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Review Article

Chylothorax after Lung Cancer Surgery: A Key Factor Influencing Prognosis and Quality of Life

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Chylothorax is caused by the accumulation of chylous fluid in the pleural cavity due to the injury of the thoracic duct or its tributaries. Chylothorax following lung cancer surgery, especially pulmonary resection and mediastinal lymph node dissection, is a raw potential postoperative complication as previously reported. Chylothorax might lead to a high mortality rate if not addressed in a timely fashion. This article reviews the anatomy of the thoracic duct, risk factors of postoperative chylothorax, diagnoses and management with chylothorax, and intraoperative prevention of chylothorax. With the development of researches on postoperative chylothorax, more effective treatment and prevention measures need to be proposed to better solve this clinical problem.

Keywords: postoperative chylothorax, thoracic surgery, managements

Introduction

Postoperative chylothorax is a major complication in pulmonary surgery, although the incidence rate is 0.25%–3%.[1,2)] The chylothorax often presents as a pleural effusion or milky effluent from the thoracic cavity with an increased chest drainage, and generally associated with feeding. It is usually caused by damage of thoracic duct and its tributaries during lobectomy or lymph node dissection. The complications of thoracic duct injury can be fatal in up to 30% patients if not treated properly.[3)]

Although there are few researches on chylothorax after lung cancer surgery so far, it is necessary to summarize and review the research progress of chylothorax after lung cancer surgery. This article reviewed the anatomical location of chylothorax, discussed the high-risk factors, clinical diagnosis and current management of chylothorax after lung cancer surgery, and summarized the existing problems, which will provide a powerful reference for the development of relevant research on chylothorax.

Anatomy of Thoracic Duct

Generally, the thoracic duct originates from the chylous cistern on the anterior surface of the spine, posterior to the right side of the aorta, and then enters the posterior mediastinum through the diaphragmatic hiatus. It is located in the left upper mediastinal segment of the esophagus, posterior to the left subclavian artery, and connected to the left mediastinal pleura. Locally, the thoracic duct starts from the right anterior part of the spine, between the azygos vein and the aorta, behind the esophagus of the thoracic cavity. This segment of thoracic duct

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is covered by the right mediastinal pleura. When ascending to the level of thoracic vertebra 4–5, the duct gradually passes through the middle line from the posterior thoracic aorta and esophagus to the left anterior spine, and finally from the superior thoracic foramen goes out of the jugular root and enters the left venous angle.

From the review of thoracic duct anatomy and previous studies, it was shown that lung cancer surgery does not always lead to the chylothorax according to its anatomical location. Postoperative chylothorax may be a result of damaging its branches which can easily happen when dissecting mediastinal lymph nodes.[4)]

High-risk factors

Extension of resection

The extension of resection may be related to chylothorax in lung surgery. The overall frequency of chylothorax has been reported by Cerfolio[1)] as 0.37% following pneumonectomy and 0.26% following lobectomy. Uchida[5)] reported 50 cases of patients with chylothorax in 1235 patients after lung cancer surgery. In these patients with chylothorax, the initial surgical procedures were pneumonectomy in 2 (4%) patients, bilobectomy in 5 (10%), lobectomy in 42 (84%; including sleeve lobectomy in 20%), and segmentectomy in 1 (2%). Kutlu[6)] reported 834 patients underwent lung resection with non-small-cell lung carcinoma, in which surgical procedure was lobectomy in 388 patients (57.6%) and pneumonectomy in 285 (42.4%). Chylothorax occurred in five patients following lobectomy (5/388, 1.28%) and pneumonectomy in two (2/285, 0.7%) ($p = 0.36$). To sum up, there is no definite conclusion as to which surgical method can minimize the incidence of chylothorax in lung cancer surgery.

Places of origin

A higher rate of occurrence has been reported following the resection of right lung cancer. In Cho's work, chylothorax occurred more frequently in patients who underwent right-sided operations (48 patients, 2.6%) than in those who underwent left-sided operations (19 patients, 1.5%) ($p = 0.033$).[7)] Byrant[8)] reviewed 41 cases of chylothorax after radical resection of lung cancer and found that the incidence of chylothorax was higher after radical resection of right lung cancer (1159 with left resection and 1679 with right resection, $p < 0.001$). Kutlu[6)] reported seven patients with chylothorax after lung surgery. Five out of the seven patients underwent right thoracotomy (5/362, 1.38%), the remaining two had left thoracotomy (2/311, 0.64%) ($p = 0.29$). Among them, the incidence of chylothorax with right side resection was also significantly higher than left.

The underlying reason might be the high morbidity of right-sided lung cancer. The boundary of right side mediastinal lymph node is more extensive, resulting in the right thoracic duct branches more vulnerable. Furthermore, the amount of chyle drained from left pleural cavity to right is larger than that from right part to the left.[9)] The high drainage amount makes chylothorax more prone to occur when the right branch is damaged.

Systematic mediastinal lymph node dissection

Kutlu[6)] suggested that systematic mediastinal lymph node dissection is the main cause of postoperative chylothorax with an incidence of 1.46%. Bryant[8)] indicated that the incidence of chylothorax was higher in pathological N2 disease ($p = 0.027$). Akin[10)] suggested that the systemic mediastinal lymph node dissection strongly correlates with postoperative chylothorax with an incidence of 1.9%. A possible explanation is that dissection of mediastinal lymph node during lung cancer surgery increases the risk of injury to adjacent thoracic ducts and/or their small branches, resulting in chyle outflow and formation of chylothorax.[6)] The adjacent thoracic duct is more likely to be damaged, especially when dissecting enlarged lymph nodes fused into subcarina and hilum of lung, or lymph nodes around the root of left subclavian artery..

Stage and histologic type of lung cancer

It is still controversial whether lung cancer staging and histologic type affect the incidence of chylothorax. Akin[10)] indicated that adenocarcinoma was the dominant histological cell type among patients who had postoperative chylothorax. Bryant[8)] noted that pathologic N2 status ($p = 0.007$) was significantly associated with the development of chylothorax. However, Kutlu[6)] believed that histology and stage of the disease do not affect the incidence of chylothorax. Due to the low incidence of chylothorax, more evidence is still needed to prove whether the staging and histopathology of lung cancer are related to the incidence of postoperative chylothorax.

The anatomical variation of thoracic duct

Wan[11)] suggested that the occurrence of chylothorax is also related to the variation of thoracic duct in pleural cavity. 17% patients have two tributaries at the lower

part of the chest, and 5% patients have two thoracic ducts. It happens to damage the tributaries even the operative procedure is away from thoracic duct and lead to postoperative chylothorax.

Others

Jiang[12] believed that the occurrence of postoperative chylothorax is also related to body mass index (BMI; <30), diabetes, pulmonary infection, tracheal intubation, acute respiratory distress syndrome, sepsis, septic shock, and hypoproteinemia. However, none of these results have come to a hard conclusion and needed to be verified by further researches.

Diagnosis

The clinical manifestations of chylothorax and essential characteristics of chylothorax are described in **Tables 1** and **2**.[13–17]

Common diagnostic methods

The examination of pleural drainage

Staats[17] and Benedix[18] suggested that a pleural fluid triglyceride value greater than 1.24 mmol/L is 99% diagnostic of a chylothorax. Values of between 0.56 and 1.24 mmol/L are considered equivocal and require lipoprotein analysis for chylomicrons, whereas a triglyceride value less than 0.56 mmol/L has a 5% chance of being chylous fluid. Fasting and malnutrition must be taken into consideration when interpreting biochemical results as these factors can contribute to lower triglyceride levels[19] Demonstration of chylomicrons remains the reference standard for the diagnosis of a chylothorax.[20]

Lymphangiography

Lymphangiography is an effective method for detecting various types of lymphatic leakage including chylothorax, chylous ascites, and lymphatic fistulae.[21–28] Previous researches have described a leakage detection rate of 64–78%.[22,23,26] Lymphangiography can assist the diagnosis of chylothorax, determine the location of chylothorax and other abnormalities, and provide an effective reference for the need for surgical treatment. However, Sachs et al.[25] thought that lymphangiography is of little value in the diagnosis of chylothorax. Le[29] believed that performing lymphangiography would bring great pain and complications to patients, and they argued the necessity of lymphangiography as a routine examination method unless the location of chylothorax was determined during the surgery.

Radionuclide lymphoid imaging

Radionuclide lymphoid imaging is a non-invasive examination that shows the structure and drainage of the lymphatic pathway by means of the lymphatic system's osmotic absorption, transport, uptake, and phagocytosis of labeled compounds colloidal particles or macromolecules. The examination is simple to carry out, with relatively low risk, and can be repeatedly applied.[30] It can not only be qualitative but also be used for localized diagnosis, as well as to monitor curative effect or prognosis.[31]

Others

If patients are unable to have lymphangiography, routine examination methods such as lymphangiography, ultrasound, computed tomography, magnetic resonance imaging, and X-ray are also diagnostic.[20,26,32]

Differential diagnosis of chylothorax and pseudochylothorax

Pseudochylothorax is a less common pleural effusion than chylothorax, usually unilateral. About one-third of the patients has no clinical symptoms. Similar to chylothorax, pseudochylothorax has higher lipid content and can be opaque or milky white in appearance, so it can be easy to get confused with chylothorax, while pseudochylothorax has different etiology, pathogenesis, and clinical characteristics.[33]

Chylothorax is mainly caused by chyle leakage into the thoracic cavity, while pseudochylothorax is mainly caused by cholesterol accumulation. The most common causes of pseudochylothorax are tuberculous pleural effusion, rheumatic pleural effusion, and hemothorax with a long course. In addition, pseudochylothorax has been reported in paragonimiasis, hydatidosis, and malignant tumors. In addition, pseudochylothorax is common in patients with pleural thickening or calcification and long-term exudates, especially those with a history of pleural effusion of more than 5 years.[34] The high concentration of cholesterol in pseudochylothorax mainly comes from the degradation of erythrocyte and neutrophil. The poor absorption of these degradation products by the thickened pleura results in the accumulation of cholesterol in the pseudochylothorax. However, in recent years, some studies have found that pseudochylothorax may also occur in patients without pleural thickening.[35] Therefore, pleural thickening and patient history may not be reliable for the diagnosis of pseudochylothorax.

Thus, a firm diagnosis relies on analysis of the pleural liquid: exudative liquid (protein >30 g/L, lactate

Table 1 Clinical manifestations of chylothorax

Clinical manifestations
Pleural effusion, mediastinal displacement
Chest tightness
Shortness of breath
Palpitation
Fever
Dyspnea (too much effusion)
Loss of chylous fluid and nutrition
Weak
Emaciation
Dehydration

dehydrogenase >200 UI/L) with a high level of cholesterol (usually >200 mg/dL), low level of triglyceride (usually <0.11g/100mL), cholesterol total/ triglyceride ratio >1, absence of chylomicron, and in some cases the presence of cholesterol crystals.[36)]

Pseudochylothorax is usually caused by benign diseases, so in most cases, no special intervention is needed, mainly for the treatment of primary diseases, but if the clinical symptoms are prominent and the amount of pleural effusion is large, pleural puncture or drainage can be performed, and pleural adhesion and fixation can be given if necessary for recurrent refractory cases. However, chylothorax often needs comprehensive treatment of drugs, diet, surgery, and other means because of the repeated and unstable condition of chylothorax.

Management

If the postoperative chylothorax cannot be addressed in a timely fashion, it may lead to dehydration, nutrient loss, and other complications within a week. Because of the relatively low incidence rate and less reported on postoperative chylothorax, there is no complete consensus on the guidelines for postoperative chylothorax. Currently, the treatment of chylothorax includes conservative treatment, surgical intervention, and thoracic duct embolization.

Conservative treatment

Conservative treatment is the optimal choice in many cases, with feasible outcomes reported.[2,7)] The strategy of conservative treatment includes the reduction of the chyle flow, inflating the lung, decreasing the dead space in the thoracic cavity, nutritional support, and the prevention of septic complications.[16)] Its main measures include drainage of the pleural cavity, drug therapy, diet control, and pleurodesis.

Drainage of the pleural cavity

Pleural drainage can decrease the pressure of pleural effusion on mediastinal organs, relieve the clinical symptoms like shortness of breath and palpitation, and also induce pulmonary recruitment.[37)] Thoracic drainage can be the first choice for conservative treatment after lung cancer resection, and a cautious investigation the appearance and the amount of drainage fluid is needed. Kutlu[6)] suggested that conservative management can be performed within postoperative day 7 unless the volume of fluid remains higher than 1000 mL per day on consecutive days, and conservative management longer than 7 days may be justified with close observation of the patient if the volume of the fluid is less than 500 mL per day on postoperative day 7. Typically, during the drainage, a chest tube without suction is always placed as suction may have negative effect on the closure of thoracic duct.[3)]

Diet control

Previous researches showed that thoracic duct chyle flow increases after meal,[38)] particularly after a high-fat one. The volume of chyle flow can be reduced by avoiding fat-containing enteral nutrition.[39)] Therefore, complete oral intake cessation, with total parenteral nutrition or a low-fat diet, was recommended in the initial treatment of chylothorax. Takuwa[2)] indicated that more than 80% of chylothorax cases after pulmonary resection could be cured with a low-fat diet management strategy. Shimizu[40)] also reported that chest tube drainage less than 500 mL during the first 24 hours after complete oral intake cessation and total parenteral nutrition predicts a better prognosis.

On the other side of the coin, total parenteral nutrition can be associated with complications such as venous line infection and mucosal integrity disorder. In contrast, oral intake and enteral nutrition have been reported to have fewer complications.[41,42)] Meanwhile, many studies of the conservative management of chylothorax have suggested that the use of total parenteral nutrition was more effective than a low-fat diet.[15,43,44)] Thus, the adoption of diet control with total parenteral nutrition and a low-fat diet remains to be further evaluated.

Drug therapy

Drug therapy, especially somatostatin, and its analogs are effective in the treatment of chylothorax after lung cancer surgery. It may because somatostatin inhibits the physiological functions of the gastrointestinal tract and pancreas, reducing the generation and leakage of chyle

Table 2 Essential characteristics of chylothorax

Characteristics of chylous fluid	
Color	café-au-lait or chocolate milk
pH	7.4–7.8
Fat (g/100 mL)	0.4–0.6
Chylomicrons	Present
Triglyceride	>1.24 mmol/l
Cholesterol	<5.18 mmol/l (0.065–0.22)
Total protein (g/100 mL)	2.21–6.0

fluid to promote spontaneous healing of chylous fistula.[45,46] Moreover, Bryant[8] shows that 90% of patients with chylothorax after lung cancer surgery can be cured by combined diet control (medium-chain triglyceride ketogenic diet) and drug therapy (somatostatin).

Pleurodesis

When the diet measures failed to resolve the chylothorax, pleurodesis was recommended.[10,47–49] Akin[10] and Cho[7] reported that during the operation of pleurodesis, chemicals (such as ok-432, tetracycline, bleomycin, talcum powder, etc.) are injected into the pleural cavity to minimize the space between visceral pleura and parietal pleura to block the surrounding pleural cavity so that the chylothorax cannot accumulate in the pleural cavity. As a whole, the pleurodesis increased the success rate of conservative management and minimized the need for surgical intervention.

Surgical intervention

A surgical intervention is needed when conservative treatments have been proven ineffective. However, the indications of surgical treatment were still controversial. Kutlu[6] and Orringer[43] reported that early surgical intervention significantly decreased the mortality rate, so they proposed that surgical intervention may be warranted earlier than day 7 in those cases where chylous leak remains above 1000 mL per day. Takuwa[2] thought that a surgical intervention was recommended if the chest tube discharge during the first 24 hours is more than 500 mL. Haniuda[50] believed that unless the patients cannot tolerate surgery, early surgical treatment should be performed. Wan[11] suggested that the drainage volume continues to be more than 1000 mL over 10 days, and not remission after conservative treatment are two indicators for surgical treatment. Zabeck[51] reported that reoperation chylothorax with chest tube drainage of more than 900 mL/day should be performed as soon as possible for postoperative chylothorax.

Thoracic duct ligation is a prior choice for patients who need surgical intervention. It has been proposed in patients subjected to oesophagectomy as it has shown a 9%–2.1% reduction in incidence of postoperative chylothorax.[15,52] Lymphangiography or preoperative enteral administration of a fat source with methylene blue added can help to locate the site of leak prior to thoracotomy.[14]

Thoracic duct embolization

Thoracic duct embolization has become a valuable treatment alternative in recent years.[53] The technique was first proposed by Dr. Constantine Cope as a first-line treatment for chylothorax, the main procedure is to locate repeatedly by means of radiology (X-ray, lymphangiography, contrast material injection, etc.) and then embolize with metal coils or protein glue.[53–56]

Itkin[57] reported outcomes of thoracic duct embolization disruption in 109 patients with chylous leaks, and the overall success rate of the entire series on an intent-to-treat basis was 71%. Chen[54] suggested that the use of a combination of coil and a liquid embolic agent is necessary to achieve optimal thoracic duct embolization as it can provide additional embolic mechanism in case of glue failure (84% vs 91%).

Complications might follow the embolization. The short-term complications of thoracic duct embolization include peritonitis, hemorrhage, pulmonary embolism, and even acute respiratory distress syndrome. Long-term complications included chronic lower limb edema, chronic diarrhea, and ascites.[58]

Prevention of Chylothorax

Zhou[59] investigated the effect of prevention of chylothorax by comparing the preoperative oral hyperlipidemic milk or the thoracic duct labeled with fat emulsion, and the results showed that fat emulsion was considered to be the best marker for the detection of thoracic duct. After the fat emulsion was injected into the gastric tube before the operation, the velocity of chylous fluid could be up to more than 100 mL/h. Therefore, the thoracic duct and its branches were filled significantly during the operation. Under the effect of minimally invasive thoracoscopic magnification, it would be easy to identify its anatomic courses and reduce the injury. On the one hand, a large amount of typical white chyle fluid can be found after injury. Even collateral damage can be detected in a timely manner, which has a significant effect on the

positioning of the fistula; on the other hand, the sealing effect can be judged timely and accurately by repairing the fistula. Moreover, it can avoid unsuccessful re-repair because of the obvious edema around orificium fistulae with easy-damaged.

Discussion

The low incidence rate of chylothorax after lung cancer surgery and the lack of relevant studies have brought great difficulties and challenges for the development of prevention and treatment measures for chylothorax after lung cancer surgery.

There are many questions that are still needed to be answered. When concerning the anatomy of thoracic duct, there are many variations in the thoracic duct, the position of the leakage of chyle fluid is also diverse. However, no relevant studies have been conducted to summarize the position of chyle fluid exposure. In terms of surgical methods, none of the existing reports compared the advantages and disadvantages of the surgical methods of chylothorax. As for surgical intervention, there is no consensus or standard for surgical indications of chylothorax after lung cancer resection. Studies on the efficacy of chylothorax after lung cancer surgery are also warranted as well as the comparison between total parenteral nutrition and oral low-fat diets. All the above problems need to be solved using current evidence-based medical data and multi-center large sample research.

Authors' Contributions

Protocol/project development: Lunxu Liu and Qiang Pu. Investigation: Jian Zhou and Nan Chen. Funding acquisition: Qiang Pu. Writing: original draft: Cong Chen and Zihuai Wang. Manuscript review and editing: Jianqi Hao and Xiaohu Hao.

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