The Amount and Concentration of Drain Amylase Together Predict Postoperative Pancreatic Fistula after Gastric Cancer Surgery More Accurately than the Concentration Alone

Miura, Susumu ; Wakahara, Tomoyuki ; Yamauchi, Saya ; Yasuhara, Yuki ; Mukubo, Hideyo ; Kanemitsu, Kiyonori ; Iwasaki, Takeshi ; Sasako,…

(Citation)
Oncology,100(7):363-369

(Issue Date)
2022-03-25

(Resource Type)
journal article

(Version)
Accepted Manuscript

Research Article

The amount and concentration of drain amylase together predict postoperative pancreatic fistula after gastric cancer surgery more accurately than the concentration alone.

Susumu Miura[1, 2], Tomoyuki Wakahara[1], Saya Yamauchi, Yuki Yasuhara, Hideyo Mukubo[1], Kiyonori Kanemitsu[1], Takeshi Iwasaki[1], Mitsuru Sasako[1], Yoshihiro Kakeji[2]

1. Department of Surgery, Yodogawa Christian Hospital, Osaka, Japan
2. Division of Gastrointestinal Surgery, Department of Surgery, Graduate School of Medicine, Kobe University, Hyogo, Japan

Short Title: Amount of drain amylase predict pancreatic fistula after gastric cancer surgery

Corresponding Author:

Full name Susumu Miura

Department of Surgery, Yodogawa Cristian Hospital, 1-7-50, Kunijima, Higashi Yodogawa Ku, Osaka, Japan 533-0024

Tel: 81-0120-364-489

E-mail: smiura@med.kobe-u.ac.jp

Number of Tables: 3

Number of Figures: 3

Word count: 2218

Keywords: Gastric cancer, Gastrectomy, Pancreatic fistula, Drain amylase concentration, Drainage fluid

Abstract

Introduction The drain amylase concentration (dAmy-C) is a useful marker for predicting pancreatic fistula after gastric cancer surgery. However, dAmy-C might be reduced in cases of high drainage volume. Therefore, we hypothesized that we could accurately assess the amount of amylase leaked from the pancreas by multiplying dAmy-C by the daily drainage volume. In this study, we investigated the clinical utility of the amount of drain amylase (A-dAmy: concentration × volume) for predicting pancreatic fistula. And, we investigated the clinical utility of the combination of dAmy-C and A-dAmy for predicting pancreatic fistula.

Methods We investigated patients who underwent gastrectomy for gastric cancer at Yodogawa Christian Hospital between 2012 and 2020. The optimal cut-off levels of dAmy-C and A-dAmy on postoperative day 1 for predicting Clavien-Dindo grade II or higher pancreatic fistula were calculated using receiver operating characteristic (ROC) curves. And, we calculate the positive predictive value and negative predictive value for predicting pancreatic fistula using these cut-off levels.

Results A total of 448 patients were eligible for analysis. Twenty-two patients experienced Clavien-Dindo grade II or higher pancreatic fistula. ROC curves identified 1,615 IU/L as the optimal cut-off level of dAmy-C predicting pancreatic fistula. When the simple cut-off level of dAmy-C was 1,600 IU/L, the positive predictive value for was 22.8% and the negative predictive value was 99.7%. ROC curves identified 177.52 IU as the optimal cut-off level of A-dAmy predicting pancreatic fistula. When the simple cut-off level of A-dAmy was 177 IU, the positive predictive value was 21.2% and the negative predictive value was 99.7%. Using these two cut-off levels together, the positive predictive value was 34.4% and the negative predictive value was 99.7%.

Conclusion A-dAmy could predict and exclude pancreatic fistula after gastrectomy as with dAmy-C. The combination of dAmy-C and A-dAmy predict pancreatic fistula more accurately than dAmy-C alone.

Introduction

Gastrectomy with extended lymphadenectomy is the standard treatment for potentially curable gastric cancer [1, 2]. However, patients who undergo this procedure experience more postoperative complications than those who receive gastrectomy with only limited lymphadenectomy [3]. Postoperative pancreatic fistula is one of the major complications after gastrectomy for gastric cancer [4, 5]. In the context of pancreatic surgery, the International Study Group of Pancreatic Fistula (ISGPF) defined postoperative pancreatic fistula as a drain amylase concentration of greater than 3 times the institutional upper limit of serum amylase (375 IU/L in our hospital) on or after postoperative day 3 (POD3) [6, 7]. In gastric surgery, the ISGPF definition is commonly used along with the Clavien-Dindo (CD) grading classification for postoperative assessment of pancreatic fistula [8-10].

The drain amylase concentration on POD1 is a very useful marker for predicting postoperative pancreatic fistula after gastric cancer surgery [11-18]. Pancreatic damage during surgery usually results in amylase leakage, resulting in pancreatic fistula. However, when there is a high volume of postoperative drainage, the amylase concentration may be diluted and its actual amount underestimated.

Therefore, we hypothesized that we could more accurately assess the amount of amylase leaked from the pancreas by multiplying the drain amylase concentration by the daily drainage volume. There are no previous reports on the relationship between the amount of drain amylase (concentration [UI/L] × drainage volume [L]) and the incidence of postoperative pancreatic fistula after gastric cancer surgery.

In this study, we examined the clinical utility of the amount of drain amylase and the drain amylase concentration on POD1 for predicting postoperative pancreatic fistula after gastrectomy for gastric cancer.

Materials and methods

Patients

We investigated the patients who underwent gastrectomy with lymph node dissection for gastric cancer at Yodogawa Christian Hospital between 2012 and 2020, and analyzed those whose drain amylase concentration was measured on POD1. We excluded patients who underwent gastrectomy for remnant gastric cancer or gastrectomy with pancreatectomy.

We performed preoperative diagnosis and clinical staging of gastric cancer by esophagogastroduodenoscopy (EGD) and computed tomography (CT). We classified patients according to the Japanese classification of gastric carcinoma, 3rd English edition [19]. Surgery was indicated in those with potentially curable gastric cancer. Surgical procedures were selected according to the Japanese gastric cancer treatment guidelines 2014 [20].

In most cases, we placed a single drain in the suprapancreatic area during surgery. In rare instances, we placed another drain under the left subphrenic space in cases of total gastrectomy. In this study, we assessed the amylase concentration and amount in the fluid obtained from the drain placed in the suprapancreatic area. We measured the drainage volume on POD1 from 23:00 on POD0 to 23:00 on POD1, according to the ward protocol at our hospital. In addition, we assessed the drain amylase concentration on POD1 and POD3 as specified by our institution's clinical pathway.

We defined postoperative pancreatic fistula as an elevated drain amylase concentration of greater than 375 IU/L (3 times the upper limit of the normal serum amylase value at our hospital) on or after POD3, according to the ISGPF definition [6, 7]. We graded pancreatic fistula according to the CD classification [8-10]: grade I did not require any treatment; grade II required only pharmacological treatment; grade III required surgical, endoscopic, or radiological intervention; grade IV was characterized by organ failure; and grade V was defined by patient death. In this study we investigated patients with pancreatic fistula of grade II or higher (≥ grade II) since it requires treatment and is therefore clinically important.

This retrospective study was approved by the ethics committee of Yodogawa Christian Hospital (No. 2021-019). Informed consent was obtained from all participants.

Analysis

First, we compared the clinical characteristics of patients with and without ≥ grade II pancreatic fistula. Drainage volume was measured in [mL], and since drain amylase concentrations were assessed as [IU/L], units of drainage volume were converted from [mL] to [L] when calculating the amount of drain amylase.

Second, the optimal cut-off levels of drain amylase concentration and the amount of drain amylase on POD1 for predicting ≥ grade II pancreatic fistula were calculated using receiver operating characteristic (ROC) curves. These cut-off levels were then used to calculate the positive predictive value, negative predictive value, sensitivity, and specificity for predicting ≥ grade II pancreatic fistula.

As a reference, we also calculated these parameters when the cut-off level of the drain amylase concentration on POD3 was set to 375 UI/L.

Third, we examined the incidence of ≥ grade II pancreatic fistula in groups classified by the optimal cut-off levels of the drain amylase concentration and the amount of drain amylase on POD1. We then drew a scatter plot to investigate the relationship between these two measurements. And, we performed regression analyses and calculated correlation coefficients.

Forth, univariate and multivariate analysis with the Cox hazard model were performed to identify predictive factors for ≥ grade II pancreatic fistula. These confounding factors were selected from factors that showed significant difference in Table 1 and predictive factors used in past studies [12, 16]

We used JMP (version 10; SAS Institute, Cary, NC, USA) for statistical analysis. We defined statistical significance at $P \leq 0.05$, and compared differences between the two groups with the t-test or chi-square test.

Results

From January 2012 to December 2020, 473 patients diagnosed with potentially curable gastric cancer underwent gastrectomy with lymphadenectomy at Yodogawa Christian Hospital. We excluded 11 patients who underwent gastrectomy for remnant gastric cancer and 9 patients who underwent gastrectomy with pancreatectomy. Excluding 3 patients in whom a drain was not placed during gastrectomy and 2 patients whose drain amylase concentration on POD1 was not measured, 448 patients were eligible for analysis.

Pancreatic fistula was classified as ≥ grade II in 22 patients, and as ≥ grade III in 14 patients. There were no cases of grade IV or V pancreatic fistula. The drain amylase concentration was > 375 IU/L on POD3 in 19 patients, while this concentration was achieved after POD3 in the other 3. Ten additional patients experienced complications other than pancreatic fistula: ≥ grade II anastomosis leak occurred in 10 patients, ≥ grade II abdominal abscess in 6, and ≥ grade II pneumonia in 6.

Table 1 shows the clinical characteristics of patients with and without ≥ grade II pancreatic fistula. There were no significant differences in age or sex between the 2 groups. The group with ≥ grade II pancreatic fistula had a significantly higher body mass index (BMI) (P=0.02), significantly longer operative time (P<0.01) and significantly higher blood loss (P<0.01). In the group with ≥ grade II pancreatic fistula, the rate of D2 lymph node dissection was higher than D1+ lymph node dissection, the rate of open surgery was higher than laparoscopic surgery and the rate of advanced cancer was higher than early cancer.

The drain amylase concentrations on POD1 and POD3 were significantly higher in the group with ≥ grade II pancreatic fistula (*P*<0.01). There was no significant difference between the 2 groups in terms of the drain drainage volume on POD1. The amount of drain amylase on POD1 was significantly higher in the group with ≥ grade II pancreatic fistula (*P*<0.01).

ROC curves identified 1,615 IU/L as the optimal cut-off level of the drain amylase concentration on POD1 for predicting ≥ grade II pancreatic fistula (Fig 1a). When the simple cut-off level of the drain amylase concentration was defined as 1,600 IU/L, the positive predictive value for predicting ≥ grade II pancreatic fistula was 22.8%, the negative predictive value was 99.7%, the sensitivity was 95.4%, and the specificity was 83.3%. As a reference, when the cut-off level of the drain amylase concentration on POD3 was set to 375 UI/L, the positive predictive value was 14.5%, the negative predictive value was 99.0%, the sensitivity was 86.3%, and the specificity was 73.7%.

ROC curves identified 177.52 IU as the optimal cut-off level of the amount of drain amylase on POD1 for predicting ≥ grade II pancreatic fistula (Fig 1b). When the simple cut-off level of the amount of drain amylase was defined as 177 IU, the positive predictive value for predicting ≥ grade II pancreatic fistula was 21.2%, the negative predictive value was 99.7%, the sensitivity was 95.4%, and the specificity was 81.6%.

Table 2 shows the incidence of ≥ grade II pancreatic fistula in groups classified by the cut-off levels of the drain amylase concentration and the amount of drain amylase on POD1. Of the 61 patients who had both a drain amylase concentration > 1,600 IU/L and an amount of drain amylase > 177 IU, 21 (34.4%) had ≥ grade II pancreatic fistula. Figure 2 shows a scatter plot of the drain amylase concentration and the amount of drain amylase. The aforementioned cut-off levels are shown on the plot. The regression line was defined as follows: Amount of drain amylase = 2.5 + 0.1 × Drain amylase concentration, R^2 = 0.71.

Table 3 showed univariate and multivariate analyses of risk factors for ≥ grade II pancreatic fistula with odds ratio (OR) and 95% confidence interval (CI). In univariate analysis, operative time ≥ 300 minutes (OR = 3.45, 95%CI; 1.14-10.3), blood loss ≥ 300ml (OR = 5.78, 95%CI; 2.35-14.1), total gastrectomy (OR = 3.57, 95%CI; 1.34-9.50), D2 lymphadenectomy (OR = 4.63, 95%CI; 1.35-15.8) pathological Stage II/III/IV (OR = 3.52 95%CI; 1.21-10.1), drain amylase concentration ≥1600 (OR= 104.9, 95%CI; 13.8-793.2) and amount of drain amylase ≥ 177 (OR = 93.6 95%CI; 12.4-707.1) were significant predictive factors. In multivariate analysis, operative time ≥ 300 minutes (OR = 12.2, 95%CI; 1.36-110.4), drain amylase concentration ≥ 1600 (OR= 21.7, 95%CI; 2.51-187.1) and amount of drain amylase ≥ 177 (OR = 19.6, 95%CI; 2.02-190.6) were significant independent predictive factors.

Discussion

In this study, we showed that a drain amylase concentration on POD1 > 1,600 UI/L and an amount of drain amylase on POD1 > 177 UI could respectively predict and exclude ≥ grade II pancreatic fistula. These 2 cutoff levels could also be used in combination to predict pancreatic fistula more accurately.

The mean BMI was significantly higher in the group with ≥ grade II pancreatic fistula. A past study also reported that a high BMI was a risk factor for pancreatic fistula [16]. Patients with a high BMI were shown to have an increased incidence of postoperative complications, longer operative time, and increased blood loss [21, 22].

The mean operative time was significantly longer and the mean blood loss was significantly higher in the group with ≥ grade II pancreatic fistula. These results are consistent with those of a past study showing that longer operative time and greater blood loss were risk factors for pancreatic fistula [16]. In addition, extended lymph node dissection was found to result in a longer operation time, more blood loss, and more postoperative complications [23, 24].

In the group with pancreatic fistula, the rate of D2 lymph node dissection was higher than D1+ lymph node dissection, the rate of open surgery was higher than laparoscopic surgery and the rate of advanced cancer was higher than early cancer. Possible reasons were as follows. The larger lymph node dissection was performed around the pancreas, the more frequent pancreatic fistula was [23, 24]. Advanced cancer required larger lymph node dissection than early cancer [19,20]. In principle, laparoscopic surgery was often performed for early cancer and open surgery was often performed for advanced cancer [19, 20].

In univariate analysis, operative time ≥ 300 minutes, blood loss ≥ 300ml, total gastrectomy, D2 lymphadenectomy and pathological Stage were also significant predictive factors. Total gastrectomy required larger lymph node dissection around the pancreas than other gastrectomy [19 20]. In multivariate analysis, operative time ≥ 300 was significant independent predictive factors among these factors. These factors could be related to each other to certain degree [16, 19, 20, 21-24]. The operation time ≥ 300 might be representative of other factors.

The mean drain amylase concentration and the mean amount of drain amylase on POD1 were significantly higher in the group with ≥ grade II pancreatic fistula. The drain amylase concentration is associated with the degree of chemical stimulation by amylase that has leaked from the pancreas. Thus, the drain amylase concentration might be related to the severity of pancreatic fistula. However, this concentration might not accurately reflect the amount of amylase leaked from the pancreas if it is diluted in a high drainage volume consisting mainly of lymphatic fluid. The amount of drain amylase might reflect the amount of leaked pancreatic amylase more accurately than the drain amylase concentration. Thus, the amount of drain amylase might be related to the degree of pancreatic damage as well as the severity of pancreatic fistula. In fact, in multivariate analysis, the drain amylase concentration and the amount of drain amylase were independent predictive factors.

In this study, the drain amylase concentration on POD1 was able to predict pancreatic fistula when the cut-off level was set to 1,600 IU/L. And, pancreatic fistula could be excluded if the concentration was below 1,600 IU/L. In a past study, there was a wide range of cut-off levels for the drain amylase concentration, ranging from 1,000 to 5,000 IU/L. The most recent study examining ≥ grade III pancreatic fistula in more than 800 patients used 2,218 IU/L as the cut-off level [16]; therefore, 1,600 IU/L seems relatively reasonable as the cutoff level for predicting ≥ grade II pancreatic fistula.

When the cut-off level of the drain amylase concentration on POD3 was set to 375 IU/L, the positive and negative predictive values were lower than those associated with the drain amylase concentration on POD1 and the amount of drain amylase on POD1. In past studies, the cut-off levels of the drain amylase concentration on POD3 were 555–2,000 IU/L [15, 16]. A drain amylase concentration on POD3 > 375 UI/L might not be optimal for predicting ≥ grade II pancreatic fistula after gastrectomy [15, 16].

The amount of drain amylase on POD1 was also able to predict pancreatic fistula when the cut-off level was set to 177 IU. And, pancreatic fistula could be excluded if the amount of drain amylase was below 177 IU/L. The positive and negative predictive values were almost the same as those obtained when using the drain amylase concentration on POD1.

However, in multivariate analysis, the drain amylase concentration and the amount of drain amylase were independent predictive factors. And, the populations by these 2 cut off levels were not exactly equivalent (Figure 2). When the scatter plot in Figure 2 was quartered using these two cut off levels, almost all patients with ≥ grade II pancreatic fistula were in upper right block (Table2). If the cut-off levels for both parameters were met (upper right block in Figure 2), there was a 34.4% incidence of ≥ grade II pancreatic fistula. On the contrary, there was almost no pancreatic fistula in blocks other than the upper right block in Figure 2 (Table2). Thus, pancreatic fistula could be predicted more accurately when the drain amylase concentration on POD1 was considered along with the amount of drain amylase on POD1.

It is clinically relevant that we could predict ≥ grade II pancreatic fistula earlier when using both the drain amylase concentration on POD1 and the amount of drain amylase on POD1 than when using the former value alone. Figure 3 shows an example of a flowchart for predicting ≥ grade II pancreatic fistula in clinical practice. By combining these two cut-off levels, patients can be divided into high- and low-risk groups. In the low-risk group, the drain can be removed earlier. In the high-risk group, prophylactically administering antibiotics and performing CT scans should be considered.

This study had several limitations. First, it was a retrospective study performed at a single hospital. Second, there were not many patients with ≥ grade II pancreatic fistula. It will be necessary to evaluate the clinical significance of the amount of drain amylase on POD1 in a future prospective, large-scale clinical study.

Conclusion

This study showed that postoperative pancreatic fistula after gastric cancer surgery could be predicted with similar accuracy by the amount of drain amylase on POD1 and by the drain amylase concentration, and an even more accurate prediction was obtained by combining the 2 parameters.

Statement of Ethics

This study protocol was reviewed and approved by the ethics committee of Yodogawa Christian Hospital, approval number [2021-019].

Written informed consent was obtained from all participants to participate in this study.

This study complied with the guidelines for human studies and should include evidence that the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors have not received any funding.

Author Contributions

Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; Susumu Miura, Tomoyuki Wakahara, Hideyo Mukubou, Kiyonori Kanemitsu

Drafting the work or revising it critically for important intellectual content; Susumu Miura, Saya Yamauchi, Yuki Yasuhara

Final approval of the version to be published; Takeshi Iwasaki, Mitsuru Sasako, Yoshihiro Kakeji

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; All authors

Data Availability Statement

Due to privacy and ethical concerns, neither the data nor the source of the data can be made available.

References

1. Chew-Wun Wu, Chao A Hsiung, Su-Shun Lo, Mao-Chin Hsieh, Jen-Hao Chen, Anna Fen-Yau Li, et al. Nodal dissection for patients with gastric cancer: a randomised controlled trial. Lancet Oncol 2006;7:309-315.

2. Songun I, Putter H, Kranenbarg EM, Sasako M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. Lancet Oncol 2010;11:439-449.

3. Bonenkamp JJ, Songun I, Hermans J, Sasako M, Welvaart K, Plukker JT, et al. Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. Lancet 1995;345:745-748.

4. Sano T, Sasako M, Yamamoto S, Nashimoto A, Kurita A, Hiratsuka M, et al. Gastric cancer surgery: morbidity and mortality results from a prospective randomized controlled trial comparing D2 and extended para-aortic lymphadenectomy--Japan Clinical Oncology Group study 9501. J Clin Oncol 2004;22:2767-2773.

5. Washio M, Yamashita K, Niihara M, Hosoda K, Hiki N. Postoperative pancreatic fistula after gastrectomy for gastric cancer. Ann Gastroenterol Surg. 2020;4:618-627.

6. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005;138:8-13.

7. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. Surgery 2017;161:584-591.

8. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-213.

9. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009;250:187-196.

10. Katayama H, Kurokawa Y, Nakamura K, Ito H, Kanemitsu Y, Masuda N, et al. Extended Clavien-Dindo classification of surgical complications: Japan Clinical Oncology Group postoperative complications criteria. Surg Today 2016;46:668-685.

11. Sano T, Sasako M, Katai H, Maruyama K. Amylase concentration of drainage fluid after total gastrectomy. Br J Surg 1997;84:1310-1312.

12. Iwata N, Kodera Y, Eguchi T, Ohashi N, Nakayama G, Koike M, et al. Amylase concentration of the drainage fluid as a risk factor for intra-abdominal abscess following gastrectomy for gastric cancer. World J Surg. 2010;34:1534-1539.

13. Miki Y, Tokunaga M, Bando E, Tanizawa Y, Kawamura T, Terashima M. Evaluation of postoperative pancreatic fistula after total gastrectomy with D2 lymphadenectomy by ISGPF classification. J Gastrointest Surg 2011;15:1969-1976.

14. Tomimaru Y, Miyashiro I, Kishi K, Motoori M, Yano M, Shingai T, et al. Is routine measurement of amylase concentration in drainage fluid necessary after total gastrectomy for gastric cancer? J Surg Oncol 2011;104:274-277.

15. Taniguchi Y, Kurokawa Y, Mikami J, Tanaka K, Miyazaki Y, Makino T, et al. Amylase concentration in drainage fluid as a predictive factor for severe postoperative pancreatic fistula in patients with gastric cancer. Surg Today 2017;47:1378-1383.

16. Kamiya S, Hiki N, Kumagai K, Honda M, Nunobe S, Ohashi M, et al. Two-point measurement of amylase in drainage fluid predicts severe postoperative pancreatic fistula after gastric cancer surgery. Gastric Cancer 2018;21:871-878.

17. Wakahara T, Kanemitsu K, Asari S, Tsuchida S, Ueno N, Toyokawa A, et al. The Combined Use of Drainage Amylase Concentration and Serum C-reactive Protein as Predictors of Pancreas-Related Complications after Elective Gastrectomy. Oncology 2020;98:111-116.

18. Wakahara T, Kanemitsu K, Miura S, Tsuchida S, Iwasaki T, Sasako M. Optimal Timing to Assess Drain Amylase Concentration after Elective Gastrectomy. J Gastric Cancer 2021;21:30-37.

19. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer 2011;14:101-112.

20. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2014 (ver. 4). Gastric Cancer 2017;20:1-19.

21. Tsujinaka T, Sasako M, Yamamoto S, Sano T, Kurokawa Y, Nashimoto A, et al. Influence of overweight on surgical complications for gastric cancer: results from a randomized control trial comparing D2 and extended para-aortic D3 lymphadenectomy (JCOG9501). Ann Surg Oncol 2007;14:355-361.

22. Sahakyan MA, Shahbazyan SS, Martirosyan A, Gabrielyan A, Petrosyan H, Sahakyan AM. Gastrectomy for Gastric Cancer in Patients with BMI 30 kg/m2. Am Surg 2020;86:158-163.

23. Danielson H, Kokkola A, Kiviluoto T, Sirén J, Louhimo J, Kivilaakso E, et al. Clinical outcome after D1 vs D2-3 gastrectomy for treatment of gastric cancer. Scand J Surg 2007;96:35-40.

24. Yonemura Y, Wu CC, Fukushima N, Honda I, Bandou E, Kawamura T, et al. Operative morbidity and mortality after D2 and D4 extended dissection for advanced gastric cancer: a prospective randomized trial conducted by Asian surgeons. Hepatogastroenterology 2006;53:389-394.

Figure Legends

Fig. 1. **ROC curve for predicting grade II or higher pancreatic fistula.** a. ROC curve of the drain amylase concentration on POD1 (cut-off level = 1,615 UI/L, area under the curve = 0.92) b. ROC curve of the amount of drain amylase on POD1 (cut-off level = 177.52 UI, area under the curve = 0.92).

Fig. 2. **Scatter plot and regression line of the drain amylase concentration on POD1 and the amount of drain amylase on POD1.** Regression line (Amount of drain amylase = 2.5 + 0.1 × Drain amylase concentration, R2 = 0.71). The 2 cutoff levels are shown.

Fig. 3. **Flowchart for predicting pancreatic fistula and incidence of ≥ grade II pancreatic fistula** By combining the cut-off levels for the drain amylase concentration on POD1 and the amount of drain amylase on POD1, patients can be divided into a high-risk group (21/61; 34.4%) and a low-risk group (1/387; 0.3%).

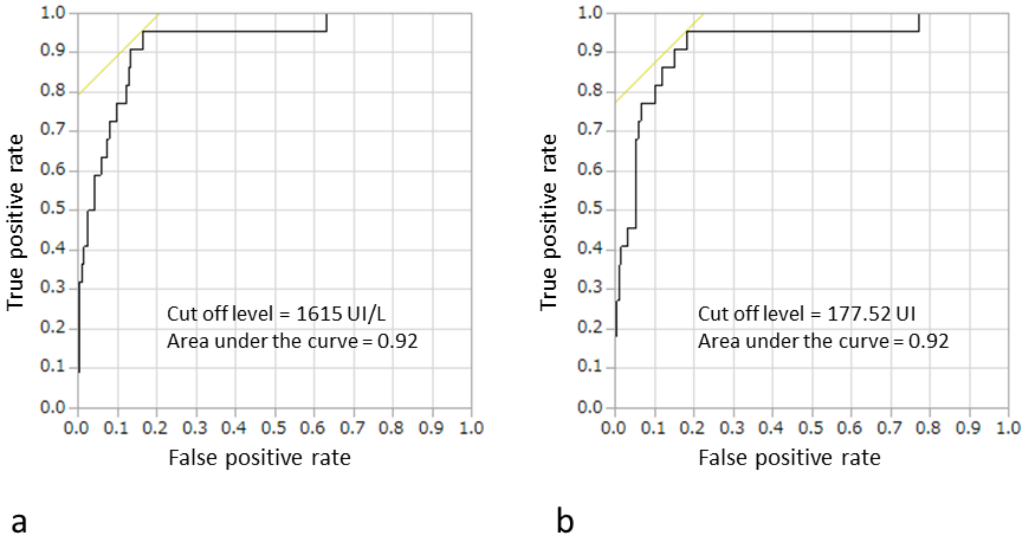

Fig. 1. **ROC curve for predicting grade II or higher pancreatic fistula.**
a. ROC curve of the drain amylase concentration on POD1 (cut-off level = 1,615 UI/L, area under the curve = 0.92)
b. ROC curve of the amount of drain amylase on POD1 (cut-off level = 177.52 UI, area under the curve = 0.92).

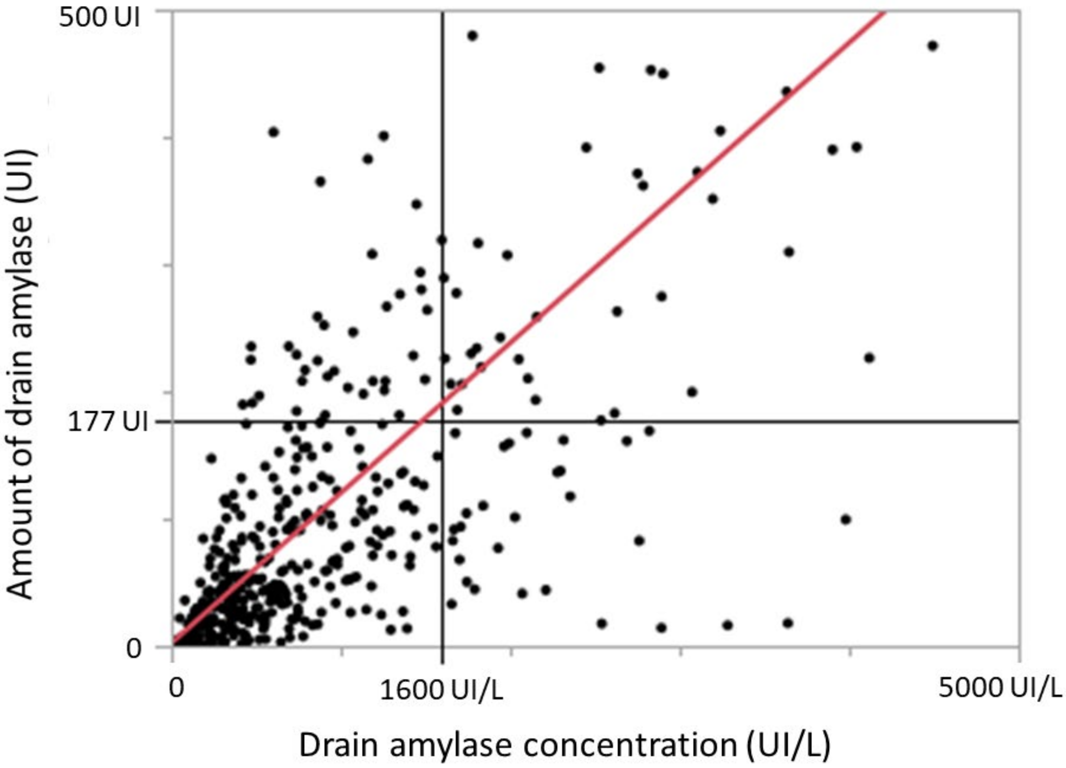

Fig. 2. **Scatter plot and regression line of the drain amylase concentration on POD1 and the amount of drain amylase on POD1.** Regression line (Amount of drain amylase = 2.5 + 0.1 × Drain amylase concentration, R2 = 0.71). The 2 cutoff levels are shown.

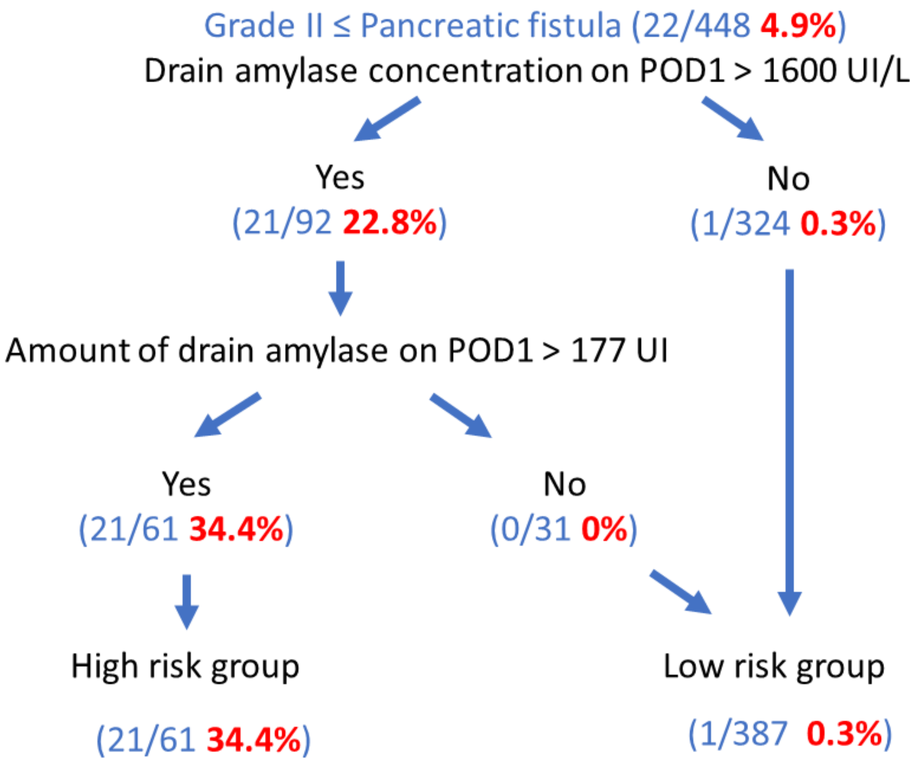

Fig. 3. **Flowchart for predicting pancreatic fistula and incidence of ≥ grade II pancreatic fistula.** By combining the cut-off levels for the drain amylase concentration on POD1 and the amount of drain amylase on POD1, patients can be divided into a high-risk group (21/61; 34.4%) and a low-risk group (1/387; 0.3%).

Table 1 Clinical characteristics of patients with and without grade II or higher pancreatic fistula.

	Grade II or higher Pancreatic Fistula		
	No (N = 426)	Yes (N= 22)	*P value*
Age (average, years)	67.7	69.1	0.58
Sex			
Male	278	17	0.23
Female	148	5	
Body Mass Index (average, kg/m^2)	22.7	24.4	**0.02**
Approach			
Open surgery	156	19	**<0.01**
Laparoscopic surgery	270	3	
Procedures			
Total Gastrectomy	102	11	0.08
Distal Gastrectomy	302	11	
Pylorus-Preserving Gastrectomy	9	0	
Proximal Gastrectomy	13	0	
Extent of lymphadenectomy			
D1+	180	3	**<0.01**
D2	246	19	
Number of lymph nodes retrieved	44.9	41.5	0.41
Neoadjuvant chemotherapy	12	1	0.48
Pathological Stage			
Stage I	265	8	**0.02**
Stage II	68	4	
Stage III	72	6	
Stage IV	21	4	
Operation time (average, minutes)	323.1	411.2	**<0.01**
Blood loss (average, ml)	235.4	723.5	**<0.01**
Drain amylase concentration on POD1* (average, IU/L)	1056.3	8952.5	**<0.01**
Drain amylase concentration on POD3* (average, IU/L)	431.5	2786.6	**<0.01**
Drainage volume on POD1* (average, ml)	126.0	141.4	0.47
Amount of drain amylase on POD1* (average, IU)	117.2	1242.6	**<0.01**

*POD postoperative day

Table 2 Incidence of grade II or higher pancreatic fistula classified by 2 cut-off levels

	Amount of drain amylase on POD1*		
	> 177 UI	≤ 177 UI	Total
Drain amylase concentration on POD1*			
> 1,600 UI/L	21/61 (34.4%)	0/31 (0%)	21/92 (22.8%)
≤ 1,600 UI/L	0/38 (0%)	1/318 (0.3%)	1/324 (0.3%)
Total	21/99 (21.2%)	1/349 (0.3%)	22/448 (4.9%)

*POD postoperative day

Table 3 Univariate and Multivariate analyses of risk factors for Grade II or higher Pancreatic fistula.

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Age (years)				
≥75				
<75	1.23 (0.39-3.87)	0.71		
Sex				
Female				
Male	1.81 (0.65-5.00)	0.25		
Body Mass Index (kg/m^2)				
<23				
≥23	1.88 (0.78-4.49)	0.15		
Operation time (minutes)				
<300				
≥300	3.45 (1.14-10.3)	**0.02**	12.2 (1.36-110.4)	**0.03**
Blood loss (ml)				
<300				
≥300	5.78 (2.35-14.1)	**<0.01**	0.96 (0.22-4.20)	0.96
Procedures				
Other Gastrectomy				
Total Gastrectomy	3.57 (1.34-9.50)	**0.01**	0.52 (0.13-2.01)	0.35
Extent of lymphadenectomy				
D1+				

D2	4.63 (1.35-15.8)	**0.01**	1.51 (0.20-11.3)	0.68
Pathological Stage				
Stage I				
Stage II / III / IV	3.52 (1.21-10.1)	**0.02**	2.12 (0.41-10.7)	0.36
Drain amylase concentration on POD1 (IU/L)				
<1600				
≥1600	104.9 (13.8-793.2)	**<0.01**	21.7 (2.51-187.1)	**<0.01**
Amount of drain amylase on POD1 (IU)				
<177				
≥177	93.6 (12.4-707.1)	**<0.01**	19.6 (2.02-190.6)	**0.01**