Daily Triglyceride Output Volume as an Early Predictor for Chyle Leak Following Pancreatoduodenectomy

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Abstract. Background/Aim: Useful prophylaxes of chyle leak (CL) after pancreatic surgery have not been established. The aim of the study was to identify an early clinical predictor for CL. Patients and Methods: Fifty-five patients who underwent subtotal stomach preserved pancreaticoduodenectomy (SSPPD) were included. Clinical factors associated with postoperative CL were evaluated. Results: Eleven patients (20%) developed a CL after SSPPD. Shorter operative time, absent pancreatic fistula, and triglyceride output volume at postoperative day (POD) two were independent risk factors for CL. The receiver operating characteristics curve of the daily triglyceride output volume at POD two indicated a cutoff point of 177 mg (AUC = 0.782; p = 0.004; 95% CI = 0.639–0.925). CL was significantly associated with prolonged postoperative hospital stay in patients who did not develop a pancreatic fistula (p = 0.003). Conclusion: Daily triglyceride output volume of >177 mg at POD two may be a predictor of CL following pancreatoduodenectomy.

Postoperative chyle leak (CL) is not a rare complication after pancreatic surgery, with an incidence up to 16% (1-3), and causes prolonged postoperative hospital stay (2). The latter is a negative factor for survival, especially in patients with pancreatic cancer, because of the resulting delay in initiation of adjuvant chemotherapy (4, 5).

Previous studies have suggested various risk factors for postoperative CL after pancreatic surgery, such as female gender (1), distal pancreatectomy (2), retroperitoneal tumor invasion (6), number of lymph nodes harvested (7), early enteral feeding (6, 8), and pancreatic fistula (2). A review article concluded that CL was mainly predicted by the extent of lymphadenectomy and lymphatic tissue dissection (9). However, there are few studies which suggest a clinical predictor for postoperative CL. Kim et al. reported that drainage fluid volume ≥335 ml by the fourth postoperative day was a useful and simple predictor for postoperative CL (10). However, drainage fluid volume is influenced by various factors such as intra-abdominal inflammation, liver function, poor nutritional state, and chronic heart diseases. Similarly, triglyceride concentration also depends on the drainage fluid volume. Hence, these factors might not be the best predictors for CL. We hypothesized that the total amount of triglyceride output volume may reflect the true leakage volume more accurately compared to the fluid volume or the triglyceride concentration in the drainage fluid. Moreover, we hypothesized that triglyceride output volume may reflect late CL even if measured in the early postoperative period.

Thus, the aim of the study was to determine whether triglyceride volume in the drainage fluid, measured before postoperative resumption of oral intake, could be a predictor of postoperative CL.

Patients and Methods

Patient cohort. This study was approved by the Internal Review Board (IRB) of the Saku Central Hospital Advanced Care Center (IRB number R201802-01) and followed the tenets set by the Declaration of Helsinki. Between August 2018 and June 2020, the medical records of all the patients who underwent subtotal stomach preserved pancreatoduodenectomy (SSPPD) at the Saku Central Hospital Advanced Care Center were reviewed. There were no exclusion criteria.

Surgical procedure. All surgeries were performed by one of three surgeons operating in the Saku Central Hospital Advanced Care Center, all of whom are authors of current article (T.S., N.O., F.S.). Following a mid-line laparotomy, the para-aortic lymph node area was sampled and examined by intraoperative frozen-section for all patients regardless of the preoperative tumor diagnosis, with an
exception of one patient with chronic pancreatitis. Patients
underwent palliative surgery if the para-aortic lymph nodes were
positive by intraoperative pathological diagnosis. Lymph nodes were
routinely dissected around the hepatoduodenal ligament, common
hepatic artery, and superior mesenteric artery for all patients using
unipolar cutting cautery or Harmonic® vessel-sealing device
(Ethicon, Tokyo, Japan). The pancreatic head and uncinate process
nerve plexuses were dissected using the same device and plexuses
of the superior mesenteric and celiac artery were preserved
circumferentially. The mesentery was dissected along with the
second jejunal artery and jejunal vein. The first jejunal artery was
ligated at its base. Based on our institutional policy, end-to-side
pancreateojunostomy with an incomplete external stent, end-to-side
hepaticojunostomy with or without ductal stent, side-to-side
gastrojunostomy, and Braun anastomosis were routinely performed
for reconstruction. From August 2018 to December 2019, we
provided early enteral nutrition to postoperative patients via a
feeding jejunostomy tube, which was placed in the upper jejunum.
Two drains were routinely placed, one anterior to the
pancreateojunostomy site, and another posterior to the
hepaticojunostomy site.

Postoperative management. Following the nasogastric tube removal
on postoperative day (POD) one, only clear liquids were allowed
and oral food intake, which contained fat, was started on POD three
if tolerated by the patient. From August 2018 to December 2019,
patients received enteral nutrition starting POD three with
continuous 20 ml/h low fat elemental diet (ELENTAL®, EA
Pharma, Tokyo, Japan) until they were able to tolerate sufficient oral
intake. All patients had their drain amylase and triglyceride levels
measured at PODs one and three. Drains were removed on POD
three if there was no pancreatic fistula or bile leakage. Pancreatic
fistula was treated with only continuous drainage therapy. No
patients received octreotide.

Identification and management chyle leak. CL was defined as an
output of any milky discharge from patients’ drains or drain sites
on or after POD three with a triglyceride content ≥110 mg/dl, in
accordance with the International Study Group of Pancreatic
Surgery (ISGPS) criteria (11). Once diagnosed, patients were
treated conservatively with seven days of diet-withholding. If the
fluid volume was less than 50 ml at the time of the diagnosis, diet-
withholding therapy was discontinued once the milky discharge
disappeared. If CL recurred after restarting oral diet, additional
diet-withholding with total parenteral nutrition was adopted until
the CL resolved.

Dairy triglyceride output volume at POD two. Since CL occurs
following oral intake, it is important to seek an early clinical
warning sign which can be identified before the postoperative
resumption of oral intake. The total amount of the drainage
triglyceride volume of POD two was determined as the sum of all
drain output amounts which were calculated by multiplying the 24-
hour (from 9 a.m. on POD two to 9 a.m. on POD three) fluid
volume with the corresponding concentration.

Statistical analysis. Summary statistics were expressed using
median and range. The association of clinical factors with CL was
analyzed by univariate analysis. Continuous data sets were analyzed
by the nonparametric Mann-Whitney U-test and discontinuous data
sets were analyzed with the Chi squared test. Factors found to be
significant on univariate analysis were subjected to multivariate
analysis using a logistic regression model. The receiver operating
characteristics (ROC) curve of the daily triglyceride drainage
volume on POD two was used to predict CL. Mann-Whitney U-test
was used for comparison of the postoperative duration of hospital
stay between the patients with, and without CL. Values of p<0.05
were considered statistically significant. These analyses were
conducted using IBM® SPSS statistics version 25.0 (IBM Japan,
Tokyo, Japan).

Results

Patient characteristics. A total of 55 consecutive patients who
underwent SSPPD were analyzed in the study. The patient
demographics and pathological characteristics of our cohort
are summarized in Table I. Median age was 73 years
(range=52-86 years) and 38 of them (69%) were males. The
median body mass index (BMI) was 22.2 kg/m² (range=16.0-
28.6 kg/m²). The pathologic diagnosis was pancreatic
carcinoma in 25 (45%), periampullary carcinoma in 20 (36%),
neuroendocrine neoplasm in 6 (11%), pancreatic intraductal
mucinous neoplasm in 3 (5%), and chronic pancreatitis in 1
patient (2%). The median operative time was 494 min
(range=330-756 min) and the median intraoperative blood loss
was 521 ml (range=100-3,100 ml). The operators were board-
certified expert surgeons in 22 (40%) and training surgeons in
the rest of cases. The median daily fluid volume and triglyceride concentrations in the fluid by POD two were 290
ml (range=68-1,680 ml) and 34 mg/dl (range=8-493 mg/dl),
respectively. The median triglyceride output volume at POD
two was 127.5 mg (range=27.5-872.2 mg). Of the 55 patients,
grade B/C pancreatic fistula was present in 23 (42%); grade
B in 20 (36%) patients; and grade C in 3 (5%). One patient
(2%) died because of deterioration of pre-existing interstitial
pneumonia. The median postoperative hospital stay was 26
days (range=15-101 days).

| Table I. Patient demographics and pathologic features (N=55). |
|-----------------------------------------------|
| Characteristics                             |     |
| Age (years), median (range)                  | 73 (52-86) |
| Gender, male                                 | 38 (69) |
| Pathologic diagnosis                         |     |
| Pancreatic cancer                            | 25 (45) |
| Intraductal papillary mucinous adenoma        | 3 (5) |
| Pancreatic neuroendocrine neoplasm           | 4 (7) |
| Pancreatitis                                 | 1 (2) |
| Bile duct cancer                             | 11 (20) |
| Ampulla carcinoma                            | 3 (5) |
| Duodenal carcinoma                           | 6 (11) |
| Duodenal neuroendocrine neoplasm             | 2 (4) |

Data are expressed as n (%) unless otherwise specified.
Incidence and risk factors for chyle leak. CL occurred in 11 patients (20%) after SSPPD. All patients diagnosed as CL, characterized by obvious milky discharge from their drainage tubes or drain site, were identified between POD 5 and POD 13. The median time to CL presentation following the postoperative resumption of oral intake was four days (range=2-7 days) and the median diet-withholding duration for the resolution of CL was ten days (range=2 to 20 days). The clinical characteristics of patients with and without CL are summarized in Table II. On univariate analysis, shorter operating time (p=0.007), absent grade B/C pancreatic fistula (p=0.034), and daily triglyceride output volume at POD two (p=0.004) were significantly associated with an increased incidence of postoperative CL. On multivariate logistic regression analysis, all these factors remained independently significant risk factors for the development of CL (Table III).

Cut-off points of the daily triglyceride output volume. All instances of CL occurred after the resumption of oral diet postoperatively, and all were resolved by diet-withholding. We, therefore, hypothesized that CL could be prevented by deferring oral intake if the daily triglyceride output volume at POD two was high (we routinely allowed oral diet intake on POD three, as noted above). Based on the ROC curve, we investigated the cut-off point for a triglyceride output volume of 177 mg with an area under the curve of 0.782 (95% CI=0.639-0.925) (Figure 1). A daily triglyceride output volume of >177 mg indicated suspicion of CL (sensitivity 72.7%, specificity 72.7%).

Association between postoperative hospital stay and complications. The association between postoperative hospital stay and complications is summarized in Table IV. For all 55 patients, CL was not associated with a longer postoperative hospital stay (p=0.83), but a pancreatic fistula was (p<0.001). We then analyzed the association between development of CL and increased postoperative hospital stay for patients who did not develop a pancreatic fistula (n=32): postoperative hospital stay in patients with a CL was found to be significantly longer than those without a CL (p=0.003).

Discussion

The incidence of CL after SSPPD in this study was 20%. This was higher than most previous studies which reported an incidence of 1.8%-16.0% (1, 3, 6-8, 10). This dissimilarity could be explained by our definition of CL which included any volume of milky discharge with a triglyceride content ≥110 mg/dl. In contrast, most previous studies which reported an incidence lower than 10%, included a criteria of daily fluid volume >100 ml or up to 600 ml (6-8). A recent large series, whose definition was the same as our study, reported the

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Table II. Variables associated with postoperative chyle leak after SSPPD.

| Variables                                      | Chyle leak (n=11) | No chyle leak (N=44) | p-Value |
|------------------------------------------------|-------------------|----------------------|---------|
| Age (years)*                                   | 73 (54-84)        | 73 (52-86)           | 0.7     |
| Gender, males                                  | 8 (73)            | 30 (68)              | 0.94    |
| BMI (kg/m²)*                                   | 20.9 (16.0-23.8)  | 22.8 (16.6-28.6)     | 0.09    |
| Operative time (min)*                          | 449 (363-539)     | 533 (330-756)        | 0.007   |
| Intraoperative blood loss (ml)*                | 498 (100-1,400)   | 721 (100-3,100)      | 0.36    |
| Operator, certified expert surgeons**          | 2 (18)            | 20 (45)              | 0.19    |
| Pancreatic fistula, ISGPF grade B/C            | 1 (9)             | 22 (50)              | 0.034   |
| Postoperative initial oral diet intake (days)* | 3 (3-6)           | 4 (3-9)              | 0.19    |
| Enteral nutritional support                    | 5 (45)            | 29 (66)              | 0.37    |
| Fluid volume of POD 2 (ml)*                   | 330 (110-1290)    | 262 (68-1680)        | 0.14    |
| Triglyceride concentration in the fluid of POD 2 (mg/dl)* | 64 (22-104) | 38 (13-493)        | 0.08    |
| Daily triglyceride output volume of POD 2 (mg)* | 186 (70-511)    | 98 (30-872)          | 0.004   |

Data are expressed as n (%) unless otherwise specified; *Values are median (range). **Certified by the Japanese Society of Hepato-Biliary-Pancreatic Surgery. SSPPD: Subtotal stomach-preserving pancreaticoduodenectomy; BMI: body mass index; ISGPF: international study group on pancreatic fistula; POD: postoperative days.

Table III. Multivariate analysis of factors associated with postoperative chyle leak after SSPPD.

|                              | OR (95% CI) | p-Value |
|------------------------------|-------------|---------|
| Operative time               | 0.05 (0.004-0.539) | 0.014   |
| Pancreatic fistula, ISGPF grade B/C | 0.06 (0.003-0.746) | 0.03    |
| Daily triglyceride output volume of POD 2 >177mg | 22.4 (2.2-232.7) | 0.009   |

SSPPD: Subtotal stomach-preserving pancreaticoduodenectomy; OR: odds ratio; CI: confidence intervals; ISGPF: international study group on pancreatic fistula; POD: postoperative days.
presence of a CL in 12.5% of patients after pancreaticoduodenectomy (PD) (2). Therefore, CL cannot be thought of as a rare complication after pancreatic surgery, especially if the definition is broader.

There are no randomized clinical trials that recommend one surgical procedure over another, nor any clinical treatment to prevent postoperative CL. Thus, it is important to look for clinical warning signs for a CL. Aoki et al. reported on the effectiveness of intraoperative “Milk Test” to prevent CL in their prospective patient cohort (12). They attempted to confirm injury to lymphatic vessels intraoperatively by administration of milk to the upper jejunum. This method is thought to be reasonable for preventing CL, but did not achieve statistically significant improvements when analyzed. This study is the first report, to the best of our knowledge, to indicate a predictor for postoperative CL by measuring the total amount of triglyceride output. We hypothesized that the triglyceride output volume reflects the true leakage volume more accurately than the drainage fluid volume or its triglyceride concentration. In this study, the daily triglyceride output volume by POD two was significantly associated with the development of postoperative CL, but the fluid volume and triglyceride concentration in the fluid at POD two did not reach significance on univariate analysis. These results follow the essence of our hypothesis that fluid volume and triglyceride concentration depends on various factors. The ROC curve for triglyceride output volume by POD two indicated that a cut-off of >177 mg could be a predictor for a CL with a sensitivity of 72.7% and a specificity of 72.7%.

Since all CLs occurred after the initiation of postoperative oral diet and were resolved by diet-withholding, this predictor may be useful if CLs can be predicted before the initiation of oral intake. In this study, the median time to CL presentation following the postoperative resumption of oral intake was four days, and the median diet-withholding duration for the resolution of CL was ten days. Therefore, delayed imitation of postoperative initial intake may possibly prevent CL in patients who satisfy our identified cut-off point. Moreover, this preventive measure may decrease the risk of prolonged hospital stay. Based on these results, however, nearly 30% of the patients who had a POD2 value >177 mg did not develop CL. Navez et al. (13) reported that early postoperative oral intake after PD was significantly associated with lower rate of severe postoperative morbidity and shorter hospital stay. Thus, further studies are expected to exclude these false-positive patients or to minimalize the duration of prophylactic diet-withholding.

There might be some debate as to whether triglyceride output measurement is an appropriate method when measured in the early postoperative and fasting state. Clinically, milky discharge is often visualized a day or two after the initiation of oral diet and remains for at least a day if therapeutic diet-withholding is initiated. This study also noted a median of four days between the initiation of oral diet and a diagnosis of CL. These clinical features indicate that some discrepancy exists between the intestinal absorption of triglyceride and the chylomicron delivery to the lymphatic vessels. Aoki et al. reported that lymphatic flow in the cisterna chili was very slow: <1 ml/min in the fasting state compared to 225 ml/min after ingestion of a fatty meal (12). Therefore, we hypothesize that triglyceride output by POD two reflects the triglyceride absorption of preoperative oral diet intake and our criteria can be feasible.
Similar to previous reports (14, 15), we found that pancreatic fistula was significantly associated with increased postoperative hospital stay, though CL was not associated with the latter when analyzing the whole population, possibly due to the stronger effect of pancreatic fistula development over increased postoperative stay. However, CL was noted to be a significant factor associated with prolonged postoperative stay in patients who did not develop a pancreatic fistula. Thus, our threshold may need to be adjusted to that limited subset of patients.

There is no consensus on whether postoperative pancreatic fistula is associated with CL (2, 10). This study revealed a significant association between CL and absent grade B/C pancreatic fistulas. The cisterna chyli is located anterior to the superior lumbar vertebrae and lies at the same level as that of the pancreatic head and neck (16, 17). Thus, it is understandable that CL occurs after pancreaticoduodenectomy, including SSPPD, due to the traumatic nature of the procedure. We hypothesize that local inflammation around the pancreaticojejunostomy site, induced by a pancreatic fistula, accelerates injured lymphatic vessel closure. More studies will be required to confirm this hypothesis, since currently there are no reports investigating the pathological relationship between pancreatic fistulas and injured lymphatic vessel closure.

The reason for the association between CL and shorter operative time is unclear. However, Kim et al. (10) reported the same result in their univariate analysis and hypothesized that lesser surrounding inflammation might preserve the lymphatic inflow, and that CL might occur easily if lymphatic ducts were injured. Operative time is also influenced by various factors such as tumor T-stage, BMI, adhesions from past operations, operator skill and technique, etc.

A major limitation of our study is that it was retrospective, single-institution study that examined a small number of patients. In order to gather more definitive evidence, further studies are needed.

In conclusion, daily triglyceride output volume >177 mg by POD two indicates a possibility of developing postoperative CL after SSPPD. Further studies are needed, which assess whether the delayed administration of postoperative initial oral intake can prevent CL in patients who meet that cut-off point.

Conflicts of Interest

All Authors disclose no conflicts of interest.

Authors’ Contributions

TI, KF and KH were involved with design of this study and manuscript. Data were collected by NO and FS and analyzed by RH, YS and KH. TI and KH proofread the manuscript. All Authors have read and approved the final version of the edited manuscript.

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