Surgery Today (2021) 51:678–685
https://doi.org/10.1007/s00595-020-02143-y

REVIEW ARTICLE

Management options for post-esophagectomy chylothorax

Vaibhav Kumar Varshney[1] · Sunita Suman[1] · Pawan Kumar Garg[2] · Subhash Chandra Soni[1] · Pushpinder Singh Khera[2]

Received: 22 May 2020 / Accepted: 3 August 2020 / Published online: 17 September 2020

Abstract

Chylothorax, although an uncommon complication of esophagectomy, is associated with high morbidity and mortality if not treated promptly. Consequently, knowledge of the thoracic duct (TD) anatomy is essential to prevent its inadvertent injury during surgery. If the TD is injured, early diagnosis and immediate intervention are of paramount importance; however, there is still no universal consensus about the management of post-operative chylothorax. With increasing advances in the spheres of interventional radiology and minimally invasive surgery, there are now several options for managing TD injury. We review this topic in detail to provide a comprehensive and practical overview to help surgeons manage this challenging complication. In particular, we discuss an appropriate step-up approach to prevent the morbidity associated with open surgery as well as the metabolic, nutritional, and immunological disorders that accompany a prolonged illness.

Keywords Chylothorax · Post-esophagectomy · Lymphangiography · Thoracoscopic ligation · Embolization

Introduction

The thoracic duct (TD) is often damaged during mobilization of esophageal cancers, via right thoracotomy or via the trans-hiatal route [1]. In the event of TD injury, chylothorax usually presents in the first week after surgery. Initial management is generally conservative, but high volume leaks require surgical management. Re-exploration either via thoracotomy or via laparotomy will add to the morbidity of esophagectomy. A minimally invasive approach via lymphangiography, with or without embolization, for post-esophagectomy chylothorax has been reported with good success rates [2, 3]. We discuss the anatomy of the TD, then review the clinical presentation of its injury and the various treatment options for post-esophagectomy chylothorax, focusing on minimally invasive approaches.

✉ Vaibhav Kumar Varshney
drvarshney09@gmail.com

1 Department of Surgical Gastroenterology, All India Institute of Medical Sciences, Basni Industrial Area, Phase-II, Jodhpur, Rajasthan 342005, India

2 Department of Diagnostic and Interventional Radiology, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India

Anatomy

The thoracic duct (TD) drains lymph from the entire body, except from the right hemithorax, upper limb, and right side of the head and neck. Consequently, it is a long structure, measuring 38–45 cm with a diameter of 2–5 mm, extending from the apex of the cisterna chyli to the neck [4]. The small lymphatic vessels converge to form the right and left lumbar trunks and the intestinal lymph trunks, which in turn unite to form the cisterna chyli, usually at the level of the L2 vertebrae and to the right of the aorta. It is found in only about 53% of lymphangiography studies [5]. The TD originates at the apex of the cisterna chyli and traverses through the aortic hiatus and ascends in the posterior mediastinum between the thoracic aorta in the left and the azygous vein in the right. Here, the vertebral column and right intercostal arteries lie posterior to the TD, and the diaphragm and esophagus lie anterior to it. The TD then turns left and enters the superior mediastinum along the left border of the esophagus, usually at the level of the T5 vertebrae. The TD then travels posterior to the arch of aorta and then the left subclavian artery, and proceeds to the cervical region, where it turns laterally at the level of the transverse process of the C7 vertebra [5]. It rises 3–4 cm above the clavicle and passes posterior to the left common carotid artery, vagus nerve, and internal jugular vein. Finally, the TD descends anterior to the first part of the left subclavian artery and, after receiving branches from the left sides of the head and neck and the left upper limb, it most commonly terminates in the internal jugular vein directly, or in the jugulo-venous angle [6] (Fig. 1). However, remarkable embryological variations occur, and this typical anatomy is found in only 50% of the population [5]. Variations include different crossover levels as well as several mediastinal trunks. Duct duplication is a common variant, which may give rise to a plexus in the mid-portion of the duct and can have varying terminations into the vascular system [7]. A recent review article found that the TD terminates in the internal jugular vein in 54.05% of people, in the jugular-venous angle in 25.79%, and in the subclavian vein in 8.16% [6].

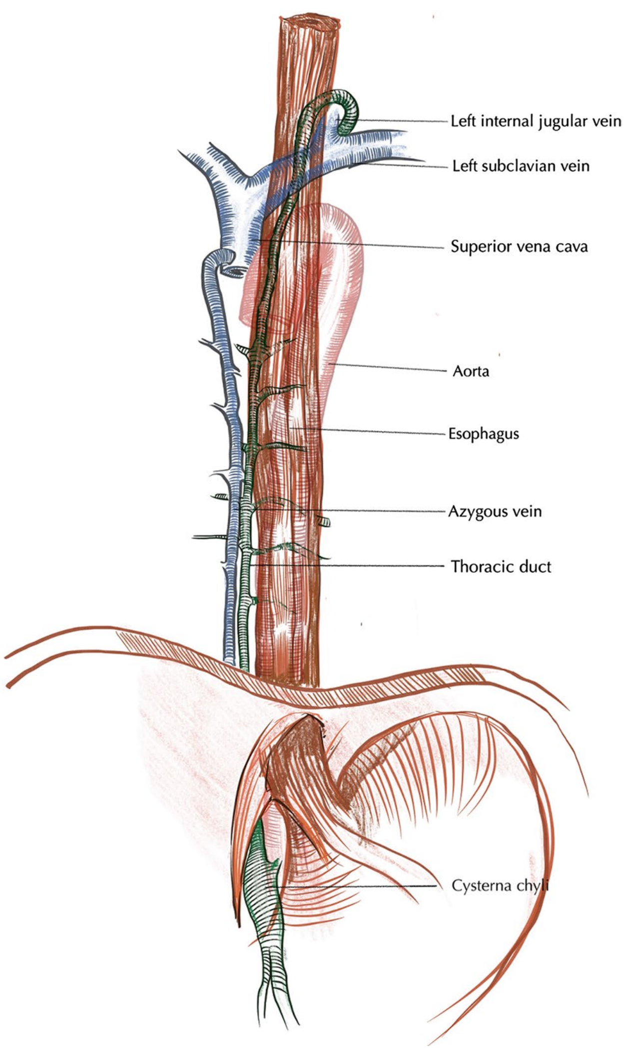

Fig. 1 Surgical anatomy of the thoracic duct showing its origin in the abdomen, the course it follows in the thorax, and its termination in the neck

Etiology of chylothorax

The TD lies in close proximity to major vessels and organs during its course and is consequently at risk during any surgery or intervention in the neck, mediastinum, or abdomen. Furthermore, it traverses a long course with frequent anatomical variance and is, thus, prone to iatrogenic injury, from thoracic, cardiac, and head and neck surgeries. Esophagectomy is one of the most common causes of chylothorax, with an incidence of 2–10% [1], followed by surgeries for congenital heart disease. TD injury may occur even in less invasive procedures, such as central line placement, particularly with a subclavian approach. Non-traumatic occlusion and leakage of the TD is much less common and may originate from both malignant and benign etiologies. Malignant lesions include lymphoma, esophageal adenocarcinoma, primary lung malignancies, and mesothelioma [8]. Benign causes of obstruction range from systemic disease and infection to primary lymphatic vessel diseases and idiopathic causes. Congenital etiology includes atresia of the TD and pleural thoracic duct fistula.

Chylothorax is a known, although infrequent, complication after esophagectomy. Injury to the TD is usually encountered during dissection of the esophagus, either in the thoracic or cervical region. In a systematic review by Kranzfelder et al., the overall incidence of post-esophagectomy chylothorax was 2.6%, with no significant difference between the trans-hiatal and transthoracic approaches [9]. Similarly, in a meta-analysis by Nagpal et al. [10], no difference was noted between minimally invasive esophagectomy and open techniques, in terms of the incidence of chyle leak. The predisposing factors for chylothorax are variable anatomy of the TD, the radicality of dissection, neoadjuvant treatment, and squamous histology [11]. A body mass index (BMI) < 18.5 kg/m^2 is another reported independent risk factor for chylothorax. Zhang et al. [12], in their meta-analysis, reported a significantly increased risk of chylous leakage in patients with a low BMI. Similar findings were reported by Miao et al. [13], who postulated that patients with a higher BMI had fatty tissue surrounding the esophagus and tumor tissue, which seemed to protect the TD. Furthermore, with the advent of neoadjuvant chemoradiotherapy (NACRT) as an established treatment for carcinoma of the esophagus and resultant fibrosis, the risk of chylothorax may increase in the near future [9, 14].

Diagnosis and evaluation

Patients with non-traumatic chylothorax usually present with progressive respiratory distress. An initial chest X-ray reveals pleural effusion and diagnosis is made following drainage and analysis of the pleural fluid. An iatrogenic chylous leak, post-procedure, is suspected when there is copious chest tube output after surgery, and it turns milky as the feed is commenced. The diagnosis of chylothorax is further confirmed by a high level of triglycerides (TGs) in the pleural fluid. If the pleural fluid TG level is > 110 mg/dL, then chylothorax is highly suspected. However, if TGs are < 110 mg/dL and the clinical history or pleural effusion appearance is consistent with possible chylothorax, then a pleural chylomicron study should be performed [15]. The presence of pleural chylomicrons confirms the diagnosis of a chylothorax, and their absence suggests an alternative etiology.

In an average adult, the TD transports up to 0.38 mL/min (550 mL/24 h) during fasting, to 3.9 mL/min in the post-prandial state [16]. This flow rate is also influenced by the fasting state, gut function, diet, drug intake, and the degree of mobility. Approximately 60–70% of dietary fat enters the systemic circulation via the TD, and lymphocytes (primarily T cells) constitute 95% of the cellular component of chyle. Electrolytes, antibodies, and enzymes concentration are similar to those in plasma [16]. Consequently, persistent leakage from the TD leads to loss of protein, albumin, fat, and vitamins [17]. Furthermore, the ongoing loss of electrolytes results in acidosis, hyponatremia, and hypocalcemia with increased risk of bacterial and viral sepsis attributable to loss of lymphocytes, antibodies, and albumin. Hence, the mortality rate associated with chylothorax is high without prompt treatment [11, 17]. The management of chylothorax also depends on factors like etiology, intercostal drain (ICD) output, and condition of the patient.

Management

The ideal management of chylothorax is contentious and the optimal timing of any intervention remains controversial. Notwithstanding, management begins with conservative therapy.

Non-surgical management

Conservative management is usually successful, if the drainage is less than 10 ml per kg body-weight per day [13, 18, 19]. Patients who are less likely to respond include those with high-output chylothorax diagnosed early in the post-operative course, which usually signifies injury to the TD rather than its tributaries. As soon as the diagnosis is confirmed, patients are either started on a low-fat, medium-chain triglyceride (MCT) diet, or kept on nil per oral (NPO) with total parenteral nutrition (TPN) support. The objective of these dietary modifications is to decrease the flow of chyle through the TD and thereby aid in spontaneous healing. Long-acting somatostatins, such as octreotide [20, 21] and alpha agonists like etilefrine [22], have been used as an adjunct and serve the same purpose. Octreotide is usually administered subcutaneously at a dose of 100 mcg every 8 h [21], but it has also been administered intravenously at dosages ranging from 50 to 200 mcg, three times a day, with good results [23]. Octreotide decreases the splanchnic blood flow, thereby decreasing the triglyceride content of chyle and subsequently aiding in spontaneous healing. A meta-analysis by Ismail et al. [20] concluded that octreotide was effective for mild-to-moderate volume chyle leak, with its benefit usually expected within 2–3 days of administration. However, their study was limited by a heterogeneous population with different pathology and surgeries. Etilefrine has also been given as an aid at doses of 120 mg per day intravenously [22], with or without octreotide. Etilefrine is a sympathomimetic drug that causes the contraction of smooth muscle fibres in the wall of the TD, leading to a narrow lumen and decreasing output. In a retrospective analysis by Guillem et al. [24], 7 of 10 patients were managed without reoperation, using etilefrine. Similarly, Tabata et al. utilized a combination of octreotide and etilefrine, but most of their patients also required pleurodesis and had a prolonged recovery [25]. As the studies on the use of these drugs are limited to case series and retrospective studies, they have only a supportive role with variable success rates. Hence, a general consensus for conservative management comprises NPO, MCT diet, TPN, and octreotide in patients with ICD output < 10 ml/kg for 5–7 days with success rates ranging from 80 to 90% [21, 26].

Percutaneous radiological interventions

The lymphangiographic approach has been reported in a series of cases, as an alternative approach for the management of chylothorax. Initially, it was used as a diagnostic tool to locate leakage of chyle preoperatively, but now lymphangiography is used as a therapeutic technique [27]. Intranodal lymphangiography (IL) is performed via ultrasound access, which is minimally invasive and requires no incision. A superficial inguinal node can be accessed directly with a 21- 23 G micro-puncture needle under local anesthesia. Iodinated contrast lipiodol (Guerbet, France), which is iodized ethyl-ester of fatty acids of poppy seed oil, is infused

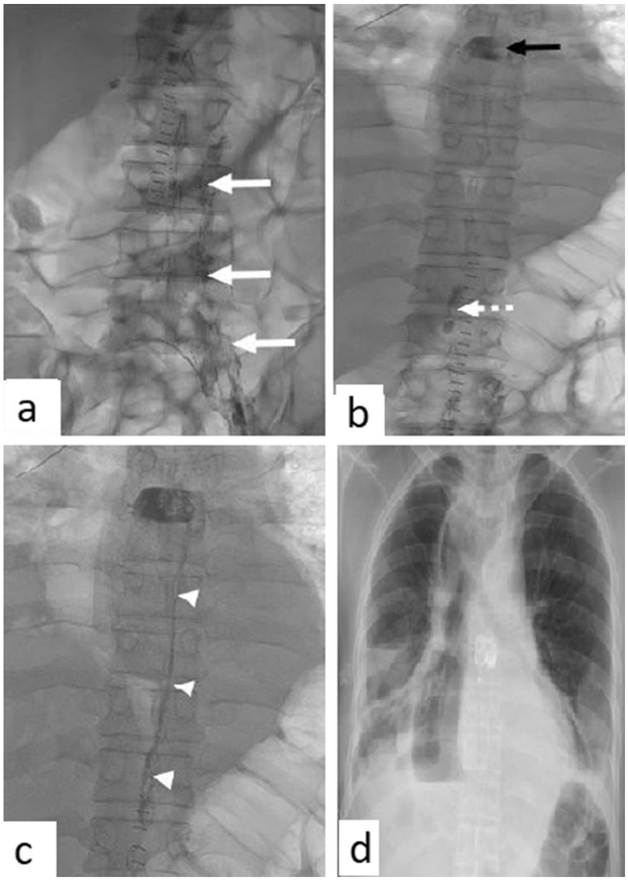

Fig. 2 Fluoroscopic images of lymphangiography and embolization: **a** Opacification of the left-sided lumbar lymphatics (white arrow) following an intranodal injection of lipiodol; **b** Further follow up showing opacification of the cisterna chyli (dashed arrow) and visualization of the leak in chest (black arrow) corresponding to the surgical site; **c** Percutaneous fluoroscopy-guided puncture of the cisterna chyli and injection of 50% glue into thoracic duct (arrowhead); **d** Chest radiograph 24 h post-procedure showing the retention of glue and lipiodol cast

slowly at 0.1–0.2 ml/min, and intermittent fluoroscopic images are taken. This oil-based iodinated contrast ascends superiorly as oil droplets from the inguinal lymph node into the lumbar lymphatics via the pelvic lymphatics (Fig. 2a). After approximately 1 h of the infusion, the contrast will opacify the cisterna chyli at the D12-L1 vertebral level and it continues to ascend to depict the leak site along the course of the TD (Fig. 2b). The next step is puncturing the cisterna chyli using a 21 G Chiba needle with fluoroscopic guidance, which requires precision, but is possible because the cisterna is opacified by contrast. Once it is punctured, a thin guidewire, 0.014 inches in diameter, is inserted into the TD in the mid-thorax. A microcatheter-like 2.7 Fr Progreat (Terumo, Japan) is then placed over the wire and into the duct and the leak is confirmed by contrast injection. Embolization of the TD with glue (N-Butyl Cyanoacrylate) and Lipiodol through a microcatheter injection leads to its obliteration and has been shown to be effective for a chylous leak (Fig. 2c–d).

Cope et al. reported the first cannulation and embolization technique to treat chylothorax with demonstrable duct leakage [28]. Following this report, there has been a gradual accumulation of experience in treating chylous effusions, with the adoption of thoracic duct embolization (TDE) to treat chylothorax. However, reproducibility and success rates vary in different centers. Several retrospective analyses have shown that the percutaneous approach achieved a successful resolution in nearly 70% of patients, even with high chyle output [29–31]. Lipiodol lymphangiography with embolization is clinically effective and should be attempted before surgical intervention for chylothorax.

Advances in lymphangiography and related interventions have given treating surgeons an alternative to invasive re-exploration for post-esophagectomy chylothorax. With satisfactory success rates ranging 55–90% for various procedures [29, 30, 32], these minimally invasive techniques represent a step-up approach preceding surgery, after failed conservative management. Surgery may be avoided in more than 50% of carefully selected patients with chylothorax. General anesthesia is not required and monitored sedation may suffice for these minimally invasive techniques, thus avoiding the associated morbidities. Newer techniques for lymphangiography, such as ultrasound-guided intranodal lymphangiography, are less time-consuming with a lower technical failure rate [33]. Studies have shown that TDE is feasible, even for patients with high-output chylothorax. Therefore, we believe that lymphangiographic approaches should be explored before opting for surgery. Even if the lymphangiographic embolization fails, it will provide the site of leak, any anatomical variations in the TD course, and a road map for future surgical intervention. TD disruption and retrograde cannulation of the TD are alternative procedures that can be done during the same sitting if a suitable lymphatic vessel is not identified for catheterization. Furthermore, complications associated with lymphangiography and associated embolization procedures are uncommon, but usually self-limiting. These include leg edema, wound infections, perihepatic hematoma at the access site, and rarely, non-target embolization of the lung or portal vein or a retained guidewire fragment [29–31]. Nadolski et al. suggested embolization of the TD below the leak, first with coils to create a scaffold on which glue can polymerize to prevent non-target embolization [31].

Surgical management

Prophylactic thoracic duct ligation (TDL) during esophagectomy may decrease the risk of post-operative chylothorax [34, 35]. Lei et al. analyzed this in their review article, and failed to show any benefit of prophylactic TDL [36];

however, it may be prudent to ligate the TD prophylactically in patients with high-risk factors, such as low BMI, difficult mediastinal dissection or post NACRT. Another proposition is intraoperative visualization of the TD with immediate ligation on injury or preservation, during the primary surgery. This can be achieved with methylene blue, olive oil or milk feeds, 6–8 h prior to surgery [37]. Shen et al., in their retrospective study, claim that it is a feasible option with a significant reduction in the incidence of post-operative chylothorax [38]. Du et al. in a propensity score matching study found that the TD was readily identified intraoperatively in all patients who had received olive oil feeds prior to esophagectomy, compared with fewer than half of the patients in the control arm, with no post-operative chyle leak in the olive oil group versus 3% in the control arm [37].

Postoperatively, if conservative therapy fails, surgical intervention with TDL via an abdominal or thoracic route is preferred. Surgery is recommended when the drain output is more than 10 ml/kg/day or chyle flow has persisted for more than 5–7 days, because of a progressive increase in associated complications [8, 10]. In a systematic review by Kranzfelder et al. [9], reoperation was performed within 2 weeks of primary surgery in more than 65% of patients. Performing re-exploration to manage chylothorax following esophageal surgery is associated with morbidity in 50% of patients and with mortality in about 10%. However, it may be argued that surgery is attempted only after conservative management fails and this generally encompasses a minimal duration of 7–10 days [11], while the patient is malnourished and immunocompromised, thereby increasing the risk of mortality and morbidity post-surgery. Hence, it is advocated that if the chylous output remains > 10 ml/kg/day after 48–72 h of conservative management, either radiological or surgical intervention should be initiated as the likelihood of spontaneous resolution is less.

Before embarking on surgery, the procedure is made easier by identifying the point of injury. This can be accomplished with preoperative lymphangiography or intraoperatively by the administration of an enteral fatty diet (usually cream or olive oil) with the addition of methylene blue. Once the focus of chyle leak is recognized, the surgeon can proceed with thoracoscopy or thoracotomy and ligate or clip the TD proximal to it [8]. This can be done with titanium clips, hem-o-lok clips (Weck systems, USA), non-absorbable sutures like polypropylene, or a combination of these [18]. However, identification of the point of leakage is not essential and failure to do so can be managed with the mass ligation of tissue in the supradiaphragmatic region between the descending thoracic aorta and azygous vein [34]. Mass ligation of the duct may be especially favorable in patients with anatomic variations in the TD and any unidentified ductal injuries [8]. The probability of anatomic variations is lowest close to the origin of the TD, and because of this, mass ligation of the TD has a success rate of 67–100% [39]. Chemical and surgical pleurodesis have been used as an adjunct, post-procedure.

Minimally invasive surgery is feasible and has been advocated by several authors, as it is associated with lower morbidity and a reasonable success rate [11, 18, 40]. A right-sided thoracic approach with a semi-prone position is preferred as the thoracic aorta does not hinder visualization of the TD [18, 41]. Usually, three ports are placed, with a posterior camera port below the scapular tip and two working ports in the 5th intercostal space along the anterior axillary line and eighth intercostal space along the mid-axillary line. If the primary surgery is done thoracoscopically, a similar port position can be used. The utmost care must be taken during manipulation of the gastric conduit to avoid inadvertent injury, and additional ports may be required to retract the gastric tube. The TD is then localized using the descending aorta and azygous vein as landmarks. A fatty solution with methylene blue given via the nasogastric tube or feeding jejunostomy 30–60 min before surgery may aid in visualization of the duct as it enlarges. Once identified, a short segment of the TD is dissected and a clip or suture is applied caudally, close to hiatus, and another clip is applied cranially, about 5 cm proximal to the previous clip [41]. The application of too many clips or excessive dissection of the TD should be avoided, as it may cause secondary injury to the duct. If the duct is not localized, mass ligation can be done with larger clips or it can be ligated with non-absorbable sutures at the supradiaphragmatic region. Hence, video-assisted thoracoscopic surgery (VATS) has become the gold standard for managing chylothorax. VATS gives a magnified view, which helps to identify the TD and has the added advantage of a minimally invasive procedure with less pain, earlier recovery, and shorter hospital stay. As thoracotomy is averted during re-exploration, so are its associated pulmonary complications, with a decreased incidence of pneumonia and sepsis. For a patient with upper thoracic or cervical TD injury, the duct can be identified at the Poirier's triangle, with its base formed by the aortic arch, its sides formed by the left subclavian artery and vertebral column, and its floor formed by the esophagus [42, 43]. After post-thoracic duct ligation, the patient improves promptly with a decrease in ICD output and stabilization of their hemodynamic parameters. Usually, they are allowed nutrition through the jejunostomy tube and then orally. The ICD is removed when the output is < 100 ml. If surgical intervention fails, there is likely to be some variable anatomy; hence, in such cases, lymphangiography should be done, if it was not done before surgery.

Newer techniques, such as Indocyanine green (ICG) lymphography, may provide real-time assessment of the TD anatomy and localize the site of injury. A few cases of successful surgical management with intraoperative ICG

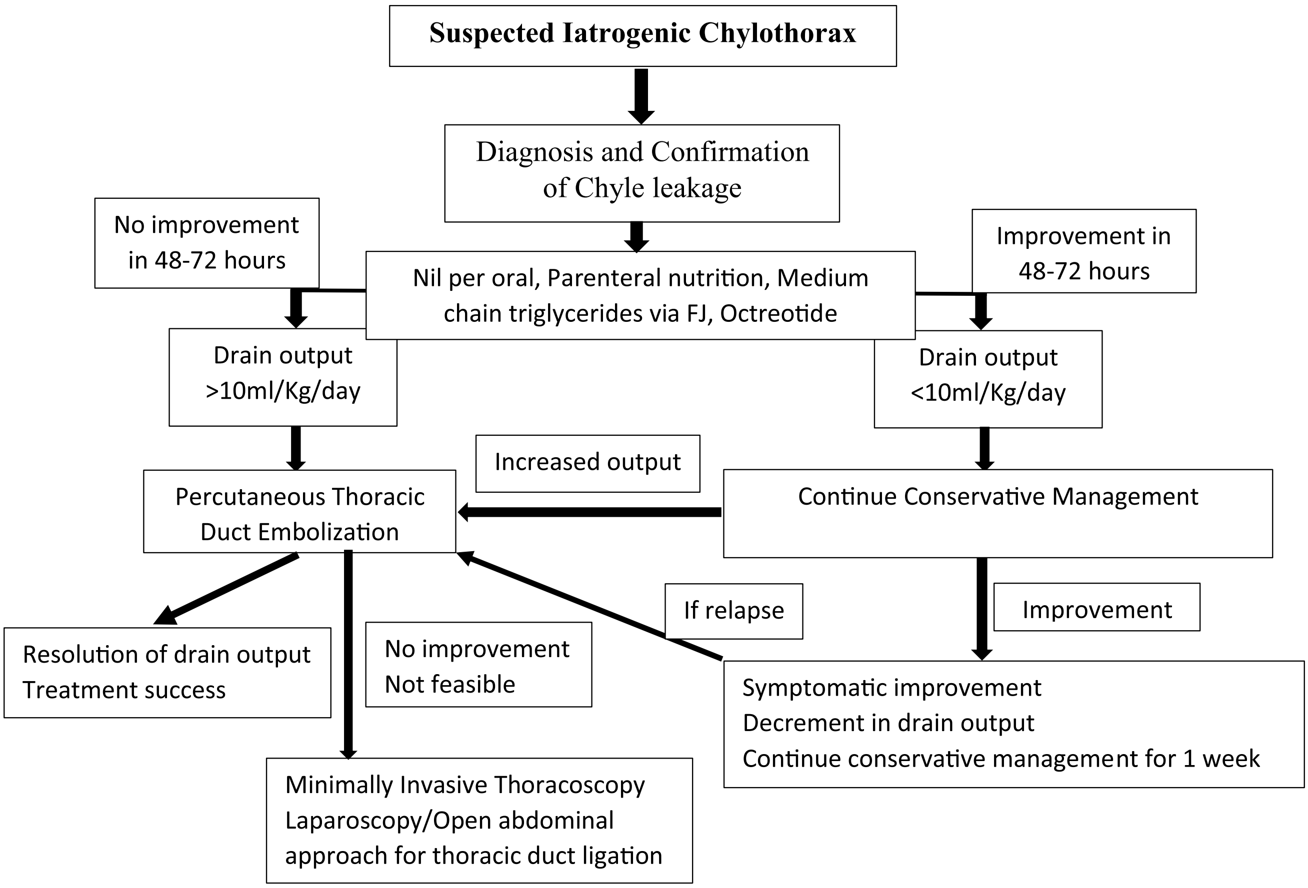

Fig. 3 Proposed treatment algorithm for the management of iatrogenic chylothorax

have been reported [41, 44, 45]. Subcutaneous ICG injection was given either in the inguinal region, in the small bowel mesentery, or between the toes, identifying the TD with a delay of only about 15 min, followed by successful ligation or clipping [46]. ICG-lymphography is potentially beneficial for the treatment of chylothorax, despite the limited evidence on this subject to date.

In conclusion, iatrogenic TD injury must be diagnosed and managed promptly to avoid severe consequences. An algorithmic approach for the management of post-esophagectomy chylothorax is proposed in Fig. 3. TD embolization for iatrogenic injury is a minimally invasive technique that is safe, effective, and has low morbidity. Hence, this option, although technically challenging, should be explored before considering surgery.

Author contributions Conception and design: VKV, SS, PKG, PSK; Provision of study materials: VKV, SS, PS; Collection and assembly of data: VKV, SS, SCS; Manuscript writing: VKV, SS, PKG, SCS; Final approval of manuscript: VKV, SS, PKG, SCS, PSK.

Funding No source of funding.

Compliance with ethical standards

Conflict of interest Vaibhav K Varshney, Sunita Suman, Pawan K Garg, Subhash C Soni and Pushpinder S Khera have no conflicts of interest to declare.

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