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Review

Perioperative immunonutrition in esophageal cancer patients undergoing esophagectomy: the first meta-analysis of randomized clinical trials

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*SUMMARY.***Although several randomized controlled trials have been published in recent years, the effect of perioperative immunonutrition in esophageal cancer (EC) patients remains unclear. This initial meta-analysis was conducted to assess whether perioperative enteral immunonutrition reduces postoperative complications in patients undergoing esophagectomy for EC. Relevant randomized controlled trials published before 1st September 2019 were retrieved from the Cochrane Library, PubMed, and EMBASE databases. After the literature was screened, two researchers extracted the information and data from eligible studies according to predefined selection criteria. Obtained data were pooled and analyzed by RevMan 5.3 software. The results were presented as risk ratios (RRs) with 95% confidence intervals (CIs). The heterogeneity among studies was tested by I^2 test. Seven high-quality randomized controlled trials were included, with a total of 606 patients, 311 of whom received immunonutrition before and after surgery, while 295 received perioperative standard nutrition. No significant difference was observed between the two groups in the incidence of postoperative infection complications, including total infection complications (RR = 0.97, CI: 0.78–1.20, P = 0.76), pneumonia (RR = 0.97, CI: 0.71–1.33, P = 0.84), wound infection (RR = 0.80, CI: 0.46–1.40, P = 0.44), sepsis (RR = 1.35, CI: 0.67–2.71, P = 0.40), and urinary tract infection (RR = 0.87, CI: 0.54–1.40, P = 0.56). The prevalence of anastomotic leakage in the two groups was 9.4 and 5.4%, but the difference was not statistically significant (RR = 0.59, CI: 0.33–1.04, P = 0.07). Perioperative enteral immunonutrition provided no benefit in terms of the incidence of infection complications and anastomotic leakage in EC patients undergoing esophagectomy. Further large-scale randomized controlled trials are needed to confirm this conclusion.**

KEY WORDS: **anastomotic leakage, esophageal cancer, esophagectomy, immunonutrition.**

INTRODUCTION

Esophageal cancer (EC) is associated with a poor prognosis and leads to more than 400,000 deaths worldwide.[1] Esophagectomy offers EC patients the best prospect of a cure, but this procedure is also associated with a high incidence of postoperative complications.[2] Perioperative enteral nutrition (EN) is essential for the recovery of EC patients undergoing esophagectomy, while enteral immunonutrition (EIN) has become a novel recommendation within the past several years. Recent meta-analyses have demonstrated that EIN potentially decreases the incidence of postoperative complications in several types of digestive tract malignancies, such as gastric and colorectal cancers.[3,4] However, the effect of EIN in EC patients remains unclear.

EIN, also known as immune-modulating or immune-enhanced nutrition, is a specialized enteral formula containing immune substances, such as arginine, ribonucleic acid (RNA), and eicosapentaenoic acid (EPA), which is a type of omega-3 polyunsaturated fatty acids.[5] Two formulae are commonly used in postesophagectomy patients: IMPACT and a formula enriched with EPA.[6] IMPACT formula, which consists of RNA, arginine, EPA, and docosahexaenoic acid, has been found to be effective for reducing the incidence of postoperative complications. A total of 17 randomized controlled trials (RCTs) were combined into a meta-analysis by Waitzberg *et al.* to assess the efficacy of IMPACT, and the results suggested that preoperative use of IMPACT could reduce the incidence of postoperative complications in patients who underwent elective

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surgery.[7] In recent years, the application of EIN in EC has become a hot issue. Nevertheless, studies on this issue have yielded controversial results.[8,9] Herein, we conducted the first meta-analysis of RCTs to explore the relationships between perioperative EIN and infection complications as well as anastomotic leakage after esophagectomy.

MATERIALS AND METHODS

Search strategy

Potential studies published before 1st September 2019 were searched in the Cochrane Library, PubMed, and EMBASE databases. The terms and keywords used in the PubMed and the Cochrane Library searches were ("esophageal cancer" OR "esophageal carcinoma" OR "esophagectomy") AND ("immunonutrition" OR "immune-enhancing" OR "immune-enhanced" OR "immune-modulating"). The main keywords used for the EMBASE search were ("esophageal cancer"/exp OR "esophageal cancer" OR "esophageal carcinoma"/exp OR "esophageal carcinoma" OR "esophagectomy"/exp OR "esophagectomy") AND ("immunonutrition"/exp OR "immunonutrition" OR "immune-enhancing" OR "immune-enhanced" OR "immune-modulating"). Citation lists of the included studies were manually screened to ensure sensitivity of the search strategy.

Selection criteria

The inclusion criteria were as follows: (i) studies associated with perioperative EIN versus EN in EC patients undergoing esophagectomy; (ii) RCTs with a total sample size greater than 30 patients; and (iii) studies that provided primary data of postoperative infection complications and anastomotic leakage. The exclusion criteria were as follows: (i) studies in which EIN was used only before or after surgery, but not both; and (ii) studies beyond the inclusion criteria or originally published in a language other than English.

Data extraction and quality assessment

Two researchers independently extracted the information and data from all eligible studies according to predefined selection criteria, and the third author evaluated the literature if a dispute arose. The quality of the publications was assessed using Jadad scores for RCTs.[10] The following details were extracted from each study: first author, publication year, institution, country, sample size, patient characteristics, EIN formula and usage, infection complications (pneumonia, wound infection, sepsis and urinary tract infection), anastomotic leakage, hospital stay, and study design. The quality assessments of eligible studies were performed using the Cochrane Collaboration's tool published in the Cochrane Handbook (version 5.3); this tool consists of the following seven parts: random sequence generation, blinding of participants and personnel, allocation concealment, blinding of outcome assessors, selective reporting, incomplete outcome data, and other biases.

Statistical analyses

Data were extracted from the publications and combined into a meta-analysis using RevMan 5.3 analysis software (Cochrane Collaboration, Copenhagen, Denmark). The heterogeneity among eligible studies was measured using chi-square and I^2 tests. A fixed-effect model was applied if no significant heterogeneity was detected ($I^2 < 50\%$) among studies; otherwise, a random-effect model was used. The results of dichotomous outcomes were presented as RRs with 95% CIs, and the results of continuous outcome data were presented as the mean difference with 95% CIs. The significance level was set as $P = 0.05$.

RESULTS

In the present meta-analysis, 135 relevant studies were retrieved: 40 from PubMed, 75 from EMBASE, and 19 from the Cochrane Library; moreover, 1 was manually retrieved. After screening, seven RCTs were eligible for the pooled analysis.[11–17] These studies included 606 patients, 311 of whom received EIN before and after surgery and 295 of whom received perioperative EN. The literature screening process is shown in Figure 1.

The characteristics and Jadad scores of the seven included studies are listed in Table 1, and the patient characteristics are shown in Table 2. Among the eligible studies, three papers aimed to compare the efficacy of IMPACT and isocaloric control standard nutrition (ICSN) in EC patients, two trials compared EPA with ICSN, one trial compared Oxepa® with ICSN[17] and the last trial compared MHN-02[18] with ICSN. All participants in the seven studies received preoperative oral immunonutrition or standard nutrition support and postoperative EIN or EN via a jejunostomy catheter. The original data on infection complications and anastomotic leakage were provided in these studies, while the biochemical and immune indicators among these papers were different. Therefore, we could not assess the effect, and this meta-analysis only evaluated the benefits of EIN in clinical outcomes of postesophagectomy patients.

Quality assessment

Most of the studies were high-quality RCTs, and their quality assessment is listed in Figure 2. Six articles reported methods of random sequence

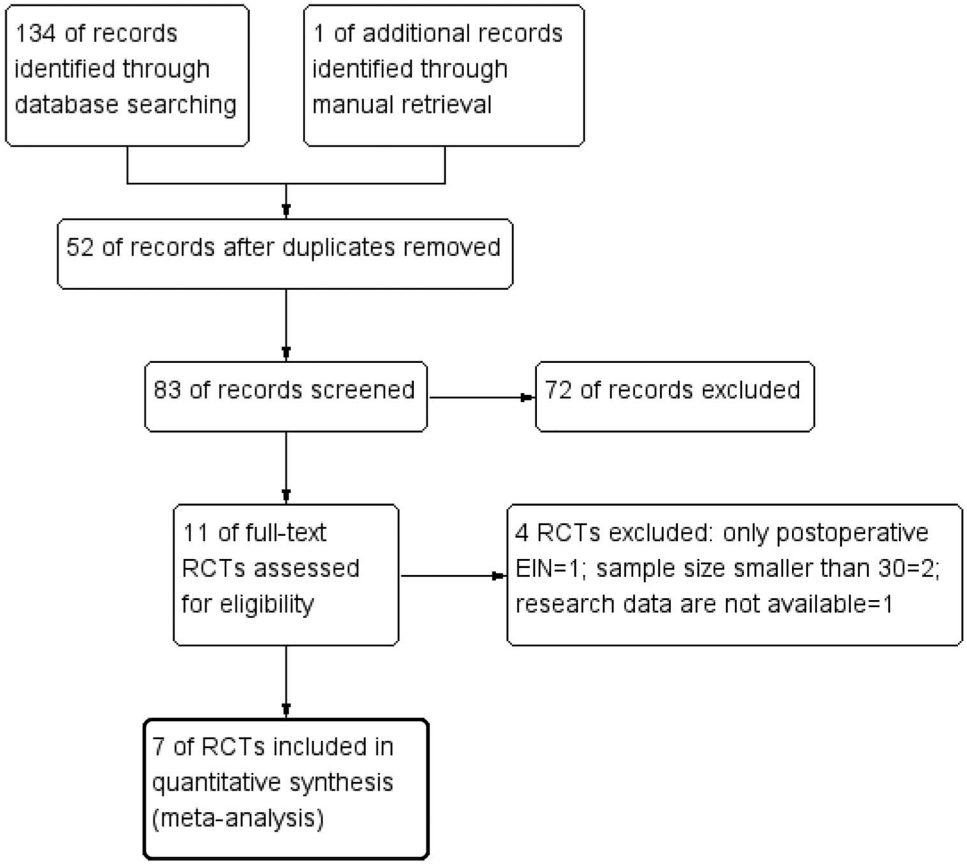

Fig. 1 The PRISMA flow chart.

Table 1 The basic characteristics of involved trials (EN/EIN)

Studies	Regions	Sample size (n)	Nutritional formula	Nutritional duration	Average LOS (d)	Jadad score
Healy 2017	Ireland	94/97	ICSN/EPA	5 d before and 1 m after surgery	NR	7
Kanekiyo 2019	Japan	20/20	Ensure/IMPACT	7 d before and after surgery	28/28	5
Kitagawa 2017	Japan	15/15	ICSN/MHN-02	5 d before and 7 d after surgery	35/32	5
Mudge 2018	Australia	62/71	ICSN/IMPACT	7 d before and 6–7 d after surgery	13/13	7
Ryan 2009	Ireland	25/28	Ensure Plus/EPA	5 d before and 21 d after surgery	NR	6
Sakurai 2007	Japan	16/14	Ensure/IMPACT	3 d before and 14 d after surgery	31/26	5
Sultan 2012	England	63/66	Ensure Plus/Oxepa	7 d before and after operation	16/16	7

Abbreviations: d, day; ICSN, isocaloric control standard nutrition; LOS, length of stay; m, month; NR, not report.

generation,[11–14,16,17] three of them used a computer,[11,14,17] and the other three used an opaque envelope.[12,13,16] Although only one study expounded that randomization was performed by an independent statistician, the specific methods were not provided.[15] All seven studies conducted the allocation concealment,[11–17] and in three studies, participants and personnel were not blinded.[12,13,16] Other details on the risk of bias outcome are shown in Figure 2.

Infection complications

All eligible studies provided the incidence of infection complications, which included pneumonia in seven studies,[11–17] wound infection in six studies,[12–17] sepsis in four studies[11,14,15,17], and urinary tract infection in two studies.[14,17] No heterogeneity was detected in the analyses of the above items ($I^2 \leq 31\%$), and thus a fixed-effect model was applied. Related articles were

Table 2 The basic characteristics of patient in involved trials (EN/EIN)

Studies	Age (years)	BMI (kg/m^2)	Neoadjuvant therapy (%)	Operation time (minutes)	Tumor stage (n)	
					0–1	2–4
Healy 2017	62/62	27.7/28.4	66/68	NR	NR	NR
Kanekiyo 2019	62/65	21.5/21.9	NR	435/419	7/7	13/13
Kitagawa 2016	66/67	19.9/21.0	NR	595/573	3/0	12/14
Mudge 2018	64/62	26.9/26.9	78/75	334/343	NR	NR
Ryan 2009	65/62	27.1/24.6	44/57	NR	14/11	14/14
Sakurai 2007	63/63	NR	NR	411/455	NR	NR
Sultan 2012	60/67	26.7/25.8	56/57	338/343	NR	NR

Abbreviations: BMI, body mass index; NR, not report.

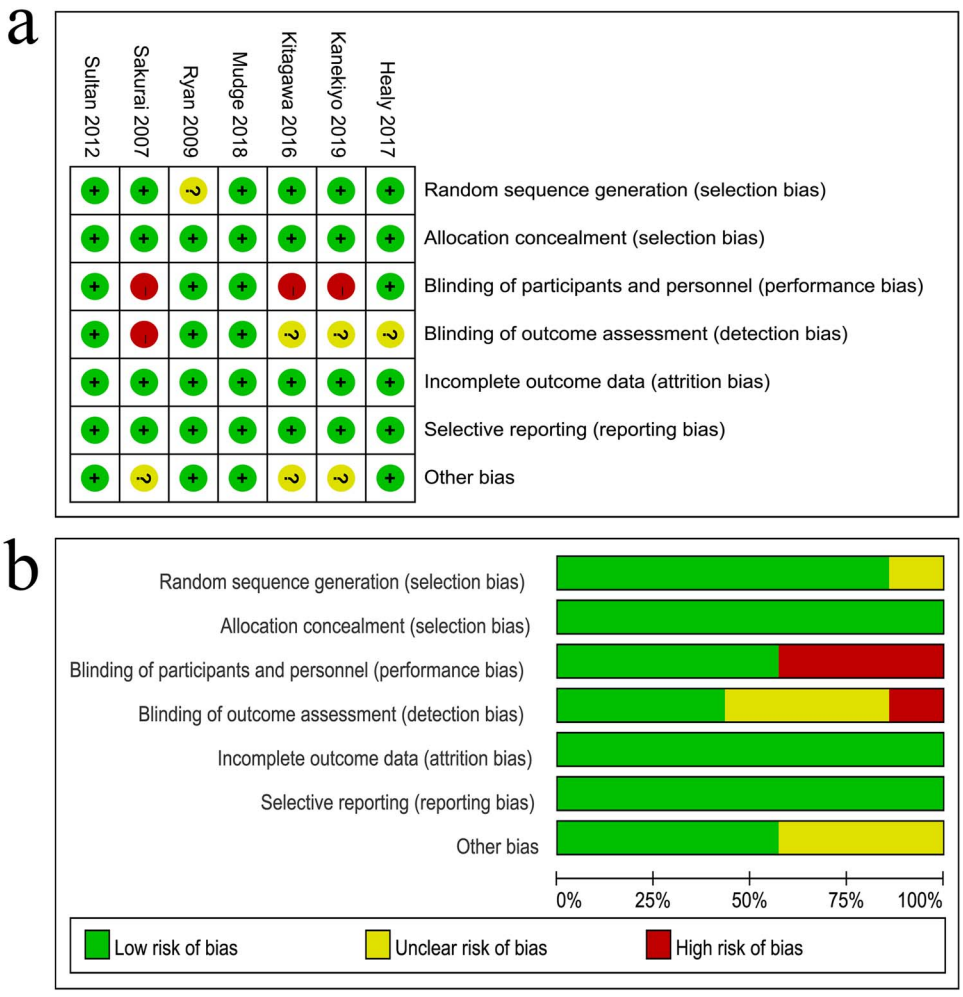

Fig. 2 Risks of bias assessment for each included study ($n = 7$). (a) Risk of bias summary; (b) risk of bias graph.

analyzed, and no significant differences were found in the infection complications between EN and EIN. All postoperative infection complications were evaluated in seven studies, with a total of 311 patients in the EIN group and 295 patients in the EN group; no significant difference was observed between the two groups in overall infection complications (RR = 0.97, CI: 0.78–1.20, $P = 0.76$) (Fig. 3) or in the occurrence of pneumonia (RR = 0.97, CI: 0.71–1.33, $P = 0.84$) (Fig. 4).

Six studies recorded the occurrence of wound infection, which was found in 214 patients in the EIN group and 201 patients in the EN group (RR = 0.80, CI: 0.46–1.40, $P = 0.44$) (Fig. 5). Sepsis was recorded in four trials and was reported in 262 patients in the EIN group and 244 patients in the EN group (RR = 1.35, CI: 0.67–2.71, $P = 0.40$) (Fig. 6). Urinary tract infection was evaluated in two trials and was found in 137 patients in the EIN group and 125 patients in the EN group (RR = 0.87, CI: 0.54–1.40,

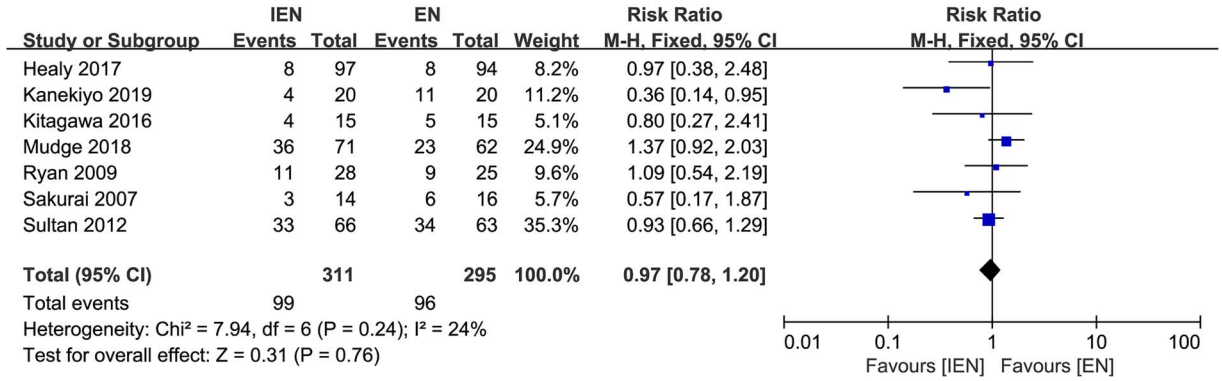

Fig. 3 Forest plot of the occurrence of total infection complications between the EIN and EN groups.

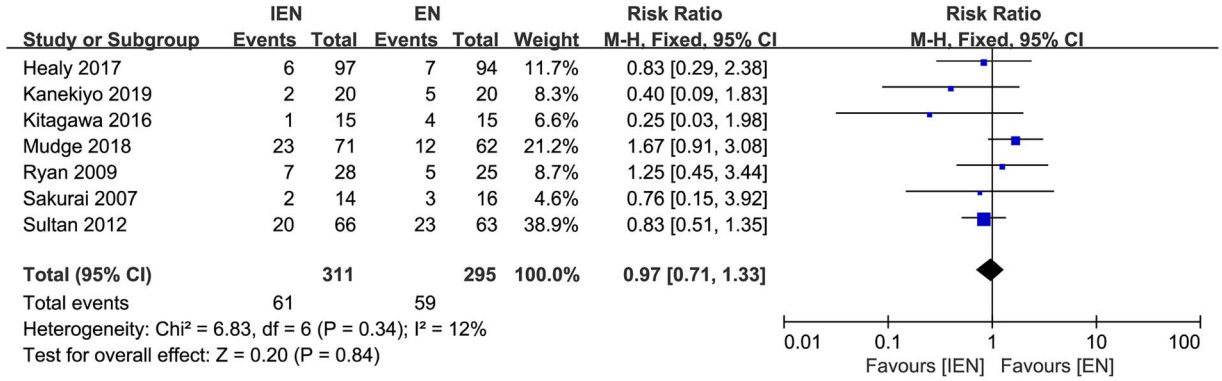

Fig. 4 Forest plot of the occurrence of pneumonia between the EIN and EN groups.

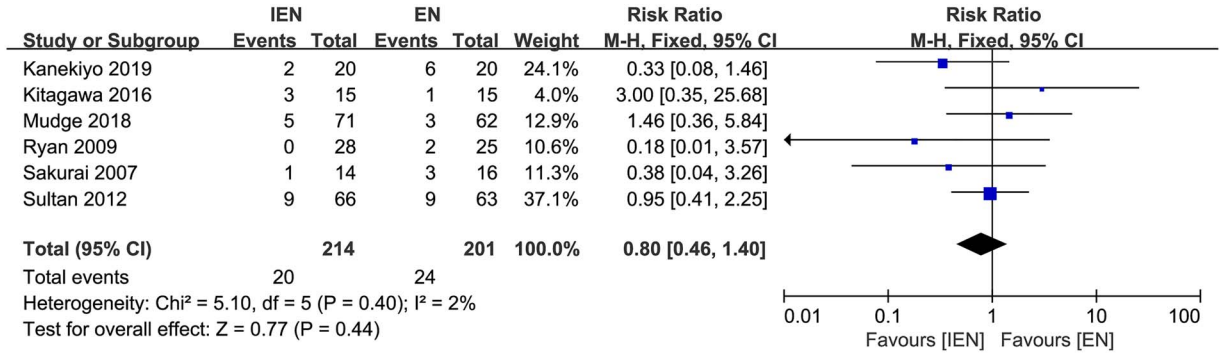

Fig. 5 Forest plot of the occurrence of wound infection between the EIN and EN groups.

$P = 0.56$) (Fig. 7). These differences were not statistically significant.

Anastomotic leakage

Data on anastomotic leakage were included in all eligible articles.[11–17] The result of the heterogeneity test was $I^2 = 0$, and thus, a fixed-effect model was applied. Pooled data showed no significant difference between the EN and EIN groups (RR = 0.59, CI: 0.33–1.04, $P = 0.07$) (Fig. 8). The prevalence of anastomotic leakage in the EN and EIN groups was 9.4% (28/295) and 5.4% (17/311), respectively. The incidence of anastomotic leakage ranged from 0 to 6.0% in the intervention group and from 4 to 12.9% in the control group.

DISCUSSION

Immunonutrition is widely used in nutritional support treatment for various types of cancer, including head and neck cancer, liver cancer, bladder cancer, and breast cancer.[19–22] In head and neck cancer patients, preoperative immunonutrition was found to contribute to a shorter hospital stay and a lower incidence of postoperative complications than standard nutrition.[19] A recent meta-analysis also produced a similar conclusion.[23] Recently, EIN was applied to EC patients and recommended in the treatment of EC patients who underwent chemoradiotherapy due to a significant decrease in inflammatory cytokines and enhancement of immune cell responses.[24,25] Nevertheless, the authors held different views on

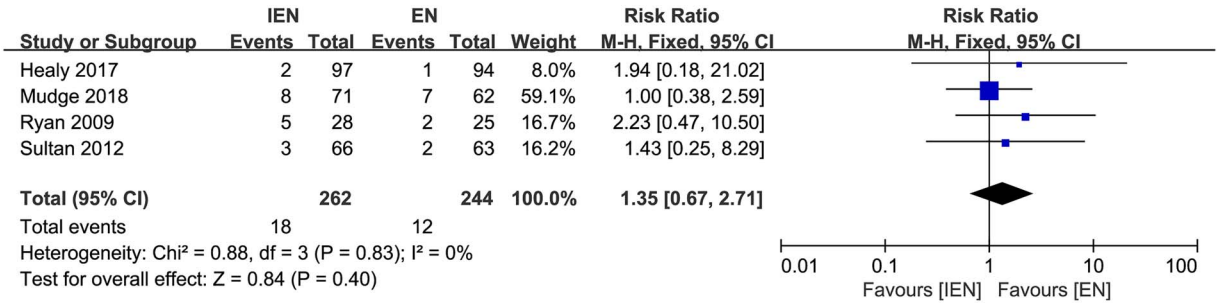

Fig. 6 Forest plot of the occurrence of sepsis between the EIN and EN groups.

Fig. 7 Forest plot of the occurrence of urinary tract infection between the EIN and EN groups.

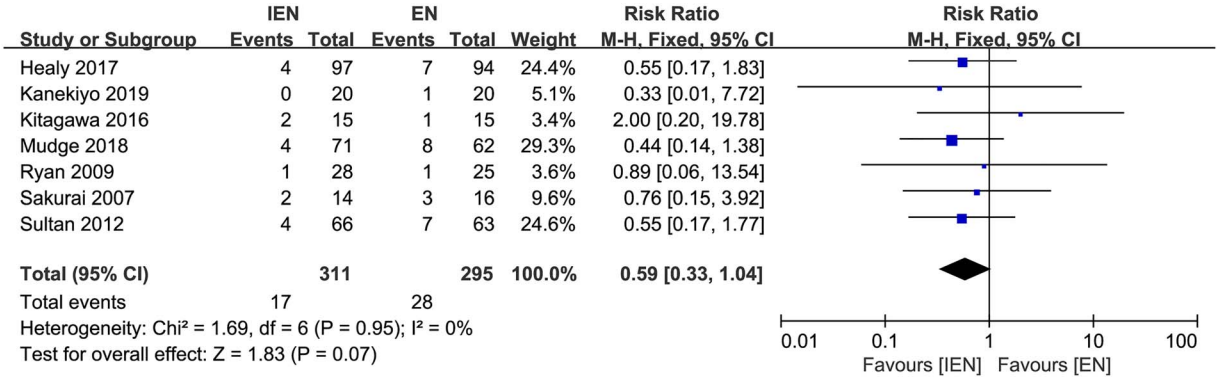

Fig. 8 Forest plot of the occurrence of anastomotic leakage between the EIN and EN groups.

whether EIN should be used in postesophagectomy patients. Mudge *et al.* conducted a multicenter 2 × 2 factorial RCT, and this large-scale RCT concluded that preoperative, postoperative, and perioperative EIN provided no benefit over standard nutrition in patients undergoing esophagectomy,[14] which was further demonstrated by other RCTs.[11,17] Another four RCTs observed slight benefits of EIN for EC patients, such as improved early postoperative nutritional status, suppressed TNF-α levels, preserved lean body mass, and increased total lymphocyte count. Notably, all studies demonstrated no significant difference in postoperative complications between EIN and EN.[12,13,15,16] Therefore, the role of EIN in postesophagectomy patients remains controversial, and no meta-analysis has been performed for EIN in this patient population.

The present meta-analysis aimed to evaluate the benefits of perioperative EIN in EC patients and indicated that perioperative EIN cannot improve clinical outcomes, including the occurrence of infection complications and anastomotic leakage. Infections are the leading cause of postdischarge complications following esophagectomy.[26] In the present article, the prevalence of total infection complications in the EIN and EN groups was 31.8% and 32.2% respectively. Only one trial conducted by Kanekiyo *et al*. demonstrated a significant reduction of total infection complications in patients with EIN compared with EN after esophagectomy.[12] These studies suggested that perioperative EIN supplementation provides no benefit for postoperative infection complications in EC patients.

The current meta-analysis showed that EIN subjects have a slightly lower prevalence of anastomotic leakage than EN subjects, but the difference was not statistically significant (5.4% vs. 9.4%, $P = 0.07$). Five trials reported a much lower incidence of anastomotic leakage in the EIN group,[11,12,14,16,17] but two other trials presented a similar incidence between the two groups.[14] Mudge *et al*. also did not detect a benefit in anastomotic leakage in patients with perioperative

EIN compared with EN, despite showing a decreased trend (5.6% and 12.9%, for EIN and EN, respectively).[14] We noticed that in the multicenter, double-blind, placebo-controlled RCT, anastomotic leakage was reduced in the EIN group (4.1 and 7.4%).[11] Overall, even though the occurrence of anastomotic leakage in the EIN group was lower than that of the EN group, the difference was not statistically significant.

This meta-analysis also provided three directions for further studies. First, although the difference did not reach statistical significance, the incidence of anastomotic leakage in the EN group was approximately twice as high as in the EIN group. Therefore, further research on this issue is necessary. Second, more studies should focus on the application of different formulae in EC. This article included four different EIN formulae, of which IMPACT was the most widely used. A subgroup analysis showed that IMPACT and EPA had no significant effect on postoperative complications (data not presented). Hence, more formulae should be applied in EC patients to decrease postoperative complications. Finally, when and how to test the biochemical and immune indicators should be standardized in further trials, so that more available data and parameters could be used for further combined analyses.

Several strengths and limitations of this meta-analysis should be described. The present article is the first meta-analysis that attempted to assess the effect of perioperative immunonutrition on clinical outcomes in postesophagectomy patients. Jadad scoring and quality assessment were performed in this strict meta-analysis. Three studies received a score of 7, two studies received a score of 6, and two studies received a score of 5. Literature quality assessment revealed a low risk of bias in most items. Additionally, no heterogeneity was found among the studies. The above results indicated that all seven eligible studies were high-quality RCTs and that the conclusion of this study is convincing. However, this meta-analysis has several limitations. First, the results of biochemical and immune indicators were diverse, and thus, we were unable to perform subgroup analyses in the present meta-analysis. Second, the number of included articles was less than 10, and hence, publication bias could not be detected. Finally, gray literature and non-English language studies were excluded in this study, which was another limitation.

CONCLUSION

In conclusion, this strict meta-analysis indicated that perioperative EIN provided no benefit in reducing the prevalence of infection complications and anastomotic leakage in EC patients undergoing esophagectomy. Further, large-scale RCTs should be conducted to confirm this conclusion.

AUTHOR CONTRIBUTIONS

Conceptualization: Wang Mingliang and Li Yongxiang; Methodology: Wang Mingliang, Ke Zhangyan and Fan Fangfang; Writing, review, and editing: Wang Mingliang, Fan Fangfang, Wang Huizhen and Ke Zhangyan; Supervision: Ke Zhangyan and Fan Fangfang; Project administration: Li Yongxiang; Wang Mingliang, Ke Zhangyan, and Fan Fangfang contributed equally to the article.

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