

## REVIEW ARTICLE

# Chyle leak after major pancreatic surgery. Is this an underestimated complication? A narrative review of the literature

Michail Vailas<sup>1\*</sup>, Maria Sotiropoulou<sup>2\*</sup>, Nikolaos Benetatos<sup>1</sup>, Francesk Mulita<sup>1</sup>, Ioannis Maroulis<sup>1</sup>, Stylianos Germanos<sup>1</sup>

<sup>1</sup>Department of Surgery, University Hospital of Patras, Patras - Rio, Greece. <sup>2</sup>Third Department of Surgery, Evangelismos General Hospital, Athens, Greece.

\*These authors contributed equally to this work.

## Summary

**Purpose:** Postoperative chyle leak, termed 'chylous ascites', is a rare complication with a reported frequency of only one in 20464 abdominal operations. The purpose of this study was to summarize the available scientific data reviewing the most relevant studies for this type of postoperative complication after pancreatic surgery, highlighting at the same time the necessity for pancreatic surgeons to retain a high level of clinical suspicion for the early diagnosis and its therapeutic management.

**Methods:** A thorough literature search in Pubmed and Google Scholar, under the terms 'chylous ascites OR chyle leak AND pancreas OR pancreatic', since the year of inception until 19<sup>th</sup> of February 2021 was conducted by the authors and the associated results are presented in this narrative review.

**Results:** Chyle leak is a rare complication following pancreatic surgery. Patients may suffer from exudative enter-

opathy and malnutrition leading to repeated infections and impaired wound healing or even death secondary to sepsis. Several studies have highlighted the issue of increased hospital stay, while others failed to reach statistical significance as far as hospital stay or survival are concerned. Researchers found that patients with diffuse chyle leak tended to have a worse 3-year survival rate (18.8%), which can be attributed to postoperative complications and early demise due to immunosuppression associated with the leak, or delayed adjuvant chemotherapy.

**Conclusion:** Further clinical research is needed to enhance prevention, diagnosis, treatment and long-term prognosis of this relevant surgical problem that shows trends of increase due to the great number of major operations which are performed nowadays.

**Key words:** chyle ascites, chyle leak, complication, pancreas, surgery

## Introduction

Pancreatic surgery has been validated as the cornerstone of treatment for pancreatic cancer cases with morbidity rates reaching almost 50%, with pancreatic fistula being the most relevant type of postoperative complication [1,2]. Undoubtedly, the number of major abdominal operations, performed by specialized surgeons worldwide, has significant-

ly increased in the last decades, a fact that might be explained from the continuous improvement and standardization of surgical techniques, treatment modalities and perioperative management [3,4].

Postoperative chyle leak, termed 'chylous ascites' (CA), is a rare complication following major abdominal surgery, with a reported frequency of

Corresponding author: Michail Vailas, MD, MSc (HPB), Pharm,D, PhD. Department of General and HPB Surgery. University Hospital of Patras, Patras Medical School, Patras - Rio, 26504, Greece.  
Tel: +30 6976815514; Email: mike\_vailas@gmail.com  
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only one in 20464 abdominal operations [5]. Surgical procedures that have been traditionally linked with this entity include retroperitoneal lymph node dissection, distal splenorenal shunts, abdominal aortic aneurysm repair, and liver transplantation [6-8]. CA occurs in 3.3–10.4% of patients after pancreatic resection operations, with all data being anecdotal and deriving from limited case reports and case series [9,10]. Strikingly enough, there are several studies reporting that CA is one of the factors that influences the prognosis of patients following this type of surgery [11]. Because of the aforementioned fact that pancreatic resections are associated with increased morbidity, chyle leak (CL) may frequently coexist with other complications that may conceal or affect its clinical relevance [12].

Due to the necessity of reporting uniformly this type of complication after pancreatic surgery and the need to better appreciate the exact causes, risk factors and their management, the International Study Group on Pancreatic Surgery has proposed a new validation system similar to those already existing about pancreatic fistula, delayed gastric emptying and postpancreatectomy haemorrhage [13]. According to this, Grade A implies a clinically irrelevant chyle leak with no prolongation of hospital stay and a conservative approach with only restrictions in the oral diet, Grade B leak requires changing in nutritional management, possible addition of drugs like somatostatin analogs or even some kind of interventional drainage by radiologists with increased hospital stay, while Grade C requires more invasive methods of treatment and admission to the intensive care unit or even implies mortality due to CL [13]. The traditional treatment for chylous ascites is dietary control with a medium-chain triglyceride (MCT) diet, total parenteral nutrition (TPN) or a combination of both, while alternative options include bipedal lymphangiography (BPLAG), somatostatin analog administration, peritoneovenous shunts, administration of etilefrine and various other less common interventions [9,14].

Due to increasing numbers of extended resections and surgical operations being performed, the incidence of CA might increase further. The true incidence of CA should be appreciated by studies involving a large cohort of patients undergoing pancreatic surgery. Up until recently, pathophysiology, risk factors, management, and prognostic implications of CA have been infrequently reported in limited number of subjects.

The purpose of this study was to summarize the available scientific data reviewing the most relevant and validated studies for this type of postoperative complication after pancreatic sur-

gery, highlighting at the same time the necessity for pancreatic surgeons to retain a high level of clinical suspicion for the early diagnosis and its therapeutic management.

## Methods

A thorough literature search in Pubmed and Google Scholar, under the terms 'chylous ascites OR chyle leak AND pancreas OR pancreatic' since year of inception until 19<sup>th</sup> of February 2021, was conducted by the authors with focus in the last 15 years and the associated results are presented in this narrative review. We included articles published in full text, written in English.

### *Lymph formation and possible causes of chyle leak after pancreatic surgery*

Lymph is comprised of cells, particles, proteins and chylomicrons that are formed by the exudation of plasma and its constituents from capillaries into interstitial compartments of the human body. The lymphatic system is a route by which this excess fluid from the interstitial spaces, that is not reabsorbed in the postcapillary venules, returns to the vascular system. Dietary long-chain triglycerides are reduced to monoglycerides and fatty acids in the small intestine. Breakdown derivatives are in turn absorbed as chylomicrons into the lymphatic system [15].

The lymphatic system of the abdomen includes cisterna chyli and its main tributaries. Cisterna chyli is a dilated sac-like formation in the retroperitoneum at the level of first and second vertebral bodies, which continues as the thoracic duct cranially [16]. In turn, the thoracic duct enters the posterior mediastinum after passing through the aortic hiatus in the diaphragm, the superior mediastinum and eventually empties into the venous system at the junction of the internal jugular and subclavian veins [15].

On account of anatomical proximity, oncological pancreatic resections with radical or even standard lymph node dissections, are linked with an increased risk of chyle leak, when compared with other major abdominal surgical operations [17]. That being said, it seems that pancreaticoduodenectomies are accompanied with greater risk of CL in contrast with distal pancreatectomies due to the nearness of the cisterna chyli to pancreatic head [10,14,18]. Concomitant vascular resection of superior mesenteric vessels and reconstruction with synthetic or autologous grafts in borderline and locally advanced pancreatic cancer cases seem predictive of chyle leaks [10]. It is quite interesting that surrounding inflammation and focal pancrea-

titis around the tumor itself has been linked with increased incidence for CL due to the necessity to perform extended dissection during surgery [19].

#### *Risk factors for the development of chyle leak*

Lately, many researchers reviewed possible risk factors associated with the development of chyle leak after pancreatic surgery (Table 1). Kuboki et al [20] reported the outcome after hepatobiliary and pancreatic surgery in a group of 2002 patients, out of whom 21 developed CA. Multivariate analysis revealed that manipulation of the para-aortic area ( $p<0.001$ ), retroperitoneal invasion ( $p=0.031$ ) and early enteral feeding after operation ( $p<0.001$ ) were independent risk factors for CL following pancreatic resection [20]. Assumpcao et al [10] reviewed 3,532

patients undergoing pancreatic resection with 47 of them (1.3%) developing a CL. After matching on tumor size, disease etiology, and resection type, the number of lymph nodes harvested and history of concomitant vascular resection predicted higher risk of chyle leak (both  $p < 0.05$ ).

In turn, pre-existing diabetes, resection for malignancy, distal pancreatectomy, duration of surgery 180 min or longer, and concomitant pancreatic fistula or abscess were independent risk factors for CL reported by Strobel et al [12] in 346 out of 3324 patients. Furthermore, Pan et al [11] retrospectively reviewed 1921 patients who underwent pancreatic resection, out of whom 49 developed CA. A multivariate analysis demonstrated that manipulating the paraaortic area and superior mes-

**Table 1.** Studies reporting risk factors associated with development of chyle leak (CL)

Author	Year of publication	Number of included patients undergoing pancreatectomy	Patients with CL n (%)	Risk factors associated with CL ( $p<0.05$ )
Russell et al [24]	2020	560	17 (3.04)	higher body mass index (mean 30.5 kg/m <sup>2</sup> (range 17-43) ( $P=0.02$ ) longer duration of operation (mean 6.2 h (range 4.3-9.0) ( $p=0.03$ ))
Strobel et al [12]	2016	3324	346 (10.4)	pre-existing diabetes, resection for malignancy, distal pancreatectomy, duration of surgery 180 min or longer, and concomitant pancreatic fistula or abscess
Pan et al [11]	2015	1921	49 (2.5)	manipulating para-aortic area and superior mesenteric artery root area; retroperitoneal invasion; malignancy; focal chronic pancreatitis and early enteral feeding
Kuboki et al [20]	2013	2002	21 (1)	manipulation of the para-aortic area ( $p<0.001$ ), retroperitoneal invasion ( $p=0.031$ ) and early enteral feeding after operation ( $p<0.001$ )
Abu Hilal et al [23]	2013	245	40 (16.3)	extensive lymphadenectomy ( $p=0.002$ ) and postoperative portal/mesenteric venous thrombosis (PVT) ( $p=0.009$ )
Noji et al [21]	2012	138	11 (8)	Early enteral feeding
Assumpcao et al [10]	2008	3532	47 (1.3)	number of lymph nodes harvested and history of concomitant vascular resection predicted higher risk of chyle leak
Van der Gaag [19]	2008	66	609 (11)	that female gender (odds ratio, 1.79; 95% CI, 1.05 to 3.03) and chronic pancreatitis at pathology (odds ratio, 2.52; 95% CI, 1.19 to 5.32)

enteric artery root area, retroperitoneal invasion malignancy, focal chronic pancreatitis and early enteral feeding were the independent risk factors for CA after pancreatic surgery [11]. Early enteral feeding was also linked with chyle leak in the study published by Noji et al [21]. Van der Gaag [19] studied 609 consecutive patients who underwent pancreaticoduodenectomy, 66 with CL, reporting that female gender (odds ratio, 1.79; 95%CI 1.05 to 3.03) and chronic pancreatitis at pathology (odds ratio, 2.52; 95% CI 1.19 to 5.32) were independently associated with development of this complication.

Increased age, female gender, the surgeon, preoperative ascites and low preoperative albumin, chronic pancreatitis, preoperative chemotherapy, retroperitoneal tumor invasion, tumors fed by the superior mesenteric artery, number of lymph nodes removed, manipulation of the paraaortic area, concomitant vascular resection, increased intraoperative blood loss, and early enteral feeding were also identified as possible factors by Weniger et al in their systematic review of medical literature in 2016 about CA after major surgery [22]. Abu Hilal et al [23] reported CL complicating 40/245 cases (16.3 %). After multivariate analysis, both extensive lymphadenectomy ( $p=0.002$ ) and postoperative portal/mesenteric venous thrombosis (PVT) ( $p=0.009$ ) were independently linked with a higher incidence of chyle leak. Finally, Russell et al [24] reviewed 560 patients who underwent pancreatoduodenectomy and reported CL in 17 with the majority of them having higher body mass index [mean  $30.5 \text{ kg/m}^2$  (range 17-43) versus  $26.7 \text{ kg/m}^2$  (22-38)] ( $p=0.02$ ) and longer duration of operation [mean 6.2 h (range 4.3-9.0) versus 5.6 (3.0-11.0)] ( $p=0.03$ ), when compared with those without chyle leak.

#### *Diagnosis of chyle leak*

A recently proposed definition of CL includes the discharge of milky, lipid-rich (triglycerides  $>110 \text{ mg/dL}$ , amylase-poor, bilirubin-poor, and chylomicron-rich) fluid from a surgical wound or drain, which is  $>100 \text{ mL/day}$  in quantity and culture-negative for microorganisms [24]. As such, CL is usually diagnosed based on clinical criteria and biochemical confirmation through analysis of the fluid. After the initiation of enteral feeding, the appearance of milky fluid in drainage tubes is characteristic of postoperative CA. After ingesting a fatty meal, lymphatic flow in the cisterna chyli is found to increase from 1 ml per min to more than 200 ml per min [19]. Most patients complain of abdominal distention.

The lack of a uniform system to describe CL has led other researchers and authors to define 200 mL/24 has the lower quantity limit to diagnose

this complication. Further typical laboratory findings included a drainage fluid/serum ratio greater than 1.0 for triglycerides and a drainage fluid/serum ratio less than 1.0 for cholesterol. The ISGPS agreed that CLs are relevant, regardless of a minimal reported volume threshold [13]. Conventional diagnostic lymphangiography detects successfully the site of lymphatic leakage in about 75% of the cases [22].

#### *Treatment of chyle leak*

Traditionally, the initial management of CL is conservative, including total parenteral nutrition (TPN) or medium chain triglyceride (MCT) diet, with or without the addition of octreotide. Resolution rates of CL have been reported in 77% to 100% of the cases with TPN alone, in almost 75% of the cases with MCT diet, and surprisingly enough in 100% of the cases with addition of octreotide to MCT diet or TPN [22]. Somatostatin analogs act by reducing splanchnic blood flow and lymph formation, whereas MCTs are not absorbed via the gut lymphatics and help increase the calorie intake of the patient postoperatively. MCT can be transported across the enterocyte and directly into the mesenteric venous circulation. This process does not require transport into the mesenteric lymphatics [13].

Kuboki et al [20] found that TPN and octreotide allowed faster removal of drains significantly earlier in patients with chylous ascites after hepatopancreatobiliary surgery (12 vs 19 days, 11 vs 9 patients), when compared to patients treated solely with TPN. Russell et al [24] proposed as initial step in management the initiation of MCT and octreotide and in case of failure total starvation of patient along with TPN. Once drain output is less than 50 mL in quantity for a 24-h period, removal of the surgical drain can be considered. octreotide therapy can be stopped, and a normal diet can be gradually re-introduced [24].

If CL is resistant to these measures and exceeds 1 L/day or is  $>500 \text{ mL}$  for five or more days, or if the patient experiences metabolic or immunologic complications, more invasive investigation and/or treatment may be followed [25]. It is then imperative to localize the site of the leak which can be done through performance of lymphoscintigraphy, magnetic resonance imaging (MRI) and lymphangiography [14,24]. Dynamic MRI imaging with intranodal contrast injection can also be used for this purpose [24]. Lymphangiography under fluoroscopy along with the injection of radioopaque contrast such as lipiodol into the groin lymph nodes may induce a localized inflammatory response and seal leaking lymphatic channels [26].

Apart from that, direct embolization of the cisterna chyli with a combination of coils and liquid



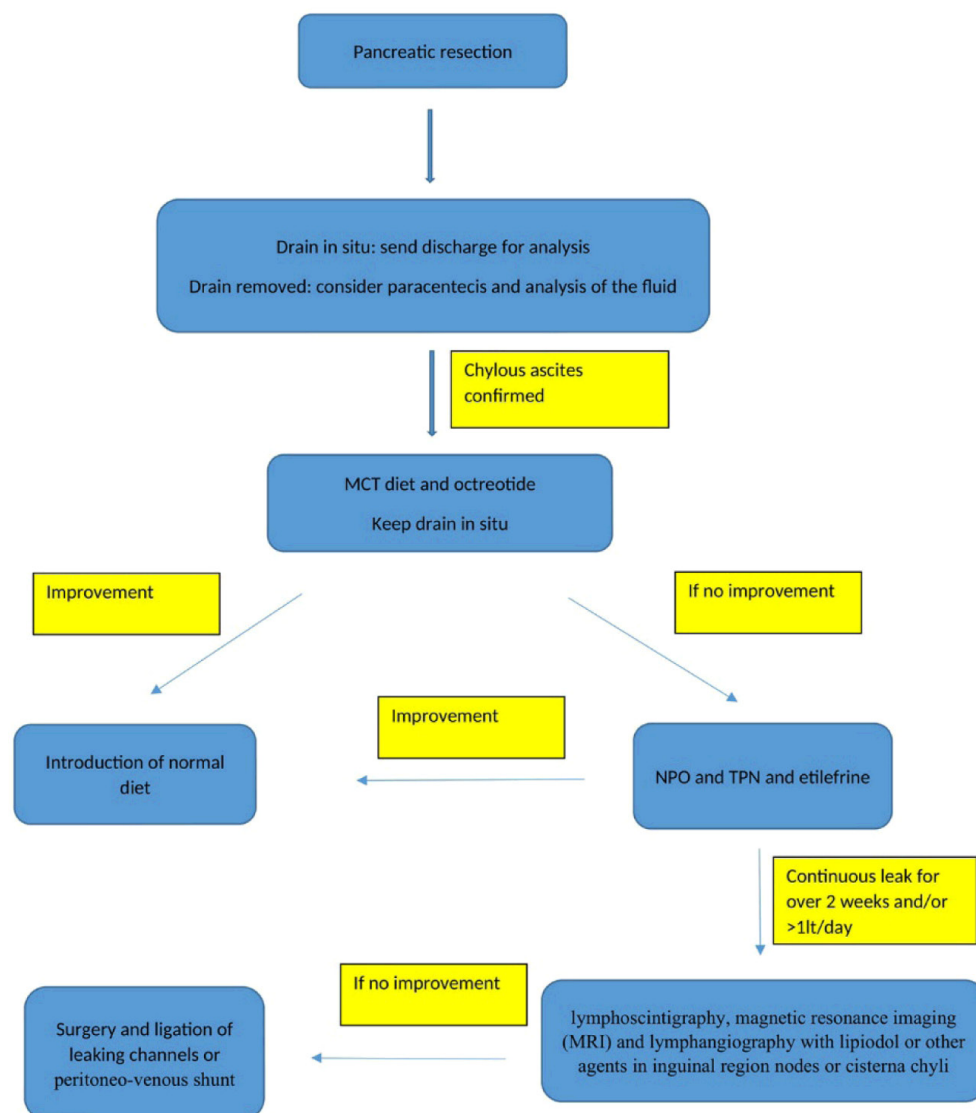
embolic, such as n-butyl cyanoacrylate or ethylene vinyl alcohol co-polymer following lymphangiographic opacification of the lymphatic system, has shown promising results. Success rates reaching 90% have been reported if the cisterna chyli can be cannulated [26]. Recently, there are case studies published reporting successful management of chylous ascites after pancreatoduodenectomy using etilefrine, which is capable of contracting the smooth muscle of the thoracic duct and decrease the flow of chyle [9].

A last resort is considering the surgical management assisted by preoperative high-fat meal that should be given along with intraoperative administration of indocyanine green or methylene blue in order to localize the site of the leak and ligate leaking channels [27]. When the site of the chyle leak cannot be identified, placement of a peritoneo-venous shunt may be another op-

tion [10]. Interestingly enough, the extensive use of energy devices nowadays raises concerns that these sources may partially or temporarily seal these lymphatic channels, which can reopen and manifest as chyle leak in the early postoperative period, thus suggesting the ligation of lymphatics instead [18].

#### *Patient related complications and economic burden of chyle leak*

CL affects long-chain triglyceride digestion and leads to important protein loss. Patients suffer from exudative enteropathy and malnutrition leading to repeated infections and impaired wound healing, immune status or even death secondary to sepsis [10,14,25]. Strobel et al [12] reported that CL may have impact on survival in cases that persisted over 14 days in patients with cancer undergoing palliative surgery. Several studies have highlighted



**Figure 1.** Proposed algorithm for the management of chyle leak.

the issue of increased hospital stay after the development of CL [13], while others failed to reach statistical significance as far as hospital stay or survival are concerned [23,24]. Other researchers found that patients with diffuse CL tended to have a worse 3-year survival rate (18.8%), which can be attributed to postoperative complications and early demise due to immunosuppression associated with the leak, or delayed adjuvant chemotherapy. As far as the economic burden is concerned, the new ISGPS classification depicted notable differences in the hospital costs among the 3 grades of CL, with a difference of €4,344 between grade A and grade B CL, €12,878 between grade A and grade C CL, and €8,534 between grade B and grade C CL [28].

## Conclusion

The true incidence of chyle leak after pancreatic surgery probably remains unknown, with the reported incidence varying between 1-11% between different series [12]. These variations may be the result of missed non-reported cases during retrospective data extraction, different definitions used among the authors reporting, and different protocols for prophylactic abdominal drainage and feeding after pancreatic surgery [12]. Hopefully, ISGPS classification will give the chance for future studies to better appreciate the exact incidence of CL following pancreatic surgery along with the best management associated with the most favorable patient outcomes.

Conservative measures usually suffice, with more invasive methods being the last resort for containment. There is also need for pancreatic surgeons to maintain high level of clinical suspicion preoperatively to successfully recognize the group of patients in risk to present with this complication. Moreover, intraoperatively they need to minimize unnecessary dissections, follow meticulous clipping and ligation of lymphatics and also place surgical drains in order to identify early chyle leak.

It is the authors' view that despite the fact that most of the cases of CL resolve after conservative treatment, those cases associated with prolonged course, especially those necessitating most invasive methods of control like surgery, might be proved harmful not only for immediate postoperative health status and survival of the patients, but also for their long-term survival after pancreatic cancer treatment. Herein, we propose a suggested algorithm for the management of CL (Figure 1). Overall, the evidence for chylous ascites is sparse and randomized controlled trials are lacking. Further clinical research is needed to enhance prevention, diagnosis, and treatment of this relevant surgical problem that shows increasing trends due to the great number of major operations which are performed in our days.

## Conflict of interests

The authors declare no conflict of interests.

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