ORIGINAL ARTICLE

RISK FACTORS FOR CHYLE LEAK AFTER ESOPHAGECTOMY

Sadaf Batool, Sana Amir Akbar, Misbah Khan, Raza Sayyed, Osama Shakeel, Aamir Ali Syed, Shahid Khattak, Ali Raza Khan

Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore-Pakistan

Background: Chylothorax is an uncommon (3–8% risk) but potentially fatal complication of esophagectomy with poorly understood risk factors. It has a high morbidity due to loss of fluids, electrolytes, and other nutrients, loss of lymphocytes and immune dysfunction. **Methods:** Retrospective chart review of adult patients who underwent esophagectomy between 2009 and 2016 was performed. Cases with chyle leak were identified according to a set criteria. Clinical features, operative findings and postoperative variables were recorded and predictors of chyle leak were analyzed. **Results:** During the study period, a total of 193 adult patients underwent esophagectomy of which 186 received neo adjuvant chemotherapy. The mean age was 53 years with 118 males and 74 females. Type of procedure performed was 3-stage esophagectomy in 98, Transhiatal esophagectomy in 79 and Ivor-Lewis esophagectomy in 15 patients. Chyle leak was identified in 9 (4.6%) patients. There was no significant association of chyle leak with age, gender, co-morbid, level of tumor, Neo-adjuvant therapy and Type of esophagectomy. Chest drain output on postoperative day 5 was significantly predictive of chyle leak (p-value<0.05). Drain output more than 1000 on day 4 was highly suggestive of chyle leak (p-value<0.05). Day on which chest drain was removed was also found to be significantly related to chyle leak (p-value <0.05). **Conclusion:** No significant preoperative risk factors were identified for chyle leak. High chest drain output on postoperative day 5 and drain output more than 1000 on day 4 are significant predictors of chyle leak.

Keywords: Thoracic duct; Chylothorax; Chylous ascites; Chest drain

Citation: Batool S, Akbar SA, Khan M, Sayyed R, Shakeel O, Syed AA, Khattak S, Khan AR. Risk factors for chyle leak after esophagectomy. J Ayub Med Coll Abbottabad 2019;31(4):506–11.

INTRODUCTION

Close anatomical relation of thoracic duct to oesophagus predisposes it to injury during oesophageal mobilization, with a 0–9% risk of iatrogenic injury.[1] Chylothorax is a rare but potentially lethal complication of esophagectomy with mortality rates of 0–50%.[2–4] It predisposes to an increased risk of pulmonary complications and sepsis.[5–7]

Most commonly caused by injury to the main thoracic duct or its tributaries.[8] Chylothorax is a leak of lymphatic fluid consisting of lymphocytes, enzymes and immunoglobins.[1,9] Diagnosis is suspected by whitish fluid in chest drain and confirmed by triglyceride levels of more than 110 mg/dL after starting enteral feed. Chyle leak is managed conservatively with Total Parenteral Nutrition (TPN), pleurodesis or surgically with chest drainage and thoracic duct ligation.[10] There is no study to predict the precise timing of re-exploration. However, conservative therapy is likely to be successful if chest drain output decreases to less than 10 ml/kg, five days after initiation of non-operative management.[11]

Due to its relatively low incidence, only few studies with a small number of cases are available on post esophagectomy chylothorax. We have analysed pre-operative, intraoperative and postoperative risk factors associated with chyle leak after esophagectomy.

MATERIAL AND METHODS

This case control study was carried out at Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore. Patients who underwent elective esophagectomy for the treatment of oesophageal carcinoma from Jan 2009 till Dec 2016 were identified from Hospital Information System and reviewed retrospectively. Following inclusion criteria were used in the present study:

1) All adult patients with oesophageal cancer who underwent subtotal esophagectomy
2) cTis-T4a and N1-N3, M0 tumours[12]

Patients were only excluded if they had

1) Emergency oesophageal surgery due to oesophageal perforation
2) Anastomotic leak (Diagnosed on radiology, clinical findings or on re-exploration)
3) T4b or M1 stage oesophageal cancers[12]

Neo-adjuvant therapy was given as concurrent chemotherapy (Paclitaxel and Carboplatin /5-FU based) and external beam

radiation (total dose of 41.4 Gy).[13] All the patients were operated by or under direct supervision of two surgeons experienced in oesophageal surgery and thoracic part by single specialist cardiothoracic surgeon. Operations were performed using transhiatal approach for gastro-oesophageal junction tumours or transthoracic approach (3 stage or Ivor Lewis esophagectomy) for mid/lower oesophageal tumours. Right sided 28–32 Fr Chest drain with negative pressure was placed in all patients who underwent esophagectomy through transthoracic approach. During transhiatal esophagectomy, the tumour and its adjacent lymph nodes were dissected en bloc. To prevent damage to the thoracic duct, the ventral wall of the thoracic aorta was chosen as the dorsal dissection plane. During right-sided transthoracic esophagectomy, thoracic duct was identified and selective ligation of thoracic duct was performed in few patients. Preoperative nutritional status was improved by placing percutaneous endoscopic gastrostomy tube in all patients with oesophageal cancer and dysphagia. Per-operative jejunostomy tube was not placed for enteral nutrition, instead all patients were kept nil per oral (NPO) and were given intravenous fluids for 5 to 6 days after operation. Before starting per oral enteral feed, upper GI contrast study was performed on all patients on the 5^{th} or 6^{th} day to rule out anastomotic leakage. Fluid output from chest drain was measured on daily basis. In general, drain was removed when the drainage volume dropped to less than 100 ml/day.

The patients with chyle leakage were initially managed conservatively, i.e., they were kept NPO and were given total parental nutrition (TPN) or a fat free diet. There were no strict criteria for surgical intervention, other than a high volume drain output for several days despite conservative management, or the patients who did not respond to conservative therapy, i.e., they remained unstable.

Patients were divided into two groups, cases and controls. Patients were included in the case group if they developed post-operative chyle leakage and in control group if had no features suggestive of this complication.

Patients were included in the case group if they had anyone of the following features:

1) Chyle leak on re–exploration.
2) The contents of the drain output became milky white (in patients who have been started with enteral nutrition on the 5^{th} or 6^{th} post-operative day).
3) Chylous output from wound.
4) Chest drain fluid triglyceride levels more than 110 mg/dl.

Patient's age, gender, BMI, endoscopic level of tumour, tumour differentiation, pre-treatment T and N stage, response to neo-adjuvant therapy on imaging, duration between neo-adjuvant therapy and surgery, preoperative serum albumin levels, operative approach, extensive adhesions and pathological T stage were evaluated as potential predisposing factors for chyle leakage between case and control groups (Table 1 and 2).

Data analysis was conducted using SPSS® Version 22.0 for Windows™ (SPSS® Inc., Chicago, III). Categorical variables were described as frequencies and percentages. Quantitative variables were described as median with interquartile range. To compare categorical data chi-square test was used for binominal variables and one-way analysis of variance for tri and tetra-nominal variables. The Mann-Whitney U test (MVU) was used to compare abnormally distributed continuous variables and student *t*-test for normal distributed continuous variable. Binary logistic regression analysis was used to determine whether certain variables could predict risk of chyle leak. *p*-value of less than 0.05 and a confidence interval of 95% were considered as a level of statistical significance.

RESULTS

During the study period 193 patients underwent esophagectomy for oesophageal cancer with curative intent at our hospital. Out of 193 patients, nine patients developed chyle leak with an incidence of 4.6 percent.

There was no statistically significant difference between patient and tumour characteristics of the two groups pre-operatively (Table-1). More than 95% of patients received neo-adjuvant chemo radiotherapy and planned surgery was performed after an interval of three-four months.

Intra-operative risk factors for chyle leak were analysed (Table-2). Extensive dissection during surgery described subjectively by operating surgeon was linked to an increase risk of chylothorax (*p*-value 0.004)

Prophylactic thoracic duct ligation was done in nine patients and was not found to lower risk for chyle leak. Type of esophagectomy performed also failed to show any significant impact on univariate analysis, this however on logistic regression analysis was found to be the only potential risk factor with a statistically significant *p*-value of <0.05 (Table-4).

Early predictors of chyle leak after esophagectomy are analysed in table-3. Chest drain output was found to be closely related to the chyle

leak. When observed in retrograde, patients with chyle leak had a high median chest drain output on day 5, (*p*-value <0.05). Chest drain output of more than 1000 on day four was significant predictor of chyle leak postoperatively (*p*-value 0.001). Additionally, the day on which chest drain was removed was significantly associated with chyle leak (*p*-value 0.007). Out of 9 patients with chyle leak, drain triglyceride level was raised only in two patients and rest of them were diagnosed by a combination of high chest drain output with milky discharge and cream test/fat loading test. Seven cases were managed conservatively with nil by mouth and total parenteral nutrition, while upfront re-exploration was done in 2 patients due to persistent high chest drain output (Figure-1).

Among patients with conservative management three cases required re-exploration due to persistent high drain output (Table-5). Chylothorax was seen in all patients who were re-explored. There was no 30-days mortality in our study population.

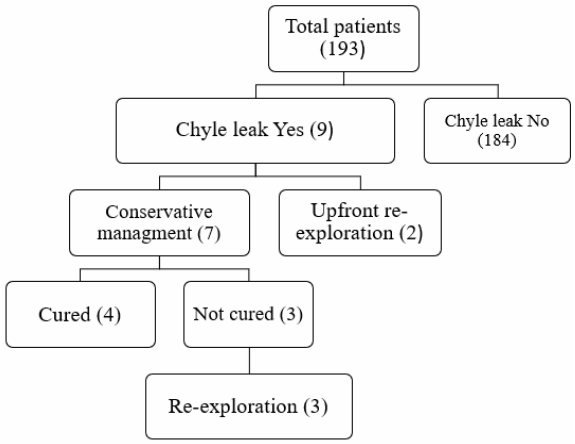

Figure -1: Hierarchy of study population

Table-1: Baseline patient and tumor characteristics

Variables	Chyle leak=NO n= 184	Chyle leak YES n= 9	*p*-value
	n (%) / Median (IQR)	n (%) / Median (IQR)	
Age (years)	54 (47–60)	53 (42–58)	0.886
Gender			
Male	115 (62%)	4 (44%)	0.277
Female	69 (38%)	5 (55%)	
BMI (kg/m^2)	21 (18-25)	22 (17-26)	0.485
Charlson Co-morbidity index[14]			
0	177 (96%)	8 (89%)	0.249
1	7 (4%)	1 (11%)	
Level of tumor (EUS)			
Middle	38 (20%)	3 (33%)	0.388
Lower	145 (80%)	6 (77%)	
Pretreatment T stage (EUS)			
Early (Tis, T1, T2)	14 (8%)	0 (0%)	0.655
Advanced (T3, T4a)	144 (92%)	9 (100%)	
Neo-adjuvant therapy			
Yes	177 (96%)	9 (100%)	0.815
No	7 (4%)	0 (0%)	
Response to neo-adj therapy on CT scan			
Reduction	123 (67%)	6 (77%)	
Progression	2 (1%)	0 (0%)	0.742
Stable	48 (26%)	3 (33%)	
Not known	4 (2%)	0 (0%)	
Duration between neo-adjuvant therapy and surgery (months)	4 (3–5)	3 (3–4.5)	0.821
Serum albumin (g/dl)	4 (3.8–4.2)	4 (3.5–4.3)	0.176
Pathological T stage			
T0	102 (55%)	5 (55%)	0.662
Early (T1, T2)	36 (20%)	3 (33%)	
Advanced (T3, T4)	46 (25%)	1 (11%)	

Table-2: Intra-op risk factor for chyle leak

Variables	Chyle leak NO (n=184) n (%)	Chyle leak YES (n=9) n (%)	*p*-value
Esophagectomy			
i) Transhiatal	78 (43%)	1 (11%)	0.081
ii) Ivor lewis	13 (7%)	2 (22%)	
iii) **3-stage**	92 (50%)	6 (77%)	
Extensive adhesions during surgery			
Yes	31 (16%)	5 (55%)	0.004
No	153 (84%)	4 (45%)	
Prophylactic Thoracic duct ligation			
Yes	9 (5%)	1 (11%)	0.411
No	175 (95%)	8 (88%)	

Table-3: Post-operative predictors of chyle leak

Variable	Chyle leak No Median (IQR)	Chyle leak Yes Median (IQR)	*p* value
Chest drain output day 1(ml)	180 (160–320)	405 (190–660)	0.167
Chest drain output on day 2 (ml)	200 (70–360)	590 (125–730)	0.461
Chest drain output day 3 (ml)	170 (60–250)	250 (40–732)	0.490
Chest drain output day 4 (ml)	110 (50–200)	245 (85–695)	0.166
Chest drain output day 5(ml)	105 (47–167)	260 ((150–525)	0.032
Chest drain output day 6 (ml)	85 (35–152)	335 (145–737)	0.153
Chest drain output day 7(ml)	95 (41–160)	324 (255–990)	0.058
Day on which enteral feeding was started	7 (6–8)	7 (5–9)	0.479
Day on which chest drain was removed	6 (5–7)	16 (11–26)	0.007
DOP more than 1000 mL/day on day four Yes No	 2 (1%) 182 (99%)	 2 (22%) 7 (78%)	 0.001

Table-4: Linear regression analysis

Variable	Significance (*p*-value)
Age	0.899
Gender	0.951
BMI	0.166
Distance of tumor from incisor	0.681
Pretreatment T stage	0.985
Neo-adjuvant therapy	0.941
Duration between therapy and surgery	0.236
Serum albumin before surgery	0.585
Type of Esophagectomy	0.043

Table-5: Details of cases with re-exploration

Re-exploration	Detection on (POD)	Detected By	Re-exploration (POD)	Dietary management
Case no. 1	10	Persistent high drain output.	11	Fat free diet for 1 day. TPN after re-exploration for 21 days.
Case no. 2	8	Abdominal distention and milky discharge from all wounds Ascites on CT abdomen.	9	TPN for 5 days after re-exploration.
Case no. 3	8	Persistent high milky white drain output. High TG levels of drain fluid.	16	TPN for 7 days before and 4 days after re-exploration.
Case no. 4	10	Milky white drain output after cream intake. Normal TG levels.	13	TPN for 4 days before re-exploraion.
Case no. 5	14	High drain output. Raised TG level.	27	TPN + Octreotide for 2 weeks before and 1 week after re-exploration

POD: post-operative day. TG: triglyceride level. NPO: nil per oral. TPN: total parental nutrition

Table-6: Chylothorax after esophageal resection – prevalence, treatment (non-operative vs reoperation), and outcome

Previous studies with year of publication	Prevalence	Conservative management		Re-exploartion	
	Chyle leak	Total	Mortality	Total	mortality
Orringer *et al*[21] 1988			-	11	0
Tam *et al*[22] 1989	4 (1.3%)	2	1 (50%)	2	1 (50%)
Bolger *et al*[23] 1991	11 (2%)	8	4 (50%)	3	1 (33%)
Dugue *et al*[25] 1998	23 (2.7%)	14	0	9	2 (22.2%)
Bonavina *et al*[26] 1998	3 (1.1%)	3	0	3	0
Merigliano *et al*[27] 2000	19 (1.1%)	11	0	15	1
Sadaf *et al*	9 (4.5%)	4	0	5	0

DISCUSSION

In this retrospective analysis of 193 patients, 9 developed chyle leak (4.6%) during the period of Jan 2009 to Dec 2015. Patients who developed chyle leak after esophagectomy at our centre were analyzed for potential risk factors and early predictors. Our incidence is similar to the one quoted in the literature (2–8.6%).[1,15]

Risk factors for esophagectomy were analysed. 3 stage esophagectomy had a higher rate as compared to other two types in our series, but results were statistically insignificant. Additionally, linear regression analysis showed type of surgery to be an

independent risk factor (p<0.05), in contrast to the previous results by Miao L *et al*. which showed no effect of the type of surgery on chyle leak. Also, both 3-stage and Ivor-Lewis were at a higher risk of potential injury to the thoracic duct in comparison to the transhiatal surgery, which in many earlier studies was found to be an adverse predictor for this specific outcome.[17] Low BMI (<25)[17] is linked to increase risk of chylothorax, however, similar results are not replicated in our study. Hou X *et al* did not find significant difference of tumour location (p=0.887), pathological T category (p=0.917), TNM staging (p=0.890), histological type (p=0.731) or preoperative therapy (p=1.000) on risk of chylothorax[17], these findings are similar to our results.

Role of Prophylactic Thoracic duct ligation has been controversial in literature. Hou X *et al* reported decrease survival rates (5-year survival 75 verses 65.3%) in patients with prophylactic duct ligation, without a significant reduction in risk of chylothorax.[17] While, Pierfilippo Crucitti *et al* reported a decreased likelihood of chylothorax (odds ratio 0.47 in favour of ligation).[18] We observed no statistically significant benefit of prophylactic ligation of thoracic duct. This might be due to damage to tributaries of duct[19] rather than the main thoracic duct or slippage of ligature. However, number of patients in whom thoracic duct was ligated is much smaller than the comparison group so a larger sample size preferably in the setting of a randomized control trial will be required to affirm this.

Increased chest drain output >13.5 ml/kg has been reported to be linked to increased incidence of chyle leak.[20] We have observed similar trend in our study with statistically significant difference between drain outputs of two groups on day five. In addition, chest drain output more than 1000 on day 4 was significantly related to the incidence of chyle leak. Patients with chyle leak are more likely to have drain retained for longer period of time due to high output and are more likely to have delay in the start of enteral feed as they are managed by TPN and fat free diet. Using a stricter criterion, we found a slightly higher incidence of chyle leak as compared to our previous reported rate.[24] This potentially accounts for inclusion of cases with minor chyle leak and addition of some newer cases.

Among 9 patients with chyle leak 5 cases required re-exploration and thoracic duct ligation. Of these five cases, case number 2 was not a typical thoracic duct injury as cisterna chyli was damaged in this case in the first operation. Two cases were planned for upfront re-exploration due to chylous ascites and pulmonary complication respectively while remaining 3 cases were re-explored after a trial of conservative management due to persistent high chest drain output. Literature review of incidence and conservative verses non operative management of chylothorax is given in table 6.[18–23]

This study was not without limitations. We did not include upper segment tumours in our study. It was a retrospective non randomized observational study, which owing to the rarity of this complication is a feasible study design. Nevertheless, a well-designed prospective trial is suggested to confirm these findings. Our institutional practice is to keep patients NPO for 5 to 6 days so drain triglyceride level could not be used as an optimal criterion to diagnose chyle leak, except for two patients who developed chyle leak after enteral feed was started.

CONCLUSION

We have concluded that there should be a high index of suspicion for chyle leak in patients with drain output of more than 1000 ml on day 4 or a high drain output on day 5, as early diagnosis and management can significantly lower morbidity and mortality.

Conflict of interest: The authors declare that they have no conflict of interest.

Ethical statement: This article does not contain any studies with human or animal subjects performed by any authors.
Institutional Review Board exemption was obtained.

AUTHORS' CONTRIBUTION

SB: Data collection, analysis and article writing. SAA: Data collection and article writing. MK: Analysis and proof reading. RS: Basic study design and questionnaire formation. OS: Data collection. AAS, SK, ARK: Write-up, proof reading, final approval of the draft.

REFERENCES

1. Dougenis D, Walker WS, Cameron EW, Walbaum. Management of chylothorax complicating extensive esophageal resection. Surg Gynecol Obstet 1992;174(6):501–6.
2. Bolger C, Walsh TN, Tanner WA, Keeling P, Hennessy TP. Chylothorax after oesophagectomy. Br J Surg 1991;78(5):587–8.
3. Collard JM, Otte JB, Reynaert M, Michel L, Carlier MA, Kestens PJ. Esophageal resection and by-pass: a 6-year experience with a low postoperative mortality. World J Surg 1991;15(5):635–41.
4. Orringer MB, Marshall B, Iannettoni MD. Transhiatal esophagectomy for treatment of benign and malignant esophageal disease. World J Surg 2001;25(2):196–203.
5. Merrigan BA, Winter DC, O'sullivan GC. Chylothorax. Br J Surg 1997;84(1):15–20.
6. Alexiou C, Watson M, Beggs D, Salama FD, Morgan WE. Chylothorax following oesophagogastrectomy for malignant disease. Eur J Cardiothorac Surg 1998;14(5):460–6.

7. Machleder HI, Paulus H. Clinical and immunological alterations observed in patients undergoing long-term thoracic duct drainage. Surgery 1978;84(1):157–65.
8. Cerfolio RJ, Allen MS, Deschamps C, Trastek VF, Pairolero PC. Postoperative chylothorax. J Thorac Cardiovasc Surg 1996;112(5):1361–6.
9. Lemaire LC, Van Lanschot JB, Stoutenbeek CP, van Deventer SJ, Dankert J, Oosting H, *et al*. Thoracic duct in patients with multiple organ failure: no major route of bacterial translocation. Ann Surg 1999;229(1):128–36.
10. Nath DS, Savla J, Khemani RG, Nussbaum DP, Greene CL, Wells WJ. Thoracic duct ligation for persistent chylothorax after pediatric cardiothoracic surgery. Ann Thorac Surg 2009;88(1):246–52.
11. Dugue L, Sauvanet A, Farges O, Goharin A, Le Mee J, Belghiti J. Output of chyle as an indicator of treatment for chylothorax complicating oesophagectomy. Br J Surg 1998;85(8):1147–9.
12. NCCN. Clinical Practice Guidelines in Oncology. Esophageal and Esophagogastric Junction Cancers. [Internet]. National Comprehensive Cancer Network [cited 2017 Jan 4]. Available from: http://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf
13. van Hagen P, Hulshof MC, Van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijinhoven BP, *et al*. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366(22):2074–84.
14. Roffman CE, Buchanan J, Allison GT. Charlson comorbidities index. J Physiother 2016;62(3):171.
15. Mishra PK, Saluja SS, Ramaswamy D, Bains SS, Haque PD. Thoracic duct injury following esophagectomy in carcinoma of the esophagus: ligation by the abdominal approach. World J Surg 2013;37(1):141–6.
16. Miao L, Zhang Y, Hu H, Ma L, Shun Y, Xiang J, *et al*. Incidence and management of chylothorax after esophagectomy. Thoracic Cancer 2015;6(3):354–8.
17. Hou X, Fu JH, Wang X, Zhang LJ, Liu QW, Luo KJ, *et al*. Prophylactic thoracic duct ligation has unfavorable impact on overall survival in patients with resectable oesophageal cancer. Eur J Surg Oncol 2014;40(12):1756–62.
18. Crucitti P, Mangiameli G, Petitti T, Condolucia A, Rocco R, Gallo IF, *et al*. Does prophylactic ligation of the thoracic duct reduce chylothorax rates in patients undergoing oesophagectomy? A systematic review and meta-analysis. Eur J Cardiothorac Surg 2016;50(6):1019–24.
19. Nair SK, Petko M, Hayward MP. Aetiology and management of chylothorax in adults. Eur J Cardiothorac Surg 2007;32(2):362–9.
20. Marts BC, Naunheim KS, Fiore AC, Pennington DC. Conservative versus surgical management of chylothorax. Am J Surg 1992;164(5):532–5.
21. Orringer MB, Bluett M, Deeb GM. Aggressive treatment of chylothorax complicating transhiatal esophagectomy without thoracotomy. Surgery 1988;104(4):720–6.
22. Tam PC, Fok M, Wong J. Reexploration for complications after esophagectomy for cancer. J Thorac Cardiovasc Surg 1989;98(6):1122–7.
23. Bonavina L, Incarbone R, Peracchia A. Thoracoscopic treatment of iatrogenic chylothorax after esophageal surgery. Proceedings of the Second International Congress of Thoracic Surgery. In 1998.
24. Merigliano S, Molena D, Ruol A, Zaninotto G, Cagol M, Scappin S, *et al*. Chylothorax complicating esophagectomy for cancer: a plea for early thoracic duct ligation. J Thorac Cardiovasc Surg 2000;119(3):453–7.

Submitted: 18 September, 2018	*Revised: 31 December, 2018*	*Accepted: 13 January, 2019*

Address for Correspondence:

Sadaf Batool, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore-Pakistan
Email: sadafbatool111@gmail.com