

Home enteral nutrition after esophagectomy for esophageal cancer

A systematic review and meta-analysis

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Abstract

Background: Not only has the placement rate of enteral feeding tubes during operations for esophageal cancer increased, but also has number of patients who choose to continue enteral feeding at home instead of removing the feeding tube at discharge. The impacts of home enteral nutrition (HEN) after esophagectomy in esophageal cancer patients are analyzed.

Methods: A systematic review was conducted in accordance with PRISMA and Cochrane guidelines. English and Chinese databases, including PubMed, Embase, Web of Science, The Cochrane Library, Scopus, CBM, CNKI, and Wan Fang were searched from inception to December 7, 2019. Randomized controlled trials evaluating the short-term outcomes of HEN following esophagectomy in cancer patients were included. The risk of bias of the included studies was appraised according to the Cochrane risk of bias tool. The summary of relative risk/weighted mean difference (WMD) estimates and corresponding 95% confidence interval (95% CI) were calculated using fixed- and random-effects models.

Results: Nine randomized controlled trials involving 757 patients were included in the meta-analysis. Compared with oral diet, HEN was associated with significantly increased body weight (WMD 3 kg, 95% CI 2.36–3.63, $P < .001$), body mass index (WMD 0.97 kg/m², 95% CI 0.74–1.21, $P < .001$), albumin (WMD 3.43 g/L, 95% CI 2.35–4.52, $P < .001$), hemoglobin (WMD 7.23 g/L, 95% CI 5.87–8.59, $P < .001$), and total protein (WMD 5.13 g/L, 95% CI 3.7–6.56, $P < .001$). No significant differences were observed in prealbumin and gastrointestinal adverse reactions. Physical (WMD 8.82, 95% CI 6.69–10.95, $P < .001$) and role function (WMD 12.23, 95% CI 2.72–21.74, $P = .01$) were also significantly better in the HEN group. The nausea/vomiting (WMD –5.43, 95% CI –8.29 to –2.57, $P = .002$) and fatigue symptoms (WMD –11.76, 95% CI –16.21 to –7.32, $P < .001$) were significantly reduced. Appetite loss (WMD –8.48, 95% CI –14.27 to –4.88, $P = .001$), diarrhea (WMD –3.9, 95% CI –7.37 to –0.43, $P = .03$), and sleep disturbance (WMD –7.64, 95% CI –12.79 to –2.5, $P = .004$) in the HEN group were also significantly less than the control group.

Conclusions: HEN improved nutrition status, physical and role function, and reduced nausea/vomiting, fatigue, appetite loss, diarrhea, and sleep disturbance compared with an oral diet in esophageal cancer patients postsurgery. HEN did not increase adverse reactions.

Abbreviations: 95% CI = 95% confidence interval, Alb = albumin, BMI = body mass index, BW = body weight, GRADE = Grading of Recommendations Assessment, Development and Evaluation, Hb = hemoglobin, HEN = home enteral nutrition, MD = mean differences, PA = pre-albumin, QOL = quality of life, RCTs = randomized controlled trials, RR = risk ratios, RR/WMD = relative risk/weighted mean difference, TP = total protein.

Keywords: esophageal cancer, esophagectomy, home enteral nutrition, meta-analysis

Editor: Neil Merrett.

Funding: This work is supported by Guangdong Esophageal Cancer Institute Science and Technology Program (No.M201917).

Authorship: QH designed the study; LL and Y-cW searched and selected the studies and drafted the manuscript; Q-wL, J-dZ, J-bL, and X-dW extracted and analyzed the data; H-yQ. revised the manuscript.

Conflict of interest: The authors report no conflicts of interest.

This work is supported by Guangdong Esophageal Cancer Institute Science and Technology Program (No.M201917).

LL and Y-cW contributed equally to this work.

The authors report no conflicts of interest.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Liu L, Wang Yc, Liu Qw, Zhong Jd, Li Jb, Wu Xd, Qin Hy. Home enteral nutrition after esophagectomy for esophageal cancer: A systematic review and meta-analysis. *Medicine* 2020;99:36(e21988).

Received: 27 March 2020 / Received in final form: 20 July 2020 / Accepted: 23 July 2020

<http://dx.doi.org/10.1097/MD.0000000000021988>

1. Introduction

Esophageal cancer is a highly malignant gastrointestinal tumor. Esophageal cancer ranks in seventh and sixth places of all malignant tumors in morbidity and mortality, respectively, and in 2018, esophageal cancer was responsible for 572,000 new cancer cases and 508,000 deaths worldwide.^[1] Although esophageal resection or esophagectomy is the primary treatment for patients with locoregional esophageal cancer,^[2] it still has high morbidity and mortality rates.^[3] Due to the complicated process of esophagectomy, nutritional status has a serious impact on the patient's overall decline.^[4]

The most common symptom of esophageal cancer is progressive dysphagia, which affects the patient's ability to eat, that in turn results in preoperative malnutrition.^[5] Postoperative stress malnutrition caused by postoperative stress also leads to high catabolic metabolism in patients. And, when combined with impaired digestion and absorption caused by digestive tract reconstruction, patient malnutrition is further aggravated.^[6] Postoperative malnutrition, such as weight loss, and weakness are present in >50% of patients who had an esophagectomy.^[7] Heneghan et al^[8] reported that the proportions of esophageal cancer patients with clinically severe weight loss ($\geq 10\%$) at 1, 6, and 18 to 24 months postoperatively were 15.6%, 31.1%, and 48.9%, respectively. Malnutrition can prolong a patient's postoperative recovery time, reduce their quality of life (QOL),^[9,10] and lower their tolerance to postoperative radiotherapy and chemotherapy, which in turn, may affect their long-term prognosis.^[11] Furthermore, patients with clinically severe weight loss after esophagectomy show an increase in overall all-cause mortality.^[12]

It is very important in esophageal patients to ameliorate their weight loss after surgery, to improve their short-term prognosis, and to promote the postoperative recovery. The benefits of enteral nutrition during hospitalization are well established^[13]; however, the effects of continuing enteral nutrition after discharge have not been intensively investigated. Therefore, the aim of this study is to determine the results of home enteral nutrition (HEN) after esophagectomy. HEN is defined as enteral tube feeding used outside the hospital.^[14]

In recent years, the rate of enteral feeding tube placement during operations for esophageal cancer has increased,^[15] and more patients are choosing to continue enteral feeding at home instead of removing the feeding tube at discharge.^[16] Although there have been some randomized controlled trials (RCTs) on HEN in patients with esophageal cancer, the sample size of these studies is small, and the conclusions on the effect of HEN for improving nutritional status and QOL are inconsistent.^[11,17–20] In addition, we were also concerned about the safety of HEN, including the incidence of gastrointestinal adverse reactions such as diarrhea and vomiting, but again, the results of existing studies are inconsistent. There has been no systematic evaluation or meta-analysis of HEN in postoperative patients with esophageal cancer. In view of these considerations, we performed a systematic review and meta-analysis of RCTs comparing HEN patients with a control group (oral diet) after esophagectomy to evaluate evidence for continuing enteral nutritional care after the discharge of postoperative patients with esophageal cancer.

2. Methods

This systematic review and meta-analysis was performed and reported according to the Preferred Reporting Items for

Systematic Review and Meta-Analyses (PRISMA) statement and Cochrane guidelines. It is not necessary to get the ethical approval and patient consent because this study is a systematic review and meta-analysis.

2.1. Search strategy

Eight medical databases were searched: PubMed, Embase, Web of Science, The Cochrane Library, Scopus, CBM, CNKI, and Wan Fang. These databases were searched from inception to December 7, 2019, and the language of publication was limited to English and Chinese. The search terms include “esophageal neoplasms,” “enteral nutrition,” “esophagectomy,” and “home.” After study screening and selection, the references of the identified studies were manually searched to locate the probable related gray and bibliographic articles. The full search strategies and the number of search results for each database are presented in the Appendix, <http://links.lww.com/MD/E779>.

2.2. Study screening and selection

Two reviewers (LL, WYC) independently assessed the eligibility of studies according to the prespecified inclusion and exclusion criteria. The inclusion criteria included: RCTs assessing whether HEN following esophagectomy for cancer influenced any of the following clinical endpoints: anthropometric parameters including body weight (BW) and body mass index (BMI), nutritional hematological parameters including body serum albumin (Alb), hemoglobin (Hb), total protein (TP), and pre-albumin (PA), nutritional assessment, gastrointestinal adverse reaction, and QOL. The selection process began with a review of titles and abstracts, followed by reading the full text to determine if the eligibility criteria were met. Trials that did not meet the inclusion criteria were excluded. Disagreements between the 2 reviewers were solved by discussion or an appeal to the third author (QHY).

2.3. Data extraction

Study characteristics and continuous or dichotomous data for the special outcomes of each eligible article were extracted by 2 independent reviewers (LL, WYC) using a predesigned table. The table included the following items: first author, year of publication, country, sample size, participant demographics (cancer stage, operation approach, age, gender), the approach and duration of the intervention group and control group, and the results with which predetermined (anthropometric parameters, hematological parameters, nutritional assessment, gastrointestinal adverse reaction, and QOL). After the independent data extraction, the 2 reviewers addressed the incomplete study data (eg, they emailed the study investigators to obtain additional information). Next, they recorded the data in an Excel spreadsheet and solved their disagreements by discussion or an appeal to the third author.

2.4. Quality assessment

Two reviewers (LL, WYC) independently assessed the quality of the selected studies using the Cochrane risk-of-bias tool, which included: randomization sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other biases. Disagreements were solved by discussion or appeal to the third author.

The quality of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system,^[21] which takes into account: statistical heterogeneity, publication bias, risk of bias, indirectness, and statistical imprecision. For interpretive scoring of the heterogeneity and downgrading of the evidence, the following system was used: $P > .05$, low heterogeneity; $.01 < P < .05$, moderate heterogeneity, downgrade evidence by 1 level; $P > .01$, high heterogeneity, downgrade evidence by 2 levels. If visual inspection of the forest plots indicated a consistent direction in study-level effect estimates, an exception was made and the quality of evidence was downgraded by 1 level even if the statistical heterogeneity was high. Our overall confidence in the reliability of the pooled data was rated as being "very low," "low," "moderate," or "high."

2.5. Statistical analysis

Statistical analyses were performed in Cochrane Collaboration's Revman Manager 5.3 software and the sensitivity analysis; Egger test was carried out using STATA 15.1. Heterogeneity was assessed using the Q test and statistical value I^2 . If $I^2 \leq 50\%$, the studies were considered to have appropriate homogeneity, and a fixed-effects model with the Mantel-Haenszel method was used for the secondary analysis. Otherwise, the following techniques were used to analyze the data: (1) a random-effects model with the DerSimonian and Laird method was adopted if there were limited included studies, or (2) a sensitivity analysis performed by excluding the trials that potentially biased the results. The intervention effect was expressed with risk ratios (RR) for dichotomous outcomes and mean differences (MD) for continuous outcome measures, with their 95% confidence intervals (95% CI). Interpretation of the intervention effects was indicated by both the 95% CI and the 2-sided P value. A 95% CI from continuous data that did not cross 0, 95% CI from dichotomous data that did not cross 1, and a P value < 0.05 were considered statistically significant. Publication biases were assessed by using the Begg and Egger tests, and a P value $> .05$ showed no publication bias was included in the study.

3. Results

3.1. Eligible studies

The literature search obtained 741 records. A total of 508 titles and abstracts were screened after removal of duplicates, and 493 studies were excluded after screening. Fifteen potential full-text articles were identified for further evaluation, and 9 studies were excluded. Finally, 9 RCTs^[17–19,22–27] were included in the meta-analysis (Fig. 1).

3.2. Study characteristics and quality assessment

This meta-analysis included 9 RCTs published between 2013 and 2019. Briefly, the studies included 757 participants (HEN vs control: 376 vs 381); the sample size of each study ranged from 25 to 75; patients' pathological stage was stage I to III; the patients were aged between 53 and 67.4; there were more men than women enrolled in the studies; and the intervention time ranged from 1 to 4 months. Each study reported a comparable baseline between 2 groups, in terms of age, sex, cancer stage, type of surgery, race, and nutritional status. In all of the included studies, the intervention group had a standard enteral nutrition

formula via jejunostomy tube in addition to an oral diet, whereas the control group only had a normal oral diet. In the included studies, the duration of HEN was 1~4 months, and the outcome measurement time was generally within 3 months. Therefore, this study only pooled the short-term efficacy of HEN patients (1~3 months). The characteristics of the included studies in this study are summarized in Table 1.

An overview of the risk of bias assessment following the Cochrane Library Handbook is presented in Figure 2. The risk of bias assessment was judged for 6 domains of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other sources of bias. A potentially high risk of selection bias was present in 2 studies^[18,28] because HEN was minimally invasive and the control group underwent an open operation. However, there was no significant difference in baseline (at discharge) between the 2 groups; they were included in the analysis. In addition, on the random sequence generation item, approximately one-quarter of the trials did not provide the exact method, and the rest were identified to be of low risk. More than half of the trials did not provide exact information when assessing selection bias and detection bias. All the trials were thought to be at low risk of attrition and reporting bias and free of other bias. In summary, although there were medium biases among the studies, they did not affect the outcomes.

3.3. Meta-analysis

The pooled relative effects and quality of overall evidence supporting each outcome are shown in Table 2.

3.3.1. Changes in anthropometric measurements. Changes in patient's BW and BMI from discharge were reported in 4^[17,22,23,25] (n=340) and 4^[17,18,23,24,26] (n=437) RCTs, respectively (Fig. 3). The meta-analysis of data from these trials showed significant outcomes between-group differences in both BW and BMI, with higher values observed in the HEN group than in the control group (BW: WMD 3 kg, 95% CI 2.36–3.63, $P < .001$; BMI: WMD 0.97 kg/m², 95% CI 0.74–1.21, $P < .001$). The statistical heterogeneity across studies was low (BW: $I^2 = 31\%$, $P = .23$; BMI: $I^2 = 0\%$, $P = .94$).

3.3.2. Change of hematological parameters. The change of body serum albumin (Alb), hemoglobin (Hb), total protein (TP), and pre-albumin (PA) from discharge was reported in 6 (n=501),^[17,18,22,24,26,27] 3 (n=286),^[18,22,26] 5 (n=393),^[22,24–27] and 3 (n=247)^[24,25,27] RCTs, respectively (Fig. 4). The χ^2 test detected heterogeneity ($P < .1$ and $I^2 > 50\%$) for all hematological parameters except hemoglobin. Therefore, the fixed model was used in the analysis of hemoglobin, whereas the random-effects model was used in the other 3 parameters considering the included studies in this part were limited. HEN resulted in statistical significantly higher concentrations of Alb (WMD 3.43 g/L, 95% CI 2.35–4.52, $P < .001$), Hb (WMD 7.23 g/L, 95% CI 5.87–8.59, $P < .001$), and TP (WMD 5.13, 95% CI 3.7–6.56, $P < .001$). No significant differences were observed in PA (WMD 23.58 mg/L, 95% CI 0.05–47.11, $P = .05$).

3.3.3. Nutritional assessment. Accurate nutritional assessment is very important for HEN patients. Unfortunately, nutrition assessment in the RCTs was recorded using different tools and presented inconsistently. Two studies including 145 participants reported the rates of nutritional risk patients at the end of their HEN; a statistically significant advantage favoring HEN group

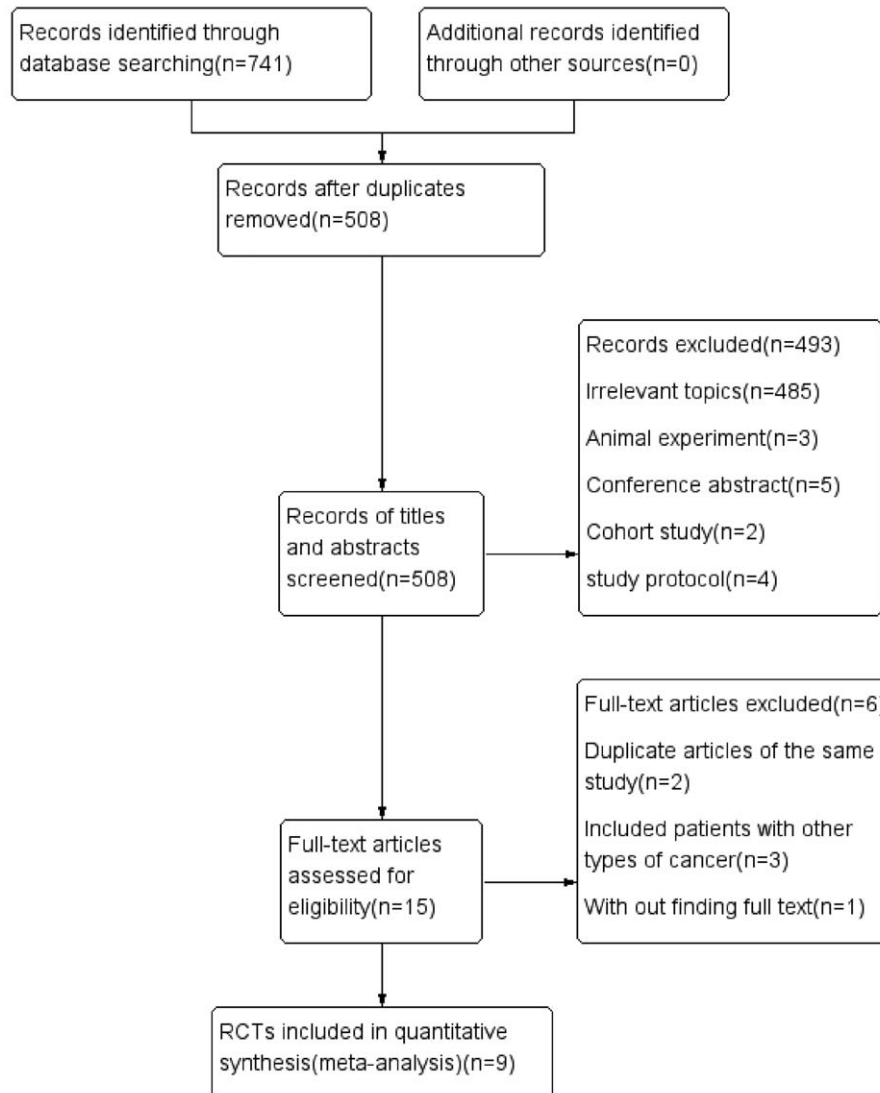


Figure 1. Flow chart of studies identified, included and excluded (PRISMA).

was observed (RR=0.64, 95% CI 0.48–0.84, $P=.001$; test for heterogeneity: $I^2=0\%$, $P=.71$) (Fig. 5A).^[19,24] The other 2 studies reported score value of PG-SGA; the PG-SGA scores of HEN group were statistically significant lower than control group (WMD -2.17 , 95% CI -2.6 to -1.74 , $P<.001$; test for heterogeneity: $I^2=0\%$, $P=.84$) (Fig. 5B).^[18,26]

3.3.4. Gastrointestinal adverse reaction. Five studies with 411 participants provided information about gastrointestinal adverse reaction rates.^[17,23–25,27] The random-effects meta-analysis showed no significant difference in gastrointestinal adverse reactions between the HEN and control groups (RR=1.13, 95% CI 0.55–2.32; $P=.74$; test for heterogeneity: $I^2=65\%$, $P=.02$) (Fig. 6A). A sensitivity analysis found that the study by Ji et al was the main source of heterogeneity,^[23] and the heterogeneity largely disappeared after excluding that study ($I^2=30\%$, $P=.23$). The fixed-effects meta-analysis of the remaining 4 studies showed that there were still no significant differences between the 2 groups (RR=1.53, 95% CI 0.95–2.49, $P=.08$) (Fig. 6B).

3.3.5. QOL. Four studies evaluated QOL using QLQ-C30 after HEN (1–3 months after discharge),^[17–19,23] the pooled effects of the 15 domains of the scale are summarized in Table 2, and the meta-analysis process (forest plots) is detailed in Supplementary Figure S1 & 2, <http://links.lww.com/MD/E779>. Global health status was not different between the HEN group and control group (WMD 0.32, 95% CI -13.6 to 14.23 , $P=.96$; test for heterogeneity: $P<.01$, $I^2=97\%$). In 5 functional domains (physical, role, cognition, emotional, and social function), physical and role function were significantly better in the HEN group than in the control group (physical: WMD 8.82/100 points, 95% CI 6.69–10.95, $P<.0001$ [test for heterogeneity: $P=0.8$, $I^2=0\%$]; role: WMD 12.23/100 points, 95% CI 2.72–21.74, $P=.01$ [test for heterogeneity: $P<.01$, $I^2=82\%$]). In the 3 symptom domains (fatigue, pain, and nausea/vomiting), nausea/vomiting and fatigue were significantly less frequent than in the control group (nausea/vomiting: WMD -5.43 /100 points, 95% CI -8.29 to 2.57 , $P=.002$ [test for heterogeneity: $P=.31$, $I^2=14\%$]; fatigue: WMD -11.76 /100 points, 95% CI -16.21 to -7.32 , $P<.001$ [test for

Table 1
Basic characteristics of included studies.

Study	Participants				Intervention and duration, mo*	Outcome Measure		
	Stage (I/II/III/IV) open/endscope	Sample size, n	Age (mean ± SD)	Sex (F/M)		Time*	Index	
Ji (2019) ^[23]	65/26/21	55	64.25 ± 6.51	17/38	JTF/ONS: SENF500–1000 mL/day + oral diet	1 mo	0, 1 mo	BW, QLQ-C30, GIAR
Liu et al (2019) ^[17]	43/69	57	65.72 ± 5.07	15/42	Oral diet	1 mo	0, 1 mo	BW, BMI, Alb, QLQ-C30, GIAR
Tong et al (2018) ^[24]	No metastatic, TNM comparable	26	62.04 ± 5.12	5/21	JTF/ONS 500 mL/day (SENF) + oral diet	1 mo	0, 1 mo	BW, BMI, Alb, QLQ-C30, GIAR
Zhang et al (2016) ^[25]	—	24	64.58 ± 5.87	10/14	Oral diet	1 mo	0, 1 mo	BW, TP, Alb, PA, NRS 2002
Wu et al (2018) ^[26]	32/53/0/0	44	62.7 ± 7.06	5/39	JTF: immune EN 600 mL/day + oral diet	1 mo	0, 1 mo	BW, TP, PA, GIAR
Zeng et al (2017) ^[19]	—	41	60.85 ± 8.08	3/38	Oral diet	1 mo	0, 1 mo	BW, TP, PA, GIAR
Wang et al 2019 ^[22]	—	41	53 ± 3.5	9/32	JTF: homogenate meals + oral diet	1 mo	0, 1 mo	BW, TP, PA, GIAR
Cao et al (2013) ^[27]	73/9	41	59 ± 4.2	12/29	oral diet	3 mo	0, 3 mo	BMI, Alb, Hb, PA, QLQ-C30, PG-SGA
Wu (2018) ^[18]	23/63/56/0	67	62 (45–80)	12/55	JTF: SENF500–1000 kcal/day + oral diet	3 mo	0, 3 mo	BMI, Alb, Hb, PA, QLQ-C30, PG-SGA
Wang et al 2019 ^[22]	67/75	75	61 (43–80)	8/67	Oral diet	1 mo	0, 1, 3, 6 mo	MNA, QOL-C30, GIAR
Wu (2018) ^[18]	1/28/31/0	30	61.7 ± 8.4	6/24	JTF: SENF + oral diet	1 mo	0, 1, 3, 6 mo	MNA, QOL-C30, GIAR
Cao et al (2013) ^[27]	—	30	59.3 ± 10.4	8/22	oral diet	4 mo	0, 2, 4 mo	BW, BMI, Alb, Hb, TP,
Zhang 2016	41/55/0/0	48	55 ± 7.25	9/39	JTF 1000 mL/day (SENF) + oral diet	4 mo	0, 2, 4 mo	BW, BMI, Alb, Hb, TP,
Zeng J 2017	0/96	48	53 ± 6.75	7/41	oral diet/ONS	3 mo	0, 3 mo	BW, Hb, Alb, TP, PG-SGA
Wu ZX 2016	8/22/20/0	25	62 (47–78)	5/25	JTF 500–1000 mL/day (SENF) + oral diet	3 mo	0, 3 mo	BW, Hb, Alb, TP, PG-SGA
Wu Z 2018	25/25	25	60 (49–74)	3/22	Oral diet	2 mo	0, 1, 3, 6 mo	TP, Alb, PA, GIAR
Wang 2019	1/36/42/0	40	65.8 (46–82)	14/26	JTF 1000 mL/day (SENF) + oral diet	2 mo	0, 1, 3, 6 mo	TP, Alb, PA, GIAR
Tong 2018	—	40	67.4 (53–80)	11/29	Oral diet	2 mo	0, 1, 3, 6 mo	TP, Alb, PA, GIAR

— = did not report, Alb = albumin, BMI = body mass index, BW = body weight, EC = esophageal cancer, F = female, GIAR = gastrointestinal adverse reactions, Hb = hemoglobin, JTF = jejunostomy tube feeding, M = male, MNA = mini-nutritional assessment, NRS2002 = nutrition risk screening, ONS = oral nutritional supplements, PA = preoperative albumin, PG-SGA = patient-generated subjective global assessment, QLQ-C30 = European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire- core 30, SD = standard deviation, SENF = standard enteral nutrition formula.
*The start of the intervention time and outcome measurement time was at discharge.

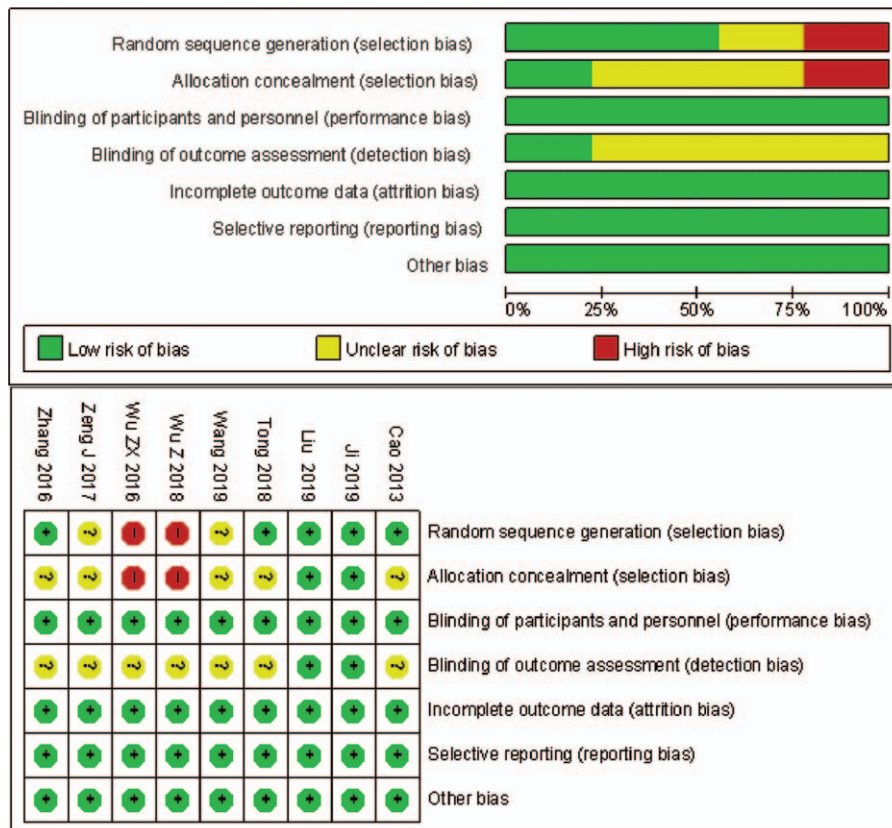


Figure 2. Risk of bias graph.

Table 2
Summary of results and overall quality of evidence.

Outcomes	Relative effect (95% CI)	P	Patients (studies)	Heterogeneity test (P, I ²)	Publication Bias		Quality of Evidence
					Begg	Egger	
BW change, kg	WMD 3.00 (2.36 to 3.3)	<.0001	340 (4)	.32, 31%	1	0.67	++++
BMI change, kg/m ²	WMD 0.97 (0.74 to 1.21)	<.0001	437 (5)	.94, 0%	0.81	0.89	+++*
Alb, g/L	WMD 3.43 (2.35 to 4.52)	<.0001	501 (6)	.001, 75%	0.71	0.43	+ + - - [†]
Hb, g/L	WMD 7.23 (5.87 to 8.59)	<.0001	286 (3)	.59, 0%	1	0.76	+++*
TP, g/L	WMD 5.13 (3.7 to 6.56)	<.0001	393 (5)	.05, 73%	0.46	0.51	+ + - - [†]
PA, mg/L	WMD 23.58 (0.05 to 47.11)	.05	247 (3)	<.01, 93%	1	0.31	+ + + - [†]
NA (score)	WMD -2.17 (-2.6 to 1.74)	<.0001	190 (2)	.84, 0%	1	—	+ + + -
NA (%)	RR 0.64 (0.48 to 0.84)	.001	145 (2)	.71, 0%	1	—	++++
GIAR (%)	RR 0.99 (0.5 to 1.95)	.74	299 (4)	.23, 30%	0.08	0.06	++++
Global QOL	WMD 0.32 (-13.6 to 14.23)	.96	362 (4)	<.01, 97%	0.31	0.23	+ + - - [‡]
Physical	WMD 8.82 (6.69 to 10.95)	<.0001	362 (4)	.8, 0%	1	0.62	+ + + -
Cognitive	WMD 1.88 (-1.03 to 4.79)	.20	302 (3)	.62, 0%	1	0.54	+ + + -
Emotional	WMD 1.45 (-4.21 to 7.11)	.62	362 (4)	<.01, 84%	0.73	0.42	+ + - - [‡]
Role	WMD 12.23 (2.72 to 21.74)	.01	360 (4)	<.01, 82%	0.31	0.25	+ + - - [‡]
Social	WMD 4.90 (-1.34 to 11.14)	.12	362 (4)	.01, 72%	0.73	0.66	+ + - - [‡]
Nausea/vomiting	WMD -5.43 (-8.29 to -2.57)	.0002	302 (3)	.31, 14%	1	0.23	+ + + -
Constipation	WMD 2.0 (-2.29 to 6.29)	.36	302 (3)	.90, 0%	1	0.90	+ + + -
Dyspnea	WMD -3.15 (-7.44 to 1.13)	.15	302 (3)	.67, 0%	1	0.50	+ + + -
Sleep disturbance	WMD -7.64 (-12.79 to -2.5)	.004	302 (3)	.73, 0%	1	0.66	+ + + -
Diarrhea	WMD -3.90 (-7.37 to -0.43)	.03	362 (4)	.15, 0%	0.31	0.58	+ + + -
Fatigue	WMD -11.76 (-16.21 to -7.32)	<.0001	362 (4)	.1, 52%	1	0.62	+ + + - [†]
Pain	WMD -4.47 (-12.62 to 3.69)	.28	362 (4)	<.01, 85%	1	0.62	+ + + - [†]
Financial impact	WMD 5.10 (-0.7 to 10.9)	.08	302 (3)	.39, 0%	1	0.99	+ + + -
Appetite loss	WMD -8.48 (-14.27 to -4.88)	.0001	302 (3)	.78, 0%	1	0.62	+ + + -

Alb=albumin, BMI=body mass index, BW=body weight, GIAR=gastrointestinal adverse reactions, Hb=hemoglobin, NA=nutritional assessment, PA=preoperative albumin.

* Downgraded by 1 level for high risk of bias.

† Downgraded by 1 level because, despite severe statistical heterogeneity, visual inspection of forest plots indicated a consistent direction in study-level treatment effects.

‡ Downgraded by 2 levels for severe statistical heterogeneity.

heterogeneity: $P=.1$, $I^2=52\%$). In 6 individual measurement domains (appetite loss, diarrhea, constipation, dyspnea, sleep disturbance, and financial impact), appetite loss, diarrhea, and sleep disturbance in the HEN group were significantly less than in the control group. The specific results were as follows: appetite loss

(WMD -8.48/100 points, 95% CI -14.27 to 4.88, $P=.001$; test for heterogeneity: $P=0.78$, $I^2=0\%$); diarrhea (WMD -3.9/100 points, 95% CI -7.37 to 0.43, $P=.03$; test for heterogeneity: $P=.15$, $I^2=0\%$); sleep disturbance (WMD 7.64/100 points, 95% CI -12.79 to 2.5, $P=.004$; test for heterogeneity: $P=.73$, $I^2=0\%$).

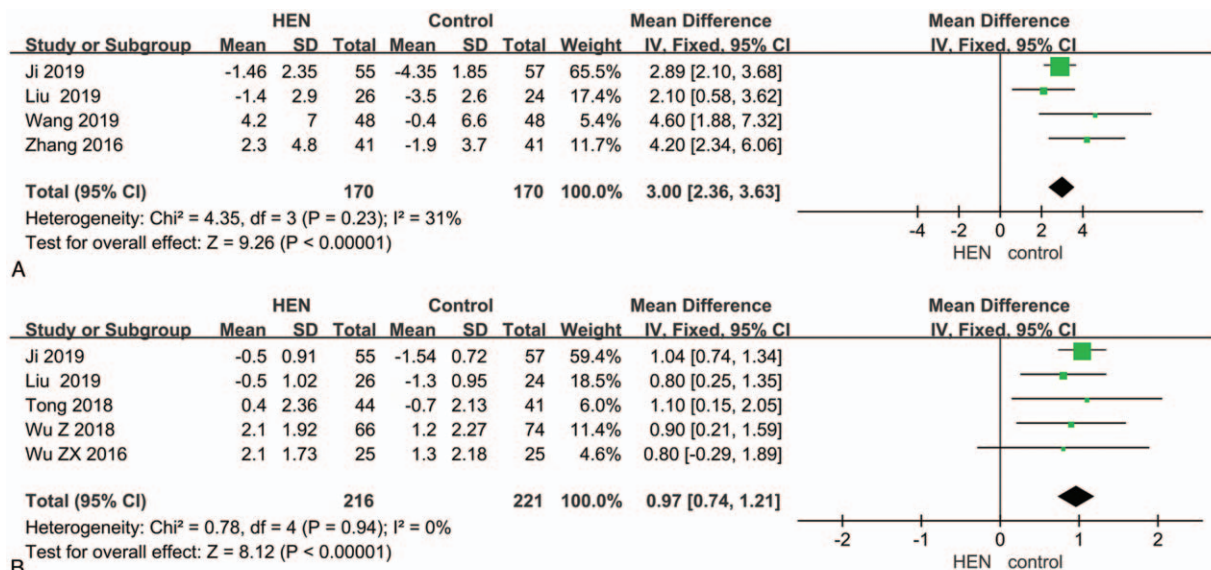


Figure 3. (A–B). Forest plots comparing the anthropometric measurements. (A) body weight, (B) body mass index.

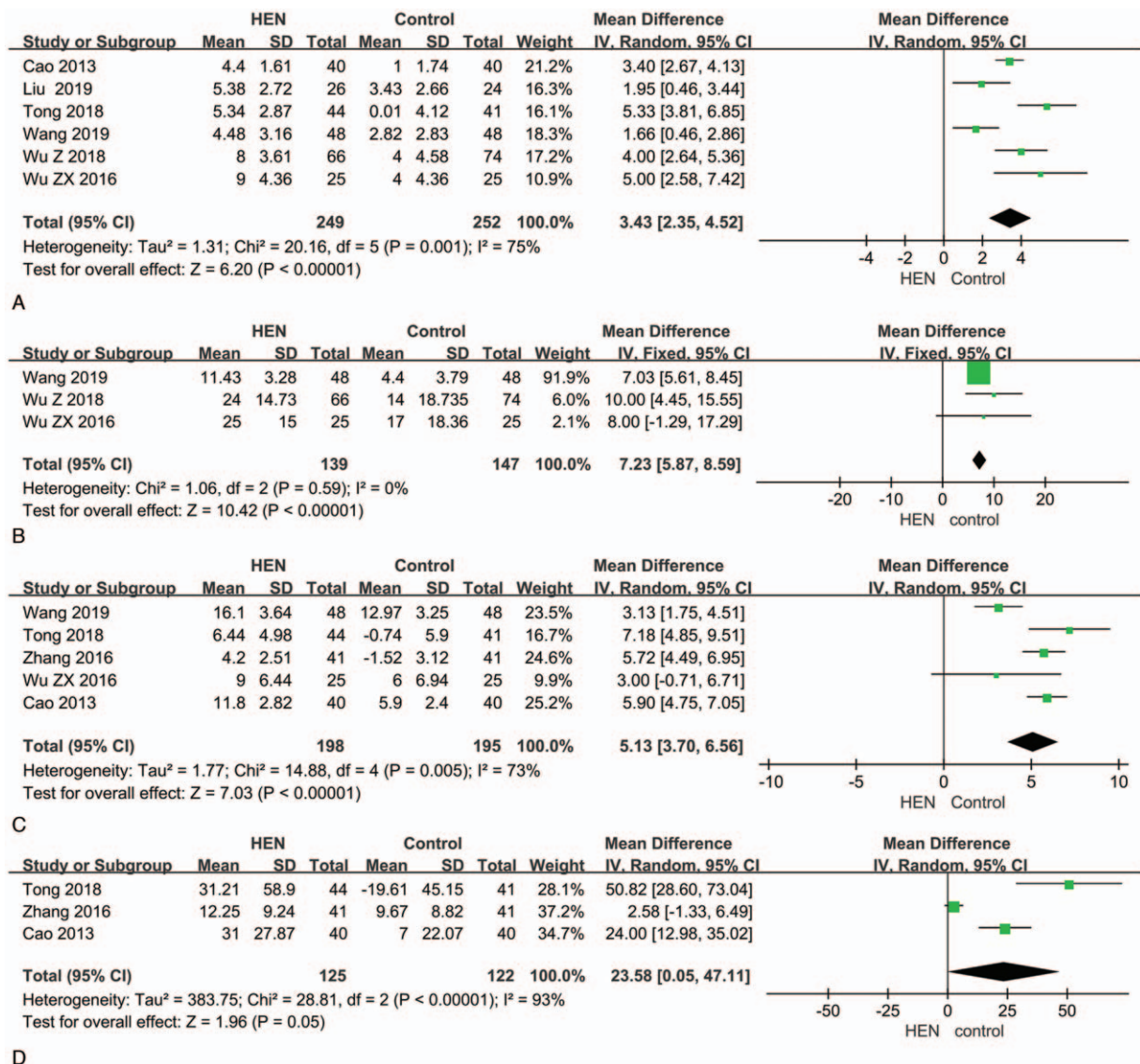


Figure 4. (A–D) Forest plots compare the change of hematological parameters from discharge. (A) serum albumin, (B) hemoglobin, (C) total protein, (D) pre-albumin.

3.4. Publication bias

Because there were <10 included studies, we used Begg and Egger tests to evaluate the publication bias for each pooled effect, and we did not observe any evidence of publication bias for the summary of estimates (Table 2).

4. Discussion

This systematic review, based on 9 RCTs containing 757 patients, was the first meta-analysis to evaluate the impact of HEN in esophageal cancer patients following an esophagectomy. Our results demonstrated that the HEN group had a more rapid improvement in nutritional status after discharge and a better QOL when compared with the control group. Although there was no difference in the incidence of gastrointestinal adverse reactions, the HEN group reported a better QOL than the control group.

Gomes et al reported that 72% of postoperative patients with esophageal cancer could not consume the required calories via

oral intake at discharge, and approximately 50% of these patients consumed <85% of the required calories.^[28] The European Society for Clinical Nutrition and Metabolism (ESPEN) suggests that if oral intake is <75% of daily requirements, nutritional status may deteriorate rapidly.^[29] Weight loss is a primary concern for esophagectomy patients, whereas nearly two-thirds of patients who undergo esophagectomy lose >10% of their preoperative BMI 6 months after discharge.^[7] HEN supplements patients' daily target requirements when they cannot be met by an oral diet. From the meta-analysis, we found that compared with an oral diet, HEN improved a patients' BW and BMI after discharge. In addition, HEN improved the nutrition-related hematological parameters that include Alb, TP, and Hb. HEN can significantly improve the nutritional status of patients.

Due to the reconstruction of the digestive tract, it can take between 3 and 9 months for patients with esophageal cancer to adapt to a new diet after surgery. Many patients have gastrointestinal adverse reactions (such as reflux, appetite loss,

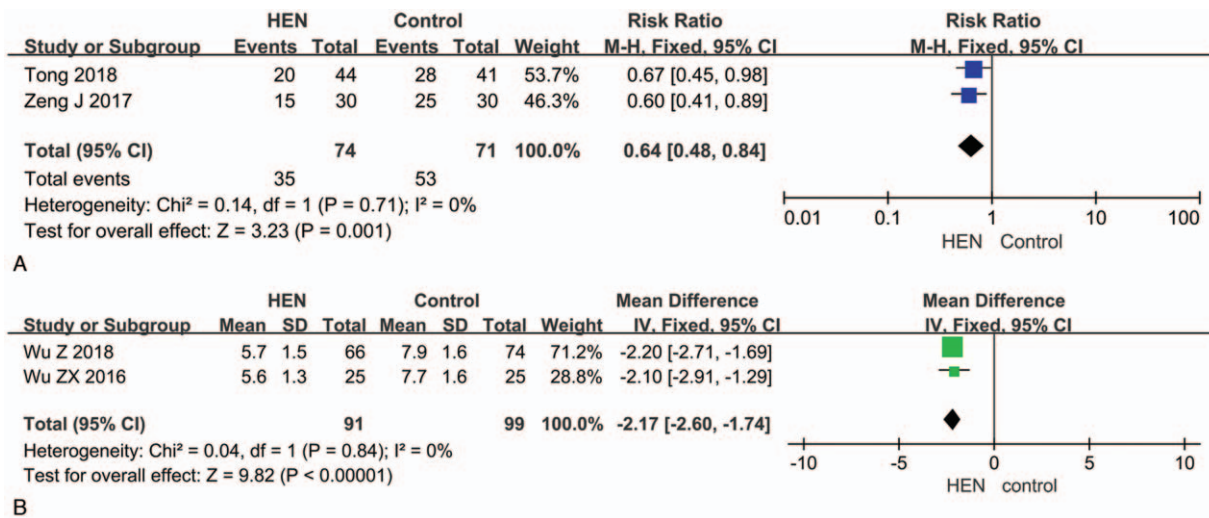


Figure 5. (A) Nutritional assessment. (B) Forest plot compared nutritional assessment.

diarrhea, and vomiting) within 1 year postsurgery.^[8,28,30] Because of these adverse reactions, some patients cannot undergo a treatment strategy that includes adjuvant therapy.^[31,32] It was important to see whether HEN increased gastrointestinal adverse reactions in patients. Bowrey et al observed no significant differences in gastrointestinal adverse reactions with upper gastrointestinal malignancy patients.^[33] Our meta-analysis also showed no adverse reactions.

Decreased physical and social functions, appetite loss, vomiting, fatigue, and sleep disturbance were common after esophagectomy.^[34–36] The EORTC QLQ-C30 is a widely used scale to assess postoperative functions and symptom.^[37] Recent

evidence shows that patients who receive a full cancer treatment are significantly associated with better physical and nutritional status,^[31,32] whereas more than half of patients with esophageal cancer did not complete their cancer treatment plan.^[2,38] Therefore, optimizing postoperative physical status and reducing symptoms are essential for esophageal cancer patients. Our results revealed that HEN improved physical status and reduced fatigue, appetite loss, diarrhea, sleep disturbance, and nausea/vomiting symptoms significantly. This contributed to patients completing a full cancer treatment and consequently increased the overall morbidity and mortality for esophageal cancer patients.

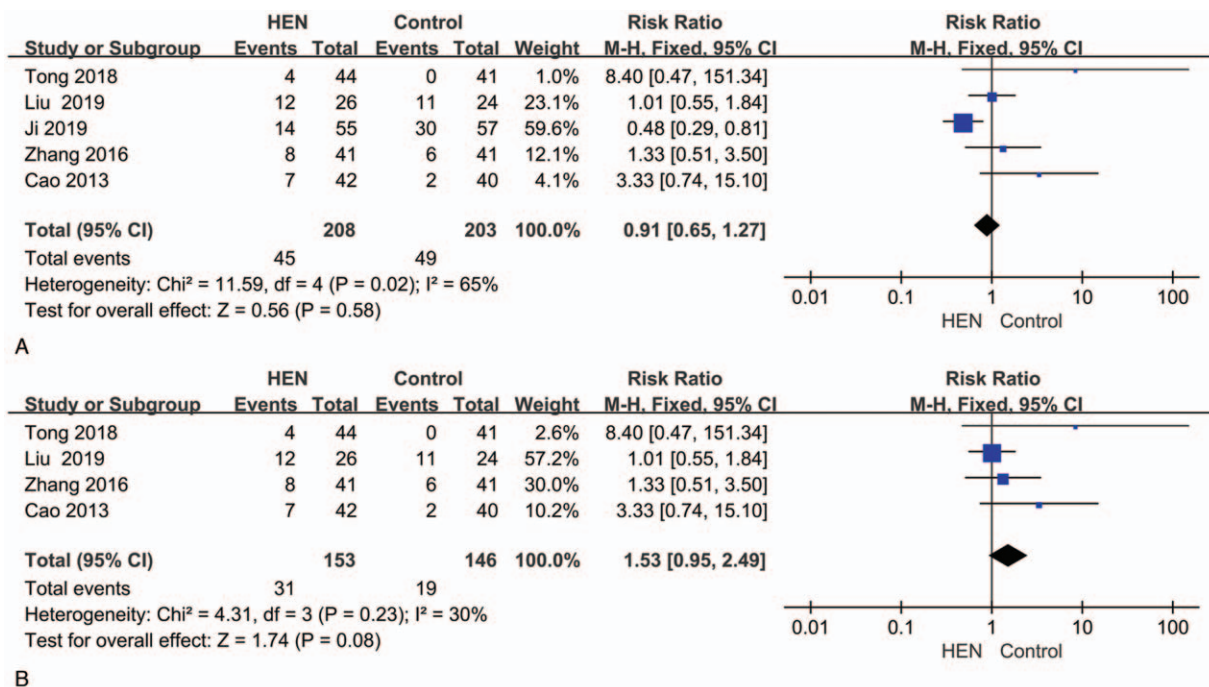


Figure 6. Forest plot comparing gastrointestinal adverse rates.

Although no long-term outcomes were analyzed in this study, the nutritional outcomes (weight, BMI, Alb, TP, Hb) improved by HEN have been demonstrated to be strongly related to reduced complications and overall survival rate following esophagectomy.^[34,39] Improving physical function and role function, and decreasing fatigue would help patients to complete the next treatment strategy,^[31,32] which, in turn, would help prolong mortality.

As the world's most populous country with a high incidence of esophageal cancer, China accounts for more than half of all new cases of and deaths from esophageal cancer worldwide.^[11] A limitation of this study is that HEN after an esophagectomy for cancer is mainly used in China, and the current evidence is therefore largely based on studies conducted in Chinese populations, so it is unknown how applicable these findings are to other regions. Trials with better methodological quality and that are conducted at multiple centers are needed to assess the effects of long-term HEN and will provide more data and evidence to reinforce our conclusions.

5. Conclusions

In conclusion, based on the meta-analysis of data from RCTs, HEN improved nutrition status and physical and role function, reduces fatigue, appetite loss, diarrhea, sleep disturbance, and nausea/vomiting compared with an oral diet in esophageal cancer patients after surgery, without increasing gastrointestinal adverse reactions in esophagectomy patients. The current findings favored the use of HEN in esophageal cancer patients after esophagectomy and post discharge.

Author contributions

H-yQ designed the study; LL and Y-cW searched and selected the studies and drafted the manuscript; Q-wL, J-dZ, J-bL, and X-dW extracted and analysed the data; H-yQ revised the manuscript.

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