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Contents

Monthly Volume 13 Number 7 July 27, 2021

OPINION REVIEW

620 Endoscopic ultrasound guided gastrojejunostomy for gastric outlet obstruction

Stefanovic S, Draganov PV, Yang D

MINIREVIEWS

633 Current status of treatments of pancreatic and peripancreatic collections of acute pancreatitis

Xiao NJ, Cui TT, Liu F, Li W

645 Closure techniques in exposed endoscopic full-thickness resection: Overview and future perspectives in the endoscopic suturing era

Granata A, Martino A, Ligresti D, Zito FP, Amata M, Lombardi G, Traina M

655 Management of early rectal cancer; current surgical options and future direction

Chavda V, Siaw O, Chaudhri S, Runau F

668 Robotic donor hepatectomy: Are we there yet?

Rammohan A, Rela M

678 Gastrectomy impact on the gut microbiome in patients with gastric cancer: A comprehensive review

Maksimaityte V, Bausys A, Kryzauskas M, Luksta M, Stundiene I, Bickaite K, Bausys B, Poskus T, Bausys R, Strupas K

ORIGINAL ARTICLE

Retrospective Study

689 Novel parameter based on lipid indicators ratio improves prognostic value of plasma lipid levels in resectable colorectal cancer patients

Gu JN, Yao S, Cao YH, Deng SH, Mao FW, Jiang HY, He YT, Li XY, Ke SQ, Li HL, Li H, Liu XH, Liu HL, Wang JL, Wu K, Liu L, Cai KL

SYSTEMATIC REVIEWS

702 Acute mesenteric ischemia and small bowel imaging findings in COVID-19: A comprehensive review of the literature

Pirola L, Palermo A, Mulinacci G, Ratti L, Fichera M, Invernizzi P, Viganò C, Massironi S

META-ANALYSIS

717 Efficacy and safety of early oral feeding in postoperative patients with upper gastrointestinal tumor: A systematic review and meta-analysis

Hao T, Liu Q, Lv X, Qiu J, Zhang HR, Jiang HP

ABOUT COVER

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS*, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc*.

INDEXING/ABSTRACTING

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META-ANALYSIS

Efficacy and safety of early oral feeding in postoperative patients with upper gastrointestinal tumor: A systematic review and meta-analysis

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Abstract

BACKGROUND

Early oral feeding (EOF) is an important measure for early recovery of patients with gastrointestinal tumors after surgery, which has emerged as a safe and effective postoperative strategy for improving clinical outcomes.

AIM

To determine the safety and efficacy of early oral feeding in postoperative patients with upper gastrointestinal tumor.

METHODS

This meta-analysis was analyzed using Review Manager version 5.3 and Stata version 14. All clinical studies that analyzed efficacy and safety of EOF for postoperative patients with upper gastrointestinal tumor were included.

RESULTS

Fifteen studies comprising 2100 adult patients met all the inclusion criteria. A significantly lower risk of pneumonia was presented in the EOF compared with TOF group [relative risk (RR) = 0.63, 95% confidence interval (CI): 0.44–0.89, P = 0.01]. Length of hospital stay was significantly shorter in the EOF group than in the TOF group [weighted mean difference (WMD) = -1.91, 95%CI: -2.42 to -1.40; P < 0.01]. Cost of hospitalization was significantly lower (WMD = -4.16, 95%CI: -5.72 to -2.61; P < 0.01), and CD4 cell count and CD4/CD8 cell ratio on postoperative day 7 were significantly higher in the EOF group than in the TOF group: CD4

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count (WMD = 7.17, 95%CI: 6.48–7.85; $P < 0.01$), CD4/CD8 ratio (WMD = 0.29, 95%CI: 0.23–0.35; $P < 0.01$). There was no significant difference in risk of anastomotic leak and total postoperative complications.

CONCLUSION

EOF as compared with TOF was associated with lower risk of pneumonia, shorter hospital length of stay, lower cost of hospitalization, and significantly improved postoperative immune function of patients.

Key Words: Early oral feeding; Gastrointestinal tumor; Safety; Efficacy; Meta-analysis; Systematic review

Core Tip: Postoperative early oral feeding (EOF) is safe and effective for improving clinical outcomes in patients with lower gastrointestinal tumor. To our knowledge, this study is the largest meta-analysis of randomized controlled trials to date, including 2100 participants, of whom 1042 received EOF protocols and 1058 received traditional oral feeding, to assess the safety and efficacy in postoperative patients with upper gastrointestinal tumor. Our review clarified that EOF results in accelerated convalescence, reduction of the risk of pneumonia, length of hospital and medical costs, and better immune status.

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INTRODUCTION

China has a 30% and 40% higher mortality of cancer than the United Kingdom and United States, respectively, and 36.4% of the cancer-related deaths are from upper gastrointestinal tract cancers (stomach, liver, and esophagus), with poor prognosis[1]. At present, surgery is still the most effective treatment. However, most of the cancer patients have accompanying malnutrition, which increases the possibility of surgical complications. Thus, it is necessary to carry out perioperative nutritional support as early as possible. Fortunately, a large number of studies have proved that early enteral nutrition is beneficial and can speed up postoperative recovery. Enhanced Recovery After Surgery (ERAS) guidelines advocate early resumption of normal oral diet to decrease surgical stress response[2,3].

Re-establishment of oral feeding as early as possible after surgery is important in the multimodal ERAS nursing strategy, which is associated with reducing morbidity, length of stay and cost[4,5]. At present, early oral feeding (EOF), *i.e.* oral intake (water or nutrient solution) within 24 h after surgery, has been widely practiced in patients with lower gastrointestinal tract surgery, and has benefited from a large number of experimental studies and reliable evidence-based medicine. However, for patients with upper gastrointestinal tract tumor, according to our observations, surgeons have a conservative attitude towards EOF, and the current method is still placing a nutrition tube or an intestinal stoma, which undoubtedly adds additional trauma and economic pressure to the patient. Although there are many studies of early oral enteral nutrition after surgery of the upper gastrointestinal tract, the results have not been consistent, and most of them are not randomized controlled trials (RCTs).

The purpose of our study was to analyze the safety and efficacy of EOF in postoperative patients with upper gastrointestinal tumors (esophagus, stomach, duodenum, and/or pancreas). Although there have been meta-analyses of EOF in patients with upper gastrointestinal tumors[6], we collected updated evidence and only included RCTs of upper gastrointestinal tumors to make our results more reliable. This is believed to be the first meta-analysis of upper gastrointestinal tumors

only including RCTs. We used postoperative complications and exhaust time as the main outcome indicators, and evaluated the changes in hospitalization time, hospitalization costs, and immune indicators after surgery.

MATERIALS AND METHODS

The present systematic review was prepared and revised according to the PRISMA 2009 Checklist. We registered the protocol with PROSPERO (International Prospective Register of Systematic Reviews), registration number CRD42021225789 (http://www.crd.york.ac.uk/PROSPERO).

Literature search

The research question was structured according to the PICOS (Population, Intervention, Comparator, Outcome and Study Design) criteria. Clinical studies that analyzed efficacy and safety of EOF for postoperative patients with upper gastrointestinal tumor were collected from PubMed, Embase, Web of Science, Cochrane Library, Chinese National Knowledge Infrastructure, Wanfang, and VIP databases until the end of December 2020. We used MeSH terms and keyword combinations when searching. The MeSH terms were: "Gastrointestinal Tract", "Upper Gastrointestinal Tract", "Esophagus", "Stomach", "Duodenum", "Pancreas" and "Neoplasms", "Anastomosis, Roux en Y", "Esophagectomy", "Esophagoplasty", "Gastrectomy", "Gastroenterostomy", "Pancreaticoduodenectomy", "Enteral Nutrition", "Nutritional Support", "Diet Therapy", "Nutrition Therapy", "Dietary Supplements", and "Feeding Methods". We also screened manually the reference lists of all included studies. Two independent researchers extracted the literature data, and the third researcher judged if there were any differences.

Inclusion and exclusion criteria

Inclusion criteria were: (1) Patients with upper gastrointestinal tumor (including esophageal, stomach, pancreatic or duodenal cancer) undergoing surgery; (2) EOF, including water or liquid, within 24 h after surgery; (3) RCTs; (4) Studies including one or more of the outcomes; (5) Control group was traditional oral feeding (TOF) or late oral feeding, including any form of enteral nutrition later than 24 h, or total parenteral nutrition; and (6) English or Chinese language. Exclusion criteria were: (1) Duplicate documents, abstract, review, case reports, animal research, and non-adult studies; (2) Non-RCTs and noncomparative studies; (3) Oral feeding after surgery later than 24 h; (4) Incomplete data or no full text; (5) Studies including non-tumor patients and lower gastrointestinal tumors; and (6) Other irrelevant research.

Study selection and data extraction

After identification of all potentially eligible studies, we evaluated the studies according to the quality evaluation criteria of the Cochrane System Reviewer Manual. The members of the research group clearly formulated the purpose of the analysis, the search procedures, and the source plan of the data. Two investigators independently extracted the literature data, and discussed with a third researcher to settle any discrepancies or divergences. The extracted content included study and baseline population characteristics (first author, publication year, country, sample size, research type, age, sex, operation type), intervention (time postoperative oral feeding started and the feeding program), comparison (time postoperative oral feeding started and the nutrition plan). Primary outcomes of interest were postoperative complications and time of gas passage. Secondary outcomes were length of postoperative hospital stay, cost of hospitalization, immune function indicators (CD4 cell count and CD4/CD8 cell ratio) (Tables 1 and 2).

Assessment of risk of bias in included studies

All included RCTs were evaluated by another two investigators separately using the risk of bias assessment tool recommended by the Cochrane Collaboration[7]. The main indicators included: (1) Randomization; (2) Allocation concealment; (3) Blinding of participants and personnel; (4) Blinding of outcome assessment; (5) Incomplete outcome data; (6) Selective outcome reporting; and (7) Other bias. Risk of bias for each included study was graded as high risk, low risk or unclear.

Table 1 Outcomes of studies

Ref.	Year	Sample size, *n*		Time of gas passage (mean ± SD, h)		LOS (mean ± SD, d)		Cost of hospitalization (mean ± SD, CNY, × 1000)		Pneumonia, *n*		Anastomotic leakage, *n*	
		EOF	TOF	EOF	TOF	EOF	TOF	EOF	TOF	EOF	TOF	EOF	TOF
Wang *et al*[15]	2017	38	42	73.5 ± 6.3	80.1 ± 8.7	8.2 ± 1.6	9.5 ± 1.7	57.2 ± 5.1	63.1 ± 4.3	5%[6]	7%[6]	0	4.8%[6]
Liu *et al*[12]	2011	30	32	2.15 ± 0.43[1]	2.97 ± 0.52[1]	NR	NR	NR	NR	1	3	0	0
Yang *et al*[18]	2013	25	25	78.8 ± 8.4	87.1 ± 11.3	7.81 ± 2.58	9.62 ± 1.91	29.6 ± 4.2	35.2 ± 3.8	NR	NR	0	0
Wang *et al*[14]	2017	60	60	67.6 ± 7.5	85.2 ± 8.5	6.5 ± 1.8	9.2 ± 2.6	NR	NR	2	6	2	3
Lin *et al*[13]	2018	47	53	2.83 ± 0.96[1]	3.56 ± 0.99[1]	11.91 ± 1.43	12.68 ± 1.42	3.56 ± 0.61[5]	3.93 ± 0.75[5]	2	10	1	2
Li *et al*[17]	2014	50	50	67.3 ± 7.9	84.6 ± 8.7	6.8 ± 1.9	9.3 ± 2.5	NR	NR	NR	NR	NR	NR
Yu *et al*[16]	2016	72	67	2.1 ± 1.2[1]	3.3 ± 1.5[1]	6.0 ± 1.8	7.7 ± 2.5	1.5 ± 0.5[5]	1.6 ± 0.8[5]	1	3	0	1
Li *et al*[12]	2015	200	200	67.3 ± 7.9	84.6 ± 8.7	6.8 ± 1.9	9.3 ± 2.5	NR	NR	NR	NR	NR	NR
Gao *et al*[10]	2019	101	97	2.05 ± 0.71[1]	2.50 ± 0.91[1]	NR	NR	NR	NR	NR	NR	1	1
Hur *et al*[20]	2011	28	26	1.9 ± 1.2[1]	2.9 ± 0.8[1]	7.2 ± 1.7	8.5 ± 2.9	7749 ± 1250[4]	8415 ± 2945[4]	1		0	1
Berkelmans *et al*[19]	2020	65	67	NR	NR	NR	NR	NR	NR	16	23	12	11
Sun *et al*[22]	2018	140	140	2 (2-3)[1,2]	3 (2-3)[1,2]	7 (7-8)[2]	10 (9-12)[2]	NR	NR	15	17	5	6
Mahmoodzadeh *et al*[23]	2015	54	55	3 (2-3)[1,2]	4 (3-4)[1,2]	6 (5.75-7)[2]	8 (7-9)[2]	NR	NR	NR	NR	2	1
Shimizu *et al*[21] (DG)	2018	70	84	2 (1-3)[1,3]	2 (1-6)[1,3]	10 (5-70)[3]	10 (5-31)[3]	NR	NR	0	2	5	2
Shimizu *et al*[21] (TG)		32	30	2 (1-4)[1,3]	3 (1-6)[1,3]	10 (7-16)[3]	12 (7-44)[3]	NR	NR	1	0	4	4
Mi *et al*[11]	2012	30	30	79.9 ± 9.5	86.6 ± 8.7	7.83 ± 2.23	9.57 ± 1.96	30.22 ± 3.22	34.6 ± 3.21	0	1	0	0

[1]The value is in days.
[2]Medians (lower quartile - upper quartile).
[3]Median (range).
[4]The walue is in USD($).
[5]The value is in CNY(¥),×10000.
[6]Incidence rate.
DG: Distal gastrectomy; EOF: Early oral feeding; LOS: Length of postoperative hospital stay; NR: No report; TG: Total gastrectomy; TOF: Traditional oral feeding.

Data collection and analysis

Statistical analysis was performed using Review Manager version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark) and Stata version 14 (StataCorp LP, College Station, TX, United States). We invited an expert in biomedical statistics (Qingshan Chen, MD, PhD, Jinan University) to evaluate the statistical methods. The results were

Table 2 Number of postoperative complications and immune function indicators (CD4 cell count and CD4/CD8 cell ratio)

Postoperative complications, *n*		CD4_PreO, (%), mean ± SD		CD4_POD1, (%), mean ± SD		CD4_POD7, (%), mean ± SD		CD4/CD8_PreO, mean ± SD		CD4/CD8_POD1, mean ± SD		CD4/CD8_POD7, mean ± SD	
EOF	TOF	EOF	TOF	EOF	TOF	EOF	TOF	EOF	TOF	EOF	TOF	EOF	TOF
13%[1]	17%[1]	43 ± 4	43 ± 4	36 ± 3	34 ± 3	42 ± 4	36 ± 4	1.8 ± 0.2	1.7 ± 0.3	1.4 ± 0.3	1.5 ± 0.3	1.8 ± 0.2	1.4 ± 0.3
7	7	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
3	4	43.2 ± 3.7	43.6 ± 4.1	35.3 ± 5.3	35.8 ± 3.6	40.6 ± 5.1	35.2 ± 3.8	1.68 ± 0.22	1.66 ± 0.27	1.52 ± 0.33	1.51 ± 0.42	1.77 ± 0.27	1.56 ± 0.31
7	17	43.4 ± 3.5	43.1 ± 3.1	30.6 ± 2.5	30.9 ± 2.4	42.4 ± 2.8	34.7 ± 2.3	1.9 ± 0.3	1.9 ± 0.2	1.5 ± 0.4	1.6 ± 0.3	1.8 ± 0.3	1.6 ± 0.3
5	16	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	43.2 ± 3.7	42.9 ± 3.3	30.4 ± 2.7	30.7 ± 2.6	42.2 ± 3.0	34.5 ± 2.5	1.8 ± 0.3	1.7 ± 0.3	1.3 ± 0.4	1.4 ± 0.4	1.7 ± 0.3	1.4 ± 0.4
10	11	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	43.5 ± 3.8	43.5 ± 3.6	31.5 ± 2.8	30.5 ± 2.5	42.1 ± 3.6	34.4 ± 2.4	1.6 ± 0.4	1.8 ± 0.3	1.6 ± 0.6	1.4 ± 0.3	1.7 ± 0.3	1.4 ± 0.8
11	10	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
7	8	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
48	56	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
6	5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
17	8	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
11	6	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
4	5	42.2 ± 3.5	42.5 ± 3.6	36.4 ± 3.1	35.7 ± 2.9	40.6 ± 3.9	34.8 ± 3.1	1.76 ± 0.21	1.75 ± 0.22	1.40 ± 0.31	1.62 ± 0.45	1.76 ± 0.28	1.46 ± 0.23

[1]Incidence rate.

EOF: Early oral feeding; NR: No report; LOS: Length of postoperative hospital stay; POD: Postoperative day; PreO: Preoperative day; TOF: Traditional oral feeding.

expressed with relative risk (RR) for the dichotomous variables and weighted mean difference (WMD) for the continuous variables, with 95% confidence intervals (CIs). If the study did not provide mean ± SD, they were obtained using an online calculator [8]. The I^2 statistic was used to evaluate statistical heterogeneity. If I^2 was > 50%, the data were regarded as having substantial heterogeneity. Thus, a random-effects model was used and we found the reason *via* sensitivity analysis; otherwise, a fixed-effects model was selected. Funnel scatterplot and Egger's test were chosen to assess publication bias. $P < 0.05$ was statistically significant. Forest plots represented the pooled RR and 95%CIs. A funnel plot was drawn to detect publication bias.

Table 3 Main characteristics of the included studies

Ref.	Year	Country	Location of cancer	Sample size, *n*		Sex, male/female, *n*		Age in yr, mean ± SD, male/female		Outcomes
				EOF	TOF	EOF	TOF	EOF	TOF	
Wang *et al*[15]	2017	China	Gastric	38	42	NR	NR	58 ± 10[1]		①②③④⑤⑥⑦⑧
Liu *et al*[12]	2011	China	Gastric	30	32	12/18	19/13	56.3[4]	57.5[4]	①②④
Yang *et al*[18]	2013	China	Gastric	25	25	15/10	16/9	57.5 ± 13.7	56.8 ± 11.9	①④⑤⑥⑦⑧
Wang *et al*[14]	2017	China	Gastric	60	60	31/29	33/27	58.6 ± 7.8	54.2 ± 8.4	①②③④⑤⑦⑧
Lin *et al*[13]	2018	China	Gastric	47	53	NR	NR	52.2 ± 6.6[1]		①②③④⑤⑥
Li *et al*[17]	2014	China	Gastric	50	50	26/24	28/22	60.8 ± 5.9	56.0 ± 7.6	④⑤⑦⑧
Yu *et al*[16]	2016	China	Gastric	72	67	57/15	49/18	57.8 ± 13.1	60.1 ± 11.8	①②③④⑤⑥
Li *et al*[12]	2015	China	Gastric	200	200	104/96	112/88	60.8 ± 5.9	56.0 ± 7.6	④⑤⑦⑧
Gao *et al*[10]	2019	China	Gastric	101	97	68/33	55/42	56.3 ± 10.2	53.9 ± 11.6	①②③④
Hur *et al*[20]	2011	South Korea	Gastric	28	26	20/8	21/5	NR (mean ± SD)		①②③④⑤⑥
Berkelmans *et al*[19]	2020	Netherlands Sweden	Esophageal	65	67	56/9	56/8	65 (59-70)[2]	65 (61-70)[2]	②③
Sun *et al*[22]	2018	China	Esophageal	140	140	92/48	103/37	62 (53-59)[2]	63 (58-69)[2]	①②③④⑤
Mahmoodzadeh *et al*[23]	2015	Iran	Both	54	55	29/25	29/26	64.2 ± 8.2	66.4 ± 7.7	①③④⑤
Shimizu *et al*[21] (DG)	2018	Japan	Gastric	70	84	36/34	54/30	64.5 (37-79)[3]	64 (25-79)3	①②③④⑤
Shimizu *et al*[21] (TG)				32	30	25/7	8/22	68.5 (48-78)[3]	68.5 (40-79)[3]	
Mi *et al*[11]	2012	China	Gastric	30	30	15/15	12/18	57.2 ± 9.5	60.0 ± 10.3	①②③④⑤⑥⑦⑧

[1]Total mean ± SD.
[2]Medians (lower quartile - upper quartile).
[3]Median (range).
[4]Total mean.
Outcomes: ①: Postoperative complications; ②: Pneumonia; ③: Anastomotic leakage; ④: Time of gas passage; ⑤: Length of postoperative hospital stay; ⑥: Cost of hospitalization; ⑦: CD4 cell count; ⑧: CD4/CD8 cell ratio. DG: Distal gastrectomy; EOF: Early oral feeding; NR: No report; TG: Total gastrectomy; TOF: Traditional oral feeding.

RESULTS

Baseline study characteristics

According to inclusion and exclusion criteria, we selected 13442 preliminary studies, including 5471 English and 7971 Chinese studies. After eliminating studies that did not meet the inclusion requirements and duplicates by rapid screening, we evaluated other studies, and removed those that did not meet the inclusion criteria and from which we could not extract data. Finally, we included 15 studies[9-23], of which seven were English and eight Chinese. The study selection process is outlined in the PRISMA flowchart (Figure 1). We evaluated the risk bias of the included studies using the Cochrane Collaboration's tool.

All 15 studies reported on 2100 patients (1042 receiving EOF and 1058 TOF). There were 12 studies of gastric cancer, 2 of esophageal cancer, and 1 of both esophageal and gastric cancer. A study of pancreatic cancer and duodenum cancer did not include EOF. Table 3 presents the main characteristics of the included studies. Assessment of the risk of bias across all included studies is presented in Figure 2. The main risk of bias was blinding among these RCTs, as it was difficult to perform double blinding in such procedural trials.

Table 4 Eliminated studies in sensitivity study of postoperative exhaust time

Ref.	Year	Sample size, *n*		Postoperative exhaust time in h, mean ± SD		Eliminate reason
		EOF	TOF	EOF	TOF	
Wang *et al*[15]	2017	38	42	73.5 ± 6.3	80.1 ± 8.7	High risk of bias
Yang *et al*[18]	2013	25	25	78.8 ± 8.4	87.1 ± 11.3	High risk of bias
Mi *et al*[11]	2012	30	30	79.9 ± 9.5	86.6 ± 8.7	High risk of bias
Li *et al*[17]	2014	50	50	67.3 ± 7.9	84.6 ± 8.7	High risk of bias
Yu *et al*[16]	2016	72	67	2.1 ± 1.2[1]	3.3 ± 1.5[1]	No data as mean ± SD
Sun *et al*[22]	2018	140	140	2 (2-3)[1,2]	3 (2-3)[1,2]	No data as mean ± SD
Mahmoodzadeh *et al*[23]	2015	54	55	3 (2-3)[1,2]	4 (3-4)[1,2]	No data as mean ± SD
Shimizu *et al*[21] (DG)	2018	70	84	2 (1-3)[1,3]	2 (1-6)[1,3]	No data as mean ± SD
Shimizu *et al*[21] (TG)		32	30	2 (1-4)[1,3]	3 (1-6)[1,3]	No data as mean ± SD

[1]The value is in days.
[2]Medians (lower quartile - upper quartile).
[3]Median (range).
DG: Distal gastrectomy; EOF: Early oral feeding; TG: Total gastrectomy; TOF: Traditional oral feeding.

Results of meta-analysis

Primary outcomes: Twelve RCTs (involving 1493 patients) reported postoperative complications as dichotomous data. The incidence of postoperative complications in the EOF group was 141 (141/746, 18.9%) and 160 (160/747, 21.4%) in the group receiving TOF. Combined analysis showed that EOF did not increase the morbidity of postoperative complications compared with TOF (RR 0.89, 95%CI: 0.68–1.16, P = 0.38), and no significant heterogeneity was found among these trials (χ^2 = 16.63; I^2 = 28%; P = 0.16) (Figure 3A).

Eleven RCTs (involving 1270 patients) provided data regarding pneumonia: 6.5% (41/631 patients) in the EOF group and 11% (68/639) in the TOF group. Pooling analysis indicated that the incidence of pneumonia was significantly reduced in the EOF group (RR = 0.63, 95%CI: 0.44–0.89, P = 0.01), and no heterogeneity was found among these trials (χ^2 = 6.61; I^2 = 0%; P = 0.76) (Figure 3B).

11 RCTs (involving 1455 patients) reported anastomotic leakage, amounting to 4.4% (32/726 patients) in the EOF group and 4.7% (34/729) in the TOF group. Pooling the results suggested that EOF did not increase anastomotic leakage compared with TOF (RR = 0.94, 95%CI: 0.60–1.48, P = 0.80), and there was no heterogeneity observed in these studies (χ^2 = 4.62; P = 0.91; I^2 = 0%) (Figure 3C).

14 studies (1968 patients) reported postoperative exhaust time. There was significantly heterogeneity among the studies (χ^2 = 104.44, I^2 = 87%, P < 0.01), and a random-effects model was adopted for the pooled analysis. The postoperative exhaust time in the EOF group was significantly earlier than that in the TOF group (WMD = -0.61, 95%CI: -0.74--0.47]; P < 0.01). When we used sensitivity to analyze the sources of heterogeneity, we found that after eliminating the studies that did not directly provide mean ± SD and those with high risk bias (Table 4), the remaining data after combined analysis showed no significant heterogeneity (χ^2 = 7.21, I^2 = 31%, P = 0.21), and the results still suggested that the EOF group could significantly shorten the exhaust time (WMD = - 0.71, 95%CI: -0.80--0.63; P < 0.01) (Figure 4).

Secondary outcomes: 12 studies (1708 patients) reported the length of postoperative hospital stay. Heterogeneity was found among these studies (χ^2 = 69.32, I^2 = 83%, P < 0.01), and a random-effects model was used for the pooled analysis. The length of postoperative hospital stay in the EOF group was significantly shorter than that in the TOF group (WMD = -1.91, 95%CI: -2.42--1.40; P < 0.01) (Figure 5A).

6 studies (482 patients) reported the cost of hospitalization. Heterogeneity was present in these trials (χ^2 = 12.14, I^2 = 59%, P = 0.03), therefore, a random-effects model was chosen for the combined analysis. The cost of hospitalization was significantly lower in the EOF group than in the TOF group (WMD = -4.16, 95%CI: -5.72--2.61]; P < 0.01) (Figure 5B).

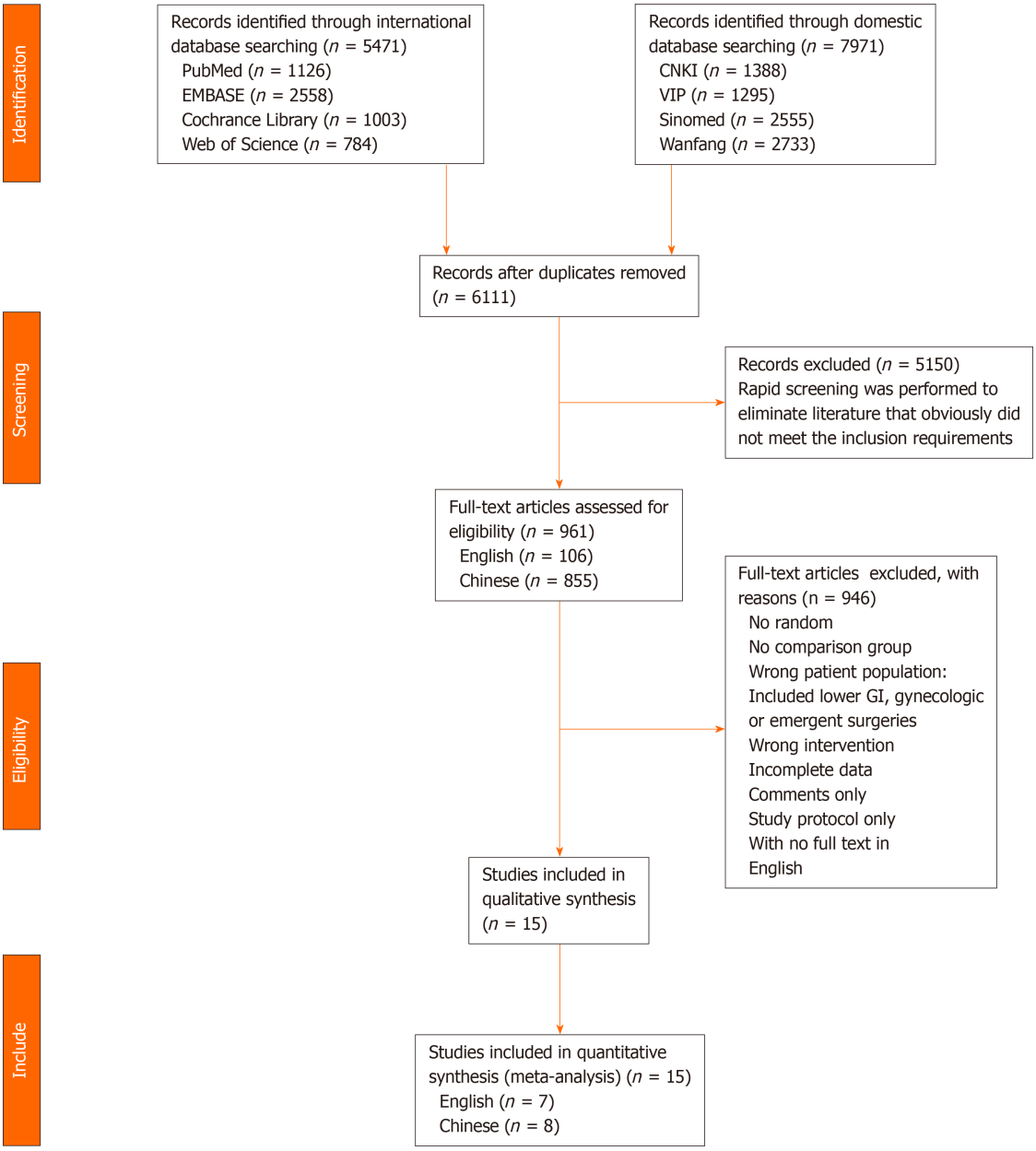


Figure 1 PRISMA flowchart of the study selection process.

6 studies (810 patients) reported CD4 cell count and CD4/CD8 cell ratio. We performed a baseline consistency check on CD4 count and CD4/CD8 ratio the day before the operation and found that the baseline was consistent: CD4 (WMD = 0.05, 95%CI: -0.45-0.55; P = 0.85), CD4/CD8 (WMD = 0.00, 95%CI: -0.11-0.11; P = 0.99). We evaluated the results on postoperative day (POD) 1 and 7 after surgery and found that CD4 count and CD4/CD8 ratio in the EOF group were higher than in the control group on POD1, but not significantly: CD4 (WMD = 0.50, 95%CI: -0.25-1.25; P = 0.19), CD4/CD8 (WMD = 0.04, 95%CI: -0.18-0.09; P = 0.53). However, on POD7, CD4 and CD4/CD8 in the EOF group were significantly higher than those in the TOF group: CD4 (WMD = 7.17, 95%CI: 6.48–7.85; P < 0.01), CD4/CD8 (WMD = 0.29, 95%CI: 0.23–0.35; P < 0.01). No significant heterogeneity was present in CD4 and CD4/CD8 results on POD7: CD4 (χ^2 = 9.66, I^2 = 48%, P = 0.09), CD4/CD8 (χ^2 = 7.50, I^2 = 33%, P = 0.19) (Figure 6).

Publication bias

Due to the obvious heterogeneity of the data analysis after combining the length of postoperative hospital stay and exhaust time, we used the funnel plot and Egger's test to detect publication bias. The analysis indicated that the publication bias was small (Figure 7).

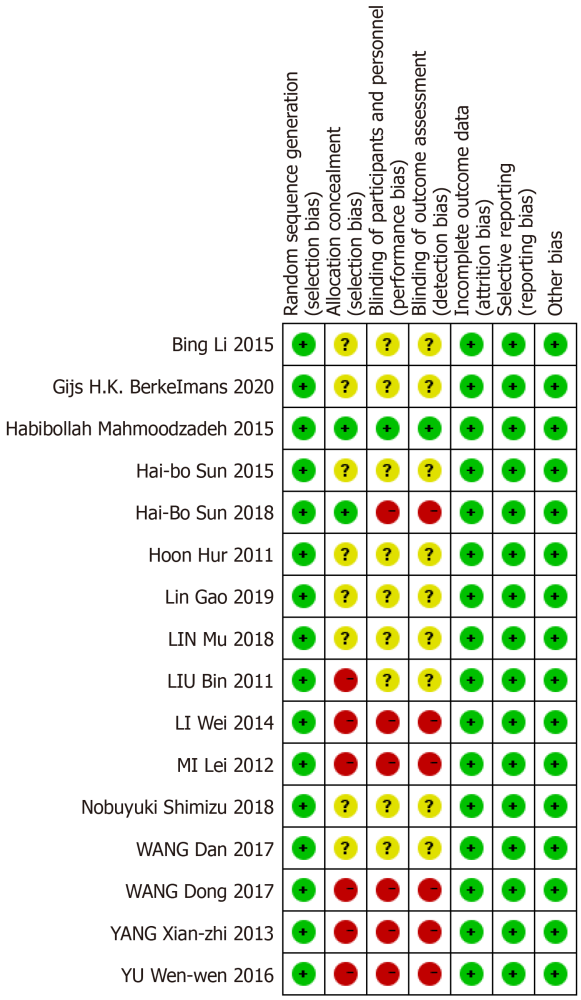


Figure 2 Risk of bias summary. Review of authors' judgments concerning each risk-of-bias item for each included study.

DISCUSSION

During the past few decades, there have been many surgical practices to keep patients nil by mouth until the return of bowel function, especially in gastrointestinal surgery with resection and anastomosis, to avoid related complications[24]. However, in recent years this routine practice has been questioned. Delayed enteral nutrition could lead to atrophic changes in the intestinal mucosa, reduction in nutrient absorption, and impairment in intestinal immune function, which have been demonstrated in animal and human studies[25,26]. As a result, tissue injury at distant sites and the development of multiple organ failure can occur[27]. Therefore, a lot of research on early enteral nutrition has appeared in the last 10 years. In these studies, there are probably 3 methods of early postoperative enteral nutrition: Early oral, jejunostomy tube or nasojejunal tube feeding. Although a nasojejunal tube or a jejunostomy tube is used in most cases, which is the best way remains to be determined.

Han-Geurts *et al*[28] showed that early oral intake did not reduce the duration of postoperative intestinal obstruction, and recovery of gastrointestinal function did not affect tolerance of an oral diet. Other researchers have proposed that resuming oral diet as soon as possible can even promote the recovery of gastrointestinal function[29,30]. Therefore, a lot of studies on EOF have been implemented recently. In the past few decades, many high-quality studies have pointed out that the safety and benefit of EOF after colorectal surgery[31,32]. Recently, the same results appeared in patients undergoing upper gastrointestinal surgery, mainly gastric and esophageal surgery[23,33,34], while there have been few operations on the pancreas and duodenum. A study on early enteral nutrition after pancreatoduodenectomy has shown that early enteral nutrition increases postoperative complications, and is not recommended in terms of safety and feasibility[35]. However, another meta-analysis[36] of enteral nutrition after pancreatoduodenectomy showed that enteral nutrition is associated with a

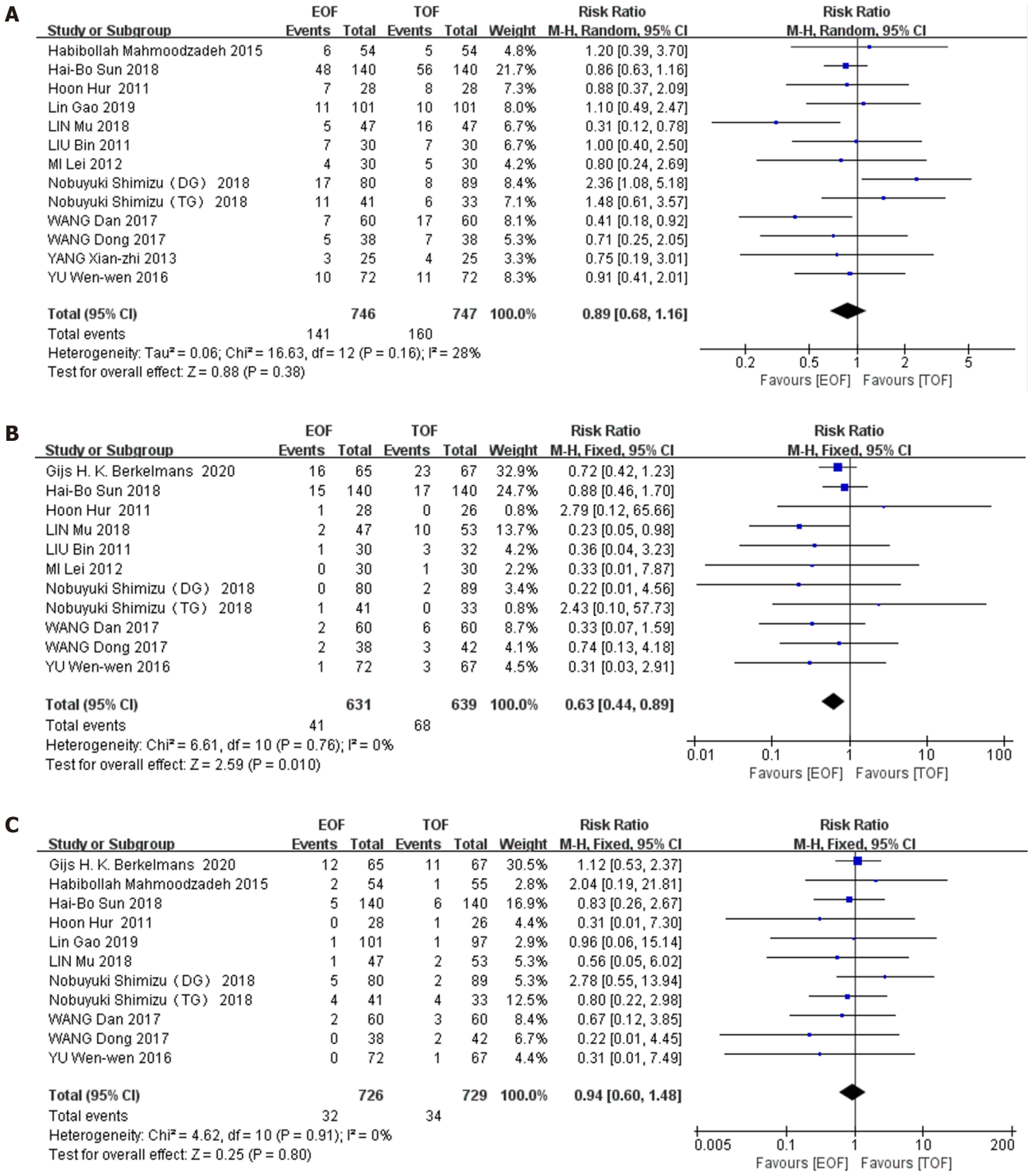


Figure 3 Forest plot evaluating the relative risk of postoperative complications. A: total postoperative complications; B: Pneumonia; C: Anastomotic leakage. EOF *vs* TOF. EOF: Early oral feeding; TOF: Traditional oral feeding.

significantly shorter length of stay compared to parenteral nutrition. In our study, we only included RCTs on gastric and esophageal cancer, and concluded that the complication of pneumonia and length and cost of hospitalization were significantly decreased. This is similar to the results of a meta-analysis on the effects of EOF in the upper gastrointestinal tract[6]. However, the results of a Japanese study were different, which concluded that EOF does not reduce the length of hospital stay after distal gastrectomy and increases the risk of complications. We consider that this might be related to the research design. They divided gastric surgery into distal and total gastrectomy, and obtained inconsistent results. Our study included esophageal and gastric surgery, and did not group the procedures, which may have caused inconsistent results. Furthermore, we counted the changes in immune indicators after

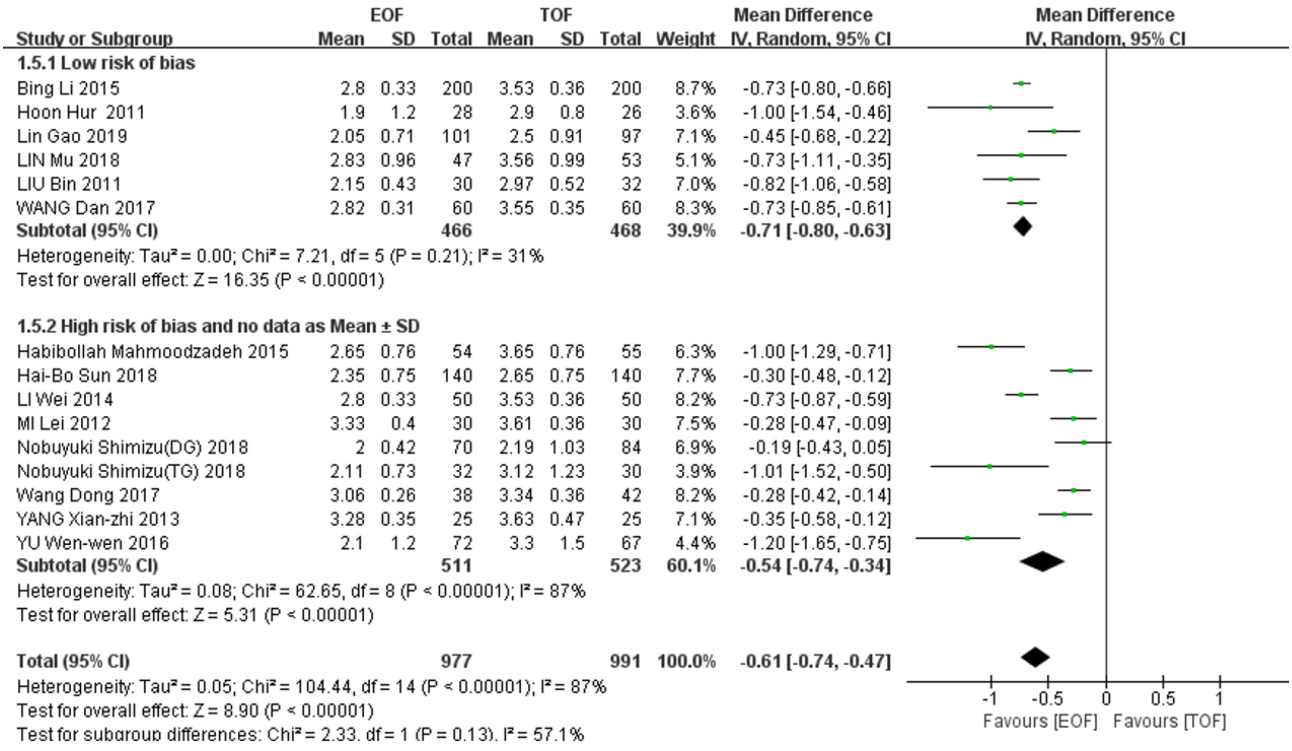


Figure 4 Forest plot evaluating the time of gas passage. EOF: Early oral feeding; TOF: Traditional oral feeding.

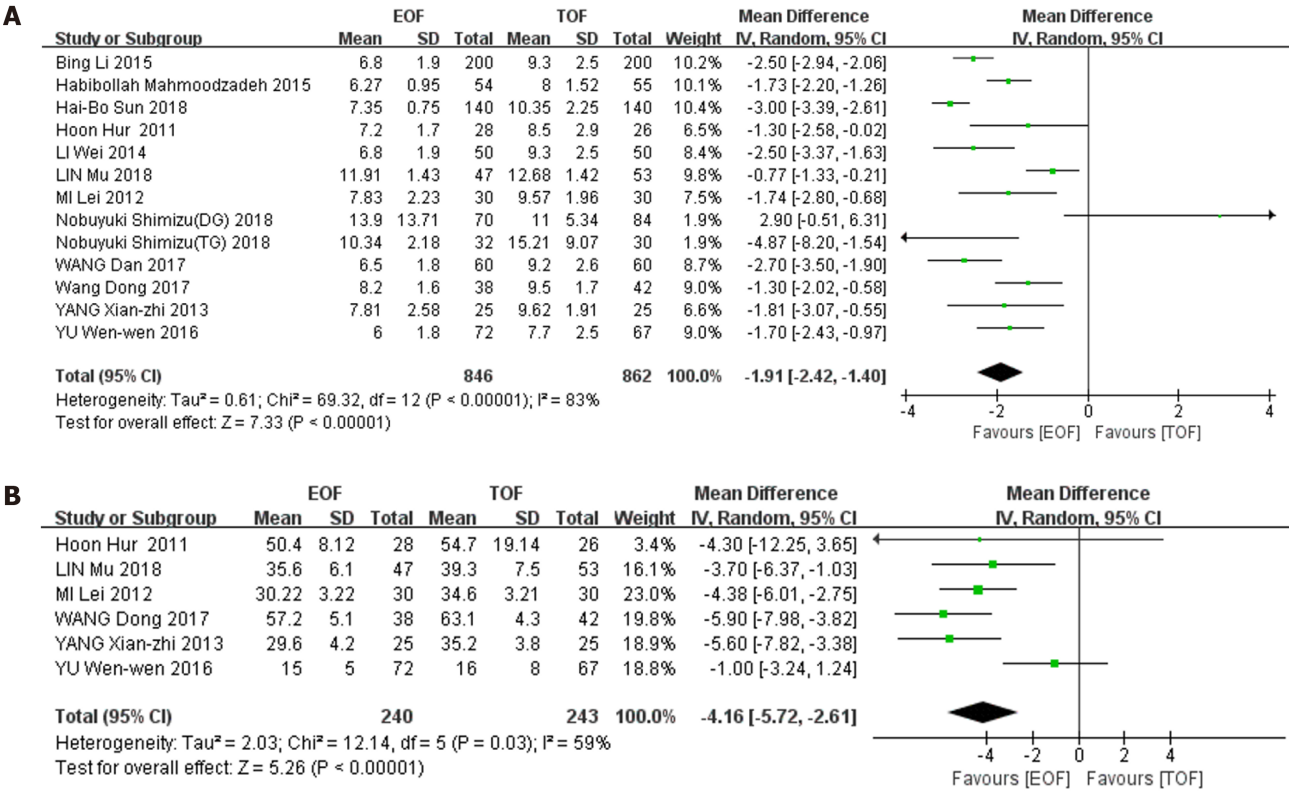


Figure 5 Forest plot evaluating length of stay (A) and cost of hospitalization (B). EOF: Early oral feeding; TOF: Traditional oral feeding.

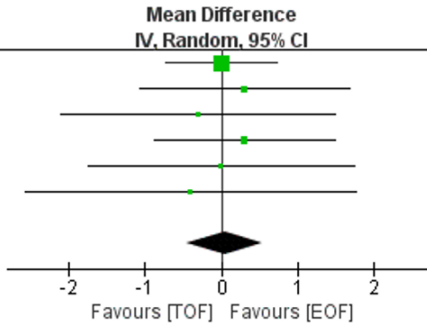
surgery. We measured CD4 cell count and CD4/CD8 cell ratio, showing that both indicators were significantly increased, indicating that EOF seems to enhance the immune system.

Meta-analyses of RCTs represent the best possible option to summarize the beneficial and harmful effects of interventions[37]. However, RCTs can have high

A

Study or Subgroup	EOF Mean	EOF SD	EOF Total	TOF Mean	TOF SD	TOF Total	Weight	Mean Difference IV, Random, 95% CI
Bing Li 2015	43.5	3.8	200	43.5	3.6	200	47.6%	0.00 [-0.73, 0.73]
LI Wei 2014	43.2	3.7	50	42.9	3.3	50	13.3%	0.30 [-1.07, 1.67]
MI Lei 2012	42.2	3.5	30	42.5	3.6	30	7.8%	-0.30 [-2.10, 1.50]
WANG Dan 2017	43.4	3.5	60	43.1	3.1	60	17.9%	0.30 [-0.88, 1.48]
WANG Dong 2017	43	4	38	43	4	42	8.1%	0.00 [-1.76, 1.76]
YANG Xian-zhi 2013	43.2	3.7	25	43.6	4.1	25	5.3%	-0.40 [-2.56, 1.76]
Total (95% CI)			**403**			**407**	**100.0%**	**0.05 [-0.45, 0.55]**

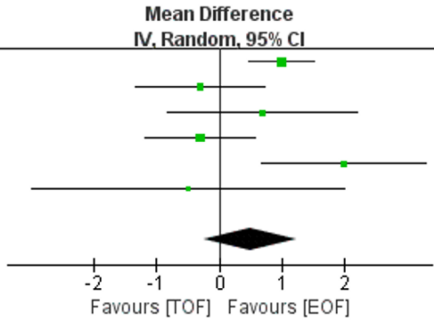
Heterogeneity: Tau² = 0.00; Chi² = 0.63, df = 5 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.19 (P = 0.85)



B

Study or Subgroup	EOF Mean	EOF SD	EOF Total	TOF Mean	TOF SD	TOF Total	Weight	Mean Difference IV, Random, 95% CI
Bing Li 2015	31.5	2.8	200	30.5	2.5	200	25.3%	1.00 [0.48, 1.52]
LI Wei 2014	30.4	2.7	50	30.7	2.6	50	18.6%	-0.30 [-1.34, 0.74]
MI Lei 2012	36.4	3.1	30	35.7	2.9	30	13.2%	0.70 [-0.82, 2.22]
WANG Dan 2017	30.6	2.5	60	30.9	2.4	60	20.7%	-0.30 [-1.18, 0.58]
WANG Dong 2017	36	3	38	34	3	42	15.3%	2.00 [0.68, 3.32]
YANG Xian-zhi 2013	35.3	5.3	25	35.8	3.6	25	6.8%	-0.50 [-3.01, 2.01]
Total (95% CI)			**403**			**407**	**100.0%**	**0.50 [-0.25, 1.25]**

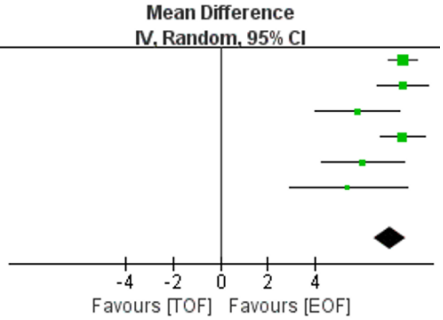
Heterogeneity: Tau² = 0.51; Chi² = 14.29, df = 5 (P = 0.01); I² = 65%
Test for overall effect: Z = 1.30 (P = 0.19)



C

Study or Subgroup	EOF Mean	EOF SD	EOF Total	TOF Mean	TOF SD	TOF Total	Weight	Mean Difference IV, Random, 95% CI
Bing Li 2015	42.1	3.6	200	34.4	2.4	200	29.7%	7.70 [7.10, 8.30]
LI Wei 2014	42.2	3	50	34.5	2.5	50	19.6%	7.70 [6.62, 8.78]
MI Lei 2012	40.6	3.9	30	34.8	3.1	30	10.7%	5.80 [4.02, 7.58]
WANG Dan 2017	42.4	2.8	60	34.7	2.3	60	22.8%	7.70 [6.78, 8.62]
WANG Dong 2017	42	4	38	36	4	42	10.9%	6.00 [4.24, 7.76]
YANG Xian-zhi 2013	40.6	5.1	25	35.2	3.8	25	6.3%	5.40 [2.91, 7.89]
Total (95% CI)			**403**			**407**	**100.0%**	**7.17 [6.48, 7.85]**

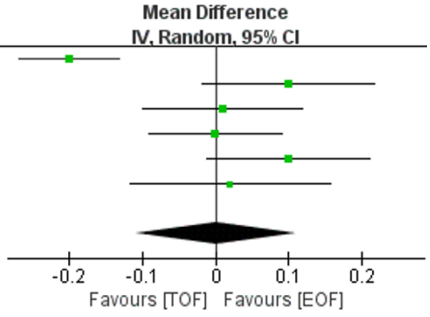
Heterogeneity: Tau² = 0.32; Chi² = 9.66, df = 5 (P = 0.09); I² = 48%
Test for overall effect: Z = 20.52 (P < 0.00001)



D

Study or Subgroup	EOF Mean	EOF SD	EOF Total	TOF Mean	TOF SD	TOF Total	Weight	Mean Difference IV, Random, 95% CI
Bing Li 2015	1.6	0.4	200	1.8	0.3	200	18.4%	-0.20 [-0.27, -0.13]
LI Wei 2014	1.8	0.3	50	1.7	0.3	50	16.1%	0.10 [-0.02, 0.22]
MI Lei 2012	1.76	0.21	30	1.75	0.22	30	16.6%	0.01 [-0.10, 0.12]
WANG Dan 2017	1.9	0.3	60	1.9	0.2	60	17.4%	0.00 [-0.09, 0.09]
WANG Dong 2017	1.8	0.2	38	1.7	0.3	42	16.5%	0.10 [-0.01, 0.21]
YANG Xian-zhi 2013	1.68	0.22	25	1.66	0.27	25	15.1%	0.02 [-0.12, 0.16]
Total (95% CI)			**403**			**407**	**100.0%**	**0.00 [-0.11, 0.11]**

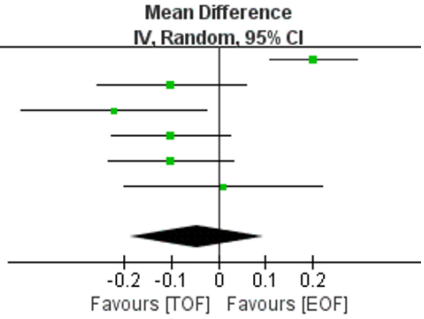
Heterogeneity: Tau² = 0.02; Chi² = 34.35, df = 5 (P < 0.00001); I² = 85%
Test for overall effect: Z = 0.01 (P = 0.99)



E

Study or Subgroup	EOF Mean	EOF SD	EOF Total	TOF Mean	TOF SD	TOF Total	Weight	Mean Difference IV, Random, 95% CI
Bing Li 2015	1.6	0.6	200	1.4	0.3	200	19.1%	0.20 [0.11, 0.29]
LI Wei 2014	1.3	0.4	50	1.4	0.4	50	16.5%	-0.10 [-0.26, 0.06]
MI Lei 2012	1.4	0.31	30	1.62	0.45	30	14.8%	-0.22 [-0.42, -0.02]
WANG Dan 2017	1.5	0.4	60	1.6	0.3	60	17.8%	-0.10 [-0.23, 0.03]
WANG Dong 2017	1.4	0.3	38	1.5	0.3	42	17.6%	-0.10 [-0.23, 0.03]
YANG Xian-zhi 2013	1.52	0.33	25	1.51	0.42	25	14.2%	0.01 [-0.20, 0.22]
Total (95% CI)			**403**			**407**	**100.0%**	**-0.04 [-0.18, 0.09]**

Heterogeneity: Tau² = 0.02; Chi² = 28.80, df = 5 (P < 0.0001); I² = 83%
Test for overall effect: Z = 0.63 (P = 0.53)



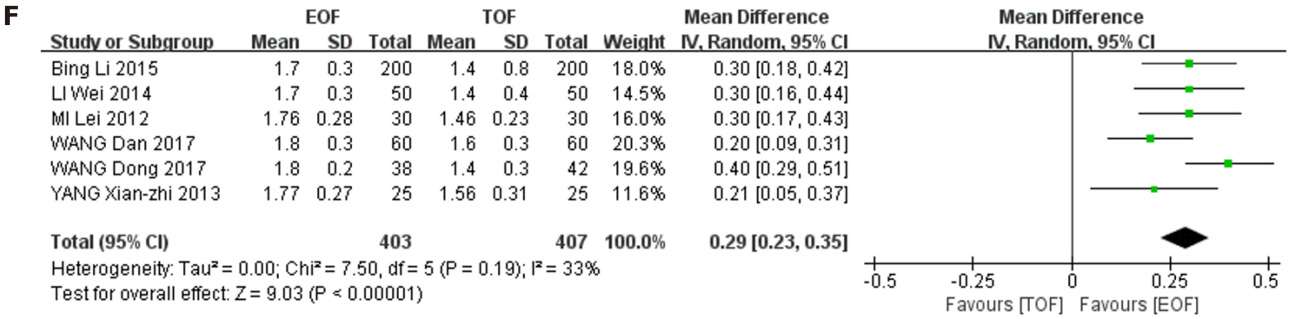


Figure 6 Forest plot evaluating CD4 cell count and CD4/CD8 cell ratio. A: CD4 preoperative day 1; B: CD4 POD1; C: CD4 POD7; D: CD4/CD8 preoperative day 1; E: CD4/CD8 POD1; F: CD4/CD8 POD7. EOF: Early oral feeding; POD: Postoperative day; TOF: Traditional oral feeding.

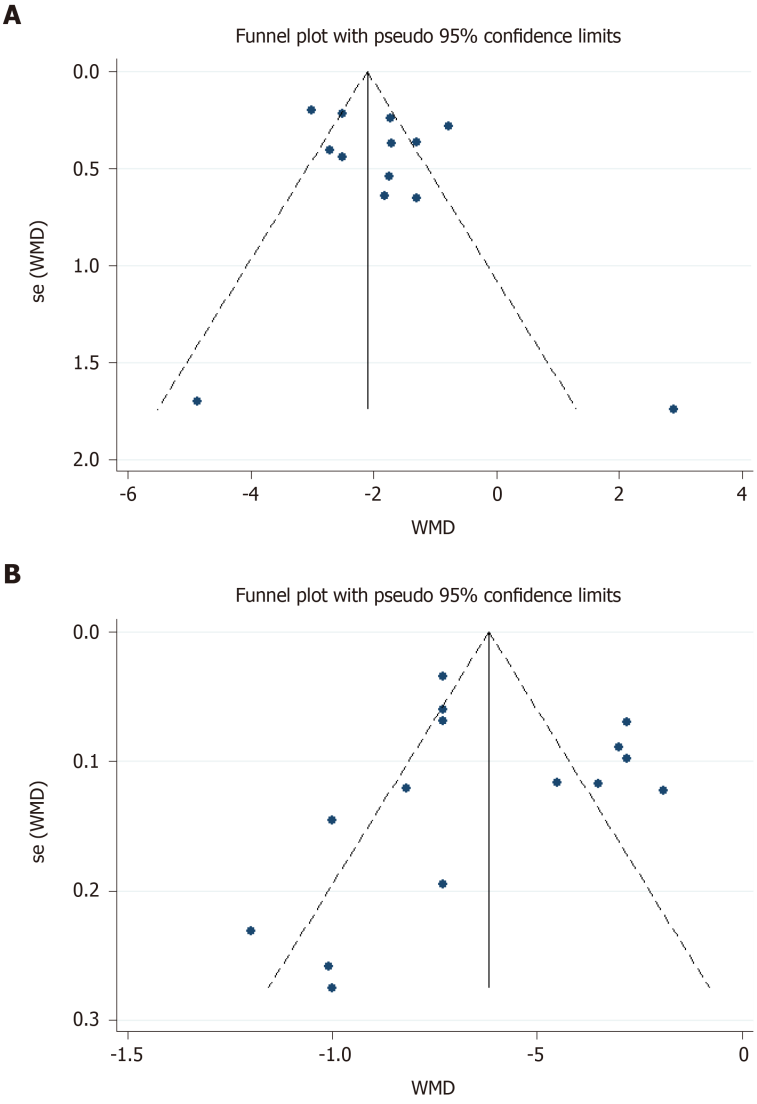


Figure 7 Funnel plot of length of hospital stay (A) and postoperative exhaust time (B) in all included studies. Egger's test: LOS, $P > 0.290$; exhaust time, $P > 0.725$.

levels of bias related to weak randomization methods, lack of blinding, and incomplete outcome data. There is no doubt that the current research had some limitations. First, although the total sample size of the study was > 2000, some of the included RCTs were smaller in size. Second, there was considerable heterogeneity in the included studies. No remarkable heterogeneity was found in the incidence of complications (including anastomotic leakage and pneumonia). However, there was significant heterogeneity in postoperative exhaust time, hospitalization costs, length of stay, and

CD4 cell count and CD4/CD8 cell ratio. This significant heterogeneity may be attributed to clinical heterogeneity, including the technical status of each institution, the inclusion of standard surgical approaches, inconsistent outcome assessments, and different EOF procedures. Third, as this study included fewer studies on esophageal cancer, we did not conduct group assessments for esophageal and gastric cancer, which increased the bias to a certain extent. However, we included most relevant RCTs and obtained positive results, which have contributed to the advancement of the application of EOF in upper gastrointestinal surgery.

CONCLUSION

The present updated meta-analysis and systematic review demonstrate that application of EOF after esophageal and gastric cancer surgery is safe and effective. EOF can significantly reduce the incidence of pneumonia, reduce hospitalization time and hospitalization costs, and significantly improve the postoperative immune function of patients. However, due to the heterogeneity of the included trials, further high-quality, large-sample and multicenter RCTs with long-term follow-up are needed. Finally, we believe that with the advancement of medical technology, EOF will be commonly used in upper gastrointestinal surgery.

ARTICLE HIGHLIGHTS

Research background

Early oral feeding (EOF) has emerged as a safe and effective postoperative strategy for improving clinical outcomes in patients with lower gastrointestinal tumor. However, controversies exist with regard to EOF practice in postoperative patients with upper gastrointestinal tumor.

Research motivation

The purpose of this systematic and meta-analysis was to evaluate the role and importance of EOF in postoperative patients with upper gastrointestinal tumor.

Research objectives

By comparing the safety and efficacy of EOF and TOF, it provided a valuable evidence and safe choice for early rehabilitation of patients in the future.

Research methods

PubMed, EMBASE, Web of Science, Cochrane Library, Chinese National Knowledge Infrastructure, Wanfang, and VIP databases were searched up to December 2020 for all available randomized controlled trials (RCTs) comparing EOF and traditional oral feeding (TOF) of postoperative patients with upper gastrointestinal tumors. Fifteen RCTs, with a total of 2100 participants, were analyzed in this study, of whom 1042 underwent EOF and 1058 TOF protocols.

Research results

In the meta-analysis of postoperative pneumonia and anastomotic leak, there was no significant heterogeneity (I^2 = 0%); therefore, a fixed-effect model was applied. A significantly lower risk of pneumonia was presented (RR = 0.63, 95%CI: 0.44–0.89, P = 0.01). In the meta-analysis of postoperative exhaust time, there was significant heterogeneity among the studies (I^2 = 87%). But, after eliminating the studies that did not directly provide mean ± SD and those with high risk bias, the remaining data after combined analysis showed no significant heterogeneity (I^2 = 31%), and the results suggested that the EOF group could significantly shorten the exhaust time (WMD = 0.71, 95%CI: 0.80-0.63; P < 0.01). No significant heterogeneity was present in CD4 cell count and CD4/CD8 cell ratio results on POD7: CD4 count (I^2 = 48%,), CD4/CD8 (I^2 = 33%); accordingly, a fixed-effect model was applied. On POD7, CD4 count and CD4/CD8 in the EOF group were significantly higher than those in the TOF group: CD4 count (WMD = 7.17, 95%CI: 6.48–7.85; P < 0.01), CD4/CD8 ratio (WMD = 0.29, 95%CI: 0.23–0.35; P < 0.01).

Research conclusions

Our unit has been committed to early postoperative rehabilitation for more than 10 years. According to our experience, this meta-analysis is consistent with the clinical situation; therefore, we suggest that EOF can be used for patients with upper gastrointestinal tumors after surgery.

Research perspectives

Early recovery after surgery has always been an important point for patients with gastrointestinal tumors. The present updated meta-analysis and systematic review demonstrate that application of EOF after esophageal and gastric cancer surgery is safe and effective. We consider that choosing appropriate patients and precise surgical operations will help the implementation of EOF. Additionally, we should conduct further high-quality, large-sample and multicenter RCTs with long-term follow-up.

ACKNOWLEDGEMENTS

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