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Evaluate the Effect of Home Enteral Nutrition Compared with Oral Diet after the Hospital Discharge of Subjects with Esophagectomy of Esophageal Cancer: A Systemic Review and Meta-analysis

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Abstract Background: We performed a meta-analysis to evaluate the effect of home enteral nutrition compared with oral diet after the hospital discharge of subjects with esophagectomy of esophageal cancer. Methods: A systematic literature search up to July 2021 was performed and 12 studies included 970 subjects with esophagectomy of esophageal cancer at the start of the study; 481 of them were using home enteral nutrition after the hospital discharge and 579 were given oral diet. They were reporting relationships between the effects of home enteral nutrition compared with oral diet after the hospital discharge of subjects with esophagectomy of esophageal cancer. We calculated the odds ratio (OR) and the mean difference (MD) with 95% confidence intervals (CIs) to assess the effects of home enteral nutrition compared with oral diet after the hospital discharge of subjects with esophagectomy of esophageal cancer using the dichotomous and contentious method with a random or fixed-effect model. Results: Home enteral nutrition had significantly higher body weight (MD, 31.4; 95% CI, 2.55–3.72, $p < 0.001$), body mass index (MD, 1.20; 95% CI, 0.66–1.74, $p < 0.001$), and serum albumin (MD, 3.14; 95% CI, 2.07–4.20, $p < 0.001$), hemoglobin (MD, 8.57; 95% CI, 6.52–10.63, $p < 0.001$), total protein (MD, 4.86; 95% CI, 2.93–6.80, $p < 0.001$), and pre-albumin (MD, 30.39; 95% CI, 1.27–59.50, $p = 0.04$) compared to oral diet after the hospital discharge of subjects with esophagectomy of esophageal cancer. Additionally, home enteral nutrition compared with oral diet after the hospital discharge of subjects with esophagectomy of esophageal cancer had no significant difference in feeding-related complications (OR, 1.04; 95% CI, 0.44–2.43, $p = 0.93$). Conclusions: Home enteral nutrition had significantly higher body weight, body mass index, and serum albumin, hemoglobin, total protein, and pre-albumin compared to oral diet after the hospital discharge of subjects with esophagectomy of esophageal cancer with no significant difference in feeding-related complications. Furthers studies are needed to confirm these findings.

Keywords: *esophageal cancer, esophagectomy, home enteral nutrition, oral diet, feeding-related complications, hematological parameters, anthropometric measurements*

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1. Introduction

Esophageal cancer is a very malignant gastrointestinal cancer. Esophageal cancer is ranked as the sixth cancer in morbidity and death rate. Esophageal cancer was accountable for more than a half-million new cancer cases and half-million deaths in the world. [1] Though esophageal resection or esophagectomy is the main management for subjects with esophageal cancer, [2] it still has high morbidity and death rates. [3] Because of the complicated procedure of esophagectomy, the nutritional condition of the subject has a serious influence on the subject's general deterioration. [4] The very common symptom of esophageal cancer is progressive dysphagia, which influences the subject's capability to eat, that results in preoperative malnutrition. [5] Moreover postoperative stress malnutrition produced by postoperative stress causes high catabolic metabolism in subjects. When that is combined with weakened digestion and absorption produced by digestive tract reconstruction, subject malnutrition is additionally intensified. [6] Postoperative malnutrition, e.g. weakness, and weight loss exists in more than 50% of subjects experiencing esophagectomy. [7] Heneghan et al showed a high extent of esophageal cancer subjects with severe

weight loss (≥10%) at 1, 6, and 18 to 24 months after the operation. [8] Malnutrition can delay a subject's postoperative recovery time, decrease their quality of life, [9] and decrease their tolerance to postoperative chemotherapy, and radiotherapy, which might influence their long-term prognosis. [10] Also, subjects with severe weight loss after esophagectomy increase overall all-cause death. [11] It is very important in esophageal cancer subjects to improve their weight after surgery, have a better short-term prognosis, and stimulate postoperative recovery. The advantage of enteral nutrition through hospitalization is well recognized [12]; though, the properties of continuing enteral nutrition after discharge have not been extensively studied. Home enteral nutrition is the enteral tube feeding used away from the hospital. [13] The rate of an enteral feeding tube through procedures for esophageal cancer has increased, [14] and more subjects are selecting to continue enteral feeding at home in place of getting rid of the feeding tube at hospital discharge. [15] Some randomized controlled trials studied home enteral nutrition in subjects with esophageal cancer, however, the sample size of these studies was small, and the conclusions on the outcome of home enteral nutrition for improving nutritional condition and quality of life were conflicting. Also, the safety of home enteral nutrition, e.g. the frequency of feeding-related complications e.g. diarrhea and vomiting is a big concern Hence, the present meta-analysis aimed to evaluate the effect of home enteral nutrition compared with oral diet after the hospital discharge of subjects with esophagectomy of esophageal cancer.

2. Materials and Methods

The present study followed the meta-analysis of studies in the epidemiology statement, [16] which was performed following an established protocol.

2.1. Study Selection

The study parameters included statistical measures of association (odds ratio [OR], mean difference [MD], frequency rate ratio, or relative risk, with 95% confidence intervals [CIs]) between the effects of home enteral nutrition compared with oral diet after the hospital discharge of subjects with esophagectomy of esophageal cancer.

Only those human studies in any language were considered. Inclusion was not restricted by study size or type. Publications excluded were review articles, commentaries, and studies that did not supply a degree of relationship. Figure 1 shows the whole study process.

The articles were integrated into the meta-analysis when the following inclusion criteria were met:

1. The study was a randomized control trial or a retrospective study.
2. The target population includes subjects with esophagectomy of esophageal cancer
3. The intervention program was home enteral nutrition compared with oral diet
4. The study included comparisons between the effects of home enteral nutrition compared with oral diet after the hospital discharge of subjects with esophagectomy of esophageal cancer.

The exclusion criteria for the intervention groups were:

1. Studies that did not determine the effect of home enteral nutrition compared with oral diet after the hospital discharge of subjects with esophagectomy of esophageal cancer
2. Studies that included managements of subjects discharge from the hospital with esophageal cancer's esophagectomy with home enteral nutrition compared with oral diet.
3. Studies that did not focus on the effect on comparative results.

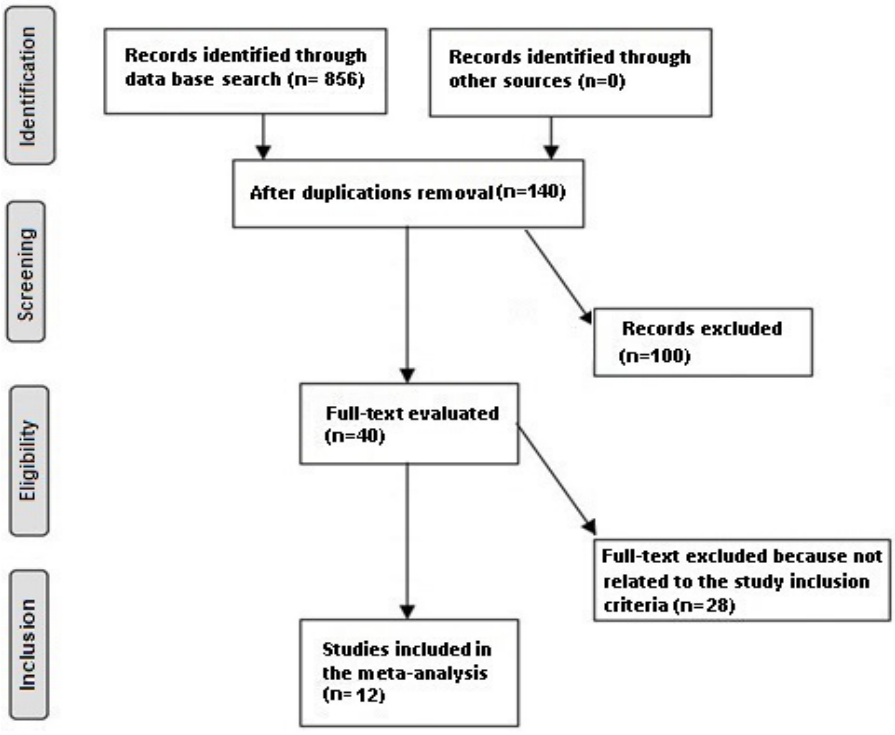

Figure 1. Schematic diagram of the study procedure

2.2. Identification

A protocol of search strategies was prepared according to the PICOS principle, [17] and we defined it as follow: P (population): subjects with esophagectomy of esophageal cancer; I (intervention/exposure): home enteral nutrition compared with oral diet; C (comparison): home enteral nutrition compared with oral diet after the hospital discharge of subjects with esophagectomy of esophageal cancer; O (outcome): feeding-related complications, hematological parameters, and anthropometric measurements; and S (study design): no restriction. [18] First, we conducted a systematic search of Embase, PubMed, Cochrane Library, OVID, China National Knowledge Infrastructure, WanFang databases, Chinese Biomedical Literature Database, and Google Scholar till July 2021, by using a blend of keywords and related words for esophageal cancer, esophagectomy, home enteral nutrition, oral diet, feeding-related complications, hematological parameters, and anthropometric measurements as shown in Table 1. All detected studies were gathered in an EndNote file, duplicates were removed, and the title and abstracts were revised to eliminate studies that did not show any relationship between the effects of home enteral nutrition compared with oral diet after the hospital discharge of subjects with esophagectomy of esophageal cancer. The remaining studies were examined for related information.

Table 1. Search Strategy for Each Database

Database	Search strategy
Pubmed	#1 "esophageal cancer"[MeSH Terms] OR "Esophagectomy"[All Fields] OR "Home enteral nutrition"[All Fields] #2 "Oral diet"[MeSH Terms] OR "esophageal cancer"[All Fields] OR "Feeding-related complications"[All Fields] OR "hematological parameters"[All Fields] OR " anthropometric measurements"[All Fields] #3 #1 AND #2
Embase	'esophageal cancer'/exp OR 'Esophagectomy'/exp OR 'Home enteral nutrition'/exp #2 'Oral diet'/exp OR 'esophageal cancer'/exp OR 'Feeding-related complications'/exp OR 'hematological parameters'/exp OR 'anthropometric measurements'/exp #3 #1 AND #2
Cochrane library	#1 (esophageal cancer):ti,ab,kw OR (Esophagectomy):ti,ab,kw OR (Home enteral nutrition):ti,ab,kw (Word variations have been searched) #2 (Oral diet):ti,ab,kw OR (Feeding-related complications):ti,ab,kw OR (hematological parameters):ti,ab,kw OR (anthropometric measurements):ti,ab,kw (Word variations have been searched) #3 #1 AND #2

2.3. Screening

Data were abridged onto a standardized form on the following basis; study-related and subject-related characteristics as follows: last name of the primary author, period of study, year of publication, country, region of the studies, and study design; population type, the total number of subjects, demographic data and clinical and treatment characteristics; categories, qualitative and quantitative method of evaluation, information source, and outcome evaluation; and statistical analysis. [19] If a study qualified for inclusion based upon the aforementioned principles, data were extracted independently by two authors. In case of disagreement, the corresponding author provided a final opinion. When the data from a particular study differed based on the assessment of the relationship between the effects of home enteral nutrition compared with oral diet after the hospital discharge of subjects with esophagectomy of esophageal cancer, we extracted the data separately. There is a risk of bias in these studies; therefore, individual studies were evaluated using two authors who independently assessed the methodological quality of the selected studies. The “risk of bias tool" from the RoB 2: A revised Cochrane risk-of-bias tool for randomized trials was utilized to evaluate methodological quality. [20] In terms of the evaluation criteria, each study was evaluated and allocated to one of the next three risks of bias-low: if all quality criteria were met, the study was considered to have a low risk of bias; unclear: if one or more of the quality criteria were partially met or unclear, the study was considered to have a moderate risk of bias; or high: if one or more of the criteria were not met, or not included, the study was considered to have a high risk of bias. Any discrepancies were addressed by a reassessment of the original article.

2.4. Eligibility

The main result concentrated on the effectiveness of home enteral nutrition compared with oral diet after the hospital discharge of subjects with esophagectomy of esophageal cancer. An assessment of these aforementioned effects was summarized.

2.5. Inclusion

Sensitivity analyses were limited to studies reporting the relationship between the effects of home enteral nutrition compared with oral diet after the hospital discharge of subjects with esophagectomy of esophageal cancer. For subcategory and sensitivity analysis, we compared the home enteral nutrition compared with oral diet.

2.6. Statistical Analysis

We calculate the odds ratio (OR) and the mean difference (MD) and 95% confidence interval (CI) using the dichotomous and contentious method with a random or fixed-effect model. We calculated the I^2 index and the I^2 index was ranging from 0% to 100%. When the I^2 index was approximately 0%, 25%, 50%, and 75% that specifies no, low, moderate, and high heterogeneity, respectively. [17] If the I^2 was > 50%, we used the random-effect; if it was < 50%, we used the fixed-effect. We stratified the original assessment as per result categories as described previously to complete the subgroup analysis. Differences among the subcategories were considered statistically significant at a p-value <0.05. Publication bias was assessed quantitatively using the Egger regression test (publication bias is present if $p \geq 0.05$), and qualitatively, by visual inspection of funnel plots of the logarithm of odds ratios versus their standard errors. [19] All the p-values were calculated via two-tailed tests. Reviewer manager version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used to do all calculations and graphs.

3. Results

A total of 856 unique studies were identified, of which 12 studies (between 2013 and 2021) fulfilled the inclusion criteria and were included in this meta-analysis. [21-32] The 12 studies included 970 subjects with esophagectomy of esophageal cancer at the start of the study; 481 of them were using home enteral nutrition after the hospital discharge and 579 were given oral diet. All studies evaluated the effects of home enteral nutrition compared with oral diet after the hospital discharge of subjects with esophagectomy of esophageal cancer.

The study size ranged from 41 to 140 subjects with esophagectomy of esophageal cancer at the start of the study. The details of the 12 studies are shown in Table 2. 7 studies reported data stratified to the effect of home enteral nutrition compared with oral diet after the hospital discharge of subjects with esophagectomy of esophageal cancer on the body weight, 5 studies reported data stratified to the effect on body mass index, 7 studies reported data stratified to the effect on serum albumin, 4 studies reported data stratified to the effect on hemoglobin, 4 studies reported data stratified to the effect on total protein, 4 studies reported data stratified to the effect on pre-albumin, and 6 studies reported data stratified to the effect on feeding-related complications.

Home enteral nutrition had significantly higher body weight (MD, 31.4; 95% CI, 2.55–3.72, $p < 0.001$) with no heterogeneity (I^2 = 11%), body mass index (MD, 1.20; 95% CI, 0.66–1.74, $p < 0.001$) with high heterogeneity (I^2 = 88%), and serum albumin (MD, 3.14; 95% CI, 2.07–4.20, $p < 0.001$) with high heterogeneity (I^2 = 86%), hemoglobin (MD, 8.57; 95% CI, 6.52–10.63, $p < 0.001$) with moderate heterogeneity (I^2 = 66%), total protein (MD, 4.86; 95% CI, 2.93–6.80, $p < 0.001$) with high heterogeneity (I^2 = 76%), and pre-albumin (MD, 30.39; 95% CI, 1.27–59.50, $p = 0.04$) with high heterogeneity (I^2 = 99%) compared to oral diet after the hospital discharge of subjects with esophagectomy of esophageal cancer as shown in Figure 2 – Figure 7. Additionally, home enteral nutrition compared with oral diet after the hospital discharge of subjects with esophagectomy of esophageal cancer had no significant difference in feeding-related complications (OR, 1.04; 95% CI, 0.44–2.43, $p = 0.93$) with moderate heterogeneity (I^2 = 61%) as shown in Figure 8.

Table 2. Characteristics of the selected studies for the meta-analysis

Study	Country	Total	Home enteral nutrition	Oral diet
Cao, 2013 [21]	China	80	40	40
Bowrey, 2015 [22]	UK	41	20	21
Gavazzi, 2016 [23]	Italy	79	38	41
Zhang, 2016 [24]	China	82	41	41
Wu, 2017 [25]	China	50	25	25
Wu, 2018 [26]	China	140	66	74
Tong, 2018 [27]	China	85	44	41
Ji, 2019 [28]	China	112	55	57
Wang, 2019 [29]	China	96	48	48
Liu, 2020 [30]	China	50	26	24
Pattamatta, 2021 [31]	Netherlands	95	48	47
Chen, 2021 [32]	China	60	30	30
	Total	**970**	**481**	**489**

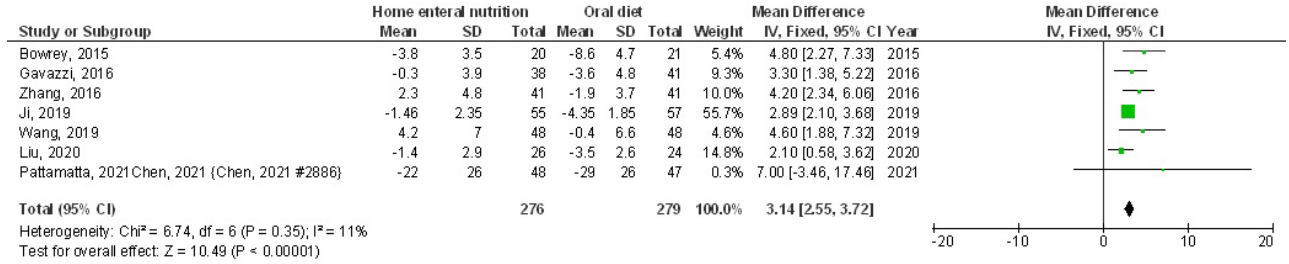

Figure 2. Forest plot of the effect of home enteral nutrition compared with oral diet after the hospital discharge of subjects with esophagectomy of esophageal cancer on body weight

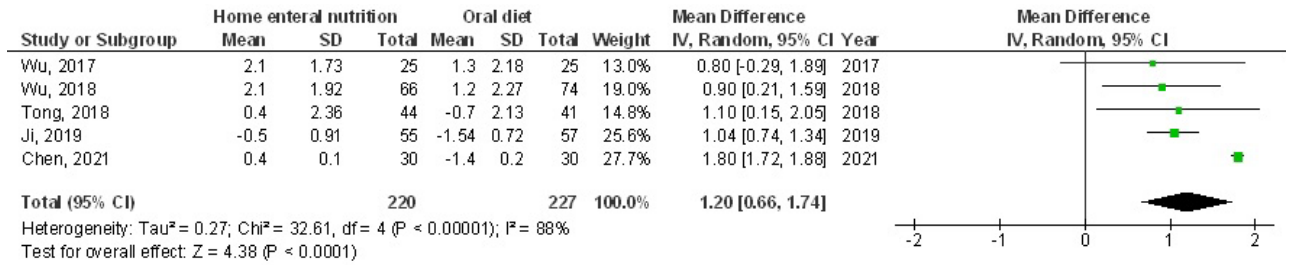

Figure 3. Forest plot of the effect of home enteral nutrition compared with oral diet after the hospital discharge of subjects with esophagectomy of esophageal cancer on body mass index

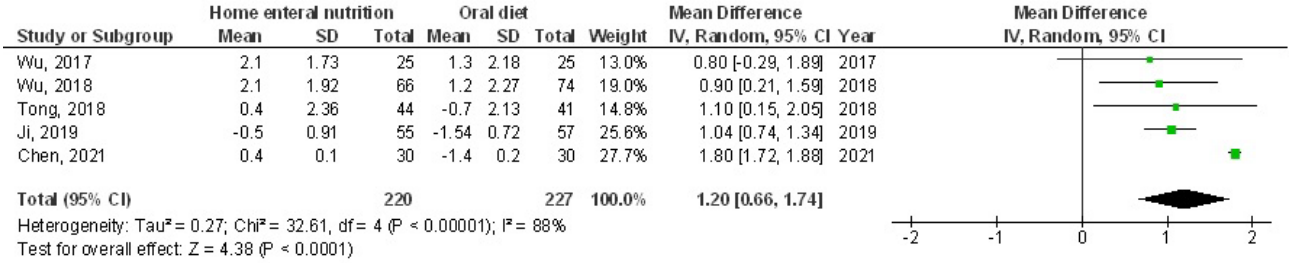

Figure 4. Forest plot of the effect of home enteral nutrition compared with oral diet after the hospital discharge of subjects with esophagectomy of esophageal cancer on serum albumin

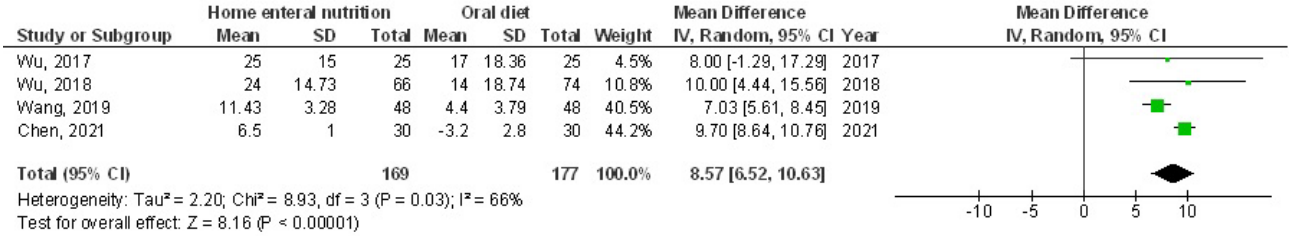

Figure 5. Forest plot of the effect of home enteral nutrition compared with oral diet after the hospital discharge of subjects with esophagectomy of esophageal cancer on hemoglobin

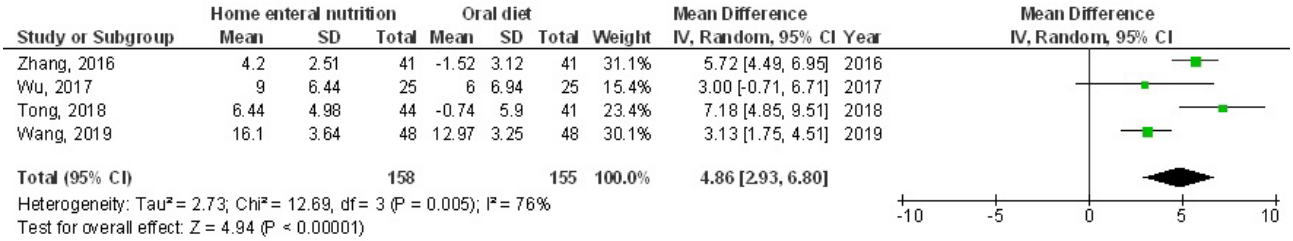

Figure 6. Forest plot of the effect of home enteral nutrition compared with oral diet after the hospital discharge of subjects with esophagectomy of esophageal cancer on total protein

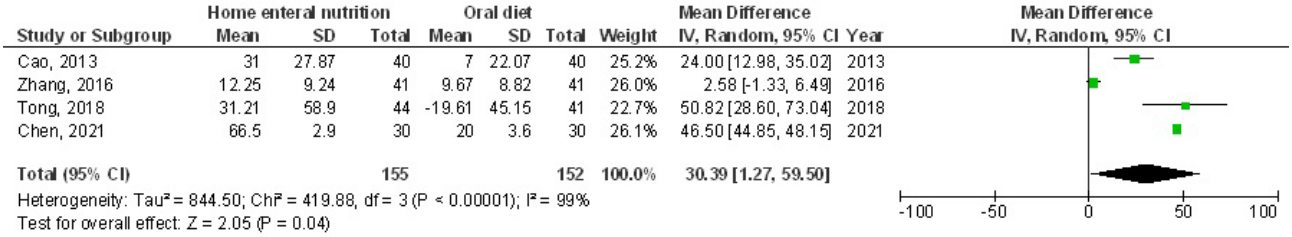

Figure 7. Forest plot of the effect of home enteral nutrition compared with oral diet after the hospital discharge of subjects with esophagectomy of esophageal cancer on pre-albumin

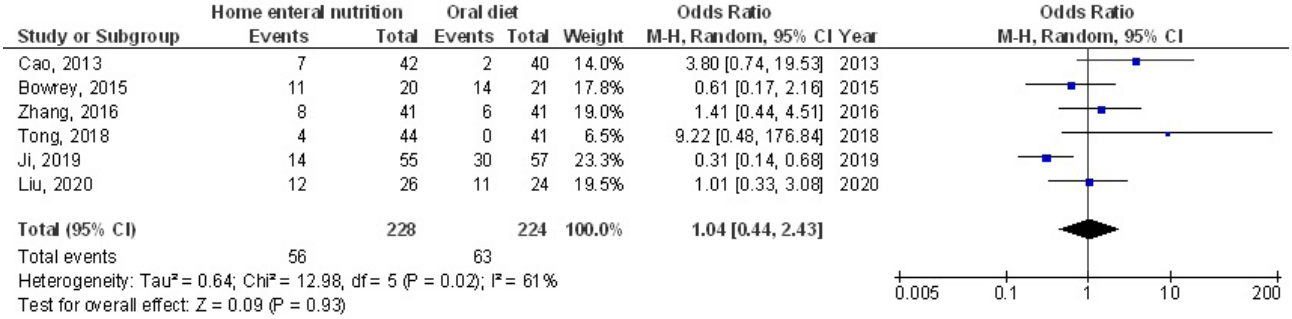

Figure 8. Forest plot of the effect of home enteral nutrition compared with oral diet after the hospital discharge of subjects with esophagectomy of esophageal cancer on feeding-related complications

Selected studies stratified analysis adjusts for age, gender, and ethnicity were not performed, since no studies reported or adjusted for these factors.

Based on the visual inspection of the funnel plot as well as on quantitative measurement using the Egger regression test, there was no evidence of publication bias (p = 0.87).

However, most of the included studies were assessed to be of low methodological quality due to their small sample size. All studies did not have selective reporting bias, and no articles had incomplete outcome data and selective reporting.

4. Discussion

This meta-analysis study based on 12 studies included 970 subjects with esophagectomy of esophageal cancer at the start of the study; 481 of them were using home enteral nutrition after the hospital discharge and 579 were given oral diet. [21-32] Home enteral nutrition had significantly higher body weight, body mass index, and serum albumin, hemoglobin, total protein, and pre-albumin compared to oral diet after the hospital discharge of subjects with esophagectomy of esophageal cancer. Additionally, home enteral nutrition compared with oral diet after the hospital discharge of subjects with esophagectomy of esophageal cancer had no significant feeding-related complications. [21-32] However, the analysis of results should be done with carefulness due to the low sample size in most of the included studies (10 studies ≤100 subjects) in the meta-analysis; recommending the requirement for more studies to confirm these findings or probably to significantly affect the confidence in the effect assessment.

Our meta-analysis aim was to systematically gather the available studies' evidence and evaluate the possible efficiency of home enteral nutrition compared with oral diet after the hospital discharge of subjects with esophagectomy of esophageal cancer. Our findings are similar to the earlier meta-analysis. [7,33] It was shown that 72% of postoperative subjects with esophageal cancer cannot take the needed calories by oral route at hospital discharge, and almost 50% of these subjects only consumed <85% of the needed calories. [34] The European Society for Clinical Nutrition and Metabolism stated that if the oral route represents <75% of daily food of subjects with esophagectomy, the nutritional condition might worsen fast. [35] Weight loss is the main concern for esophagectomy subjects, while almost 60% of subjects who experience esophagectomy lose more than 10% of their preoperative body mass index 6 months after hospital discharge. [7] Home enteral nutrition gives subjects daily needed foods when they could not take them by oral route. From our meta-analysis, we found that home enteral nutrition compared with oral diet enhanced a subjects' body weight and body mass index after hospital discharge. Also, home enteral nutrition enhanced the nutrition-associated hematological parameters e.g. albumin, total protein, pre-albumin, and hemoglobin. Hence, home enteral nutrition could significantly progress the nutritional condition of the subjects with esophageal cancer because the reconstruction of the gastrointestinal tract could take up to 9 months to adjust to a new diet after esophagectomy. Many subjects have feeding-related complications e.g. appetite loss, diarrhea, reflux, and vomiting in 1-year post esophagectomy. [8,34] Due to these feeding-related complications, some subjects could not undertake the management plan that comprises adjuvant therapy. [36] Similar to our results, Bowrey et al observed no significant differences in feeding-related complications in subjects with esophageal cancer and other upper gastrointestinal malignancy. [22] Reduced appetite, fatigue, reduced physical and social functions, sleep disturbance, and vomiting were frequent after esophagectomy. [37,38,39] The European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire-C30 is the used scale to evaluate postoperative functions and symptoms. [40] Current evidence confirms that subjects who obtain full cancer management are significantly related to better physical and nutritional condition, [36] while it was shown that more than 50% of subjects with esophagectomy of esophageal cancer did not complete their cancer management plan. [2] Consequently, improving postoperative physical condition and decreasing symptoms are important for esophageal cancer subjects. This added to subjects to complete the full cancer management and therefore reduces the overall morbidity and death for esophageal cancer subjects.

Correct nutritional assessment is vital for home enteral nutrition subjects. Nutrition assessment in the randomized controlled trials was documented using different techniques and presented inconsistently. That is why we could not study nutritional assessment and we suggest standardizing the technique of measurement to help to provide a proper recommendation about it. Though no long-term results were analyzed in this meta-analysis, the nutritional results e.g. body weight, body mass index, albumin, pre-albumin, total protein, hemoglobin were enhanced by home enteral nutrition. These have been confirmed to be associated with decreased complications and improved overall survival rate after esophagectomy. [39] Improving physical function and declining fatigue will help subjects to complete the management plan. [36]

This meta-analysis showed the relationship between the effects of home enteral nutrition compared with oral diet after the hospital discharge of subjects with esophagectomy of esophageal cancer. However, further studies are needed to validate these potential associations. Also, further studies are needed to deliver a clinically meaningful difference in the results. This was suggested in another meta-analysis which showed a similar effect of home enteral nutrition compared with oral diet after the hospital discharge of subjects with esophagectomy of esophageal cancer. [7,33] This requires further investigation and explanation since no clear rationale was found to explain these results. Well-designed studies are also needed to assess these factors including the combination of different ages, gender, and ethnicity; since our meta-analysis study could not answer whether these factors are associated with the results.

In summary, Home enteral nutrition had significantly higher body weight, body mass index, and serum albumin, hemoglobin, total protein, and pre-albumin compared to oral diet after the hospital discharge of subjects with esophagectomy of esophageal cancer. Additionally, home enteral nutrition compared with oral diet after the hospital discharge of subjects with esophagectomy of esophageal cancer had no significant difference in feeding-related complications. Furthers studies are required to validate these findings.

4.1. Limitations

There may be a selection bias in this study since so many of the studies found were excluded from the meta-analysis. However, the studies excluded did not satisfy the inclusion criteria of our meta-analysis. Moreover, we could not determine if the results were associated with age, gender, and ethnicity or not. The study designed to evaluate the association between the effects of home enteral nutrition compared with oral diet after the hospital discharge of subjects with esophagectomy of esophageal cancer was based on data from previous studies, which might cause bias induced by incomplete details. The meta-analysis was based on 12 studies with a low sample size in most of the selected studies (10 studies ≤100 subjects). Factors including the age, gender, compliance, ethnicity, and nutritional condition of subjects were also possible bias-inducing factors. Some unpublished studies and missing data may cause a bias in the pooled effect. Subjects were using different main pharmacological medicines, different management schedules, dosages, and health care systems.

5. Conclusions

Home enteral nutrition had significantly higher body weight, body mass index, and serum albumin, hemoglobin, total protein, and pre-albumin compared to oral diet after the hospital discharge of subjects with esophagectomy of esophageal cancer with no significant difference in feeding-related complications. Furthers studies are needed to confirm these findings. However, the analysis of results should be done with carefulness due to the low sample size in most of the included studies in the meta-analysis; recommending the requirement for more studies to confirm these findings or probably to significantly affect the confidence in the effect assessment.

Conflict of Interest

The authors have no conflicts of interest to declare.

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