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Association between low-fat enteral nutrition after esophagectomy and a lower incidence of chyle leakage: A call for more and better evidence

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Abstract

Objective: Reliable methods to prevent chyle leakage after esophagectomy are needed. This retrospective study was performed to evaluate the correlation between low-fat nutrition and the incidence of chyle leakage after esophagectomy.

Methods: This multicenter retrospective case–control study involved patients who underwent Ivor Lewis esophagectomy from December 2012 to August 2017. Tube feeding was started on postoperative day 1 with a normal fat-containing formula (control group, 203 patients) or low fat-containing formula (241 patients).

Results: The patients in the control group and low-fat group had a similar incidence of chyle leakage (7 [3.4%] vs. 19 [9.4%], respectively) and anastomotic leakage (4 [2.0%] vs. 11 [5.4%], respectively). The multivariate logistic regression indicated that high-volume surgeon experience (performance of $\geq$100 esophagectomies per year) was correlated with a lower incidence of chyle leakage (odds ratio, 0.280; 95% confidence interval, 0.110–0.712), whereas low-fat nutrition was correlated with an increased risk of anastomotic leakage (odds ratio, 5.995; 95% confidence interval, 1.201–29.925).

Conclusion: Prophylactic low-fat enteral nutrition following esophagectomy might not decrease the risk of chyle leakage. More and better evidence is needed.

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Introduction

Postoperative chyle leakage following surgical treatment for esophageal cancer is not rare. Early enteral low-fat elemental nutrition is reportedly a potentially useful method of preventing chyle leakage after transthoracic esophagectomy with three-field lymphadenectomy.[1] A recent study also revealed that the incidence of chylothorax after esophagectomy was significantly lower in the low-fat tube feeding group than in the normal-fat group (15 [13.4%] vs. 29 [33.0%], respectively; $p = 0.001$).[2] Furthermore, the normal-fat formula was associated with an increased risk of chylothorax (odds ratio [OR], 5.1; 95% confidence interval [CI], 2.1–12.1).[2]

Although low-fat feeding is considered a reasonable technique to lower the incidence of post-esophagectomy chyle leakage, it has not been established as a standard protocol in clinical guidelines because of the lack of high-quality evidence. The present retrospective study from two tertiary hospitals was conducted in accordance with the basic principles of an intention-to-treat analysis and real-world study. The aim was to assess the correlation of prophylactic low-fat enteral nutrition with the incidence of chyle leakage after Ivor Lewis esophagectomy.

Patients and methods

Study population and design

This multicenter retrospective case-control study involved consecutive patients from two tertiary hospitals who underwent esophagectomy for primary esophageal cancer from December 2012 to August 2017.

Ethics statement

All procedures were performed in accordance with the ethical standards of the institutional research committee and the Helsinki declaration. Written informed consent was obtained from every individual patient, and the study was approved by the Institutional Review Board and the Medical Ethics Committee of Xuzhou Central Hospital Affiliated to Southeast University. All data are presented anonymously.

Patient selection

The inclusion criteria were (1) squamous cell carcinoma or adenocarcinoma in the middle or lower third of the esophagus or esophagogastric junction (epicenter within the proximal 2 m of the gastric cardia) without recurrent laryngeal nerve palsy or distant lymph nodes on contrast-enhanced computed tomography according to the 8th edition of the TNM staging system for esophageal or esophagogastric cancer (cT1/3N0/3M0, I–III)[3]; (2) an American Society of Anesthesiologists score and cardiopulmonary function appropriate for radical esophagectomy; i.e., a performance status score of 0 to 2 on a 5-point scale (with higher numbers indicating greater disability) and a forced expiratory volume in 1 second of $\geq$1.0 L; and (3) performance of standard Ivor Lewis esophagectomy with extended two-field lymphadenectomy followed by stapled end-to-side anastomosis with the gastric conduit. The exclusion criteria were (1) a history of chest surgery or currently undergoing simultaneous surgical/medical therapy for another malignancy; (2) intraoperative thoracic duct ligation or resection for any reason; (3)

colon interposition for tract reconstruction other than the gastric conduit; (4) palliative, McKeown, or Sweet esophagectomy or endoscopic submucosal dissection; (4) malnutrition on admission with a serum albumin concentration of <35 g/L (reference range, 35–55 g/L) or weight loss exceeding 15% in 6 months before cancer diagnosis; and (5) treatment with total parenteral nutrition or direct oral feeding since postoperative day (POD) 0 to 1 (early oral feeding).

The patients in the control group received a normal enteral diet through jejunostomy. If chyle leakage in the thorax or abdomen was diagnosed in these patients, low-fat tube nutrition was scheduled. The patients in the low-fat group received enteral nutrition from POD 1 to removal of the chest drainage tube or discharge from the hospital. However, the surgeons chose prophylactic low-fat feeding mainly according to their personal experience regarding the risk of esophagectomy-related chylous leakage and anastomotic leakage (AL); a standardized criterion was lacking in this study. Low-fat nutrition was considered when the tumor had invaded the mediastinal tissue and dissection of the esophagus was expected to be difficult because intraoperative injury of the thoracic duct was seemingly unavoidable.

Surgical procedure

Preoperative medical, physical, and mental rehabilitation was implemented individually. The operations were performed by two surgeons whose experience was graded as either low-volume (<50 esophagectomies/year) or high-volume (≥100 esophagectomies/year). Open or hybrid minimally invasive Ivor Lewis esophagectomy with curative intent became the standard procedure for treatment of non-metastatic esophageal cancer in 2014, after training with a learning curve without extra morbidity had been achieved

Hybrid surgery involved laparoscopic gastric mobilization and open thoracotomy. The first step was gastric mobilization and lymphadenectomy with a laparoscopic approach. The lesser curvature of the stomach was divided with an Endo GIA linear stapler (Medtronic, Minneapolis, MN, USA) to create a 3- to 4-cm-wide gastric conduit. Next, a muscle-sparing posterior lateral thoracotomy was created in the fifth intercostal space for access to the right pleural cavity and mediastinum, without division of the latissimus or serratus muscle. Surgical quality was assured by standardization of the technique (esophagectomy and gastric tube reconstruction followed by intrathoracic end-to-side esophagogastrostomy using a stapler). Extended two-field lymph node dissection was carried out, including the upper thoracic paraesophageal, bilateral recurrent nerve, and tracheobronchial lymph nodes as previously described.[4]

Milk/olive oil to facilitate identification of the thoracic duct and pleurodesis was not used in this cohort. However, thoracic duct ligation was performed when intraoperative chyle leakage was identified.

An ultrasound-guided serratus anterior plane block for postoperative analgesia was applied to promote early mobilization of the patients.

Postoperative nutritional support

Patients began to drink clean water on POD 1 while the nasogastric tube was still in place. On POD 5 to 7, the nasogastric tube was removed and an oral diet was begun with soft and smooth food if the absence of AL and delayed gastric emptying was confirmed by a contrast swallow test. Furthermore, the chest tubes were removed at a threshold of 300 mL/day after the absence of atelectasis was confirmed on a radiograph. For patients with chyle leakage, the tubes were removed if the effluent rate continued to be $\leq$50 mL/day.

Enteral tube feeding via jejunostomy was started on POD 1 except when contraindications such as ileus were present. The patients in the low-fat group initiated treatment with a low fat-containing enteral feeding formula (ELENTAL®; Ajinomoto Pharmaceuticals Co., Ltd., Tokyo, Japan) continually until removal of the chest tubes (at least 7 days). The nutritional regimen in the present study was similar to that in a study by Moro et al.[1] The patients in the control group started treatment with an enteral diet with a standard fat-containing polymeric formula (ENSURE LIQUID®; Abbott Japan Co., Ltd., Tokyo, Japan). The median maximal amount of feeding administered to these patients ranged from 1,500 to 2,000 mL/day and 30 to 35 kcal/kg of body weight per day.

Management of complications

Chyle leakage was diagnosed based on the triglyceride concentration (>110 mg/dL) or the presence of chylomicrons (positive Sudan III stain) in the pleural fluid.[5] Based on the standard treatment options for chylothorax, patients in the control group who were diagnosed with postoperative chyle leakage were administered a low-fat diet or total parental nutrition. If the chylous fluid exceeded 500 mL/day for 5 days after conservative treatment, surgical intervention was considered.

AL was defined as a full-thickness gastrointestinal defect involving the esophagus, anastomosis, staple line, or conduit. Patients with leakage often first presented with a postoperative fever or leukocytosis. Contrast esophagography was commonly performed on POD 5 to 7 for the detection of AL or conduit leakage. Computed tomography or endoscopy (if necessary) helped to determine the extent and location of the fistula.

The major endpoint of this study was the incidence of chylothorax and AL.

Statistical analysis

Continuous data are presented as mean ± standard deviation. The statistical analysis was performed using Statistical Package for the Social Sciences software version 23.0 for Windows (IBM Corp., Armonk, NY, USA). Student's t test or the Wilcoxon test was used to compare continuous data. Pearson's χ^2 test was used to compare categorical data, except for variables with expected values of <5; in such cases, Fisher's exact test was used. Risk factors for chylothorax and AL were assessed by multivariate logistic regression analysis, with chyle leakage or AL as the dependent variable, respectively (probability for stepwise regression was defined as 0.50 in this study). The OR with 95% CI was calculated. A two-sided p-value of <0.05 was considered statistically significant.

Results

Patient demographics

In total, 444 patients were included in the statistical analysis (normal-fat group, n = 203; low-fat group, n = 241). The patients comprised 109 women and 335 men with a mean age of 62.3 years (range, 32–85 years). The process of data collection is shown in Figure 1.

The interval between neoadjuvant therapy and surgery was 4 weeks. As shown in Table 1, there was no significant difference in sex, body mass index (BMI), pathological T stage, smoking history, alcohol history, or the distribution of surgeon experience between the two groups. However, significant differences were found in the age distribution ($p < 0.001$),

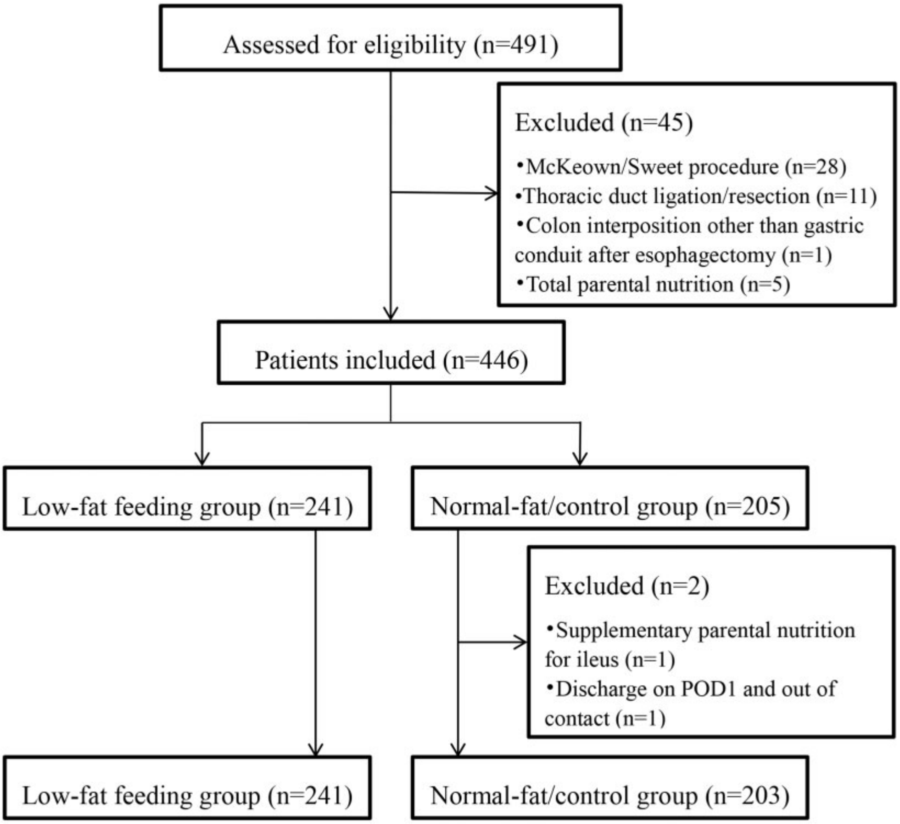

Figure 1. Flow chart of data collection. POD, postoperative day.

proportion of patients who had received neoadjuvant chemotherapy ($p = 0.041$), and tumor location ($p < 0.001$).

Operative features

No 30-day mortality, intraoperative major bleeding, bronchopleural fistula, heart/respiratory failure, pulmonary embolism, or deep vein thrombosis was encountered in this cohort. All patients achieved pathological R0 resection. In addition, the patients in the low-fat nutrition group had a shorter operation time than the patients in the control group (164.5 ± 34.0 vs. 172.7 ± 33.2 min, respectively; $p = 0.011$). However, the intraoperative blood loss, stations and numbers of dissected lymph nodes, incidence of complications, chest tube duration, overall drainage volume, and postoperative hospital stay were similar between the two groups (Table 2).

Postoperative chyle leakage and AL

Chyle leakage in the thorax or abdomen was diagnosed in 26 patients (5.9%), without a significant difference between the low-fat group and the control group (19 [9.4%] vs. 7 [3.4%], respectively). Furthermore, AL occurred in 11 patients (5.4%) in the low-fat group and 4 patients (2.0%) in the control group after esophagectomy, also without a significant difference.

Table 1. Patients' baseline demographic and clinical characteristics.

	Control group (n = 203)	Low-fat feeding group (n = 241)	p value
Age, years	64.3 ± 7.8	64.2 ± 7.8	0.896
>65	98 (48.3)	10 (4.1)	<0.001
≤65	105 (51.7)	231 (95.9)	
Sex			0.060
Female	41 (20.2)	68 (28.2)	
Male	162 (79.8)	173 (71.8)	
Body mass index, kg/m^2	23.9 ± 2.7	24.2 ± 3.2	0.260
Lean (<18.5)	4 (2.0)	6 (2.5)	0.630
Normal (18.5–23.9)	99 (48.8)	116 (48.2)	
Overweight (24.0–27.9)	87 (42.9)	96 (39.8)	
Obese (>28.0)	13 (6.3)	23 (9.5)	
Smoking history			0.056
Never	100 (49.3)	141 (58.5)	
Previous or current	103 (50.7)	100 (41.5)	
Alcohol history			0.292
Never	118 (58.1)	127 (52.7)	
Previous or current	85 (41.9)	114 (47.3)	
Neoadjuvant chemotherapy	28 (13.8)	18 (7.5)	0.041
Comorbidity	61 (30.0)	77 (32.0)	0.088
Pulmonary disease	2 (1.0)	10 (4.1)	
Diabetes mellitus	18 (8.9)	15 (6.2)	
Coronary artery disease requiring PCI	23 (11.3)	10 (4.1)	
Hypertension	9 (4.4)	7 (2.9)	
ASA score			0.462
1–2	2 (1.0)	5 (2.1)	
3	201 (99.0)	236 (97.9)	
FEV1, L	2.4 ± 0.7	2.3 ± 0.6	0.457
LVEF, %	64.8 ± 2.8	65.1 ± 2.7	0.270
Tumor location			<0.001
Lower third	8 (3.9)	51 (21.2)	
Middle third	195 (96.1)	190 (78.8)	
Pathological T stage			0.101
pT1–2	126 (62.1)	130 (53.9)	
pT3	77 (37.9)	111 (46.1)	
Pathological N stage			0.195
pN0–1	188 (92.6)	214 (88.8)	
pN2–3	15 (7.4)	27 (11.2)	
Experience of the operators			0.086
Low-volume	104 (51.2)	103 (42.7)	
High-volume	99 (48.8)	138 (57.3)	

Data are presented as mean ± standard deviation or number (%).
High-volume experience was defined as ≥100 esophagectomies per year (Surgeon C.Z.), and low-volume experience was defined as <50 esophagectomies per year (Surgeon H.Z.).
PCI, percutaneous coronary intervention; ASA, American Society of Anesthesiologists; FEV1, forced expiratory volume in 1 second; LVEF, left ventricular ejection fraction.

Table 2. Patients' perioperative details.

	Control group (n = 203)	Low-fat feeding group (n = 241)	p value
Procedure for esophagectomy			0.701
Open surgery	83 (40.9)	103 (42.7)	
Hybrid MIE	120 (59.1)	138 (57.3)	
Stations of lymph node dissection	8.2 ± 1.8	8.1 ± 1.8	0.674
≤9	81 (40.0)	97 (40.2)	1.000
>9	122 (60.0)	144 (59.8)	
Harvested lymph nodes	20.8 ± 2.5	20.3 ± 2.8	0.498
≤12	25 (12.3)	33 (13.7)	0.675
>12	178 (87.7)	208 (86.3)	
Operation time, minutes	172.7 ± 33.2	164.5 ± 34.0	0.011
≤180	105 (51.7)	135 (56.0)	0.390
>180	98 (48.3)	106 (44.0)	
Blood loss, mL	121.3 ± 87.0	112.0 ± 71.1	0.215
Chest tube duration, days	6.7 ± 5.7	7.0 ± 6.2	0.652
Postoperative complications	33 (16.3)	46 (19.1)	0.081
Chyle leakage in thorax or abdomen	7 (3.4)	19 (9.4)	0.066
Anastomotic leakage	4 (2.0)	11 (5.4)	0.187
Vocal cord paralysis	16 (7.9)	10 (4.9)	0.107
Delayed gastric conduit emptying	5 (2.5)	3 (1.5)	0.478
Aspiration	1 (0.5)	3 (1.5)	0.629
Severity of complications*			0.457
Grade I	31 (15.3)	40 (16.6)	
Grade II	2 (1.0)	6 (2.5)	
Postoperative hospital stay, days	10.5 ± 5.8	10.6 ± 5.9	0.901

Data are presented as mean ± standard deviation or number (%).
MIE, minimally invasive esophagectomy.
*According to the Clavien–Dindo Classification of Surgical Complications.

Multivariable analyses of risk factors for chyle leakage and AL

The variables possibly associated with chyle leakage were added to the multivariable logistic model. No statistical significance was found for age, sex, BMI, alcohol or smoking history, T stage, tumor location, neoadjuvant treatment, surgical procedures, operation time, stations or numbers of dissected lymph nodes, or low-fat feeding. However, high-volume surgeon experience was correlated with a lower incidence of chyle leakage (OR, 0.280; 95% CI, 0.110–0.712; p = 0.007) (Table 3).

Similarly, another multivariate logistic analysis was conducted to estimate the potential indicators of AL. No significant correlation was found for age, BMI, comorbidity, surgical procedures, operation time, or stations or numbers of dissected lymph nodes. Neoadjuvant chemotherapy was a positive risk factor for AL (OR, 12.015; 95% CI, 2.932–49.241; p = 0.001), whereas high-volume surgeon experience was a negative indicator of AL (OR, 0.165; 95% CI, 0.043–0.633; p = 0.009) (Table 4). Furthermore, low-fat tube feeding was correlated with an increased risk of AL (OR, 5.995; 95% CI, 1.201–29.925; p = 0.029).

Table 3. Multivariate analysis of factors correlated with chyle leakage after Ivor Lewis esophagectomy.

	Odds ratio (95% confidence interval)	p value
Sex (male vs. female)	1.493 (0.521–4.280)	0.456
Age (> 65 vs. ≤65 years)	0.276 (0.074–1.033)	0.056
Body mass index (high vs. low)	0.798 (0.429–1.487)	0.478
pT (T3 vs. T1–2)	1.679 (0.720–3.918)	0.230
pN (N2–3 vs. N0–1)	0.598 (0.235–1.523)	0.281
Tumor location (lower third vs. middle third of esophagus)	2.011 (0.585–6.916)	0.267
Pulmonary comorbidities (yes vs. no)	2.737 (0.504–14.873)	0.244
Coronary artery disease (yes vs. no)	1.880 (0.370–9.564)	0.447
Smoking history (current/previous vs. none)	0.611 (0.240–1.555)	0.301
Alcohol history (current/previous vs. none)	0.713 (0.288–1767)	0.465
Neoadjuvant treatment (yes vs. no)	1.901 (0.559–6.457)	0.303
Operative time (>180 vs. ≤180 minutes)	1.677 (0.718–3.917)	0.232
Dissected lymph nodes (>12 vs. ≤12)	0.557 (0.191–1.625)	0.284
Experience of surgeon (high-volume vs. low-volume)	0.280 (0.110–0.712)	0.007

Table 4. Multivariate analysis of factors correlated with anastomotic leakage after Ivor Lewis esophagectomy.

	Odds ratio (95% confidence interval)	p value
Age (>65 vs. ≤65 years)	3.699 (0.678–20.177)	0.131
Body mass index (high vs. low)	0.672 (0.283–1.594)	0.367
Coronary artery disease (yes vs. no)	3.672 (0.703–19.187)	0.123
Diabetes mellitus (yes vs. no)	0.462 (0.077–2.782)	0.400
Alcohol history (current/previous vs. none)	1.626 (0.527–5.020)	0.398
Neoadjuvant treatment (yes vs. no)	12.015 (2.932–49.241)	0.001
Operative time (>180 vs. ≤180 minutes)	0.379 (0.113–1.265)	0.115
Stations of dissected lymph nodes (>9 vs. ≤9)	0.593 (0.187–1.880)	0.375
Experience of surgeon (high-volume vs. low-volume)	0.165 (0.043–0.633)	0.009
Tube feeding (low fat vs. normal fat)	5.995 (1.201–29.925)	0.029

Discussion

Most patients lose body weight after esophagectomy because of their compromised nutritional status.[6,7] Early enteral feeding after surgery can be given via jejunostomy or a nasojejunal tube.[8] However, Berkelmans et al.[9] reported that more than half of the patients in their study deviated from the intended feeding protocol after esophagectomy and that AL, chyle leakage, and acute respiratory distress appeared to be the main reasons for feeding deviation. Immunonutrition may attenuate stress after esophagectomy.[10]

Prevention of chyle leakage and AL following esophagectomy is a challenge. Chyle is made primarily of chylomicrons, an aggregate of long-chain triglycerides, cholesterol esters, and phospholipids. The normal rate of chyle production is around 2.4 L/day.[5] Chyle leakage causes significant loss of fluid, electrolytes, proteins, and lymphocytes, leading to deleterious effects on wound healing and immunity.

Low-fat enteral nutrition is useful for preventing chyle leakage because of the lower triglyceride content in low-fat than normal-fat nutritional formulas, thereby facilitating the healing of lymphatic defects during esophagectomy.[1,2] However, a standard formula for postoperative nutritional support is still controversial. As an effective therapy for chyle leakage,[11] a low-fat diet might play a role in reducing the incidence of this complication. Nevertheless, efficacy data are still lacking. As shown in the present study, a prophylactic low-fat diet was not associated with a decreased incidence of chyle leakage after Ivor Lewis esophagectomy. The two currently available reports regarding the effect of low-fat enteral nutrition after esophagectomy are shown in Table 5. However, a definite conclusion could not be drawn because the level of evidence was estimated to be 4 (low-quality) according to the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence.[12]

Small- and medium-chain fatty acids can be provided in the diet, and long-chain fatty acids can be supplemented intravenously.[13] Trioctanoin may be a preferable medium-chain triglyceride substrate for nonsurgical treatment of chylothorax.[14] Moreover, chylothorax is associated with a higher incidence of vascular thrombosis in adults undergoing Ivor Lewis esophagogastrectomy.[15] However, the risk factors for postoperative chyle leakage in the thorax or abdomen remain unclear. One review showed that a post-chemoradiotherapy status and a high intraoperative fluid balance were predictors of chylothorax after esophagectomy.[16] Other independent factors include a transthoracic approach, neoadjuvant chemoradiotherapy, and the preoperative BMI.[11]

Knowledge of the anatomy of the lymphatic system and its variations is essential in planning esophagectomy with curative intent. As shown in our study, high-volume surgeon experience was correlated with a decreased risk of chyle leakage. Kranzfelder et al.[17] reported that the rates of chylothorax were low in high-volume centers (2%–3%). Therefore, one of the major concerns regarding how to diminish post-esophagectomy chyle leakage should be surgical training.

The effect of prophylactic thoracic duct ligation in reducing chylothorax is also controversial. One systematic review showed that prophylactic ligation of the thoracic duct is an effective preventative measure to reduce the incidence of chylothorax after esophagectomy for cancer.[18] However, an updated meta-analysis showed no significant effect of intraoperative thoracic duct ligation in reducing the incidence of chylothorax.[19] In addition, it has been reported that prophylactic thoracic ligation might reduce the overall survival of patients with esophageal cancer.[20] Oral administration of olive oil 8 hours before esophagectomy might also be effective to minimize postoperative chylothorax.[21] Similarly, preoperative oral administration of milk facilitates visualization of the thoracic duct and decreases the risk of iatrogenic injury during esophagectomy.[22] Preventive octreotide was not associated with a reduced risk of chylothorax after mediastinal lymph node dissection.[23]

The potential mechanisms by which the incidence of AL increased in the low-fat

Table 5. Previous reports evaluating the effect of low-fat enteral feeding on chyle leakage after esophagectomy.

	Moro et al. (2016)[1]	Schurink et al. (2019)[2]	Present study
Design	Retrospective case-control study	Retrospective case-control study	Retrospective case-control study
Level of evidence*	4	4	4
Sample size (low-fat vs. normal-fat group)	21 vs. 53	112 vs. 86	241 vs. 203
Nutritional formula			
Normal-fat group	Fat, 3.5 or 2.2 or 2.8 g/100 kcal (ENSURE LIQUID®/RACOL®/IMPACT®, Japan)	Long-chain triglycerides, 37.3 g/L (Nutrison Protein Plus, Netherlands)	Fat, 3.5 g/100 kcal (ENSURE LIQUID®, Japan)
Low-fat group	Fat, 0.17 g/100 kcal (ELENTAL®, Japan)	Long-chain triglycerides, 8.04 g/L (Nutrison Advanced Peptisorb, Netherlands)	Fat, 0.17 g/100 kcal (ELENTAL®, Japan)
Start of enteral nutrition (low-fat vs. normal-fat group)	(mean) POD 1.0 vs. 2.6	POD 1	POD 1
Duration of low-fat enteral nutrition, days	5 (range, 3–11)	First 7 PODs	9 (range, 7–16)
Neoadjuvant treatment (low-fat vs. normal-fat group)	11 (52.4%) vs. 25 (47.2%)	95 (84.8%) vs. 67 (77.9%)	18 (7.5%) vs. 28 (13.8%)
Experience of surgeons (high-volume/low-volume)			
Low-fat group	NA	NA	138 (57.3%) vs. 103 (42.7%)
Normal-fat group			99 (48.8%) vs. 104 (51.2%)
Surgical procedure	Transthoracic esophagectomy and three-field lymphadenectomy	Transhiatal/transthoracic (Ivor Lewis/McKeown)	Open/hybrid MIE and two-field lymphadenectomy
Preoperative oral milk/oil, n	NA	NA	0
Intraoperative thoracic duct ligation/resection, n (low-fat vs. normal-fat group)	7 (33.3%) vs. 46 (86.8%), $p < 0.001$	94 (83.9%) vs. 70 (81.4%)	0

(continued)

Table 5. Continued.

	Moro et al. (2016)[1]	Schurink et al. (2019)[2]	Present study
No. of dissected lymph nodes (low-fat vs. normal-fat group)	NA	23.0 (18.0–33.0) vs. 18.5 (14.8–28.0)	20.3 ± 2.8 vs. 20.8 ± 2.5
Operation time, minutes (low-fat vs. normal-fat group)	528 ± 113 vs. 471 ± 76	NA	164.5 ± 34.0 vs. 172.7 ± 33.2
Incidence of chyle leakage (low-fat vs. normal-fat group)	1 (4.8%) vs. 5(9.4%), p = 0.668	15 (13.4%) vs. 29 (33.7%), p = 0.001	19 (9.4%) vs. 7 (3.4%), p = 0.066
Incidence of anastomotic leakage (low-fat vs. normal-fat group)	NA	29 (33.7%) vs. 24 (21.4%), p = 0.053	11 (5.4%) vs. 4 (2.0%), p = 0.187

POD, postoperative day; NA, not available; MIE, minimally invasive esophagectomy.
*Quality of evidence was categorized according to Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence [http: //www.cebm.net/index.aspx?o=5653].

group are unknown, but the difference was probably ascribed to the obvious bias of this study. Low-fat tube feeding was a risk factor for AL compared with the normal-fat formula; however, the nutritional status of these patients was not quantitatively measured. Although high-volume surgeon experience was correlated with a lower incidence of chyle leakage and AL, the propensity for the esophageal anastomosis to heal is actually impacted by many parameters, including but not limited to systemic, local, and technical factors. The incidence of AL after esophageal resection is about 5% to 20%, which can result in a 30-day mortality rate of 2.1% to 35.7%.[24] van Workum et al.[25] reported that the mean incidence of AL following minimally invasive esophagectomy decreased from 18.8% during the learning phase to 4.5% after the plateau had been reached, and 36 extra patients developed AL during the learning curve; this could have been avoided if the patients had undergone the operations by experienced surgeons. Therefore, the occurrence of both chyle leakage and AL was determined to a considerable extent by the operator's surgical skills, including but not limited to minimizing trauma to the gastric conduit and vascular axis alongside the greater curvature.

Limitations

Based on the principles of intention-to-treat analysis and real-world study, a propensity score-matched analysis was not used. Accordingly, this study was notably limited by its small sample size, patient selection bias, and retrospective nature. The low-fat enteral feeding group contained a significantly lower proportion of patients aged >65 years. There was also a significantly low proportion of patients with tumors located in the middle third of the esophagus. Another source of bias is that low-fat enteral feeding was performed for patients with more difficult surgical conditions or worse clinical conditions. Furthermore, based on our previous experience in the treatment of chyle leakage, a low-fat diet or total parental nutrition was administered for 7 patients in the control group and 19 patients in the low-fat group who were diagnosed with chyle leakage. The patients' unmatched backgrounds might have significantly affected the clinical outcome of this study. Moreover, there may have been some inherent bias caused by the surgical experience and preference of the different surgeons, although they had all finished the learning curve of open and minimally invasive Ivor Lewis esophagectomy. Before the incorporation of low-fat tube nutrition into a guideline, more well-designed trials are warranted to verify the role and mechanisms of low-fat nutrition in esophagectomy.

Conclusion

Prophylactic low-fat enteral feeding does not lower the incidence of chyle leakage following Ivor Lewis esophagectomy. However, we could not reach a definite conclusion because of the significant heterogeneity, bias, and small sample of this study. Therefore, we call for more and better evidence to verify the effect and mechanisms of low-fat nutrition after esophageal resection.

Data availability

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

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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Ethical approval

The Ethics Committee of Xuzhou Central Hospital approved the present retrospective analysis of anonymous data.

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