Original Article

Analysis of related factors and treatment effect of chylothorax after lung surgery

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Background: Chylothorax is a seldom encountered complication following lung surgery. However, due to the widespread practice of lung surgery, postoperative complications have inevitably arisen. Chylothorax significantly affects a patient's discharge and recovery. This study investigates the risk factors for postoperative chylothorax at our center and analyzes various treatment modalities and prognostic outcomes.

Methods: A retrospective analysis was conducted on all postoperative lung resections performed between January 2018 to August 2021 that met the inclusion criteria. Inclusion criteria covered patients undergoing various thoracic surgeries for lung conditions, while exclusion criteria included postoperative referrals for surgeries unrelated to lung tumors.

Results: Postoperative chylothorax occurred in 42 of 5,706 patients after lung surgery. General information and disease-related data of the chylothorax and control group were analyzed by univariate and multivariate analyses. Multivariate analysis showed that serum albumin before surgery [odds ratio (OR) =0.86, 95% confidence interval (CI): 0.81–0.91, P<0.001], γ-glutamyl transferase level before surgery (after logarithmic transformation, OR =1.01, 95% CI: 1.00–1.01, P=0.01), squamous cell carcinoma (OR =2.77, 95% CI: 1.37–5.6, P=0.008), right mediastinal lymph node dissection (OR =3.15, 95% CI: 1.62–6.14, P<0.001) were independent risk factors for postoperative chylothorax. Among the 42 cases of postoperative chylothorax, 26 patients were improved with conservative treatments, and 6 patients were improved with chemical pleurodesis. Eight patients with postoperative chylothorax underwent thoracoscopic thoracic duct ligation. Three patients experienced severe postoperative complications: one was discharged after prolonged treatment, while the remaining two either succumbed or were discharged against medical advice.

Conclusions: The incidence of chylothorax after lung surgery closely correlates with the intraoperative trauma and nutritional status of patients during the perioperative period. The majority of patients with postoperative chylothorax experienced relief through conservative measures, somatostatin administration, and chemical pleurodesis. Nevertheless, substantial postoperative chylothorax necessitated surgical intervention, involving thoracic duct ligation or drug pleurodesis.

Keywords: Chylothorax; lung surgery; risk factors; postoperative complications

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Introduction

Lung cancer is the leading cancer among males and ranks second among females in China (1). Surgery remains the primary treatment modality for stages I through certain stages of IIIb non-small cell lung cancer (NSCLC) (2). Despite the advancements and increasing application of video-assisted thoracoscopic surgery (VATS), postoperative complications present considerable challenges. These complications, which include lung infections, chylothorax, cutaneous emphysema, and bronchopleural fistula (3), can significantly extend hospital stays and impede patient recovery. Chylothorax, a rare but serious complication mainly associated with thoracic lymph node dissection and the potential damage to lymphatic vessels (4) is of particular concern. The inadvertent injury to these vessels during surgery, especially given their complex anatomical variations, can precipitate chylothorax. Its clinical significance is underscored by the thoracic duct's critical role in fat absorption, processing over 1.5 liters of chyle daily (5). The thoracic duct carries vital nutrients, including triglycerides, proteins, electrolytes, lymphocytes, lipid-soluble vitamins, and antibodies, essential for maintaining homeostasis, protein synthesis, and immune competence (6). Consequently, substantial chyle leak can profoundly impact the body, leading to severe complications such as prolonged fasting, significant protein loss, malnutrition, postoperative infections, and potentially bronchopleural fistulas (4). Conservative treatments typically involve dietary restrictions, parenteral nutrition (PN), and albumin supplementation (7), but surgical intervention may be necessary if conservative treatments fail (8,9). These treatment modalities profoundly influence recovery duration, hospitalization length, and healthcare costs. Recent studies highlight the complexity and significance of postoperative chylothorax after lung surgery. The incidence ranges from 0.25% to 3%, often due to thoracic duct injuries during mediastinal lymph node dissection in lung cancer surgeries. Key risk factors include lobectomy, right-sided surgeries, robotic procedures, and pathological N2 disease (10,11). This study aims to identify risk factors for postoperative chylothorax following lung surgery, analyze various treatment modalities, and assess their prognostic outcomes. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-692/rc).

Highlight box

Key findings

- Chylothorax is a rare complication following lung surgery but can significantly impact patient recovery.
- Risk factors for postoperative chylothorax include intraoperative trauma and nutritional status.
- Conservative treatments, somatostatin administration, and chemical pleurodesis are commonly used to manage chylothorax.

What is known and what is new?

- This study identifies specific risk factors for postoperative chylothorax, including serum albumin levels, γ-glutamyl transferase levels, squamous cell carcinoma, and right mediastinal lymph node dissection.
- It provides insights into the effectiveness of various treatment modalities, including conservative measures, somatostatin administration, chemical pleurodesis, and surgical interventions such as thoracoscopic thoracic duct ligation.

What is the implication, and what should change now?

- Understanding the risk factors identified in this study can help clinicians anticipate and manage postoperative chylothorax more effectively.
- The findings suggest the importance of preoperative assessment of nutritional status and careful intraoperative management to reduce the risk of chylothorax.
- Clinicians should consider conservative measures as the first-line approach for managing chylothorax but be prepared to escalate to surgical intervention in severe cases.
- Further research may be needed to explore additional factors contributing to chylothorax and to optimize treatment strategies.

Methods

Inclusion and exclusion criteria

This retrospective analysis was conducted on patients who underwent only pulmonary surgeries at the Department of Thoracic Surgery, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, from January 2018 to August 2021. We included patients subjected to traditional thoracotomies, multi-port VATS, single-port VATS, and robot-assisted lobectomies, as well as those who had segmentectomies or sublobar resections. This encompassed cases with or without systematic mediastinal lymph node dissection and sampling. Nodal sampling was performed on at least three stations of mediastinal lymph nodes. The scope of lung surgeries included not only cases with known or suspected malignant tumors but also secondary lung tumors, such as metastases. We utilized lymph node forceps, ultrasonic scalpels, and electrocautery hooks for nodal sampling/dissection procedures. Additionally, fibrin glue was employed as part of our prophylactic measures. Exclusion criteria comprised of patients who were referred postoperatively for chylothorax management from other hospitals, patients operated on for lung bullae or hyperhidrosis, lung transplant and those who had empyema drainage or exploratory thoracotomy without tumor resection. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of Sir Run Run Shaw Hospital Affiliated with the Zhejiang University School of Medicine (No. 20240169) and individual consent for this retrospective analysis was waived.

Data acquisition

The study included 5,706 patients, from whom we systematically gathered data across several dimensions: (I) basic demographics and health metrics such as age, gender, body mass index (BMI), and smoking history; (II) postoperative details such as daily drainage volume, fluid characteristics, timing of chest tube removal, and hospital stay duration; (III) post-surgery pathological reports detailing the surgical approach and site, lymph node involvement, and histopathological classification; (IV) laboratory metrics before and after surgery, focusing on baseline health indicators including lipid profiles [triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C)], glucose, uric acid, liver enzymes [alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), γ-glutamyl transferase (GGT), albumin (ALB), total protein (TP)], renal function markers [blood urea nitrogen (BUN), creatinine (CRE)], blood uric acid (UA), total bilirubin (TBIL), and inflammation marker [C-reactive protein (CRP)]. Diagnosis of postoperative chylothorax was based on clinical signs and pleural fluid assessment. The treatment strategy flowchart of this study showed in *Figure 1*.

Diagnosis of chylothorax

In this study, we employed a combined approach of laboratory diagnosis and clinical assessment to diagnose chylothorax, aiming to enhance accuracy and reliability, outlined by the following criteria: (I) clinical manifestations: sudden increases in post-surgical chest drainage, particularly postprandial volume changes and altered fluid characteristics, along with symptoms like chest discomfort and breathing difficulty after tube removal, warrant suspicion for chylothorax (*Figure 2*). (II) Therapeutic diagnosis: a diet free of fats and cessation of oral intake may reduce drainage volume and clear the fluid, supporting a chylothorax diagnosis. (III) Fluid analysis: a triglyceride concentration over 1.24 mmol/L in drainage fluid typically indicates chylothorax. Concentrations between 0.56–1.24 mmol/L also suggest this condition (12). The Sudan-3 lipid stain, while highly sensitive, lacks specificity, revealing a 25% chance of false positives (13). (IV) Differential diagnosis: pleural fluid in chylothorax may not always appear milky; bloody or reduced lipid intake can alter its color (14). Cholesterol effusions, marked by pleural fluid cholesterol above 5.18 mmol/L and triglycerides below 1.24 mmol/L, and empyema, indicated by elevated white cell counts and potential fever or infection signs, must be distinguished from chylothorax, often via bacterial culture.

Treatment of chylothorax

The treatment strategy commences upon chylothorax diagnosis and is contingent on the initial drainage volume. Although this is a retrospective study, the therapeutic management of postoperative chylothorax followed a management protocol that has been used consistently at our center. Patients with a drainage volume >500 mL/24 h are prescribed fasting coupled with PN. Those with lesser volumes may attempt a non-fat diet; however, if the drainage does not substantially reduce, fasting with PN is implemented. Short-term recovery prospects lead to partial PN (PPN), while extended fasting necessitates total PN (TPN). In cases unresponsive to dietary measures, somatostatin (SST) or analogs like octreotide are administered to mitigate gastrointestinal activity and lower chyle output. Persistent drainage above 300 mL/24 h across five days may prompt medication pleurodesis, with our center favoring an olive oil emulsion, pending malignancy confirmation and informed patient consent. Should daily drainage surge past 1,500 mL or average above 500 mL across five days, thoracoscopic ligation of the thoracic duct is considered. Success is indicated by reduced drainage. If drainage remains low, post-diet resumes, and tube is removed, with subsequent chest radiography performed 1–2 days after to confirm that there is no progression before discharge. A low-fat diet persists for two weeks post-discharge, with follow-up imaging to verify chylothorax resolution. Severe nutritional deficits leading to

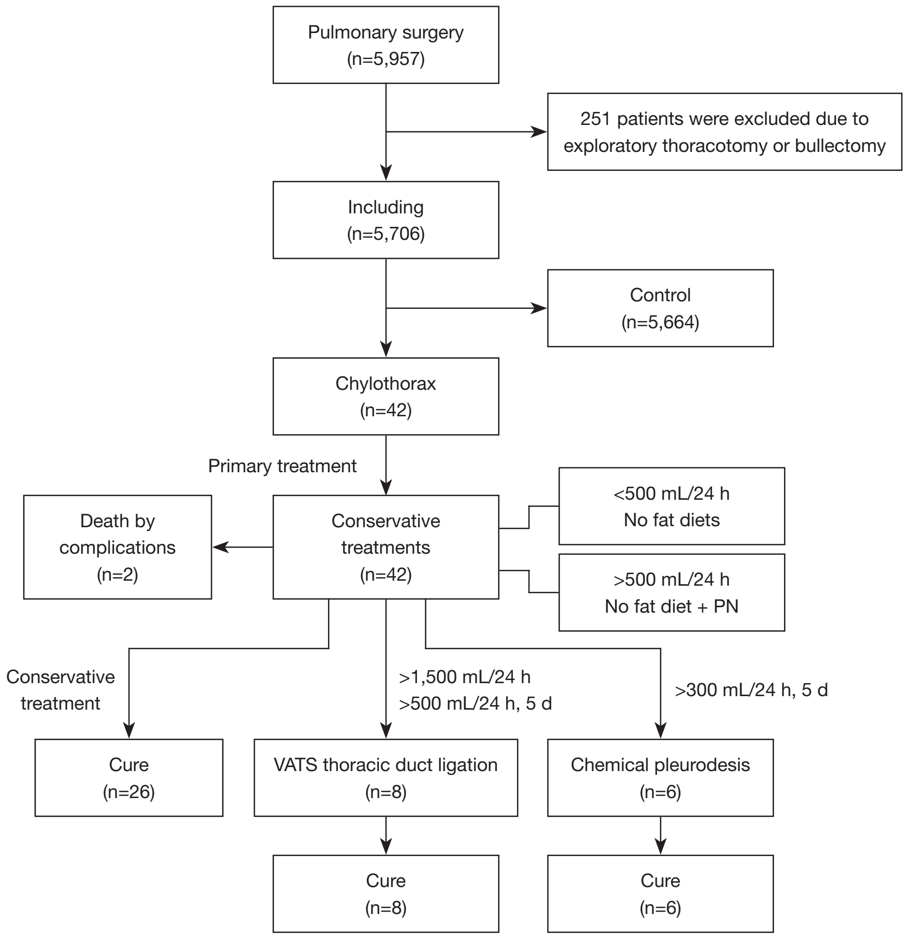

Figure 1 The treatment strategy flowchart in this study. PN, parenteral nutrition; VATS, video-assisted thoracoscopic surgery.

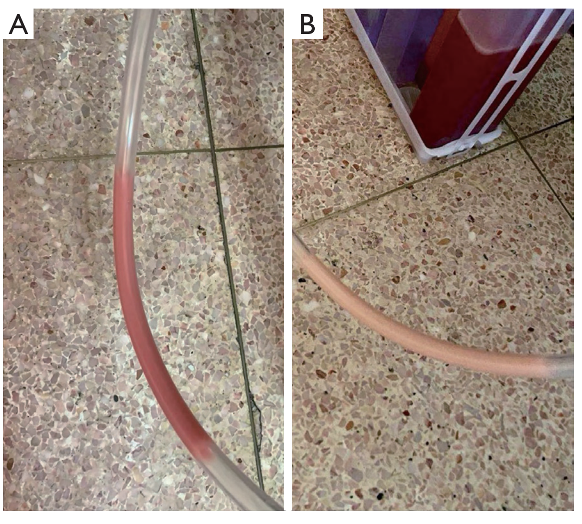

Figure 2 Photos from two patients' drainage fluid diagnosed as postoperative chylothorax (A,B). Drainage fluid is often milky white or creamy due to the presence of chyle, a lipid-rich lymphatic fluid.

complications like bronchopleural fistula or fatal pulmonary infections are categorized as mortality due to postoperative chylothorax.

Surgical procedure for thoracic duct ligation

Active surgical intervention via thoracic duct ligation using VATS is considered for patients with significant nutritional impact from chyle leaks (drainage >1,500 mL/24 h) or prolonged ineffectiveness of conservative treatments (drainage >500 mL/24 h for 5 consecutive days). All operation to ligate the thoracic duct was performed through VATS. The procedure involves inserting a gastric tube to administer a high-fat liquid, identifying the chyle leakage site, and securing it with sutures or titanium clips. The thoracic duct is ligated between T9 and T10, and the area is monitored for 30 minutes for any persistent leakage before concluding the surgery.

Statistical analysis

Data analysis employed R (version 4.0.3) with ggplot2 (version 3.3.5) for visualization. Continuous variables were tested for normality with the Shapiro-Wilk test, with normally distributed data presented as mean ± standard deviation (SD). *T*-tests or Wilcoxon rank-sum tests were used depending on normality, after log transformation where applicable. Categorical data were expressed as frequencies and analyzed with Pearson's Chi-square or Fisher's exact test. Missing data were addressed with multiple imputation (mice, version 3.14.0). Multivariable analysis used logistic regression (rms, version 6.2-0), with area under the curve (AUC) and receiver operating characteristic (ROC) curves plotted (pROC, version 1.18.0). Nonparametric multiple group comparisons utilized the Kruskal-Walli's test. A P value <0.05 was deemed significant.

Results

Univariate analysis of postoperative chylothorax

A retrospective study was conducted on all patients who underwent lung resection surgery at our center from January 1, 2018, to August 31, 2021. After excluding patients that met the exclusion criteria, a total of 5,706 patients were included in the study. Among them, 42 patients were diagnosed with chylothorax based on clinical manifestations and pleural fluid analysis, and were included in the chylothorax group, while the remaining 5,664 patients were included in the control group. Therefore, the incidence rate of postoperative chylothorax at our center during the study period was approximately 0.74%.

Males were more likely to develop chylothorax than females (41.7% *vs.* 64.3%, P=0.005, *Table 1*). There was no significant difference in age between the two groups, suggesting that the occurrence of chylothorax was not related to age. There was no significant difference in BMI between the two groups (23.2±3.1 *vs.* 22.4±3.7 kg/m^2, P=0.22). The rate of smoking was higher in patients with chylothorax compared to the control group [1,412 (24.9%) *vs.* 20 (47.6%), P=0.001], which may be related to a higher smoking rate among males.

Among the postoperative conditions of the two groups, patients with chylothorax had a significantly longer average length of hospital stay than the control group (4.1±2.8 *vs.* 12.6±5.3 days, P<0.001), and the postoperative drainage volume was significantly higher than that of the control group (174.6±110.8 *vs.* 421.1±192.9 mL, P<0.001).

Regarding the surgical approach, there was no significant difference in the occurrence of chylothorax between left and right-side surgeries, but surgeries involving the lower right lung were more prone to chylothorax. The left- and right-side surgeries mentioned here do not include mediastinal lymph node dissection. A comparison of mediastinal lymph node dissection on the left and right sides will be discussed in the subsequent multivariate analysis. There were more patients who underwent lobectomy in the chylothorax group (34.7% *vs.* 57.1%). The lymph node statistics followed the 8th edition of the International Association for the Study of Lung Cancer (IASLC) TNM (tumor, nodes, metastasis) 8 classification for grouping (15). The results indicated that the majority of patients with chylothorax underwent mediastinal lymph node dissection or sampling (62.1% *vs.* 90.5%), but there were still four cases where mediastinal lymph node dissection was not performed. Among the 38 cases in the chylothorax group who underwent mediastinal lymph node dissection or sampling, two cases had postoperative pathology indicating mediastinal lymph node metastasis. Regardless of malignant or benign tumors, chylothorax can occur after surgery, and squamous cell carcinoma accounted for a higher proportion in the chylothorax group compared to the control group (7.2% *vs.* 31.0%).

Differences in preoperative and postoperative day 1 laboratory indicators

There were significant differences observed in ALB and TP between the two groups (*Figure 3A,3B*, Figure S1A,1B). Preoperative ALB and postoperative day 1 ALB were significantly lower in the chylothorax group compared to the control group (preoperative ALB: 43.2±3.9 *vs.* 38.9±6.9, P<0.001, *Figure 3A*; postoperative day 1 ALB: 35.9±3.2 *vs.* 31.8±5.3, P<0.001, *Figure 3B*). Since ALB is an important component of TP, TP also showed similar differences (preoperative TP: 71.7±6.2 *vs.* 65.6±9.6, P<0.001, Figure S1A; postoperative day 1 TP: 59.9±5.1 *vs.* 53.7±7.0, P<0.001, Figure S1B). Additionally, a difference in HDL-C between the two groups was observed (preoperative HDL-C: 1.32±0.33 *vs.* 1.18±0.31, P=0.007, Figure S1C postoperative day 1 HDL-C: 1.18±0.26 *vs.* 1.05±0.30, P=0.007, Figure S1D), indicating a potential protective effect of HDL-C on the occurrence of chylothorax. Among the liver function indicators, only GGT showed a difference between the two groups (preoperative GGT: 29.5±30.8 *vs.* 54.0±59.9, P=0.009, *Figure 3C*; postoperative day 1 GGT:

Table 1 Summary of basic information and clinical pathological data of the control group and the chylothorax group

Variates	Control group (n=5,664)	Chylothorax group (n=42)	*T* or χ^2 values	P
Sex [M (%)/F (%)]	2,364 (41.7)/3,300 (58.3)	27 (64.3)/15 (35.7)	7.801	0.005*
Age (years)	57.5±11.7	59.4±9.1	−1.328	0.20
BMI (kg/m^2)	23.2±3.1	22.4±3.7	1.254	0.22
Smoking†	1,412 (24.9)	20 (47.6)	10.081	0.001*
Post-operative hospitalization (days)	4.1±2.8	12.6±5.3	−10.389	<0.001*
Average postoperative daily drainage (mL)	174.6±110.8	421.1±192.9	−8.071	<0.001*
Surgical site				
Left side	2,270 (40.1)	10 (23.8)	–‡	0.12
Right side	3,449 (60.9)	32 (76.2)		
Bilateral	55 (0.97)	0		
Tumor site				
Left upper lobe	1,544 (27.3)	6 (14.3)	2.922	0.09
Left lower lobe	1,068 (18.9)	5 (11.9)	0.903	0.34
Right upper lobe	2,180 (38.5)	18 (42.9)	0.177	0.67
Right middle lobe	687 (12.1)	7 (16.7)	0.435	0.51
Right lower lobe	1,458 (25.7)	19 (45.2)	5.521	0.007*
Pathological type				
Squamous carcinoma	406 (7.2)	13 (31.0)	–‡	<0.001*
Adenocarcinoma	4,459 (78.7)	27 (64.3)		
Benign nodule	707 (12.5)	2 (4.8)		
Other malignant or borderline tumors	92 (1.6)	0		
Surgical procedures				
Wedge operation	1,834 (32.4)	3 (7.1)	–‡	<0.001*
Segmental lung surgery	634 (11.2)	2 (4.8)		
Lobectomy	1,964 (34.7)	24 (57.1)		
Multi-lobectomy	1,232 (21.8)	13 (31.0)		
Lymph node dissection				
Not performed	1,741 (30.7)	2 (4.8)	–‡	<0.001*
Mediastinal lymph node + N1 group dissection	3,520 (62.1)	38 (90.5)		
N1 group lymph node dissection	404 (7.1)	2 (4.8)		
90-day mortality	8 (0.1)	2 (4.8)	27.90	<0.001*

Data are presented as n (%) or mean ± standard deviation. *, statistical significance was set at P<0.05, the *t*-value and P value were calculated using multiple imputation method for the cases with unknown information; †, smoking includes both current smokers and former smokers; ‡, Fisher's exact test is used when the chi-square statistic cannot be applied. M, male; F, female; BMI, body mass index.

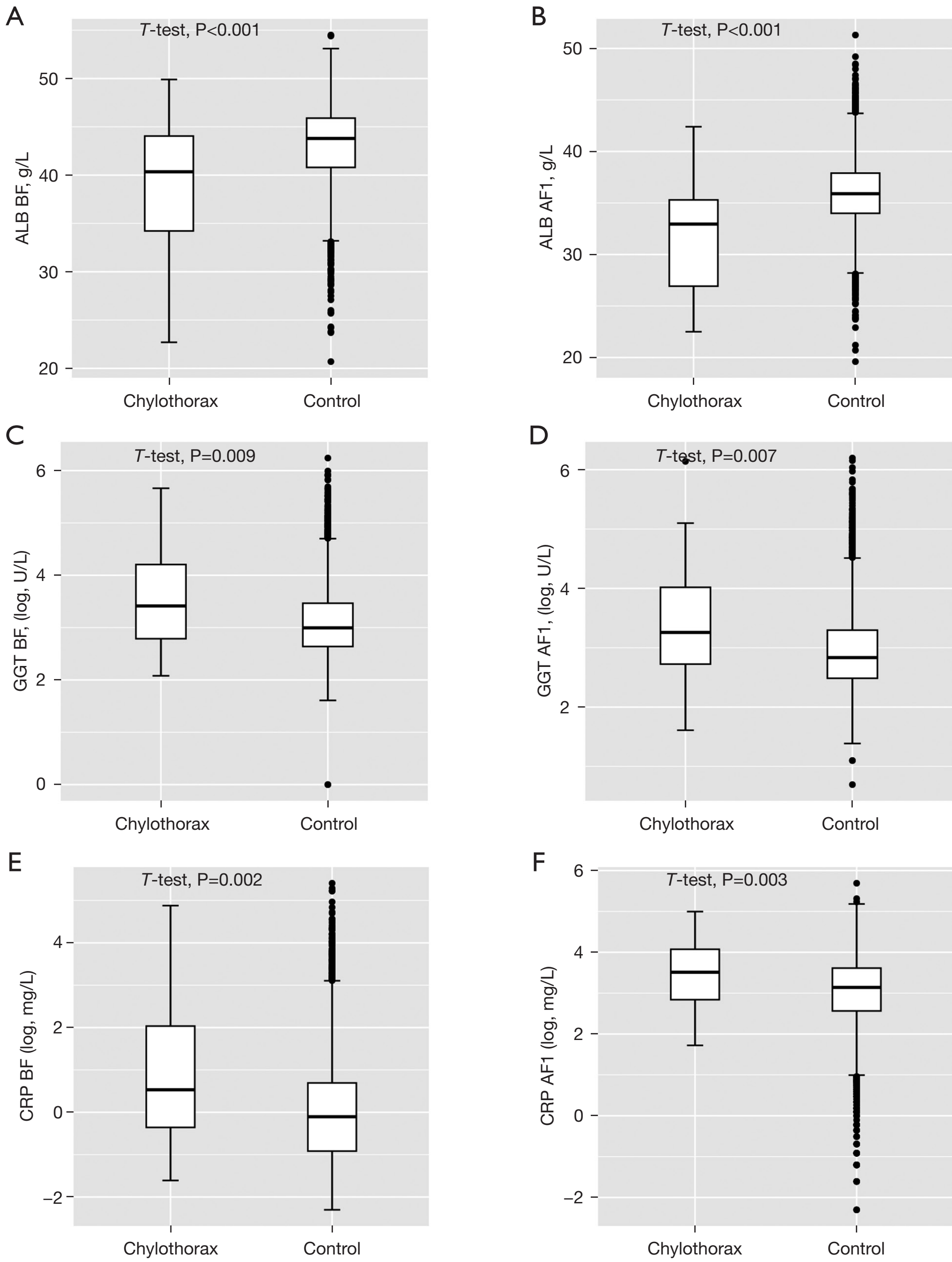

Figure 3 Differences in preoperative and postoperative day 1 laboratory indicators. ALB, albumin; BF, preoperative day; AF1, postoperative day 1; GGT, γ-glutamyl transferase; CRP, C-reactive protein.

25.4±29.3 *vs.* 54.5±78.3, P=0.007, *Figure 3D*). Further analysis of the GGT/HDL-C ratio revealed differences as well (preoperative GGT/HDL-C: 24.4±27.3 *vs.* 51.7±69.9, P=0.02; postoperative day 1 GGT/HDL-C: 23.3±36.3 *vs.* 59.5±93.7, P=0.02). Additionally, CRP showed differences between the two groups (preoperative CRP: 0.9±1.6 *vs.* 1.7±7.1, P=0.002 after logarithmic transformation, *Figure 3E*; postoperative day 1 CRP: 23.1±24.1 *vs.* 33.5±41.7, P=0.003 after logarithmic transformation, *Figure 3F*). However, there were no significant differences in LDL-C, TC,

Table 2 Multivariate analysis of factors contributing to postoperative chylothorax

Variates	Regression coefficient	Standard error	OR	95% CI	Reference values	P value
Sex	−0.249	0.383	0.78	0.37–1.65	–	0.51
Preoperative ALB	−0.135	0.034	0.87	0.82–0.93	40.0–55.0g/L	<0.001
Preoperative HDL-C	−0.120	0.549	0.89	0.30–2.60	>1.04 mmol/L	0.83
Preoperative GGT†	0.006	0.002	1.01	1.00–1.01	7–45 U/L	0.02
Preoperative CRP†	0.009	0.006	1.01	1.00–1.02	>5.0 mg/L	0.27
Adenocarcinoma	0.873	0.776	2.39	0.52–10.96	–	0.21
Squamous carcinoma	1.484	0.805	4.41	0.91–21.38	–	0.04
Lobectomy	0.138	0.382	1.15	0.54–2.43	–	0.72
Segmental lung surgery	−0.488	0.781	0.61	0.13–2.84	–	0.51
Wedge operation	−0.917	0.703	0.40	0.10–1.58	–	0.16
Right lower lung lobe surgery	0.616	0.382	1.85	0.88–3.91	–	0.11
Left mediastinal lymph node dissection	0.325	0.600	1.38	0.43–4.48	–	0.58
Right mediastinal lymph node dissection	0.858	0.542	2.36	0.81–6.82	–	0.10

†, after logarithmic transformation. ALB, albumin; HDL-C, high-density lipoprotein cholesterol; GGT, γ-glutamyl transferase; CRP, C-reactive protein; OR, odds ratio; CI, confidence interval.

Table 3 Construction of a logistic model for postoperative chylothorax

Variates	Regression coefficient	Standard error	OR	95% CI	Reference values	P value
Preoperative ALB	−0.150	0.028	0.86	0.81–0.91	40.0–55.0g/L	<0.001
Preoperative GGT†	0.007	0.002	1.01	1.00–1.01	7–45 U/L	0.01
Squamous carcinoma	1.018	0.359	2.77	1.37–5.6	–	0.008
Right mediastinal lymph node dissection	1.147	0.341	3.15	1.62–6.14	–	<0.001

†, after logarithmic transformation. ALB, albumin; GGT. γ-glutamyl transferase; OR, odds ratio; CI, confidence interval.

TG, Glu, UA, ALT, AST, ALP, BUN, CRE, and TBIL (Figure S1E-S1Z) between the two groups before surgery and on postoperative day 1.

Multivariable analysis of postoperative chylothorax

Variables that showed statistical significance in the univariate analysis were selected for multivariable analysis (*Table 2*). Logistic regression was performed on these variables, and the results suggested that preoperative ALB [odds ratio (OR) =0.87, 95% confidence interval (CI): 0.82–0.93, P<0.001], preoperative GGT (after logarithmic transformation, OR =1.01, 95% CI: 1.00–1.01, P=0.02), and squamous cell carcinoma (OR =4.41, 95% CI: 0.91–21.38, P=0.04) may be independent risk factors for postoperative chylothorax. After removing variables with smaller effects and refitting the model, the following four variables with smaller P values were selected for model construction: (I) preoperative ALB; (II) preoperative GGT; (III) squamous cell carcinoma; (IV) right mediastinal lymph node dissection (*Table 3*). The chi-square test comparing the two models showed a non-significant chi-square value (P=0.28), indicating similar goodness of fit between the two models. The new model had an AUC of 0.786 (*Figure 4*), demonstrating good predictive ability for postoperative chylothorax. Therefore, preoperative ALB level (OR =0.86, 95% CI: 0.81–0.91, P<0.001), preoperative GGT level (after logarithmic transformation, OR =1.01, 95% CI: 1.00–1.01,

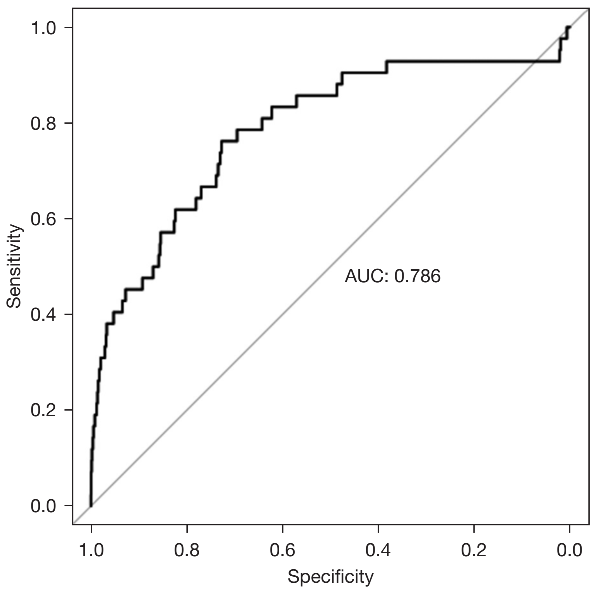

Figure 4 ROC curve of the logistic regression. AUC, area under the curve; ROC, receiver operating characteristic.

P=0.01), squamous cell carcinoma (OR =2.77, 95% CI: 1.37–5.6, P=0.008), and right mediastinal lymph node dissection (OR =3.15, 95% CI: 1.62–6.14, P<0.001) can be considered as independent risk factors for the occurrence of postoperative chylothorax. Following the presented results, we conducted Bonferroni correction, setting α_{Bonf}=0.0125 (four parameters). As all variables' P values remained below this threshold, it helps mitigate the issue of multiple comparisons.

Treatment and outcomes of postoperative chylothorax

This study included a total of 42 patients: 26 patients showed improvement after conservative medical treatment, 6 patients showed improvement after chemical pleurodesis (intrapleural injection of olive oil emulsion), 8 patients underwent VATS thoracic duct ligation and 2 patients died after treatment. Among the three patients diagnosed with postoperative chylothorax, severe postoperative complications were observed, with one patient being discharged after long-term treatment and two patients either dying or being discharged against medical advice. The gender, age, surgical site, surgical approach, mediastinal lymph node dissection, positive lymph nodes/cleared lymph nodes, average daily drainage after surgery, TNM stage, treatment methods, and outcomes of the chylothorax group are presented in Table S1. Additionally, a line graph depicting the postoperative daily drainage volume for four characteristic cases is provided for further illustration in Figure S2.

In this study, four patients did not undergo mediastinal lymph node dissection. Among these patients, two who had chylothorax following both in only intrapulmonary lymph node dissection. One patient did not undergo mediastinal lymph node dissection due to the high risk of mediastinal calcified lymph nodes, and one patient underwent simultaneous surgery for posterior mediastinal paraganglioma.

The initial treatment for postoperative chylothorax was a fat-free diet or fasting + PN. If the drainage volume did not significantly decrease after 5 days of initial treatment or if the drainage volume continued to increase, it was considered ineffective. The 6 cases in which initial treatment was ineffective and were subsequently treated with chemical pleurodesis (intrapleural injection of olive oil emulsion) were included in the chemical pleurodesis group. The eight cases in which initial treatment was ineffective and subsequently underwent VATS thoracic duct ligation were included in the VATS thoracic duct ligation group. The remaining 26 patients were included in the conservative treatment group (*Table 4*). There was no statistically significant difference in the time from surgery to the diagnosis of postoperative chylothorax among the three groups (P=0.70). However, the VATS thoracic duct ligation group had a higher drainage volume than the chemical pleurodesis and conservative treatment groups before the onset of chylothorax (803.5±234.4 *vs.* 613.3±160.8 *vs.* 450.0±325.3 mL, P=0.01, *Figure 5*). Before treatment initiation, the group undergoing VATS thoracic duct ligation exhibited a significantly higher drainage volume compared to the chemical pleurodesis group (792.3±277.3 *vs.* 494.0±83.5 mL, P=0.01), and their waiting time was also longer (12±7.5 *vs.* 4.0±1.5 days, P=0.04). There was no significant difference in the drainage volume and length of hospital stay between these two groups after pleurodesis or surgery (drainage volume: 387.6±181.7 *vs.* 200.3±77.0 mL, P=0.07; treatment to discharge time: 6.0±3.0 *vs.* 6.5±1.0 days, P=0.84). There were no cases where chemical pleurodesis treatment was ineffective and subsequently converted to VATS thoracic duct ligation.

Table 4 Comparing drainage volume and duration of postoperative chylothorax among three treatment methods with improvement

Variates	Conservative treatment (N=26)	Chemical pleurodesis (N=6)	VATS thoracic duct ligation (N=8)	P value
Days from diagnosis to surgery	2.0±2.0	2.0±0.8	1.0±1.0	0.70
Pre-diagnosis daily drainage volume (mL)	450.0±325.3	613.3±160.8	803.5±234.4	0.01*
Days from diagnosis to discharge	7.0±4.5	11.0±3.5	15.5±7.8	0.004*
Post-diagnosis daily drainage volume (mL)	280.7±143.0	337.6±81.0	621.5±187.6	<0.001*
Days from diagnosis to treatment	–	4.0±1.5	12±7.5	0.04*
Pre-treatment daily drainage volume (mL)	–	494.0±83.5	792.3±277.3	0.01*
Days from treatment to discharge	–	6.5±1.0	6.0±3.0	0.84
Post-treatment daily drainage volume (mL)	–	200.3±77.0	387.6±181.7	0.07

Data are presented as mean ± standard deviation. *, statistical significance was set at P<0.05.

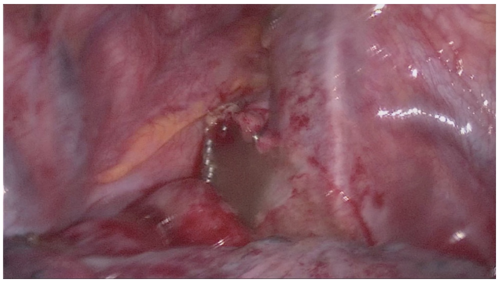

Figure 5 Photo from one of the VATS thoracic duct ligation procedures. During the surgery, a residual branch of the thoracic duct was observed above the right brachiocephalic vein arch, and a grayish-white oily fluid was seen flowing out. After precise localization, titanium clips were used for closure, and the surgery was concluded after observing no significant fluid leakage for 30 minutes. VATS, video-assisted thoracoscopic surgery.

Discussion

The incidence rate of postoperative chylothorax in our center is approximately 0.74% (excluding cases transferred from other hospitals, surgeries involving lung bullae, pneumothorax, thoracoscopy, etc.), which falls within the range of 0.25–3% reported in the literature (7,11,16). This study retrospectively analyzed 5,706 cases of pulmonary resection surgery performed from January 2018 to August 2021 and identified 42 postoperative chylothorax cases.

The incidence of postoperative chylothorax was notably higher in patients undergoing surgery on the right lower lobe compared to other lobes, with no significant difference between right and left-side surgeries. These observations were contrary to previous literature where Cho *et al.* observed a higher incidence in the right upper lobe (17), and Liu *et al.* reported a higher occurrence on the right side (18). Our study included a broad array of lung surgeries, encompassing early-stage lung cancer surgeries for ground-glass nodules, multi-lobar surgeries, and those without mediastinal lymph node dissection. As a result, our study involved sublobar resections, which differs from previous reports that mainly focused on single or double lobectomies. With the increasing popularity of low-dose CT screening, more patients are undergoing surgery at earlier stages of lung cancer, altering the disease spectrum. Sublobar resection is now deemed sufficient for complete R0 resection in ground-glass nodules (19). Sublobar resections constituted up to 43% of our cases, with 21.8% involving complex multi-lobar surgeries. This may explain the discrepancy between our findings and prior reports. Additionally, multivariate analysis indicated that the side of surgery might not be a risk factor for postoperative chylothorax, possibly due to the large number of sublobar resections that did not include systematic lymph node dissection or sampling.

The majority of postoperative chylothorax cases are believed to be related to mediastinal lymph node dissection (4). Systematic lymph node dissection and lymph node sampling are commonly used in our center for mediastinal lymph node dissection. Both lymph node sampling and systematic lymph node dissection can lead to postoperative chylothorax (20). After multivariate analysis of right-side mediastinal lymph node dissection, it was suggested as a risk factor. A study by Akin *et al.* showed that a higher incidence of mediastinal lymph node dissection on the right might be related to the higher prevalence of lung cancer and a more extensive distribution of mediastinal lymph nodes on that side (21). Zhang *et al.* identified right-side mediastinal lymph node dissection as a risk factor for post-surgery complications (22). Liu *et al.* found that dissection of the 4R lymph node group could lead to chylothorax, suggesting preventive ligation of the thoracic duct during 4R lymph node dissection (23). In our study, we have integrated certain preventive measures into our surgical practices, such as initiating prophylactic ligation of the thoracic duct upon identification of potential injury intraoperatively. Notably, patients who underwent thoracic duct ligation surgery exhibited a concentration of leak sites primarily in the 2+4 and 7 lymph node groups on the right side. Metastatic mediastinal lymph nodes can also increase the occurrence of postoperative chylothorax, as metastatic cancer tissue may invade the mediastinal lymphatic system, causing increased pressure (24). However, the low rate of mediastinal lymph node metastasis in patients with chylothorax in this study does not confirm this factor. The thoracic duct has many variations, and its course in the posterior mediastinum is not always in the form of a single duct; about 50% of individuals have a lymphatic plexus scattered in the posterior mediastinum, forming an intricate network with surrounding veins (25). If adhesions are found in the thoracic cavity during surgery, the potential pathways of the thoracic duct and its branches could be damaged during separation. Hence, postoperative chylothorax can occur not only in patients who underwent mediastinal lymph node dissection or sampling. In this study, four patients with postoperative chylothorax did not undergo mediastinal lymph node dissection, but these patients improved after conservative treatment, and the exact location of chyle leakage remains unclear. Therefore, regardless of whether sublobar or lobectomy is performed, care should be taken to avoid injury to the thoracic duct drainage area, which could lead to postoperative chylothorax.

The risk factors altered by the evolving disease spectrum of lung cancer also include pathological types. While many studies consider adenocarcinoma to be common post-surgery, our study identified squamous carcinoma as a risk factor for chylothorax (21,26). This could be related to the higher number of early-stage adenocarcinoma patients in our study, who are often associated with having ground-glass nodules, early-stage postoperative pathology, and are typically given lymph node sampling. Conversely, squamous carcinoma patients, usually older male smokers with lower rates of chest CT screening, are often diagnosed later due to symptomatic presentation, leading to more extensive mediastinal lymph node dissection and a higher incidence of chylothorax. It's crucial to closely monitor and promptly diagnose chylothorax in postoperative patients with these identified risk factors. Early detection and treatment are essential in optimizing patient outcomes and minimizing complications associated with chylothorax.

Lower ALB and TP might be associated with later-stage tumors in chylothorax patients, reflecting a catabolic state of malignancy. However, with no BMI differences between groups, short-term nutritional status seems connected to chylothorax occurrence. Poor nutrition predisposes one to chylothorax, creating a vicious cycle post-surgery, which emphasizes the need for enhanced perioperative nutritional management. Pre and postoperative lipid and cholesterol levels showed no significant difference between the groups. Zhang's study indicated that a perioperative low-fat diet does not significantly protect one against chylothorax (27). Our findings also suggest that GGT is a risk factor for chylothorax, with the GGT/HDL-C ratio being notably higher in the chylothorax group. Xing *et al.* proposed that GGT and HDL-C are associated with hepatic fat metabolism, warranting further research into this correlation (28). Above all, that nutritional status and liver function may be modifiable factors during the perioperative period. We believe that preoperative nutritional assessment and intervention, when indicated, may contribute to better surgical outcomes, including reduced risk of complications such as chylothorax. However, the decision to delay surgery to enhance nutrition should be carefully weighed against the urgency of the surgical intervention and the overall clinical condition of the patient. However, further prospective research is needed to validate these findings.

Choosing the appropriate treatment strategy for postoperative chylothorax can reduce hospital stay. Patients with less than 24-hour drainage can try a fat-free diet or fasting with PN. Most patients avoid pleurodesis or surgery through conservative treatment. For patients with short-term high-volume drainage (>1,500 mL/24 h), aggressive VATS thoracic duct ligation should be considered. Such surgical treatment effectively minimizes the systemic impact of chyle leak and shortens postoperative hospitalization (26). In cases where patients may experience prolonged high drainage output (VATS: >500 mL/24 h average over 5 days; pleurodesis: >300 mL/24 h average over 5 days), VATS duct ligation or pleurodesis was considered as potential interventions. Pleurodesis, which is less invasive than surgery, showed good results in this study. With these strategies, most patients with postoperative chylothorax improved and showed no recurrence of pleural effusion upon discharge follow-up.

The initial treatment for chylothorax patients in this study was a fat-free diet or fasting with PN support. Seven patients improved with a fat-free diet, which is preferred over fasting due to the maintenance of gastrointestinal function (29). However, a long-term fat-free diet can lead to insufficient calorie and fatty acid intake. Medium chain triglycerides (MCTs) can be absorbed by enterocytes and directly reach the liver through the portal vein, bypassing the lymphatic system. Thus, MCT diet can help reduce the production of chylomicrons while ensuring the intake of fatty acids (30). Machado *et al.* have also seen good results by including small amounts of short-chain fatty acids in a low-fat diet (31). Fasting and PN are the most widely used and definitive conservative treatments, reducing chyle production and thoracic duct flow to promote fistula closure (17). Madhavan's review suggests that SST or octreotide can effectively reduce chylothorax drainage and can be a supplementary conservative treatment (32). Several cases in this study received SST, with a noticeable drainage reduction in some (6/11) within 1–2 days of administration. Other medical centers have reported the use of weight-loss drugs to treat chylothorax, such as orlistat. Orlistat reduces fat absorption by inhibiting gastric and pancreatic lipases in the gastrointestinal lumen. This medication has low systemic absorption, good tolerability, and its main side effect is loose stools (30).

Common complications of non-surgical treatment for chylothorax patients include pulmonary complications (respiratory failure and pneumonia), infection, and cardiac arrhythmias (16). Postoperative chylothorax patients with ineffective conservative treatment or high daily drainage should consider surgical intervention. Uchida and others suggest that postoperative drainage volume is a critical determinant for thoracic duct ligation surgery (8). In this study, the eights cases that underwent surgical treatment had an average drainage of 792.3±277.3 mL from diagnosis to pleural fixation or before surgery, significantly higher than the cases treated with medical pleurodesis and conservative treatment. With significant chyle loss, electrolyte and nutritional balance are greatly disrupted, prompting most thoracic surgeons to favor aggressive VATS ligation. Reisenauer's study suggests surgical intervention when drainage exceeds 1,100 mL/24 h, while Misthos *et al.* considers it for an average drainage above 200 mL over 7 days. In this study, an indication for VATS ligation was drainage >1,500 mL/24 h on a single day or an average >500 mL/24 h over 5 days (33,34). High-fat diets, often oral olive oil, are given preoperatively to help identify the leak during surgery. In Uchida's study, the thoracic duct was ligated at the leakage point if identified, otherwise at the diaphragmatic level (8). Fluorescence navigation VATS with indocyanine green has also been used to find leaks (35,36).

Considering the invasiveness of VATS ligation, pleurodesis appears to be a more acceptable treatment. In this study, patients with an average drainage >300 mL/24 h over five days were considered for pleurodesis, with pre-treatment drainage averaging 494.0±83.5 mL/24 h, higher than conservative cases but lower than VATS (*Table 4*). Common pleurodesis agents include talc, OK-432, autologous blood, and hypertonic glucose (37). Considering the potential heavy metal content and carcinogenicity of talc in China, our center commonly uses intrapleural injection of olive oil emulsion as a chemical pleurodesis method. Olive oil emulsion can induce an inflammatory reaction in the pleural cavity, resulting in a milder chemical pleurodesis effect (38). Six patients improved with intrapleural injection of olive oil emulsion, and the post-treatment drainage and length of hospital stay were not significantly different from the cases that underwent VATS thoracic duct ligation (*Table 4*), suggesting a similar treatment efficacy despite avoiding surgery.

Lymphangiography, not yet adopted at our center, was not included in this study's treatment approach. It serves not only for diagnosis but also as a therapeutic method (39). Elevated levels of triglycerides in pleural fluid and a high pleural fluid triglyceride/serum triglyceride ratio indicate positive lymphangiography in patients with chylothorax (40). In Alejandre-Lafont *et al.*'s research, 79% of patients had the chyle leak site located during lymphangiography, with the success rate correlated with drainage volume (41). Existing studies often combine lymphangiography with CT scans or for a more precise leak location (42,43). The deposited iodine oil can be clearly seen under CT, delineating the thoracic duct's course. Another approach achieved by magnetic resonance lymphangiography could provide the leak site (44). Lymphangiography aids in understanding the chyle fistula, informing surgical decisions, and successful intranodal embolization can avoid surgery. Some studies have used a mixture of n-butyl cyanoacrylate and iodine oil (tantalum powder) for embolization with certain success (45,46). The development of lymphangiography and embolization techniques is mainly limited by the difficulty and availability of the procedure. And, retroperitoneal lymph node needle disruption as an alternative treatment option reported by Kagawa *et al.* (47). In this study, only one patient underwent lymphangiography in an external hospital to accurately locate the chylothorax site, and the leakage site was ligated during surgery. Lymphangiography, as a less invasive treatment method compared to surgery, has the potential to replace most VATS thoracic duct ligation procedures.

This study also has its limitations. (I) Some patients with minor chylothorax, not undergoing pleural fluid biochemistry or chylous tests, might have been omitted from the chylothorax group, introducing recall bias. Minor cases that were not subjected to these tests may have been missed, potentially underestimating the true incidence of chylothorax in our study population. Therefore, it's important to acknowledge that the actual occurrence of chylothorax in our study cohort may be higher than reported due to these potential omissions. (II) Being a single-center retrospective study conducted in a provincial thoracic surgery center, our study is susceptible to selection bias. This bias arises from the inherent tendency to admit complex cases. (III) Due to the low incidence of postoperative chylothorax, the sample size in the chylothorax group remains small even after three and a half years, limiting a detailed analysis of additional risk factors. Moving forward, performing a propensity score matching analysis could enhance our understanding of the risk factors. Future research endeavors should focus on prospective cohort studies to validate identified risk factors and explore additional contributors to postoperative chylothorax. Comparative analyses between different surgical techniques and perioperative management strategies can provide insights into optimal approaches. Multicenter collaborations are essential to gather diverse patient populations for enhanced generalizability and subgroup analyses. Interventional studies evaluating preventive measures and treatment modalities are warranted to establish evidence-based guidelines. Longitudinal investigations with extended follow-up periods will elucidate the long-term consequences of chylothorax, informing comprehensive patient care strategies.

Conclusions

This study suggests that preoperative ALB, GGT, histological type of squamous cell carcinoma, and right mediastinal lymph node dissection are independent risk factors for postoperative chylothorax. The occurrence of postoperative chylothorax in the lungs is closely related to surgical procedures, especially the dissection of right mediastinal lymph nodes. It is also associated with the perioperative nutritional status of the patients. Most patients with postoperative chylothorax can be relieved through conservative medical treatment. For patients with a high volume of short-term drainage, early intervention with VATS thoracic duct ligation is recommended. For patients with a high volume of long-term drainage, VATS thoracic duct ligation or chemical pleurodesis can be considered.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of Sir Run Run Shaw Hospital Affiliated with the Zhejiang University School of Medicine (No. 20240169) and individual consent for this retrospective analysis was waived.

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