

ORIGINAL ARTICLE

Incidence and management of chylothorax after esophagectomy

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Introduction

Chylothorax after esophagectomy is an uncommon but potentially lethal complication, with a reported incidence of 0.4–4%.^{1–4} It generally occurs secondary to injury to the thoracic duct or lymphatic tributaries. In adults, the thoracic duct can transport up to 4 L of chyle daily, rich in fluid, lipid, protein, and lymphocytes.⁵ Persistent chyle loss leads to hypovolemia, malnutrition, and immunosuppression, which have a significant impact on postoperative outcome after esophagectomy.

Because of the low incidence of this complication, management of chylothorax remains controversial. Some authors advocate conservative management, while others argue that a

Abstract

Background: Chylothorax is a rare but serious postoperative complication in esophageal cancer patients. The aim of this study was to identify risk factors associated with chylothorax and the indication for surgical intervention.

Methods: A consecutive series of 1290 patients who underwent esophagectomy for esophageal cancer was included. Peri-operative data, including postoperative morbidity and mortality, were analyzed.

Results: Thirty-four patients (2.6%) developed chylothorax and had significantly higher instances of pneumonia (26.5% vs. 11.1%, $P = 0.012$) and arrhythmia (17.6% vs. 2.9%, $P = 0.001$), and a longer hospital stay (22 vs. 18 days, $P < 0.001$). Reoperation was performed in 11 patients at a rate of 77.8%, 42.9%, 20%, and 0% for chylothorax diagnosed in two, three, four, and ≥ 5 days, respectively, after esophagectomy ($P < 0.001$). After three days of conservative therapy, the chest tube output was significantly greater in patients whose medical management had failed than in those successfully treated ($P < 0.001$). All patients who required reoperation had ≥ 13.5 ml/kg of drainage (sensitivity 100%); four of 23 patients with successful medical management had a chest tube output ≥ 13.5 ml/kg (specificity 83%). Logistic regression analysis showed that body mass index (BMI) < 25 was an independent risk factor for chylothorax (hazard ratio = 9.256, $P = 0.029$).

Conclusions: Patients with a BMI < 25 are more likely to develop chylothorax after esophagectomy. Operative therapy should be seriously considered in patients who develop chylothorax early postoperatively. In addition, a high daily chylous output of ≥ 13.5 ml/kg after three days of conservative therapy might be a reliable indicator for reoperation.

planned early reoperation may significantly reduce mortality.^{6–8} There is no generally accepted consensus on the indication and timing of surgical intervention.

The aim of this study was to identify potentially predisposing factors associated with chylothorax and to evaluate the management of chylothorax, especially the indication for surgical intervention.

Patients and methods

Study population

One thousand two hundred and ninety consecutive patients who underwent open Ivor-Lewis esophagectomy for thoracic

Table 1 Clinicopathologic characteristics of patients who underwent an esophagectomy

Variable	Chylothorax <i>n</i> = 34	No chylothorax <i>n</i> = 1256	<i>P</i> -value
Age (median,range)	60 (48–75)	60 (32–78)	0.405
Male (<i>n</i> , %)	30 (88.2%)	1029 (81.9%)	0.496
BMI			0.005
<25 kg/m ²	33 (3.3%)	980 (96.7%)	
≥25 kg/m ²	1 (0.4%)	276 (99.6%)	
Cigarette-smoking history	24 (70.6%)	774 (61.6%)	0.371
Hypertension	9 (26.5%)	291 (23.2%)	0.681
Diabetes	1 (2.9%)	62 (4.9%)	0.726
Histological type			0.879
Squamous cell carcinoma	33 (2.7%)	1199 (97.3%)	
Adenocarcinoma	0	20 (100%)	
Others	1 (2.6%)	37 (97.4%)	
Tumor in upper or middle esophagus	16 (47.1%)	645 (51.4%)	0.729
Tumor invasion (T3 or T4)	19 (55.9%)	732 (58.3%)	0.861
Tumor length (median,range)	4 cm (1–7)	3 cm (0.8–13)	0.185
Lymph node metastasis	17 (50%)	586 (46.7%)	0.730
Number of lymph nodes resected ≥ 21	19 (55.9%)	633 (50.4%)	0.603

BMI, body mass index.

esophageal cancer in our hospital from February 2007 to December 2012, were included in the present retrospective study. The institutional review board of Fudan University Shanghai Cancer Center approved the database of esophageal carcinoma used.

Surgical procedure

During open Ivor-Lewis esophagectomy, extended two-field lymphadenectomy (including upper mediastinal node dissection) was performed and prophylactic thoracic duct ligation was routinely conducted. In all patients, jejunostomy for intra-intestinal nutrition was performed, and enteral feeding was started on postoperative day one or two.

Data collection

Chylothorax was diagnosed by either a change in the quality of chest tube drainage to milky white drainage, regardless of chest tube output, or confirmation of chylomicrons in the pleural drainage in patients with high-volume drainage.

Pre-operative characteristics, comorbidities, and tumor-specific variables were evaluated as potential risk factors for chylothorax. To assess the impact of chylothorax on postoperative outcome, the incidence of additional complications (pneumonia, intrathoracic leak, and arrhythmia), length of hospital stay, and in-hospital mortality were evaluated. Chest tube drainage volume was collected in all chylothorax patients.

Statistical analysis

Statistical analysis was performed using the SPSS software program (SPSS Inc., Chicago, IL, USA). Descriptive statistics were summarized with frequencies and percentages for categorical variables and median for continuous variables. A Chi-square or Fisher's exact test was used to compare categorical data and a Mann-Whitney U test was used for continuous data. The results were considered significant at $P < 0.05$. Multivariate logistic regression was used to determine factors associated with an increased risk of chylothorax. In selecting variables for the multivariate logistic regression model, a cut-off P value of 0.05 was used. Receiver operating characteristic (ROC) curve analysis was used to derive the optimal cut-off value for pleural fluid drainage in predicting the failure of medical management.

Results

Risk factors for chylothorax

Postesophagectomy chylothorax occurred in 34 of 1290 patients (2.6%). Associations between chylothorax and patient characteristics, comorbidities, and tumor-specific properties were examined (Table 1). A body mass index (BMI) < 25 was the only significant risk factor for chylothorax by univariate analysis ($P = 0.005$). We selected potential contributing factors that might be associated with chylothorax for multivariate analysis. Only BMI < 25 was confirmed to be independently associated with an increased incidence of chylothorax (hazard ratio [HR] = 9.256; 95% confidence interval [CI]: 1.260–68.007, $P = 0.029$) (Table 2).

Table 2 Multivariate analyses of risk of chylothorax

	Hazard ratio	95% CI	P-value
BMI (<25/ ≥ 25)	9.256	1.260–68.007	0.029
Lymph node metastasis (yes/no)	1.091	0.550–2.165	0.803
Upper or middle esophageal cancer/lower esophageal cancer	0.836	0.421–1.661	0.608
Squamous cell carcinoma/non-squamous cell carcinoma	1.605	0.214–12.032	0.645

BMI, body mass index; CI, confidence interval.

Table 3 Impact of chylothorax on postoperative outcome

	Chylothorax n = 34	No chylothorax n = 1256	P-value
Pneumonia	9 (26.5%)	140 (11.1%)	0.012
Intrathoracic leak	2 (5.9%)	46 (3.7%)	0.364
Arrhythmia	6 (17.6%)	36 (2.9%)	0.001
Reoperation	11 (32.4%)	19 (1.5%)	<0.001
Hospital stay (median, IQR)	22 (15–56)	18 (9–161)	<0.001
In-hospital mortality	1 (2.9%)	13 (1.0%)	0.313

IQR, interquartile range.

Impact of chylothorax on postoperative outcome

Chylothorax was the second main cause of reoperation in the series. Patients with chylothorax had significantly higher instances of pneumonia (26.5% vs. 11.1%, $P = 0.012$) and arrhythmia (17.6% vs. 2.9%, $P = 0.001$). The median length of stay was also significantly longer (22 vs. 18 days, $P < 0.001$). One patient with chylothorax died postoperatively. Chylothorax was not significantly associated with increased mortality (2.9% vs. 1.0%, $P = 0.313$) (Table 3).

Management of chylothorax

Chylothorax was identified on a median of four days (interquartile range 2–9) after esophagectomy. All patients with chylothorax were initially managed conservatively (total parenteral nutrition, no enteral intake, and octreotide), resulting in the successful treatment of chylothorax in 23 patients (68%). In 11 patients (32%), conservative treatment did not successfully stop the chylous leak.

Surgical intervention was indicated when there was no response to conservative therapy and a high flow rate of chylothorax. Mass ligation of the thoracic duct, which is an en masse ligation above the diaphragmatic hiatus between the aorta and the vertebral bodies via rethoracotomy, was performed at a median of five days (range: 3 to 12 days) from the day of chylothorax diagnosis. Thoracic duct ligation resolved the chylothorax in all patients.

Predictors for failed medical management

The risk of failed medical management increased when chylothorax developed early after surgery. The reoperation rate

was 77.8%, 42.9%, 20%, and 0% for chylothorax diagnosed in two, three, four, and ≥ 5 days after esophagectomy ($P < 0.001$). (Table 4)

Chest tube output on the third day after the initiation of conservative therapy was significantly greater in patients for

Table 4 Characteristics of patients with postoperative chylothorax who underwent medical or surgical treatment

	Reoperated n = 11	No reoperation n = 23	P-value
Days from esophagectomy to diagnosis			<0.001
2 days	7 (77.8%)	2 (22.2%)	
3 days	3 (42.9%)	4 (57.1%)	
4 days	1 (20%)	4 (80%)	
≥5 days	0	13 (100%)	
Bilateral chylothorax	2 (18.2%)	6 (26.1%)	0.694
Duration of chest tube drainage (days)			0.445
Median	13	12	
Range	8–24	6–29	
Chest tube output after conservative therapy (ml/Kg)			
Day 1†			0.091
Median	23.5	18.6	
Range	10.5–40.2	3.5–32.7	
Day 2†			0.055
Median	22.1	15.2	
Range	10.7–36.2	2.3–30.2	
Day 3†			<0.001
Median	23.8	9.6	
Range	13.8–35.5	2.1–20.9	

†Day 1, 2 and 3 are defined as 1, 2, and 3 days after the initiation of conservative therapy.

whom medical management had failed ($P < 0.001$) (Table 4). ROC analysis suggested that the optimal cut-off value for failed medical management was chest tube drainage volume ≥ 13.5 ml/kg (in the third day after the initiation of conservative therapy). All patients who required reoperation had ≥ 13.5 ml/kg of drainage after three days of conservative therapy. Only four of 23 patients with successful medical management had a chest tube output ≥ 13.5 ml/kg. The sensitivity and specificity were 100% and 83%, respectively.

Discussion

In this large series of esophageal cancer patients, chylothorax was a rare but serious complication of esophagectomy. Chylothorax was associated with higher rates of pneumonia and arrhythmia, and a longer hospital stay, but not with postoperative mortality. A BMI < 25 was identified as an independent risk factor for chylothorax. Reoperation is more likely required when chylothorax develops early after surgery (before the fourth postoperative day). Moreover, a persistence of high volume chest tube drainage, equal or greater than 13.5 ml/kg/day after three days of conservative therapy predicted medical therapy failure.

In this series of 1290 patients, we encountered 34 patients (2.6%) with chylothorax. This is in line with earlier published series.^{4,9,10} The chyle is rich in lipids, proteins, and lymphocytes. Continued loss of chyle can lead to immunosuppression, resulting in infection-related complications.⁵ Lagarde *et al.* and Shah *et al.* reported that chyle leakage could lead to pneumonia.¹² In this study, we also found that patients with chylothorax had significantly higher frequencies of pneumonia. Pneumonia is the leading cause of mortality after esophagectomy, which reflects the seriousness of chylothorax.¹¹ Aggressive treatment should be immediately undertaken if postoperative chylothorax develops.

The mortality of chylothorax increases to 50% when conservative management is used as the mainstay of treatment.¹² With surgical intervention, the mortality rate has reportedly decreased to 0%–17.7%.¹² Some authors recommend early surgical ligation of the thoracic duct to decrease the risk of mortality.^{7,8} However, there is no consensus on how early and what volume of chyle output should indicate a need for surgical intervention. In the present study, reoperation was performed at a median of five days (range: 3 to 12 days) from the day of chylothorax diagnosis, which is consistent with published data.^{1,2} We were interested in predictive factors for surgical intervention. We found that medical management was more likely to fail in patients who had a chest tube drainage volume ≥ 13.5 ml/kg on the third day after initiation of conservative therapy. Using this cut-off value to predict the need for reoperation, the sensitivity and specificity was 100% and 83%, respectively. Dugue *et al.* achieved a similar result in that the drainage volume on the fifth day after diagnosis of chylo-

thorax could predict if thoracic duct ligation was required. In their study, all patients required reoperation when the chylous loss ≥ 10 ml/kg/day.⁹

Another finding in this study was that surgical management was more likely required when chylothorax developed early postoperatively. In this series, no patient required reoperation when the chylothorax was recognized after the fifth postoperative day. The reason for this is not clear. It is likely that these patients had damage to the collateral lymphatic vessels, rather than injury to the main thoracic duct; therefore it is easy to seal off with time. Chalret *et al.* argued that if chylothorax developed early, surgical management should be proposed.¹³

In the literature, indications for surgical intervention are rarely reported. It is generally advised that a continuation of conservative treatment for more than two weeks should be avoided.¹⁴ On the basis of the data from this study, if a patient developed chylothorax within four days postoperatively, with a drainage volume of ≥ 13.5 ml/kg after three days of conservative therapy, early surgical ligation of the thoracic duct should be conducted.

The thoracic duct is always revealed more clearly in normal or underweight patients compared with overweight patients. Interestingly, we found that patients with a BMI < 25 had a higher risk of developing chylothorax. One recent meta-analysis focusing on BMI reported that a higher BMI was associated with a decreased incidence of chylothorax after esophagectomy.¹⁵ A possible explanation is that as the BMI increases, there is more fatty tissue surrounding the tumor and esophagus. More fatty tissue leads to better protection of the thoracic duct. The thoracic duct should be protected more carefully in normal or underweight patients.

Squamous cell cancer (SCC) was reported as a risk factor for postoperative chylothorax.² In the current study, the major histological type was SCC; 33 of 1199 (2.7%) patients with SCC developed chylothorax compared with 0/20 (0%) of patients with adenocarcinoma. However, we could not draw a conclusion because of the small number of adenocarcinoma cases. Tumor location and lymph node metastasis were identified as risk factors in previous studies, but were not confirmed to be associated with postoperative chylothorax in this series.¹⁴ Differences in sample size, inclusion criteria, and histological type may have contributed to these inconsistent results.

Although prophylactic thoracic duct ligation was routinely performed in this study, the incidence of chylothorax was 2.6%. The result is comparable to that of Dugue *et al.* who reported a 2.7% incidence of postoperative chylothorax after preventive ligation of the thoracic duct.⁹ Duplicate or triplicate thoracic ducts can be observed in up to 40% of patients.¹⁶ The thoracic duct may also form a plexus draining into a unique duct or separately into the right and left subclavian veins. The anatomic variation is probably responsible for the

failure of prophylactic thoracic duct ligation. In the 11 reoperated patients, the main cause of the chylothorax was that the ligation did not include all the collaterals of the main thoracic duct; one patient was associated with prophylactic thoracic duct ligation (the ligation was too tight to damage the thoracic duct. In these 11 patients, a repeat ligation was successfully performed. Although prophylactic thoracic duct ligation is not a guarantee against chylothorax, a recent randomized controlled trial argued that a prophylactic thoracic duct ligation could minimize the risk of postoperative chylothorax.¹⁷

In this series, patients from a single institute within a short period underwent a consistent operative approach; thus, the data were more homogenous. The limitations of the study are acknowledged. We could not evaluate some of the potential contributing factors for chylothorax, such as surgical approach and histological type. Another limitation is the retrospective nature of the analysis.

Conclusion

In conclusion, postoperative chylothorax is associated with significant postoperative morbidity. Patients with a BMI < 25 are more likely to develop chylothorax after esophagectomy. Operative therapy should be seriously considered in patients who develop chylothorax early postoperatively. In addition, a high daily chylous output of ≥ 13.5 ml/kg after three days of conservative therapy might be a reliable indicator for reoperation.

Disclosure

No authors report any conflict of interest.

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