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# Elemental diet preventative effects for adverse events during chemotherapy in patients with esophageal cancer – A systematic review and meta-analysis

*Efectos preventivos de la dieta elemental para eventos adversos durante la quimioterapia en pacientes con cáncer de esófago: una revisión sistemática y metaanálisis*

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## Abstract

The effectiveness of an elemental diet (ED) for preventing adverse events (AEs) during chemotherapy for patients with esophageal cancer (EC) remains unclear. The aim of this meta-analysis was to comprehensively assess the efficacy of ED for preventing AE in EC patients during chemotherapy. Medline (via PubMed), Embase, the Cochrane Library, and Web of Science were searched to retrieve prospective and randomized studies published before April 12, 2023. The odds ratio (OR) of each AE was calculated using Review Manger 5.4.1. The risk of bias was assessed, and a random effect model-based meta-analysis was used to analyze the available data. Four prospective and randomized studies involving 237 patients were identified after a systematic search. Regarding gastrointestinal toxicities, the findings indicated a trend toward a decrease in the risk of mucositis (OM) (OR = 0.54, 95 % CI: 0.25-1.14), constipation (OR = 0.87, 95 % CI: 0.49-1.53), and anorexia (OR = 0.99, 95 % CI: 0.32-3.05), as well as an increasing trend in the risk of diarrhea (OR = 1.48, 95 % CI: 0.79-2.79), among patients treated with ED. However, none of these reached statistical significance. For hematological toxicities, the risk of all-grade neutropenia (OR = 0.28, 95 % CI: 0.14-0.57), grade ≥ 2 leucopenia (OR = 0.43, 95 % CI: 0.22-0.84), grade ≥ 2 neutropenia (OR = 0.34, 95 % CI: 0.17-0.67), and grade ≥ 3 neutropenia (OR = 0.28, 95 % CI: 0.12-0.63) was significantly decreased. There is no firm evidence confirming the preventive effect of an ED against OM or diarrhea. However, an ED may potentially be helpful in preventing neutropenia and leucopenia.

**Keywords:**

Elemental diet. Esophageal cancer. Adverse event. Meta-analysis.

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## Resumen

La efectividad de una dieta elemental (DE) para prevenir eventos adversos (EA) durante la quimioterapia en pacientes con cáncer de esófago (CE) sigue sin estar clara. Este metaanálisis evalúa la eficacia de DE para prevenir EA en pacientes con CE durante quimioterapia. Se realizaron búsquedas en Medline (con PubMed), Embase, Biblioteca Cochrane y Web of Science para recuperar estudios prospectivos y aleatorios publicados antes del 12/04/2023. La razón de probabilidad (RP) de cada EA se calculó usando Review Manger 5.4.1. Se evaluó el riesgo de sesgo y se utilizó un metaanálisis basado en modelo de efectos aleatorios para analizar los datos disponibles. Después de una búsqueda sistemática, se identificaron cuatro estudios prospectivos y aleatorios con 237 pacientes. En cuanto a las toxicidades gastrointestinales, los hallazgos indicaron una tendencia hacia una disminución en el riesgo de mucositis (OM) (OR = 0,54, IC 95 %: 0,25-1,14), estreñimiento (OR = 0,87, IC 95 %: 0,49-1,53) y anorexia (OR = 0,99, IC 95 %: 0,32-3,05) y una tendencia creciente en el riesgo de diarrea (OR = 1,48, IC 95 %: 0,79-2,79) entre los pacientes tratados con DE. Sin embargo, no hubo muestras estadísticas significativas. Para toxicidades hematológicas, el riesgo de neutropenia de todos los grados (RP = 0,28; IC del 95 %: 0,14-0,57), leucopenia grado ≥ 2 (RP = 0,43; IC del 95 %: 0,22-0,84), neutropenia grado ≥ 2 (RP = 0,34; IC del 95 %: 0,17-0,67) y neutropenia grado ≥ 3 (RP = 0,28; IC del 95 %: 0,12-0,63) disminuyó significativamente. Ninguna evidencia firme confirmó el efecto preventivo de DE frente a OM o la diarrea. Una DE sería útil previniendo neutropenia y leucopenia.

**Palabras clave:**

Dieta elemental. Cáncer de esófago. Evento adverso. Metaanálisis.

## INTRODUCTION

Esophageal cancer (EC) is the eighth most diagnosed cancer, accounting for 3 % of annual cases globally. In total, 604,100 new cases of EC were associated with 544,100 deaths globally in 2020 (1). According to the Global Burden of Disease 2019, the number of disability-adjusted life years (DALYs) was 11,666,016.56, and the percentage of DALYs was 0.46 for EC in 2019 (2). EC triggers a series of consequences for patients and society that include reduced quality of life, increased financial burdens, and increased consumption of social resources (3).

Chemotherapy is still the first-line treatment for most end-stage patients with EC due to its excellent effect of inhibiting tumor growth and preventing distant metastases (4). However, chemotherapy causes adverse events (AEs) in 99 % of EC patients. KEYNOTE-590, which is a randomized clinical trial of first-line chemotherapy with or without pembrolizumab for patients with EC, reported nausea (59 %), anemia (44 %), decreased appetite (32 %), decreased neutrophil count (29 %), vomiting (27 %), stomatitis (25 %), and decreased white blood cells (19 %) as the common chemotherapy-related AEs among EC patients (5). A novel treatment direction for early-stage EC involves neoadjuvant immunotherapy with chemotherapy. When chemotherapy is accompanied by immunotherapy, the risks of treatment-related AEs (odds ratio, OR = 1.28, 95 % confidence interval, CI: 1.21-2.84) (6), serious AEs (pooled risk ratio, RR: 1.36, 95 % CI: 1.15-1.61), and discontinuation of treatment caused by AEs (pooled RR: 1.82, 95 % CI: 1.55-2.14) were elevated (7).

Oral mucositis (OM) is one of the most common and clinically significant AEs induced by chemotherapy among patients with EC. Oral pain, inability to eat, weight loss, twice the risk of infection, and systemic expansion of local inflammation are all potential effects of OM. In addition, high-grade OM can lead to patients receiving dose-reduced chemotherapy, delaying the initiation of their anticancer treatment, worsening their prognosis, and increasing their risk of death four-fold compared to patients undergoing chemotherapy without mucositis (8). Various gastrointestinal AEs, such as diarrhea, anorexia, and OM, correlate with each other can cause malnutrition in patients with EC, with an incidence of up to 65-80 %, which is the highest among all cancer patients (9). A poor nutritional status may negatively influence survival, while nutritional supplementation helps improve the prognosis (10). Patients treated with innovative neoadjuvant chemoradiotherapy (11) or immune checkpoint inhibitors plus anti-angiogenic agents combined with chemoradiotherapy (12) often experience neutropenia and leucopenia, which are the most common grade 3 or 4 treatment-related AEs in EC patients, with an incidence ranging from 40-80 %.

The elemental diet (ED) refers to the daily intake of a single powder dissolved in water containing essential amino acids, carbohydrates, fat, minerals, and vitamins. It lacks complete proteins, eliminating the need for digestion (13). To the best of our knowledge, Elemental® is the sole brand in the field utilizing enteral supplements to reduce chemotherapy-related AEs among patients with EC. In all included clinical trials, the experimental groups (EG) employed Elental®. Currently, ED is widely used to prevent OM during chemotherapy in patients with EC and has been found to have and positive impact on changes in body weight, prealbumin, C-reactive protein, leucopenia (13), transferrin, total amino acids, essential amino acids (14), and lean body mass (15) when compared with the control group (CG). However, the effect of ED on OM remains controversial. Some clinical studies demonstrate that ED can prevent OM in patients with EC during chemotherapy (13,16-18), while others do not support its preventive effect (14,15). A previous meta-analysis suggested that ED could reduce the risk of developing all grade OM (OR = 0.35 CI: 0.12-0.99 $P_{statistics} = 0.04$; $I^2 = 61$ %) (17). However, this result was unreliable, as one included study (Registration number: UMIN000010860) was grouped based on treatment completion rather than the predetermined scheme (19). This study (Registration number: UMIN000010860) might just suggest that ED could be a test approach, but not a confirmed strategy for the treatment of OM. In addition, the previous meta-analysis just searched the Medline database (via PubMed) and evaluated the risk of OM only. Therefore, in this meta-analysis, we comprehensively and scientifically evaluate the preventive effect of ED on various AEs among esophageal cancer patients treated with chemotherapy.

## METHODS

Our study followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the Cochrane Collaboration Handbook recommen-

dations (20,21). Relevant information is presented in the supplementary materials. This study was based on previously published studies. Ethical approval or patient consent was required. The systematic review is registered on INPLASY: 202260021.

## SEARCH STRATEGIES

A systematic search for associated English studies published before April 12, 2023, was conducted in Medline (via PubMed), Embase, Web of Science, and the Cochrane Library. The search terms were ("food, formulated" or "elemental diet") and ("esophagus cancer" or "esophageal neoplasms"). Furthermore, conference proceedings, gray literature, similar meta-analyses, and systematic reviews were reviewed to find studies that met the standards as much as possible. Two reviewers (HL and HZ) independently searched and evaluated potential studies. If discrepancies appeared, the corresponding author would make the final decision. All records were independently imported into EndNote 20.3 by two reviewers (HL and HZ). The integrity and honesty of the studies were then confirmed.

## ELIGIBILITY CRITERIA AND SELECTION PROCESS

Studies were included if they met the PICOS criteria as follows.

*Participants:* (1) eligible patients were confirmed using histological or cytological pathological examinations including, but not limited to, squamous cell carcinoma; (2) eligible patients were at least 18 years old; (3) eligible patients were scheduled to undergo chemotherapy or chemoradiotherapy; and (4) eligible patients maintained adequate hematologic, liver, renal, and cardiac functions.

*Interventions:* patients received an elemental diet.

*Comparators:* patients received regular nutritional supplements.

*Outcomes:* the incidence of AEs in EC patients during chemotherapy treated with ED or a regular diet included OM, diarrhea, nausea, constipation, anorexia, leucopenia, anemia, neutropenia, and thrombocytopenia. The severity of AEs in these studies was classified according to the Common Terminology Criteria for Adverse Events (CTCAE). The risk of all-grade AEs, the incidence of grade ≥ 2 AEs, and the incidence of grade ≥ 3 AEs were assessed.

*Study design:* prospective and randomized studies were included.

The identified study was excluded if any of the following situations occurred: (1) uncontrolled infection, poor diabetes control, or insulin treatment; (2) receiving an elemental diet with other nutritional supplements, such as glutamine; or (3) if it was a single arm study, case report, observational study, or retrospective study.

All of the studies were first imported into EndNote 20.3, and the automation tools removed duplications. In addition, two reviewers (HL and HZ) independently screened the titles and abstracts. Subsequently, they reviewed the full text to retrieve potentially eligible studies. If inconsistencies emerged, the corresponding author made the final decision.

## DATA EXTRACTION AND RISK OF BIAS ASSESSMENT

The data in the study were independently extracted by two reviewers (HL and HZ), and any dispute was adequately resolved through discussion. The following data were collected: first author, publication year, country, age, treatment, control arms, number of patients, the percentage of males, characteristics of patients, study period, grading system, the incidence of outcomes, and study methods.

The recommendations of the Cochrane Collaboration Handbook were utilized to evaluate the bias risk, and it was classified as "low", "unclear", and "high" in several areas (21). These areas included the following: "random sequence generation", "allocation concealment", "blinding of participants and personnel", "blinding of outcome assessment", "incomplete outcome data", "selective reporting", and "other bias". If other oral medications or comfort nursing were utilized in a study, "other bias" was considered high risk.

## STATISTICAL ANALYSES

This study was based on the recommendations of the Cochrane Collaboration Handbook recommendations (22). First, the odds ratio (OR) was calculated to evaluate the pooled effect sizes for dichotomous variables. The standard mean differences (SMD) were calculated for the effect sizes referring to the continuous outcome expressed by group means and standard deviations (SDs). A 95 % confidence interval (CI) was used to measure uncertainty (23). Forest plots were drawn to visually display the results. Second, in this meta-analysis, heterogeneity was evaluated using $I^2$ statistics. When $I^2$ reached 50 %, heterogeneity was assessed as high (24). If heterogeneity existed, a random effect model was used. Otherwise, a fixed model was used. Furthermore, the significance level for the $P_{heterogeneity}$ value was set at 0.1. The included studies were excluded on an individual basis to detect potential bias. Third, funnel plots were drawn to detect potential bias using intuitive vision, and the Egger test was conducted in which the significance level for the $P_{egger}$ value was set at 0.05 (25). Review Manager 5.4.1 and Stata MP 16.0 for Windows (64-bit 86-64) software were utilized for all of the statistical analyses.

## RESULTS

Figure 1 shows the flow diagram of the study (PRISMA 2020). The search yielded 294 potential studies, of which 102 were duplicates. Two reviewers (HL and HZ) independently selected titles and abstracts and excluded 181 articles for not following the inclusion criteria. Two reviewers thoroughly reviewed the entire text, and four studies were finally included in the meta-analysis (13-16). One study in which the EG received an ED along with other nutritional supplements was excluded (18).

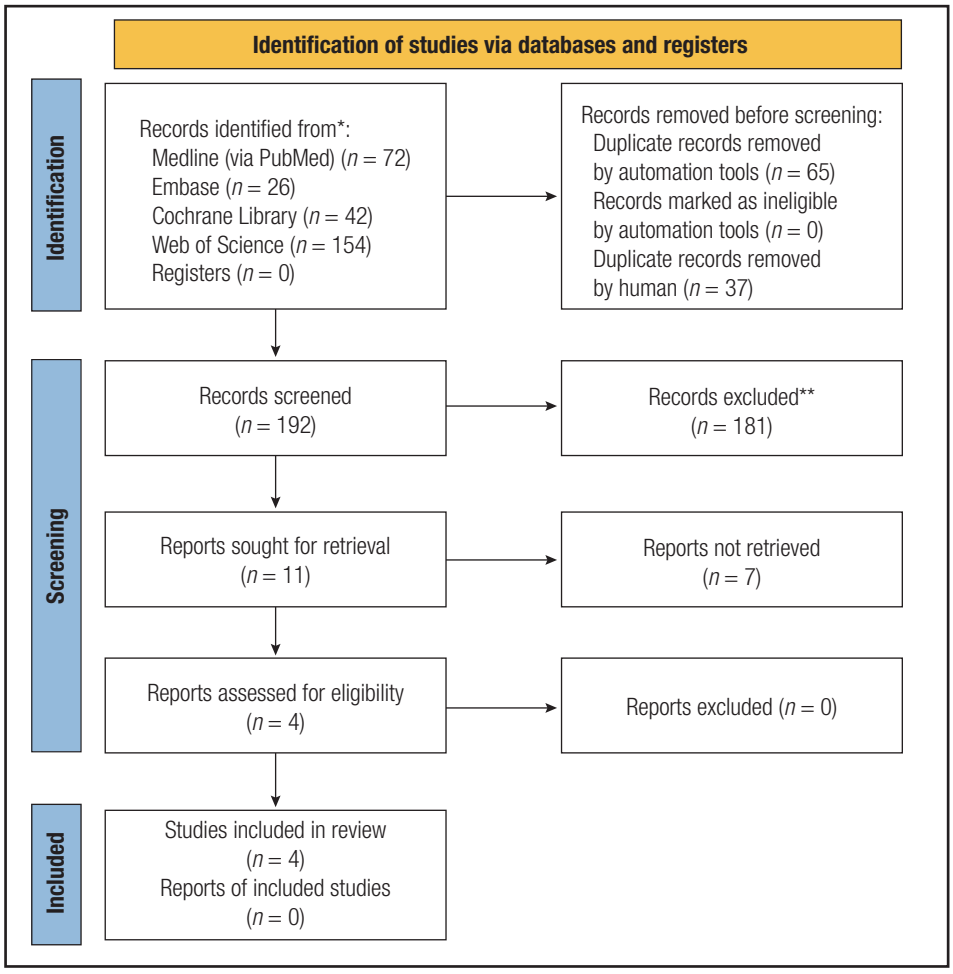


**Figure 1.**

Literature review flowchart. Modified from Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. DOI: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

## STUDY CHARACTERISTICS

Table I summarizes the primary features of the qualified studies. All four studies were conducted in Japan and published between 2016 and 2021. A total of 237 patients were included, while the CG consisted of 120 participants. A total of 82.7 % ($n$ = 196) of the patients were men. Patients received chemotherapy alone in three studies, while in one study they received chemoradiotherapy and radiation therapy. In all of the included studies, the EG received an ED (300 kcal/day or 600 kcal/day), while the CG was treated with a regular diet. In one study, the CG received azulene to relieve OM (15). The treatment course lasted 2 to 9 weeks. The grading system utilized the Common Terminology Criteria for Adverse Events.

## QUALITY OF THE INCLUDED STUDIES

Regarding performance bias, three trials were not blind for the patient (13-15), and one trial did not explain the details of blinding for patients (16). Regarding detection bias, three trials did not explain the details of blinding for doctors (14-16), and one trial was evaluated by blinded dental oncology specialists (13). Regarding other biases, two trials used a gargle containing 0.08 % lidocaine or azulene to relieve oral pain. Hence, the other bias was high (15,16). Figure 2 summarizes the biases in the included studies.

## GASTROINTESTINAL TOXICITIES

Three trials investigated the risk of OM between the ED and non-ED groups, and the results showed that the ED was unable to take effect for preventing OM for EC compared to the CG (OR = 0.54, 95 % CI: 0.25-1.14, $P_{statistics}$ = 0.10; $I^2$ = 0.0 %; Figure 3). Then the references were then excluded on a case-by-case basis. Each value of $I^2$ was 0.00 %, hence, no heterogeneity was observed. The funnel plot and the quantitative Egger test ($P_{egger}$ = 0.57) showed that there was no publication bias. Among the four included trials, the risk of grade ≥ 2 OM events (OR = 0.46, 95 % CI: 0.17-1.27, $P_{statistics}$ = 0.13; $I^2$ =58 %) and grade ≥ 3 OM events (OR = 0.45, 95 % CI: 0.11-1.77, $P_{statistics}$ = 0.40; $I^2$ = 0 %) did not have statistical significance between the ED and non-ED groups (Fig. 3). However,

**Table I.** Demographic characteristics of previous studies

| UMIN | UMIN000,025,412 | UMIN000,007,960 | UMIN000,007,609 | UMIN000,004,898 |
|---|---|---|---|---|
| Author | Tanaka Y et al. | Ishikawa T et al. | Katada C et al. | Okada T et al. |
| Year | 2021 | 2016 | 2021 | 2017 |
| Country | Japan | Japan | Japan | Japan |
| Age | Median<br>68.0 (44.0, 86.0)/68.0 (34.0, 83.0) | Median<br>68.0 (50.0-76.0)/ 66.0 (44.0-79.0) | Mean<br>67.8/66.7 | Mean<br>65.3/67.1 |
| % male | 78.1 %/86.2 % | 87.5 %/ 76.5 % | 83.3 %/ 82.9 % | 90.0 %/80.0 % |
| Number | 55/58 | 16/17 | 36/35 | 10/10 |
| Treatment arms control | ED (600.0 kcal/day)<br>ED (-) | ED (300.0 kcal/day)<br>Azulene (+) | ED (600.0 kcal/day)<br>ED (-) | ED (300.0 kcal/day)<br>ED (-) |
| Therapy | Chemotherapy | Chemotherapy or chemoradiotherapy | Chemotherapy | Chemotherapy |
| Grading system | CTCAE | CTCAE | CTCAE | CTCAE |
| Study period | 9 weeks | 4 weeks | 9 weeks | 2 weeks |

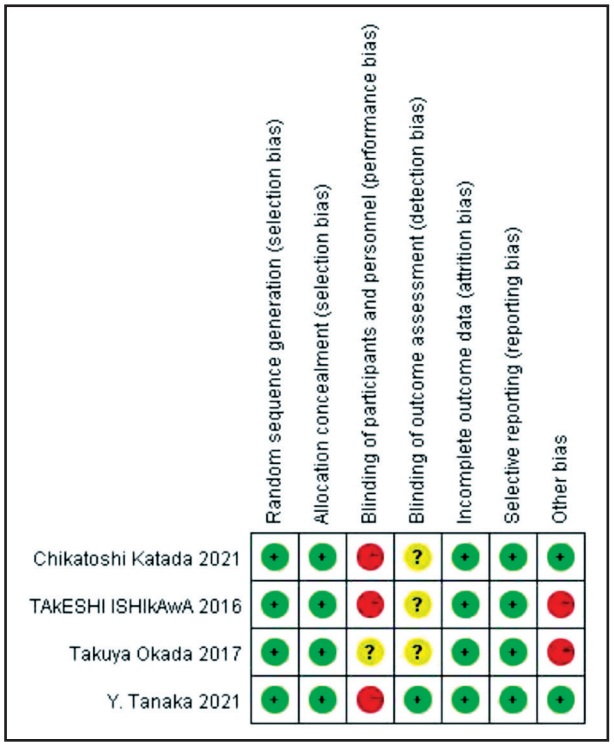


**Figure 2.**
Risk of bias graph.

the occurrence of OM tended to be reduced in the ED group compared to the CG, although none of these results were statistically significant, in contrast to some previous studies. The heterogeneity for grade ≥ 3 OM events ($I^2$ = 0 %) was low. The heterogeneity for grade ≥ 2 OM events ($I^2$ = 58 %) was high. To explore the heterogeneity, the references were excluded on a case-by-case basis. The heterogeneity of grade ≥ 2 OM was reduced when the study by Katada et al. was excluded (OR = 0.29, 95 % CI: 0.14-0.64, $P_{statistics}$ < 0.05; $I^2$ = 0 %).

There was no statistical significance between the ED and non-ED groups for the risk of diarrhea (OR = 1.48, 95 % CI: 0.79-2.79, $P_{statistics}$ = 0.22; $I^2$ = 0 %), nausea (OR = 0.82, 95 % CI: 0.34-1.99, $P_{statistics}$ = 0.66; $I^2$ = 47 %), constipation (OR = 0.87, 95 % CI: 0.49-1.53, $P_{statistics}$ = 0.62; $I^2$ = 0 %), and anorexia (OR = 0.99, 95 % CI: 0.32-3.05, $P_{statistics}$ = 0.99; $I^2$ = 56 %) (Table II). The funnel plot and the quantitative Egger test showed no evidence of publication bias. In addition, there were no statistical differences among the risks of high grade (grade ≥ 2 and grade ≥ 3) diarrhea, nausea, constipation, and anorexia between the ED and non-ED groups (Table II).

## HEMATOLOGICAL TOXICITIES

Hematological toxicities were involved in three studies. Compared to the CG, patients received an ED had a significantly decreased risk of neutropenia (OR = 0.28, 95 % CI: 0.14-0.57, $P_{statistics}$ < 0.05; $I^2$ = 0 %, Fig. 4). In addition, the same method was used to analyze the risk of leucopenia (OR = 0.50, 95 % CI: 0.25-1.00, $P_{statistics}$ = 0.05; $I^2$ = 0 %), anemia (OR = 1.06, 95 % CI: 0.44-2.55, $P_{statistics}$ = 0.90; $I^2$ = 0 %), and thrombocytopenia (OR = 1.26, 95 % CI: 0.64-2.48, $P_{statistics}$ = 0.50; $I^2$ = 29 %) (Table II). There was no difference between the ED and non-ED groups. The funnel plot and the quantitative Egger test showed no publication bias.

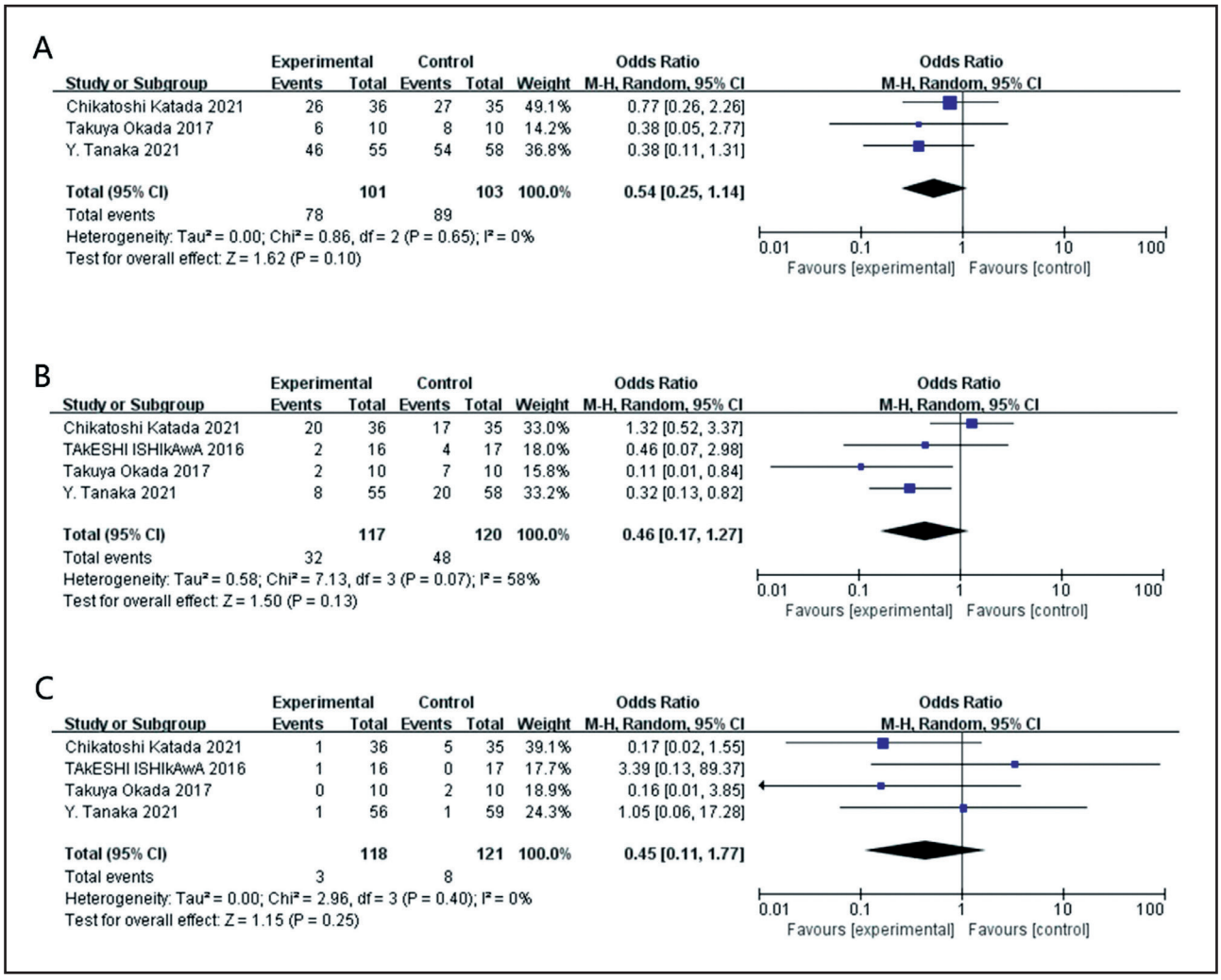


**Figure 3.**

Incidences of oral mucositis in the ED and non-ED groups: A. All-grade oral mucositis; B. Grade ≥ 2 oral mucositis; C. Grade ≥ 3 oral mucositis.

**Table II.** Primary results of adverse events in esophageal cancer during chemotherapy

| Meta-analyses variables | No. of studies | No. of patients | | Pool effect size | $I^2$ | *p* |
|---|---|---|---|---|---|---|
| | | ED | NO-ED | | | |
| **Gastrointestinal toxicities** | | | | **Pooled ORs (95 % CI)** | | |
| *Oral mucositis* | | | | | | |
| All-grade | 4* | 78/101 | 89/103 | 0.54[0.25,1.14] | 0 % | 0.10 |
| Grade ≥ 2 | 4 | 32/117 | 48/120 | 0.46[0.17,1.27] | 58 % | 0.13 |
| Grade ≥ 3 | 4** | 3/118 | 8/121 | 0.45[0.11,1.77] | 0 % | 0.25 |
| *Diarrhea* | | | | | | |
| All-grade | 4 | 40/117 | 32/120 | 1.48[0.79,2.79] | 0 % | 0.22 |
| Grade ≥ 2 | 4 | 16/117 | 10/120 | 1.72[0.73,4.07] | 0 % | 0.22 |
| Grade ≥ 3 | 4*** | 4/119 | 4/122 | 1.02[0.25,4.23] | 0 % | 0.98 |

*(Continues on next page)*

**Table II (cont.).** Primary results of adverse events in esophageal cancer during chemotherapy

| Meta-analyses variables | No. of studies | No. of patients | | Pool effect size | $I^2$ | *p* |
|---|---|---|---|---|---|---|
| | | ED | NO-ED | | | |
| **Gastrointestinal toxicities** | | | | **Pooled ORs (95 % CI)** | | |
| *Nausea* | | | | | | |
| All-grade | 3 | 44/107 | 47/110 | 0.82[0.34,1.99] | 47 % | 0.66 |
| Grade ≥ 2 | 3 | 18/107 | 21/110 | 0.56[0.10,3.26] | 71 % | 0.52 |
| Grade ≥ 3 | 3** | 9/108 | 8/111 | 1.10[0.40,3.08] | 0 % | 0.85 |
| *Constipation* | | | | | | |
| All-grade | 3 | 65/107 | 70/110 | 0.87[0.49,1.53] | 0 % | 0.62 |
| Grade ≥ 2 | 3** | 8/108 | 9/111 | 0.88[0.32,2.41] | 0 % | 0.80 |
| Grade ≥ 3 | 3*** | 3/109 | 3/112 | 1.03[0.20,5.24] | 0 % | 0.97 |
| *Anorexia* | | | | | | |
| All-grade | 3 | 81/107 | 77/110 | 0.99 [0.32, 3.05] | 56 % | 0.99 |
| Grade ≥ 2 | 3 | 40/107 | 40/110 | 1.02 [0.53, 1.98] | 0 % | 0.95 |
| Grade ≥ 3 | 3 | 17/107 | 10/110 | 1.88 [0.76, 4.66] | 0 % | 0.17 |
| **Hematological toxicities** | | | | **Pooled ORs (95 % CI)** | | |
| *Leucopenia* | | | | | | |
| All-grade | 3* | 40/71 | 54/75 | 0.50 [0.25, 1.00] | 0 % | 0.05 |
| Grade ≥ 2 | 3* | 27/71 | 44/75 | 0.43 [0.22, 0.84] | 0 % | 0.01 |
| Grade ≥ 3 | 3 | 41/107 | 53/110 | 0.41 [0.15, 1.13] | 22 % | 0.08 |
| *Anemia* | | | | | | |
| All-grade | 3 | 96/107 | 98/110 | 1.06 [0.44, 2.55] | 0 % | 0.90 |
| Grade ≥ 2 | 3 | 43/107 | 46/110 | 0.92 [0.47, 1.82] | 24 % | 0.81 |
| Grade ≥ 3 | 3** | 8/108 | 11/111 | 0.72 [0.28, 1.88] | 0 % | 0.51 |
| *Neutropenia* | | | | | | |
| All-grade | 3* | 26/71 | 50/75 | 0.28 [0.14, 0.57] | 0 % | < 0.01 |
| Grade ≥ 2 | 3* | 26/71 | 45/75 | 0.34 [0.17, 0.67] | 0 % | < 0.01 |
| Grade ≥ 3 | 3 | 45/107 | 63/110 | 0.28 [0.12, 0.63] | 0 % | < 0.01 |
| *Thrombocytopenia* | | | | | | |
| All-grade | 3 | 55/107 | 50/110 | 1.26 [0.64, 2.48] | 29 % | 0.50 |
| Grade ≥ 2 | 3 | 8/107 | 14/110 | 0.55 [0.21, 1.44] | 0 % | 0.22 |
| Grade ≥ 3 | 3** | 3/108 | 1/111 | 2.05 [0.34, 12.16] | 0 % | 0.43 |

*CI: confidence interval; ED: elemental diet; OR: odds ratio; SMD: standard mean differences. *All patients suffered from this disease in one study. We exclude one study. **All patients did not suffer from this disease in one study. We correct the data. ***All patients did not suffer from this disease in two studies. We correct the data.*

The risk of grade ≥ 2 leucopenia (OR = 0.43, 95 % CI: 0.22-0.84, $P_{statistics} < 0.05$; $I^2 = 0$ %, Fig. 5), grade ≥ 2 neutropenia (OR = 0.34, 95 % CI: 0.17-0.67, $P_{statistics} < 0.05$; $I^2 = 0$ %, Fig. 4), and grade ≥ 3 neutropenia (OR = 0.28, 95 % CI: 0.12-0.63, $P_{statistics} < 0.05$; $I^2 = 0$ %, Fig. 4) were decreased in the ED group. The risk of grade ≥ 3 anemia showed a decreasing trend (OR = 0.72, 95 % CI: 0.28-1.88, $P_{statistics} = 0.51$; $I^2 = 0$ %, Table II). No significant differences were found among the risk of grade ≥ 2 anemia, grade ≥ 2 thrombocytopenia, and grade ≥ 3 thrombocytopenia between the ED and non-ED groups (Table II).

## DISCUSSION

According to the statistical analysis above, the central conclusion is that the existing evidence cannot support the hypothesis that ED can prevent the occurrence of OM in patients with EC during chemotherapy. However, there is a possibility that an ED can reduce the risk of leucopenia and neutropenia.

OM is among the most common and severe AEs in EC during chemotherapy. Due to its easy absorption when intestinal villi are damaged by chemotherapy (26), an ED is considered to have po-

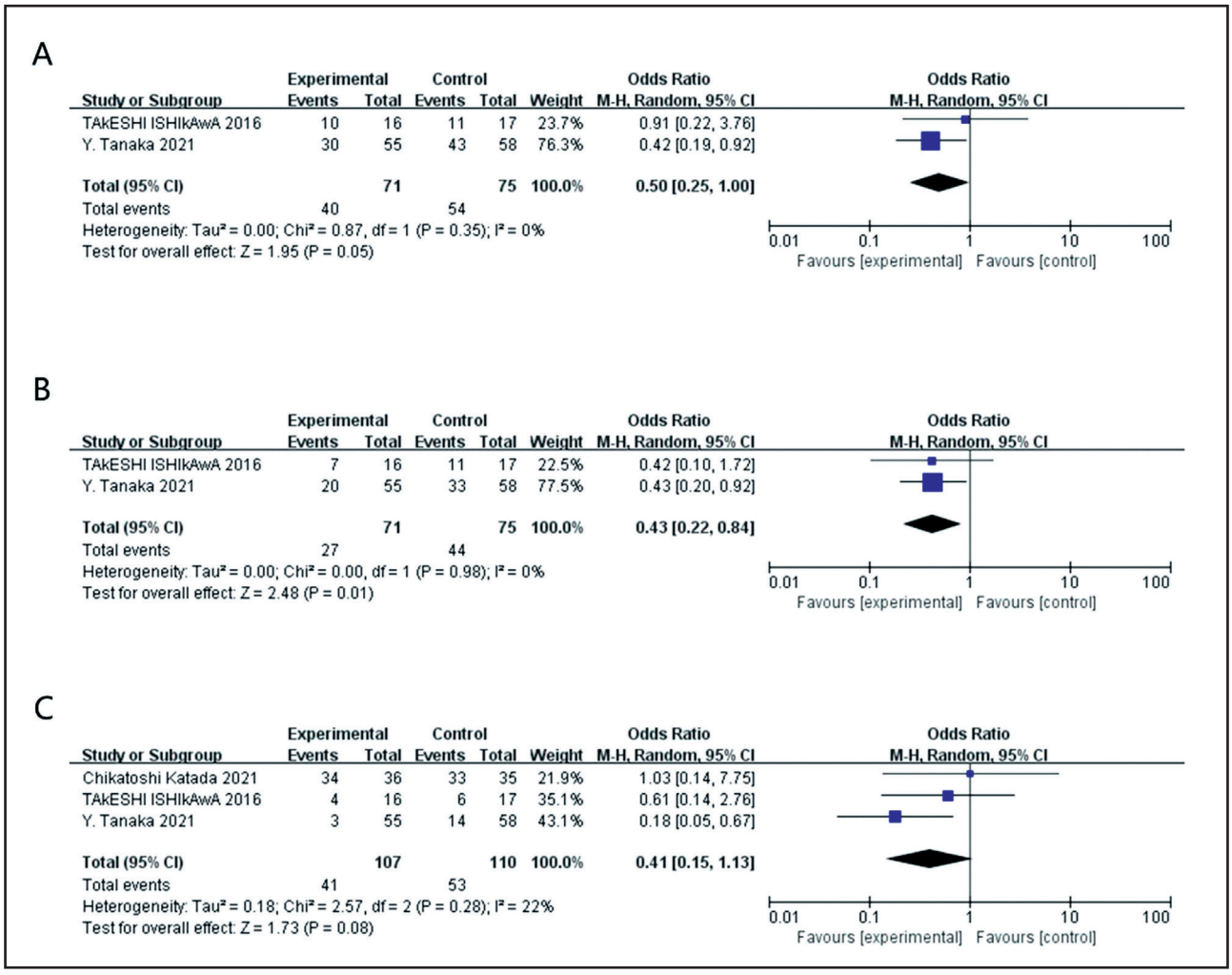


**Figure 4.**

Incidences of neutropenia in the ED and non-ED groups: A. All-grade neutropenia; B. Grade ≥ 2 neutropenia; C. Grade ≥ 3 neutropenia.

tential therapeutic effects and has been widely used, particularly in Japan. However, the clinical efficacy of ED remains controversial. Some studies have found that it is effective (13,16-18), but other studies could not prove its effectiveness (14,15). Therefore, this quantitative meta-analysis synthesized the existing evidence and can be used to guide clinical decision-making. Our results showed that the risk of all-grade OM had a decreasing trend in the ED group compared to the CG, but without statistical differences. These results do not for conclusively support the effectiveness of prevention of ED, and we must interpret the marginal results with caution. In mouse models and human keratinocyte cell lines, an ED accelerates mucosal and skin recovery through FGF2 induction and reepithelization (27) and reduces the expression of cytokines (TNF-$\alpha$, IL-1$\beta$, and IL-6) by inhibiting NF-kB activation (28). The results of these studies imply that an ED is probably effective in the treatment of a variety of cutaneous inflammatory disorders, even externally (29). Whether or not the administration of an ED can reduce the risk of OM remains controversial. Hence, more large-scale random controlled trials (RCTs) are required to guide clear clinical decisions.

OM, anorexia, and nutritional disorders are interrelated and constitute a vicious circle of adverse reactions to chemotherapy (30). As a result, gastrointestinal AEs are drawing increasing amounts of attention. However, in this meta-analysis, no direct evidence was found to confirm that an ED could reduce the risk of diarrhea, nausea, constipation, or vomiting. Similarly, compared to the CG, an ED could not reduce the risk of gastrointestinal adverse reactions such as nausea, vomiting, diarrhea, and bloating for Crohn's disease (31). A possible explanation is that chemotherapeutic drugs induce nausea and vomiting by activating neurotransmitter receptors in the area postrema and the vagal afferents (32). Hence, receptor antagonists, such as ondansetron instead of ED, can have satisfactory effects (33). Furthermore, the majority of patients included in the meta-analysis had an Eastern Cooperative Oncology Group performance status of 0-2, which indicated that they were ambulatory and capable of all self-care. Given the abovementioned performance, fewer gastrointestinal adverse reactions occurred, and the efficacy could have been underestimated.

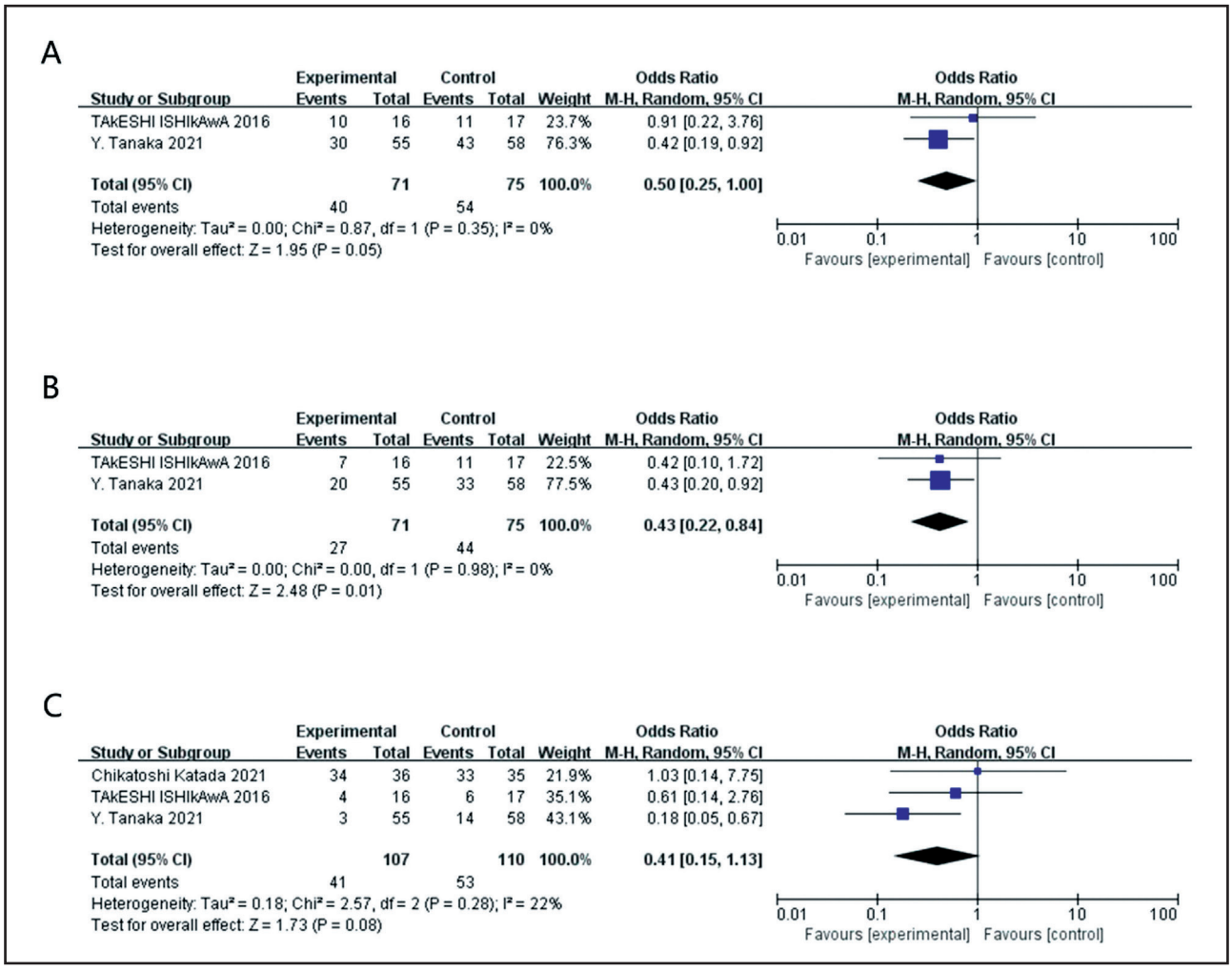


**Figure 5.**

Incidences of leucopenia in the ED and non-ED groups: A. All-grade leucopenia; B. Grade ≥ 2 leucopenia; C. Grade ≥ 3 leucopenia.

Our results showed that an ED helped to reduce all-grade neutropenia, grade ≥ 2 neutropenia, grade ≥ 3 neutropenia, and grade ≥ 2 leucopenia. An ED may also have a positive impact on grade ≥ 3 anemia. Neutropenia easily progresses to febrile neutropenia and even death (34). Leukopenia can be fatal to the patient, especially when they have agranulocytosis and fever (35). Severe anemia can lead to lethargy and heart failure (36). Avoiding these AEs is crucial for maintaining anti-tumour treatment. Several possible reasons might explain this preventive effect. Chemotherapy suppresses the proliferation of the hematopoietic system and restricts the differentiation of progenitor cells into functioning cells (37). An ED contains a variety of amino acids, among which many amino acids can play a mitigating role. Histidine has an antioxidant effect, reducing free radicals induced by cytotoxic therapy (38). Isoleucine can activate the mammalian target of rapamycin complex 1, which plays a critical role in hematopoietic stem cell homeostasis (39). Appropriate arginine and leucine can maintain cell proliferation, especially from the G1 phase to the S and G2/mitotic phases, oxidative metabolism, and protein translation in mouse embryonic stem cells (40).

We found during the data analysis that the ED group had a tendency for higher levels of aspartate transferase (AST) and alanine transaminase (ALT). Two investigations found that the ED group frequently had elevated AST and ALT levels compared to the CG (13,15). This consequence may due to the metabolism of multiple amino acids is closely related to the liver (38), and excessive amino acids increase the burden on the liver of tumor patients, increasing ALT. Further experiments are required to prove this speculation. However, in general, this suggests that clinicians should assess the liver function of patients with esophageal cancer in advance when using an ED to avoid causing a more significant burden on the liver.

We also closely examine the influence of compliance with the ED and the compare total calorie/protein intake. In one study, it was found that completing the ED diet may predict a decrease in the occurrence of OM in EC patients during chemotherapy (19). It is possible that patients who can complete the ED have better physical conditions, making them more capable of receiving chemotherapy entirely. However, one of the four articles

included in this study indicated that patients achieving 100 % compliance with the ED were more likely to tolerate complete chemotherapy compared to those who could not receive a complete the ED diet. Surprisingly, it did not lead to a reduction in the incidence of OM (13). The difference between the two studies could be explained as follows: first, in the initial study, the severity of OM in patients was higher, allowing the ED to demonstrate a more pronounced preventive effect; and second, the sample size in both studies were not large, making the statistical results somewhat unreliable. In the future, a larger sample size and a more objective evaluation system will be necessary. Regarding the total calorie/protein intake, most studies lack relevant information, and only one study suggests that the difference in calorie intake between the two groups is not significant, and the protein intake in the ED diet tends to be higher, with potential statistically significant differences (14). Compared to a normal diet, an ED can significantly increase the levels of amino acids in the blood of EC patients undergoing chemotherapy (14), which may help prevent chemotherapy-related AEs (41). Glutamine has also captured the attention of many researchers. We do not know if the control group has an additional intake of immune nutrients, as the control group uses regular diet. We believe it is unlikely that this will have an impact on the research results because the EG is supplemented with an ED on the basis of a conventional diet, and the immune nutritional content of the conventional diet was not as high as ED, and the nutrients in the conventional diet were not as easy to absorb and utilize as those in the ED. Furthermore, an additional study suggested that ED plus glutamine was more effective in preventing chemotherapy-related AEs in EC patients compared to glutamine alone or regular diet (18). Patients with advanced or postoperative EC often require 4-6 cycles of chemotherapy; however, the study period of the trials that were included was 2-9 weeks, which translates 1-3 cycles. This inconsistent trial duration may affect ED's ability to prevent treatment-related AEs in EC patients, as some chemotherapy reactions have additive effects, including hematological toxicity. More outstanding clinical trials that can offer comprehensive reference materials for the clinical role of ED would be helpful in the future.

## STRENGTHS AND LIMITATIONS

This meta-analysis had the following strengths. First, to our knowledge, this was the first meta-analysis to comprehensively evaluate the preventive effect of an ED on AEs during chemotherapy in patients with esophageal cancer. The results could help clinicians to fully understand the role of an ED. Second, the previous meta-analysis involved the preventive effect of an ED for OM during chemotherapy in EC by simply searching on Medline (via PubMed) and including articles from non-randomized controlled studies. We searched four databases and read the full text to ensure all studies were randomized and controlled. We corrected retrieval and inclusion errors and hoped to reach more scientific and rigorous conclusions. Third, we found that an ED can help prevent leucopenia and neutropenia during chemotherapy in EC. This finding could help to broaden the scope of ED applications and establish it as an adjunct to EC with chemotherapy as a way to reduce hematologic toxicities.

This meta-analysis had the following limitations. First, only four clinical studies were enrolled, and some indicators were only involved three studies, which must be considered when interpreting the results. Second, the primary features contained clinical heterogeneity, including therapy (chemoradiotherapy or chemotherapy) and the study period. Parts of the trials used a gargle containing 0.08 % lidocaine or azulene to relieve symptoms. Third, the production of a suitable placebo was technically and ethically problematic, meaning that the blinding of participants and personnel was not particularly strict. Fourth, it is important to note that the four clinical studies were carried out only in Japan, and the findings may not be regarding extrapolated to other populations. To enhance the reliability of the results regarding whether an ED can help prevent treatment-related AEs among cancer patients worldwide, additional high-quality and multicenter clinical studies are needed. Fifth, there are limitations on the applicability of the conclusion to other brands, as only Elental® was included in our study. To address this gap, further clinical trials investigating various brands are required.

## CONCLUSIONS

In this study, it was found that an elemental diet may decrease the risk of leucopenia and neutropenia during chemotherapy in EC. However, no significant improvement in other side effects was observed. As such, whether to use an ED requires a detailed evaluation by clinicians, and agreement should be reached through patient communication.

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