sample size of individual study was between 29 and 191, with a total participants of 1071. All studies were two-arm design except for one study(44), which was designed as three-arm. Details of characteristics of included studies were summarized in Table 1.

Table 1
Basic characteristics of included studies.

Study	Country	Sample size	Age, yrs	EIN regime	Time of intaking EIN			Outcomes
					PrO	*PtO*	*PeO*	
Aiko, 2015	Japan	15/14	(60 ± 2)/(64 ± 5)	EIN (ω-3 fatty acid, arginine, RNA, and ω-6 fatty acid) was fed through nasoenteral from 1d to 7 d after surgery.		٦		Pneumonia, anastomotic leak, wound infection, LOH
Sakurai, 2007	Japan	16/14	(63 ± 4)/(63 ± 5)	EIN (ω-3 fatty acid, arginine, and RNA) was fed through oral and nasoenteral accordingly from 3d before surgery until to 7d after surgery.			٦	Pneumonia, anastomotic leak, wound infection, LOH
Mudge, 2018	Australia	73/66	(62.5 ± 9.6)/(64.6 ± 8.2)	EIN (ω-3 fatty acid, DHA, RNA, and arginine) was orally intaked from 7d before until to 6−7 d after surgery.			٦	Infectious complication, pneumonia, sepsis, anastomotic leak, wound infection, LOH
Kanekiyo, 2019	Japan	20/20	65(60−70)/62(60−72)	EIN (ω-3 fatty acid, arginine, RNA, ω-6 fatty acid, EPA, and DHA) was fed through oral and nasoenteral accordingly 7 d before and after operation.			٦	Infectious complication, pneumonia, LOH

Study	Country	Sample size	Age, yrs	EIN regime	Time of intaking EIN			Outcomes
					PrO	PtO	PeO	
Kitagawa, 2017	Japan	14/15	(67.1 ± 5.8)/(66.8 ± 8.3)	EIN (ω-3 fatty acid, arginine, RNA, and ω-6 fatty acid) was orally intaked 7d before surgery.	�			Infectious complication, pneumonia, anastomotic leak, wound infection, LOH
Ryan, 2009	Japan	28/25	(62 ± 11)/(65.7 ± 9)	EIN containg EPA was fed through oral and nasoenteral accordingly from 5d before surgery until to 21d after surgery.			�	Pneumonia, sepsis, anastomotic leak, wound infection
Healy, 2017	Ireland	94/97	n.r.	EIN containg EPA was fed through oral and nasoenteral accordingly from 5d before surgery until to 30d after surgery.			�	Infectious complication, pneumonia, sepsis, anastomotic leak
Sultan, 2012	England	63/66	67(42–79)/60(42–79)	EIN containg ω-3 fatty acids was fed through oral and nasoenteral accordingly 7d before and after operation.			�	Infectious complication, pneumonia, sepsis, anastomotic leak, wound infection

Study	Country	Sample size	Age, yrs	EIN regime	Time of intaking EIN			Outcomes
					PrO	*PtO*	*PeO*	
Li, 2020	China	53/50	(62.13 ± 6.51)/(61.52 ± 5.97)	EIN (arginine, RNA, and ω-3 fatty acids) was fed through oral and jejunal tube accordingly 7d before and after operation.			�	Infectious complication, pneumonia, wound infection, anastomotic leakage, LOH
Matsuda, 2017	Japan	35/37	(64.1 ± 8.3)/(64.6 ± 6.4)	EIN (EPA, γ-linolenic acid and antioxidants) was fed through jejunostomy 2-21d after surgery.	�			Pneumonia, anastomotic leak, wound infection, LOH
Takeuchi, 2007	Japan	6/14/20	(61.5 ± 5.0)/(65.0 ± 7.4)/(64.6 ± 7.6)	EIN (arginine, ω-3 fatty acids, and RNA) was fed through jejunostomy from 1d until to 14d after surgery or from 5d before surgery until to 14d after surgery.	�		�	Infectious complication, pneumonia, sepsis, anastomotic leak, wound infection
Zhou, 2012	China	30/30	(41−62)/(43−64)	EIN (arginine and ω-3 fatty acids) was fed through nasoenteral from 2-7d after surgery.	�			Pneumonia, wound infection
Xu, 2017	China	30/30	(59.0 ± 2.7)/(59.5 ± 2.9)	EIN (arginine and ω-3 fatty acids) was fed through jejunostomy from 1-7d after surgery.	�			Pneumonia, anastomotic leak, wound infection, LOH

Study	Country	Sample size	Age, yrs	EIN regime	Time of intaking EIN			Outcomes
					PrO	*PtO*	*PeO*	
Xu, 2019	China	47/49	(64.8 ± 3.1)/(65.1 ± 2.9)	EIN (arginine and ω-3 fatty acids) was fed through jejunostomy from 1-7d after surgery.		✓		Pneumonia, LOH
yrs, years; EIN, enteral immunonutrition; Pro, preoperation; PtO, postoperation; PeO, perioperation; LOH, length of hospitalization; n.r., not reported.								

Risk of bias

Among 14 eligible studies, nine(13, 14, 37, 38, 40−42, 45, 46) reported the details of generating random sequence such as computerized random program and random number table. Eight studies(13, 14, 37, 39−43) correctly performed allocation concealment, and three studies(13, 14, 42) did not blind participant, personnel or outcome assessor. Details of the risk of bias were summarized in Fig. 2.

Total infectious complications

Thirteen studies(13, 14, 37−47) reported the incidence of total infectious complications after surgery, and evidence structure was displayed in Fig. 3A. Pair-wise suggested no statistical difference between EIN and standard EN (OR = 0.74; 95%CI = 0.52−1.03; p = 0.19; I2 = 24%) (Figure S1 in the appendix). However, subgroup analysis indicated that postoperative EIN was associated with decreased incidence of total infectious complications compared to standard EN (OR = 0.47; 95%CI = 0.26−0.84; p = 0.01; I2 = 0%) (Figure S1), which was further established by network meta-analysis (OR = 0.44; 95%CrI = 0.20−0.98) (Fig. 4A). Node-splitting analysis established the consistency between direct and indirect evidence (p = 0.15) (Table 2). Ranking probability suggested that postoperative EIN has the highest probability of being optimal option (0.63), followed by perioperative EIN (0.42), preoperative EIN (0.39) and SEN (0.54) (Figure S2 in the appendix).

Table 2
Assessment of inconsistency based on node-splitting analysis

1. total infectious complications				
Node	Direct effect	Indirect effect	Overall	*P*
PeO, PtO	0.90 (-1.19, 3.01)	-0.74 (-1.70, 0.21)	-0.53 (-1.37, 0.49)	0.15
2. pneumonia				
PeO, PtO	0.66 (-1.55, 2.87)	-0.85 (-1.97, 0.14)	N/A	0.21
3. wound infection				
PeO, PtO	1.73 (-1.23, 6.31)	0.14 (-2.08, 2.54)	N/A	0.35
4. anastomotic leakage				
PeO, PtO	-9.67 (-32.49, 0.85)	0.25 (-1.29, 1.75)	0.20 (-1.20, 1.54)	0.08
PtO, postoperation; PeO, perioperation; N/A, not applicable.				

Pneumonia

All eligible studies(13, 14, 36−47) reported the incidence of postoperative pneumonia, and pair-wise meta-analysis suggested no statistical difference between EIN and SEN (OR = 0.79; 95%CI = 0.57−1.10; p = 0.17; I2 = 0%). However, subgroup analysis indicated that postoperative EIN was associated with decreased incidence of pneumonia compared to SEN (OR = 0.47; 95%CI = 0.25−0.90; p = 0.02; I2 = 0%) (Figure S3 in appendix), which was further established by network meta-analysis (OR = 0.45; 95%CrI = 0.19−0.99) (Fig. 4B). Node-splitting analysis established the consistency between direct and indirect evidence (p = 0.21) (Table 2). Ranking probability suggested that preoperative EIN has the highest probability of being optimal option (0.83), followed by postoperative EIN (0.75), perioperative EIN (0.60) and SEN (0.64) (Figure S4 in appendix).

Wound infection

Among 14 eligible studies, 11(13, 14, 36, 38−44, 47) reported the incidence of wound infection after surgery. Pair-wise meta-analysis suggested no difference between EIN and SEN (OR = 0.77; 95%CI = 0.47−1.27; p = 0.30; I2 = 0%) (Figure S5 in the appendix), and subgroup analysis also did not detect statistical differences (Figure S5), which were consistent with results from network meta-analysis (Fig. 4C). However, network meta-analysis indicated that the difference between perioperative EIN and SEN was greatly closed to statistically significant (OR = 0.44; 95%CI = 0.11-1.00). Node-splitting analysis established the consistency between direct and indirect evidence (p = 0.35) (Table 2). Ranking probability suggested that perioperative EIN has the highest probability of being optimal option (0.75), followed by postoperative EIN (0.38), SEN (0.56), and preoperative EIN (0.80) (Figure S6 in the appendix).

Sepsis

Total 5 studies(37, 40, 41, 43, 44) reported the incidence of postoperative sepsis, and pair-wise meta-analysis suggested no difference between EIN and SEN (OR = 1.44; 95%CI = 0.71−2.92; p = 0.31; I2 = 0%) (Figure S7 in the appendix), and subgroup analysis also did not detect statistical differences (Figure S7), which were

consistent with results from network meta-analysis (Fig. 4D). Inconsistency test based on node-splitting analysis was not performed. Ranking probability suggested that SEN has the highest probability of being optimal option (0.50), followed by perioperative EIN (0.52) and postoperative EIN (0.72) (Figure S8 in the appendix).

Urinary tract infection

Two studies(40, 43) reported the incidence of urinary tract infection, and pair-wise meta-analysis suggested no statistical difference between perioperative EIN and SEN (OR = 0.82; 95%CI = 0.41−1.62; p = 0.56; I2 = 0%) (Figure S9 in the appendix), which was consistent with network meta-analysis (OR = 0.83; 95%CrI = 0.39−1.79) (Fig. 4E). Inconsistency test based on node-splitting analysis was not performed. Ranking probability suggested that perioperative EIN has the highest probability of being optimal option (0.68), followed by SEN (0.68) (Figure S10 in the appendix).

Anastomotic leakage

Total 12 studies(13, 14, 36−45) reported the incidence of anastomotic leakage after surgery, and evidence structure was displayed in Fig. 3B. Pair-wise meta-analysis suggested no statistical difference between EIN and SEN (OR = 0.63; 95%CI = 0.39−1.03; p = 0.06; I2 = 0%) (Figure S11 in the appendix). Subgroup analysis also indicated no statistical differences when various EIN regimes compared to SNE (Figure S11), which was further established by network meta-analysis (Fig. 4F). Node-splitting analysis established the consistency between direct and indirect evidence (p = 0.08) (Table 2). Ranking probability suggested that perioperative EIN has the highest probability of being optimal option (0.40), followed by postoperative EIN (0.29), SEN (0.49) and preoperative EIN (0.48) (Figure S12 in the appendix).

Length of hospitalization

Seven eligible studies reported the LOH after surgery, and the evidence structure was depicted in Fig. 3C. Pair-wise meta-analysis suggested no statistical difference between EIN and SEN (MD=-0.10; 95%CI=-0.15 to 0.14; p = 0.14; I2 = 71%) (Figure S13 in the appendix), however subgroup analysis indicated that postoperative EIN statistically shorten the LOH compared to SEN (MD=-1.01; 95%CI=-1.44 to -0.57; p < 0.001; I2 = 0%) (Figure S13), which was supported by network meta-analysis (MD=-1.06; 95%CrI=-2.56 to -0.10) (Fig. 4G). Inconsistency test based on node-splitting analysis was not performed. Ranking probability suggested that postoperative EIN has the highest probability of being optimal option (0.70), followed by perioperative EIN (0.39), SEN (0.52) and preoperative EIN (0.76) (Figure S14 in the appendix).

Publication bias

Among three primary outcomes, the accumulated number of two outcomes including total infectious complications (Figure S15 in the appendix) and anastomotic leakage (Figure S16) was more than 10, and symmetric funnel plots indicated absence of publication bias.

Discussion

As one of the most common gastrointestinal malignant tumors(1), EC has been estimated to have 0.60 million new cases and 0.54 million cancer-related deaths in 2020(3). To date, esophagectomy remains

the preferred therapeutic option for the treatment of EC patients. However, patients will experience a series of serious complications after surgery such as infection and anastomotic leakage due to immunosuppression and inflammatory response(8, 10). Therefore, it is critically important to supply immune-modulating substances such as arginine and omega-3-fatty acids to SEN, which was defined as EIN(7, 17). Although the effectiveness of EIN in patients receiving gastrointestinal surgery has been established(8–10), the role of EIN in EC patients undergoing esophagectomy remains controversial. We therefore performed this network meta-analysis to determine the effectiveness of EIN for improving clinical outcomes among patients undergoing surgery for EC. Our findings suggested that postoperative EIN decrease the incidence of total infectious complications and pneumonia and shorten the LOH after surgery compared to SEN. Meanwhile, ranking probability suggested that postoperative EIN has the highest probability of being optimal nutritional prescription.

To date, two meta-analyses(17, 18) investigating the effectiveness of EIN for treating EC patients receiving esophagectomy have been published. Li and colleagues performed a meta-analysis of six articles to compare the effectiveness between EIN and SEN in patients receiving oesophagectomy, and found that impact of EIN on immunological status, biological status or clinical outcomes remains unclear(17). However, this finding must be cautiously interpreted because this meta-analysis missed four eligible studies(37, 39, 43, 44). In the same year, Wang and colleagues also reported a meta-analysis of investigating the comparative effectiveness between perioperative EIN and SEN, suggesting no statistical significance(18). It must be noted that this meta-analysis correctly included a study which focused on preoperative EIN into analysis(14) and also missed an eligible study(44). Compared to previous meta-analyses, the present network meta-analysis has several strengths: (a) we incorporated Chinese studies with high quality to increase the statistical power; (b) we designed subgroup analysis for specifically investigating the comparative effectiveness of various EIN regimes, which were categorized according to the initiation time and duration, and SEN(10); and (c) we used network meta-analysis method to determined the ranking of various EIN regimes. Based on these strengths stated above, the present network meta-analysis generated more reliable, accurate and detailed results, which can provide golden references for clinical decision.

We must acknowledge several limitations in our network meta-analysis. First, regardless of the fact that more eligible studies were included in this network meta-analysis, the sample size of individual study was small, which may have negative impact on the robustness of pooled results. Second, most eligible studies investigated the comparative effectiveness between postoperative or perioperative EIN and SEN, however only one study compared preoperative EIN with SEN, and thus more future studies investigating the direct comparison between preoperative EIN and SEN must be performed in order to further establish our findings. Third, formulas of EIN were different across eligible studies, however we did not design subgroup or sensitivity analysis to determine the comparative effectiveness of various formulas(11) due to insufficient number of eligible studies. Forth, duration of each individual regime such as perioperative EIN was also variation across studies, insufficient number of eligible studies failed to support further designing subgroup analysis.

Conclusions

At the basis of available best evidence, we concluded that postoperative EIN is the optimal nutritional regime for the treatment of patients undergoing surgery for EC because this regime was associated with decreased incidence of total infectious complications and pneumonia and shortened LOH.

Abbreviations

EC, Esophageal cancer; EN, enteral nutrition; PN, parenteral nutrition; EIN, enteral immunonutrition; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; OSF, Open Science Framework; CNKI, China National Knowledgement Infrastructure; MeSH, Medical subject heading; LOH, length of hospitalization; SD, standard difference; CI, confidence interval; OR, odds ratio; MCMC, Markov Chain Monte Carlo; PSRF, potential scale reduction factor.

Declarations

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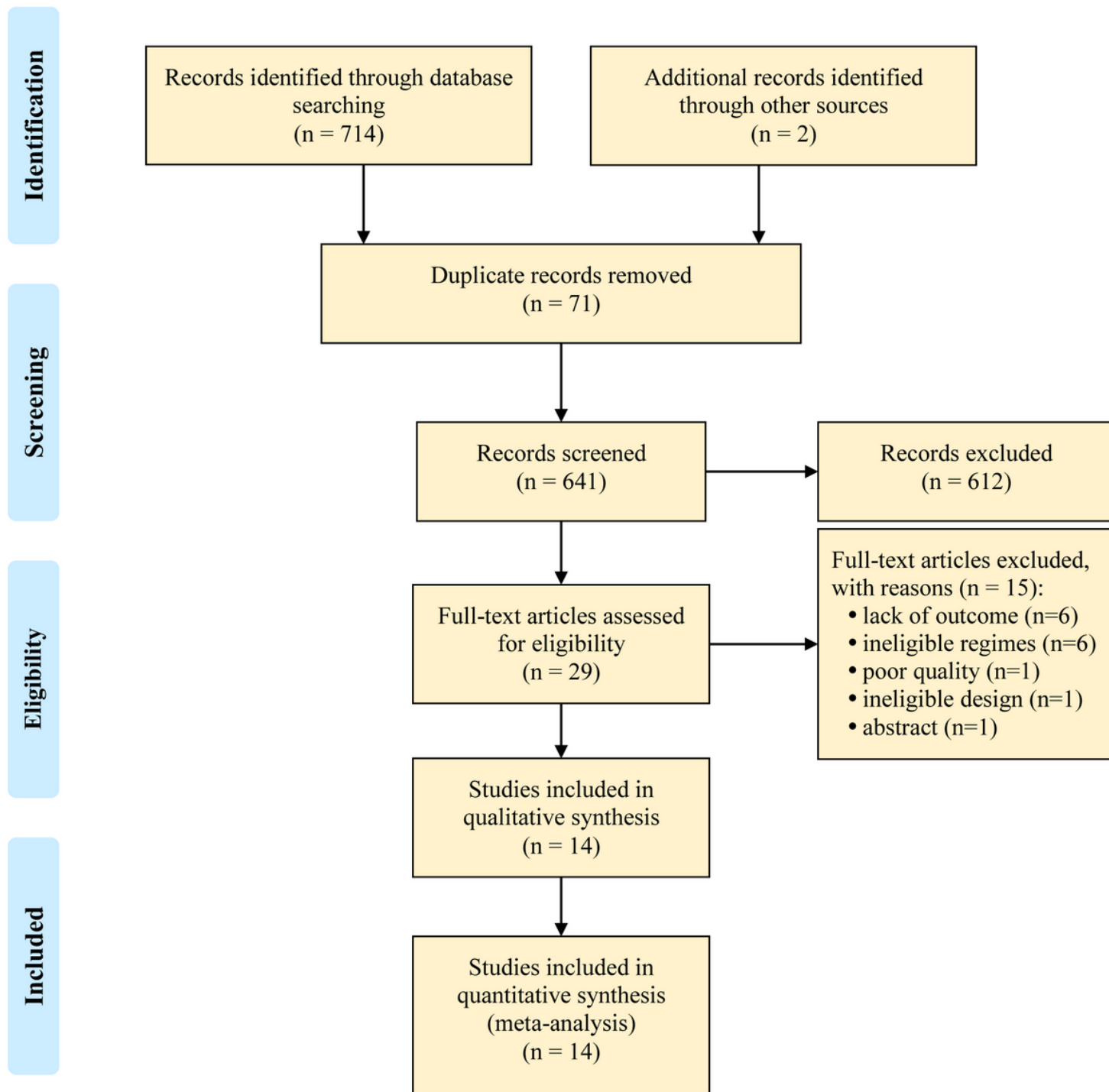
Figures

Figure 1

Flow diagram of retrieval and selection of studies. We identified 212, 315, 93, and 94 records in PubMed, EMBASE, Cochrane library, and China National Knowledgement Infrastructure (CNKI), respectively.

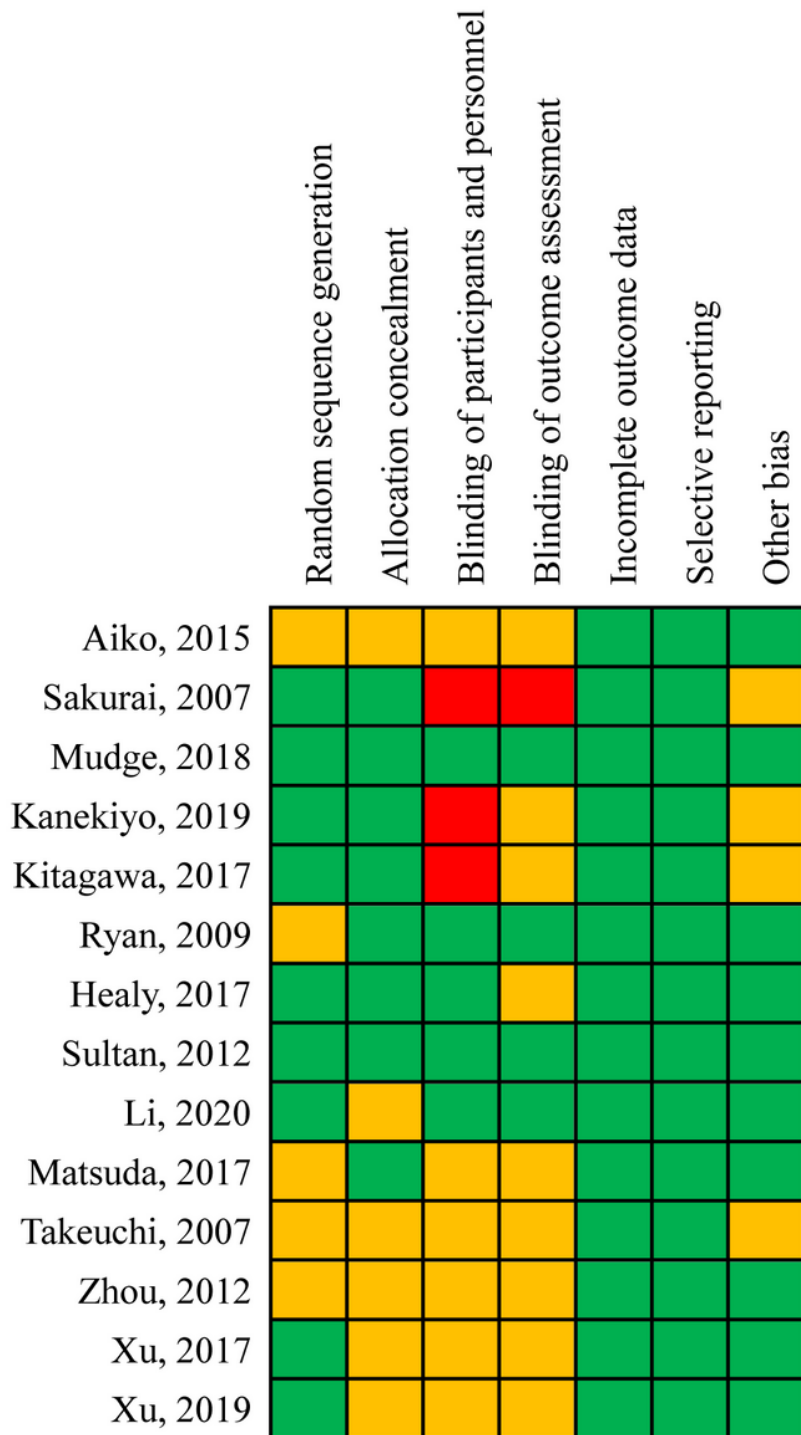|	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Aiko, 2015	🟡	🟡	🟡	🟡	🟢	🟢	🟢
Sakurai, 2007	🟢	🟢	🔴	🔴	🟢	🟢	🟡
Mudge, 2018	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Kanekiyo, 2019	🟢	🟢	🔴	🟡	🟢	🟢	🟡
Kitagawa, 2017	🟢	🟢	🔴	🟡	🟢	🟢	🟡
Ryan, 2009	🟡	🟢	🟢	🟢	🟢	🟢	🟢
Healy, 2017	🟢	🟢	🟢	🟡	🟢	🟢	🟢
Sultan, 2012	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Li, 2020	🟢	🟡	🟢	🟢	🟢	🟢	🟢
Matsuda, 2017	🟡	🟢	🟡	🟡	🟢	🟢	🟢
Takeuchi, 2007	🟡	🟡	🟡	🟡	🟢	🟢	🟡
Zhou, 2012	🟡	🟡	🟡	🟡	🟢	🟢	🟢
Xu, 2017	🟢	🟡	🟡	🟡	🟢	🟢	🟢
Xu, 2019	🟢	🟡	🟡	🟡	🟢	🟢	🟢

Figure 2

Risk of bias. Assessment of risk of bias was performed with Cochrane risk of bias assessment tool. Red, yellow, and green square represents high, unclear, and low risk of bias, respectively.
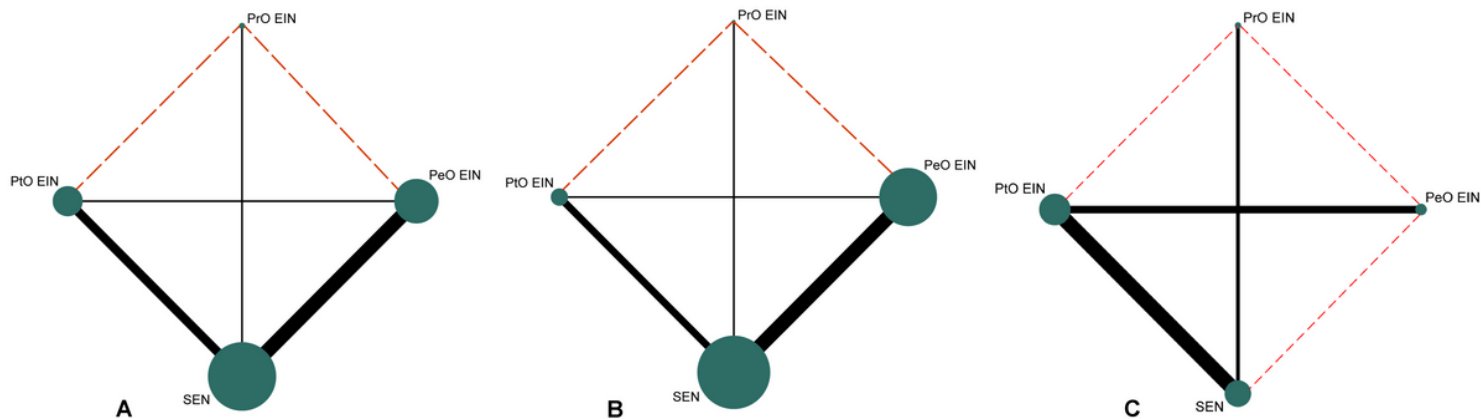
Figure 3

Evidence structure of (A) total infectious complications, (B) anastomotic leakage, and (C) length of hospitalization. The numbers (and numbers in parentheses) refer to the number of trials (and number of the combined number of participants in these trials), and the thickness of the connecting line corresponds to the number of trials between comparators.

A

Perioperative EIN			
1.01 (0.14, 7.33)	Preoperative EIN		
1.71 (0.62, 3.93)	1.65 (0.19, 11.38)	Postoperative EIN	
0.77 (0.42, 1.20)	0.75 (0.11, 4.71)	**0.44 (0.20, 0.98)**	SEN

B

Perioperative EIN			
6.76 (0.55, 273.45)	Preoperative EIN		
2.04 (0.71, 5.13)	0.32 (0.01, 4.10)	Postoperative EIN	
0.89 (0.51, 1.48)	0.13 (0.00, 1.56)	**0.45 (0.19, 0.99)**	SEN

C

Perioperative EIN			
0.09 (0.00, 1.96)	Preoperative EIN		
0.53 (0.07, 2.65)	5.81 (0.20, 614.55)	Postoperative EIN	
0.44 (0.11, 1.00)	4.85 (0.23, 346.99)	0.82 (0.17, 3.61)	SEN

D

Perioperative EIN			
N/A	Preoperative EIN		
0.33 (0.01, 12.78)	N/A	Postoperative EIN	
1.19 (0.36, 3.86)	N/A	3.78 (0.09, 94.30)	SEN

E

Perioperative EIN			
N/A	Preoperative EIN		
N/A	N/A	Postoperative EIN	
0.83 (0.39, 1.79)	N/A	N/A	SEN

F

Perioperative EIN			
0.51 (0.04, 6.34)	Preoperative EIN		
0.82 (0.21, 3.32)	1.55 (0.10, 25.77)	Postoperative EIN	
0.55 (0.28, 1.04)	1.04 (0.10, 11.75)	0.69 (0.20, 2.13)	

G

Perioperative EIN			
-10.00 (-35.26, 24.53)	Preoperative EIN		
0.97 (-1.16, 3.07)	11.04 (-23.52, 36.53)	Postoperative EIN	
-0.07 (-1.97, 1.36)	9.91 (-24.53, 34.99)	**-1.06 (-2.56, -0.10)**	SEN

Figure 4

Network meta-analysis of various nutritional regimes in terms of total infectious complications (A), pneumonia (B), wound infection (C), sepsis (D), urinary tract infection (E), anastomotic leakage (F), and length of hospitalization (G). The numerical result represents the ratio of intervention situated right divided by intervention situated above. Bold number in this figure indicates statistical significance. N/A, not available.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Appendix.docx
- TableS1.Searchstrategy.docx