

## ORIGINAL ARTICLE

# Is immunonutrition superior to standard enteral nutrition in reducing postoperative complications in patients undergoing esophagectomy? A meta-analysis of randomized controlled trials

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## Summary

**Purpose:** Perioperative enteral nutrition supports are recommended in esophagus cancer patients. Immunonutrition contains immuno-enhancing nutrients in addition to standard formula. These new nutrients are thought to be efficacious in reducing inflammatory response and improving postoperative immune response and they have been proved to be better than standard enteral nutrition in reducing postoperative complications in gastric cancer. However, if it would lead to a better clinical outcome in patients undergoing esophagectomy remains controversial.

**Methods:** A systematic literature search was performed in the online database of PubMed, Medline, EMBASE and Cochrane Library. The relevant studies were screened out of the results by reading titles and abstracts. Then, we read the full-texts to finally confirm the studies included in this meta-analysis.

**Results:** Six randomized controlled trials having enrolled 638 patients were included in the final analysis. The pooled analysis didn't show statistically significant difference between immunonutrition group and standard nutrition group in reducing postoperative complications.

**Conclusions:** The postoperative complications are comparable between immunonutrition and the standard enteral nutrition in patients undergoing esophagectomy, but its value in severe malnutrition patients is undetermined, whereas the high tolerance and other advantages brought by the immunonutrition should not be overlooked and need to be further proved.

**Key words:** enteral nutrition, esophagectomy, postoperative complication, meta-analysis

## Introduction

Esophagectomy with lymphadenectomy as the standard surgery for resectable esophageal cancer (EC) is a highly invasive procedure which involves thorax, abdomen and even the neck [1]. As a result of dysphagia and disease consumption, EC patients tend to have varying degrees of malnutrition [2]. Perioperative nutritional status affects the rehabilitation and prognosis of EC patients [3,4]. Therefore, nutrition support is quite an important part of

perioperative managements in such patients [5]. A meta-analysis showed enteral nutrition is superior to parenteral nutrition in decreasing the morbidity of postoperative complications in EC patients [2]. On the basis of standard enteral nutrition formula, new formulas with new nutrients are being designed. Immunonutrition contains the arginine, omega-3 polyunsaturated fatty acids eicosapentaenoic acid (EPA) and nucleotide in addition to

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the traditional nutrients of standard formula [6,7]. These new nutrients are thought to be efficacious in reducing inflammatory response and improving postoperative immune response. A meta-analysis has shown the superiority of immunonutrition in reducing the postoperative complications in patients undergoing gastrectomy [8]. However, whether these changes in immunological and hematological indexes would lead to a better clinical outcome in patients with EC remains inconclusive. So we pooled the related randomized controlled trials together to see if the immunonutrition is more efficient in reducing the postoperative complications in EC patients than standard nutrition

## Methods

Our protocol adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [9].

A systematic search was performed in the online database of PubMed, Medline, EMBASE and Cochrane Library on 13th September 2018 to find out potentially relevant publications. The searching strategy was consisted of following terms: (nutrition OR nutrient OR immunonutrition OR enhanced recovery) AND (esophagus OR oesophagus OR esophageal OR esophagectomy OR oesophagectomy) AND (cancer OR neoplasm OR carcinoma OR tumor).

### Inclusion and exclusion criteria

Inclusion criteria: a) studies comparing immunonutrition and standard enteral nutrition; b) studies enrolling patients undergoing esophagectomy for EC; c) studies providing data on postoperative complications.

Exclusion criteria: a) not randomized controlled trial; b) the following publication types: review, meta-analysis, case report, conference, letter and reply.

The included studies should meet all the three inclusion criteria, and any study meeting any one of the exclusion criteria was excluded.

### Study screening and quality assessment

By reading the titles and abstracts, potentially relevant studies were screened out of the searching results. Then, the full-texts of these studies were carefully read and related data were extracted to finally confirm the studies included in the meta-analysis. The Cochrane Collaboration's tool published in the Cochrane Handbook (version 5.3) which contained seven items was used to evaluate the quality of included studies. All the works were done by two authors (Zhuo and Luo) independently who then checked each other. Disagreements were resolved by discussing with another author (Lin).

### Major outcomes

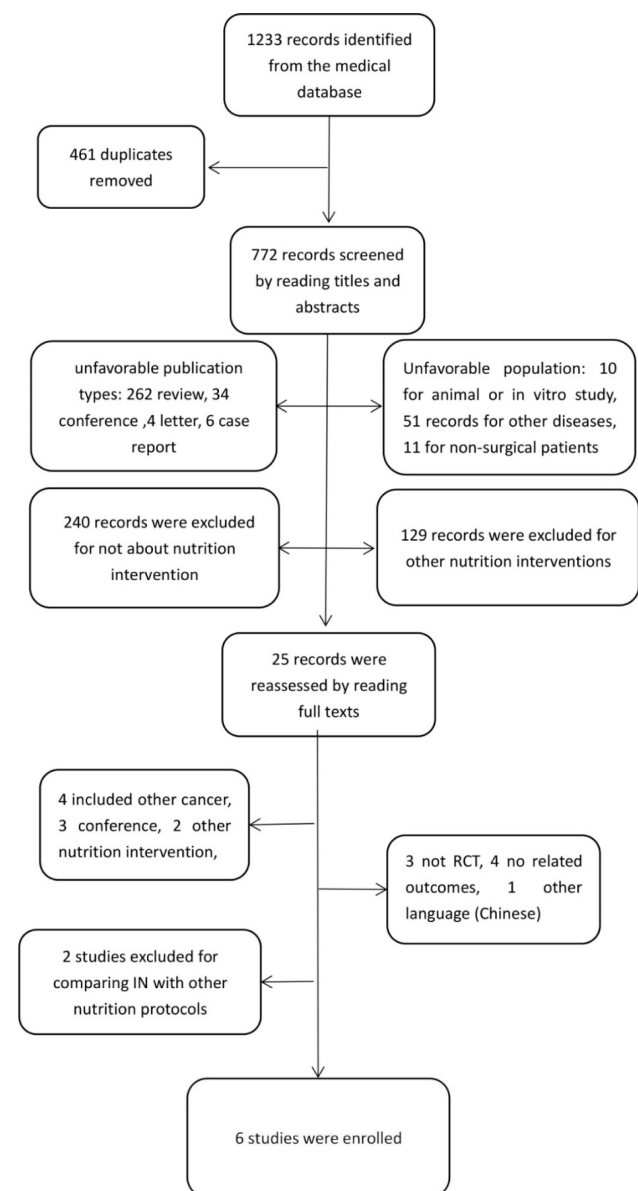
The major outcome in this study was the postoperative complications including anastomosis leakage, pulmonary infection, wound infection, sepsis and so on.

### Statistics

Data analysis was performed by Review Manager Version 5.3 and STATA Version 12.0 software (Stata Corporation, College Station, TX, USA). Odds Ratio (OR) was used in the comparison of dichotomous data. We used  $I^2$  as the indicator of heterogeneity.  $I^2 < 25\%$ ,  $25\% \leq I^2 < 50\%$  and  $I^2 \geq 50\%$  indicated low, moderate and high heterogeneity. When high heterogeneity was detected, a random effects model was adopted otherwise fixed effects model was adopted. Begg's and Egger's tests were used to detect the publication bias. P value less than 0.05 was considered to be statistically significant.

## Results

The screening procedures are shown in Figure 1. Finally, six randomized controlled trials (RCTs)



**Figure 1.** Flow diagram showing the procedures of study selection.

enrolled 638 patients (391 in the immunonutrition group) were included in the meta-analysis. The baseline characteristics of the included studies are shown in Table 1. Among the six RCTs, three articles [10-12] compared the perioperative administration of the immunonutrition with the standard enteral nutrition, one study [13] administered immunonutrition after the surgery, one study [14] gave the immunonutrition before surgery and another 2×2 factorial RCT [15] compared preoperative, postoperative and perioperative administration of immunonutrition with the standard enteral nutrition. All the patients in the RCTs underwent open or minimal invasive esophagectomy with two or three-level lymphadenectomy.

#### Postoperative complications

Although the immunonutrition group had a lower rate of anastomosis leakage (9.0% versus 10.9%), the difference didn't reach statistical significance (OR=0.75, 95%CI (0.43, 1.31), *p* value=0.32, Figure 2A). The immunonutrition group had a lower rate of wound infection (8.8% versus 9.8%),

but it didn't show statistical significance (OR=0.99, 95%CI 0.49, 2.00, *p* value=0.98) Figure 2B). The incidence of pulmonary infection was also comparable between the immunonutrition (IN) group and standard nutrition (SN) group (18.7% in IN, 14.6% in SN, OR=1.04, 95%CI (0.65, 1.65), *p* =0.88, Figure 2C). Only three studies provided about sepsis, and the pooled analysis didn't show statistically significant difference (6.1% in IN, 5.5% in SN, OR=0.92, 95%CI 0.42, 2.02, *p* value=0.84) Figure 2D). Since limited studies reported the other complications, the analyses of other complications were summarized in Table 2.

#### Heterogeneity and publication bias

Only the analysis of sepsis showed a moderate heterogeneity ( $I^2=28\%$ ), the pooled analyses of other complications showed a low heterogeneity ( $I^2<25\%$ ). Egger's and Begg's test detected no publication bias in all analyses. The quality assessment result is shown in Figure 3. The binding of participants or personnel and the binding of outcome assessment were unavailable in four studies. The

**Table 1.** Baseline characteristics of included studies

Study	No. of patients (IN/SN)	Time of IN	Duration of preoperative intervention	Duration of postoperative intervention	Surgery type	Immuno-enhancing substances
Sakuri 2007	16/14	Perioperative	3 days	14 days	OE	A,B,C
Ryan 2009	28/25	Perioperative	5 days	21 days	OE or MIE	A
Healy 2017	97/94	Perioperative	5 days	30 days	OE or MIE	A
Kitagawa 2017	14/15	preoperative	5 days	unavailable	MIE	A,C
Matsuda 2017	35/37	postoperative	Unavailable	21	OE or MIE	A
Mudge 2018	65/62	postoperative	7 days	7 days	OE or MIE	A,B,C
Mudge 2018	65/62	preoperative	7 days	7 days	OE or MIE	A,B,C
Mudge 2018	71/62	perioperative	7 days	7 days	OE or MIE	A,B,C

IN=immunonutrition, SN=standard nutrition, OE=open esophagectomy, MIE=minimal invasive esophagectomy, A=arginine, B= omega-3-unsaturated fatty acid, C= nucleotide

**Table 2.** Summary of other complications in the six randomized control trials

Complication	Number of studies	Complication rate in IN (event/total)	Complication rate in SN (event/total)
ARDS	2 studies [10, 15]	1.31% (3/229)	1.15% (1/87)
Chylothorax	1 study [15]	5.96% (14/201)	5.26% (2/62)
Urinary tract infection	1 study [15]	2.99% (6/201)	3.23 (2/62)
Respiratory failure	1 study [11]	5.15% (5/97)	7.45% (7/94)
Atrial fibrillation	1 study [11]	17.53% (17/97)	20.21% (19/94)
Recurrent nerve palsy	1 study [14]	28.57% (4/14)	40.00% (6/15)
Renal failure	1 study [10]	3.57% (1/28)	12.00% (3/25)
Gastrointestinal complication	1 study [12]	18.75% (3/16)	28.57% (4/14)

IN=immunonutrition, SN=standard nutrition, ARDS: acute respiratory distress syndrome

binding of Random sequence generation and allocation concealment were unavailable in one study. The left items were well described in all studies.

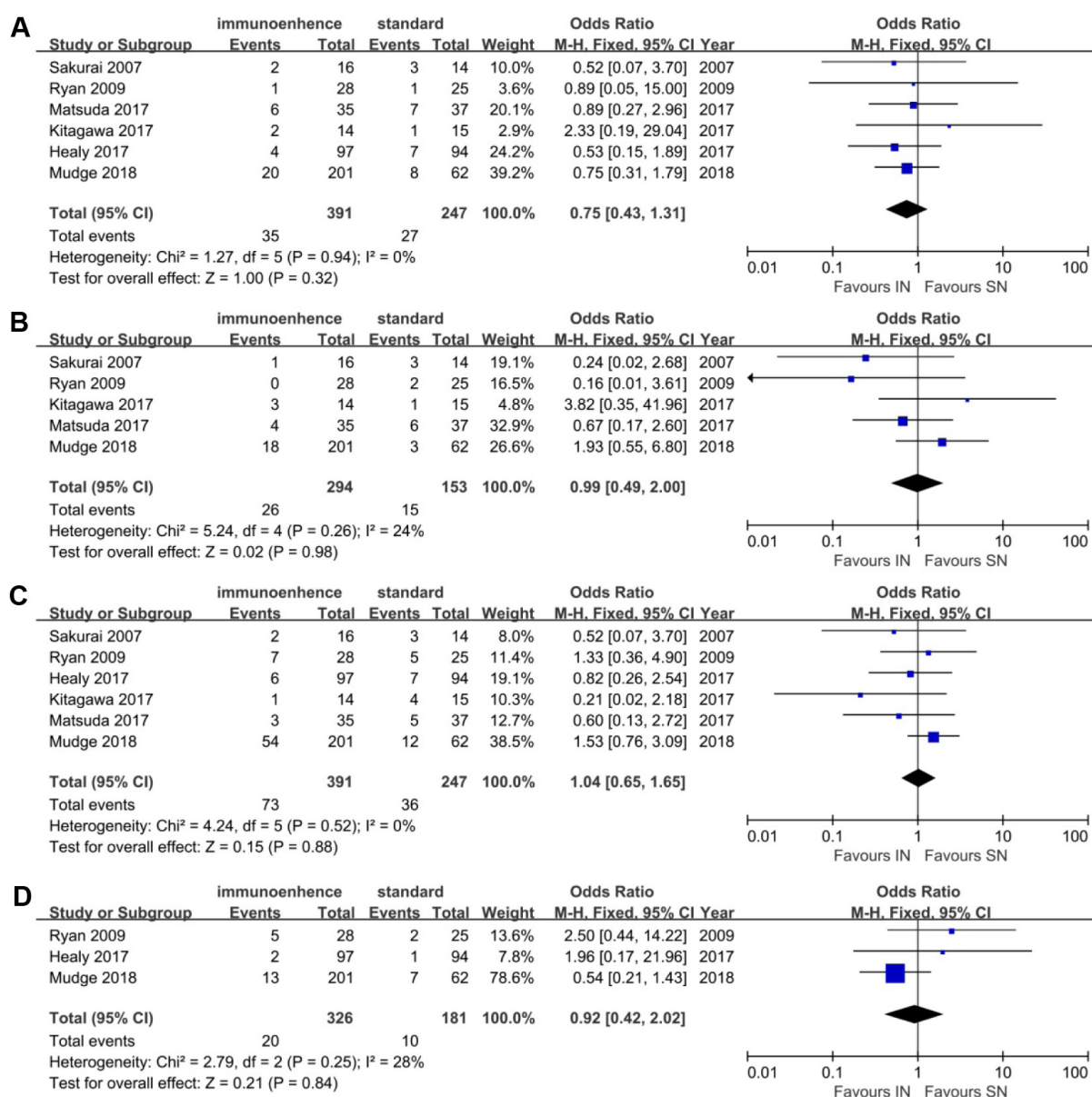
## Discussion

All the pooled analyses of postoperative complications showed no statistically significant difference between immunonutrition and standard nutrition. So the improvements of immunological and hematological indexes brought by immunonutrition failed to reduce the incidence of postoperative complications in EC patients.

Severe surgical trauma results in metabolic responses that mobilize substrate from body stores to support vital organs, thus enhance the resistance

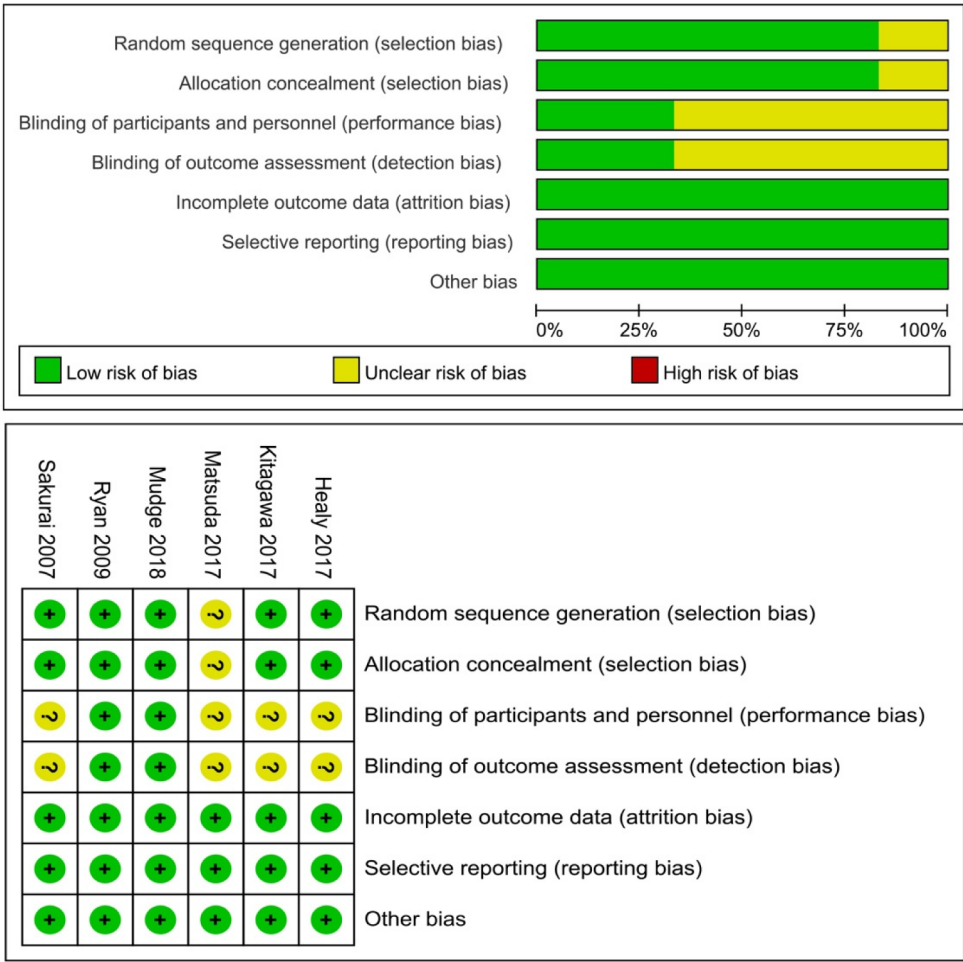
to infection, and promote wound healing [16,17]. So perioperative nutrition support is necessary in patients undergoing highly invasive surgery. Otherwise, this protein-consuming state could lead to prolonged convalescence, diminished immunity, and poor wound healing.

Enteral nutrition has been believed to bring more benefits to surgical patients than parenteral nutrition [18]. The standard enteral nutrition focuses on providing adequate energy and protein to the body. As an improvement of standard nutrition formula, arginine, nucleotide and high concentration of omega-3-unsaturated fatty acids bring more functions to the immunonutrition. Omega-3-unsaturated fatty acids have been shown to inhibit inflammatory lipid mediators produced from



**Figure 2.** Forest plot for postoperative complications (**A**: anastomosis leakage; **B**: wound infection; **C**: pulmonary infection; **D**: sepsis).





**Figure 3.** Study quality assessments based on review author’s judgement about risk of bias item for each eligible study.

n-6 fatty acids, as well as the TNF- $\alpha$  and IL-1 production. Arginine could significantly reduce body weight loss and nitrogen consumption. They help modulate immuno-dysfunction associated with surgical stress [19]. Kitawaga et al [20] reported preoperative immunonutrition suppressed the elevation of the TNF- $\alpha$  level after thoracoscopic esophagectomy. Sakuri et al [19] reported immunonutrition caused a significant increase in the total lymphocyte count and caused a shift toward B cell proliferation in EC patients. These findings support the benefits of immunonutrition in improving the immune and inflammation indexes in EC.

Several meta-analyses have shown immunonutrition is efficient in reducing postoperative complications in patients with gastric cancer and colorectal cancer [8,21]. However, in our meta-analysis its superiority was not statistically significant. But we should not overlook the value of the immunonutrition in other aspects. Mutsuda, et al [13] showed the patients in the immunonutrition group had a higher postoperative oxygenation. Ryan et al [10] showed a better control of body weight loss, while Ohkura et al [22] found a significant higher

rate of completion of enteral nutrition in the immunonutrition group. These benefits or strengths brought by the immunonutrition should be emphasized and further studied.

To our knowledge, this was the most informative meta-analysis comparing the efficacy of immunonutrition with the standard nutrition in reducing the postoperative complications in patients undergoing esophagectomy for EC. It enrolled six RCTs providing high level of evidence on this topic and it didn't show a statistically significant difference between immunonutrition and standard enteral nutrition in reducing the postoperative complications. Limited studies provide the data on immunological or inflammatory indexes, so we failed to run a meta-analysis on these indexes. Future studies focusing on severe malnutrition patients may highlight the efficacy of immunonutrition in reducing postoperative complications in EC. Other advantages of immunonutrition, such as a higher rate of completion of enteral nutrition, less body weight and so on are needed to be further proved and the data on immune and inflammatory index are also in great need.

## Conclusion

In this meta-analysis, immunonutrition didn't show superiority in reducing the postoperative complication in EC patients when comparing with the standard enteral nutrition. This result needs to be further studied, while the high tolerance and other advantages brought by the immunonutrition should not be overlooked.

## Author's contribution

Ze-Guo Zhuo and Jun Luo collected data and drafted the manuscript. Gang Li and Tie-Niu Song

analyzed the data under the guidance of Han-Yu Deng. Gu-ha Alai and Xu Shen found the full-texts of relevant studies. Yi-Dan Lin designed the study and revised the manuscript. All authors read and approved the final manuscript. We sincerely thank all the authors of the original articles for their efforts in this area.

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## Conflict of interests

The authors declare no conflict of interests.

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