Total Amylase Value in Drains After Gastrectomy for Predicting Postoperative Pancreatic Fistula

Objective: Postoperative pancreatic fistula (POPF) is defined using the ratio of the bilirubin concentration in abdominal drainage fluid to the upper normal range of serum amylase level. However, we hypothesized that the total amylase value in discharge (AVD) on POD 3 may be more sensitive for predicting grade II or higher severe POPF sPOPF, and compared the predictive power of the conventional definition of POPF and AVD for sPOPF. Methods: One hundred and fifty-one patients who underwent gastrectomy between October 2011 and February 2013 were analyzed. A drainage tube was placed in all the cases through the stump of the right gastroepiploic vein and the front of the pancreas to the back of the anastomotic site. The drainage volume and amylase concentration in the discharge were examined on POD 1, 3, and 5. AVD was calculated by multiplying the volume by the amylase concentration. Results: Eight patients (5.3%) developed sPOPF. In univariate analysis, both AVD and the amylase concentration ratio was significantly correlated with sPOPF (P = 0.002 and 0.007, respectively). AVD on POD 3 showed the best predictive performance compared with the amylase concentration ratio on POD 3 (area under the curve 0.876 vs. 0.844). Based on the cutoff values calculated from the ROC curves, AVD was more specific than amylase concentration ratio in predicting sPOPF (specificity: 97.6% vs. 86.0%; PPV: 62.5% vs. 23.1%). Conclusion: AVD on POD 3 is a more specific parameter than conventional amylase concentration ratio in predicting sPOPF.
Total Amylase Value in Drains After Gastrectomy for Predicting Postoperative Pancreatic Fistula

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Conflicts of Interest and Source of Funding:
Authors have no conflicts of interest to disclose.
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ABSTRACT

Objective: Postoperative pancreatic fistula (POPF) is defined using the ratio of the amylase concentration in abdominal drainage fluid to the upper normal range of serum amylase level. However, we hypothesized that the total amylase value in discharge (AVD) on POD 3 may be more sensitive for predicting grade II or higher severe POPF sPOPF, and compared the predictive power of the conventional definition of POPF and AVD for sPOPF.

Methods: One hundred and fifty-one patients who underwent gastrectomy between October 2011 and February 2013 were analyzed. A drainage tube was placed in all the cases through the stump of the right gastroepiploic vein and the front of the pancreas to the back of the anastomotic site. The drainage volume and amylase concentration in the discharge were examined on POD 1, 3, and 5. AVD was calculated by multiplying the volume by the amylase concentration.

Results: Eight patients (5.3%) developed sPOPF. In univariate analysis, both AVD and the amylase concentration ratio was significantly correlated with sPOPF ($P = 0.002$ and 0.007, respectively). AVD on POD 3 showed the best predictive performance compared with the...
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collection ratio in predicting sPOPF (specificity: 97.6% vs. 86.0%; PPV: 62.5% vs. 23.1%).

**Conclusion:** AVD on POD 3 is a more specific parameter than conventional amylase
concentration ratio in predicting sPOPF.

**KEY WORDS:** amylase value, gastrectomy, postoperative pancreatic fistula, predictive

factor
INTRODUCTION

Gastric cancer is the third most common cause of cancer death in the world [1] and is the most prevalent cancer in Eastern Asia [2]. Gastrectomy with adequate lymphadenectomy is a well-established and widely accepted procedure to cure gastric cancer [3-12]. However, postoperative pancreatic fistula (POPF) is one of the major postoperative complications after both laparoscopic and open gastrectomy accompanying lymphadenectomy [13-15], resulting in abscess formation, pseudoaneurysm of exposed arteries, and subsequent postoperative hemorrhage [16].

POPF is caused by the leakage of protease from the injured pancreas during dissection of the peripancreatic lymph nodes, which are then activated by the enzyme enterokinase near the anastomosis [17, 18]. Although it is reasonable to examine protease activation as a predictor of POPF, amylase concentration of the discharge is examined because of convenience [19]. In 2005 and 2016, the international study group on pancreatic fistula (ISGPF) broadly defined POPF as output of drain fluid of any measurable volume via an operatively placed drain on or after postoperative day (POD) 3, with an amylase content > 3 times the upper normal serum value (amylase concentration ratio) [20, 21]. According to the ISGPF classification, the Clavien–Dindo classification also defined POPF after
gastrostomy using the amylase concentration of the discharge [22]. However, clinically
significant grade II or severer POPF (sPOPF) is still difficult to predict using the current
definition of POPF.

The criteria for the grade I POPF after gastrectomy is too broad to predict sPOPF,
with a large discrepancy between the two grades. In addition, the amylase concentration in
drainage fluid can change with the amount of drainage fluid [21]. To date, few studies have
investigated the total value of amylase in drains (AVD) as a predictive factor for sPOPF
development [23]. In this study, we hypothesized that AVD on POD 3 is more closely related
to POPF than amylase concentration. We determined AVD on POD 3 by multiplying amylase
content by drain volume, and evaluated AVD as a predictive parameter of POPF after
gastrectomy.

PATIENTS AND METHODS

Patients

Between October 2011 and February 2013, 196 consecutive patients with gastric
cancer underwent gastrectomy with lymphadenectomy at Toranomon Hospital, Tokyo, Japan.
Tumor depth and lymph node metastasis were assessed by endoscopy and computed
tomography (CT). All tumors were histologically diagnosed as gastric carcinoma.

Pathological stage was classified according to the Japanese Classification of Gastric Carcinoma, third English edition [24, 25]. Data on daily drainage output or amylase concentration in the drainage was lacking in 45 patients, leaving 151 patients for analysis in this study.

Surgery

All operations were performed by experienced surgeons using standardized procedures. Lymphadenectomy was performed with ultrasonically activated coagulating shears and electric cautery, as described in detail previously [15, 26-28]. Lymph node dissection was performed according to the Japanese gastric cancer treatment guidelines 2010 [25]. The stomach was resected using endoscopic linear staplers and Roux-en-Y anastomosis was performed for reconstruction. At the end of every operation, a drain (J-VAC/BLAKE; Ethicon, US) was placed through the stump of the right gastroepiploic vein and the front of pancreas to the back of the anastomotic site.

Definition of Pancreatic Fistula

POPF was defined according to the Clavien–Dindo classification and sPOPF was defined as POPF ≥ grade II.
Data Collection

Patients’ clinical, surgical, and pathological records were collected from our hospital database. The volume of drain discharge and AVD was examined on POD 1, 3, and 5. Patients were divided into two groups depending on the occurrence of sPOPF.

Statistical Analysis

Data are expressed as mean ± standard deviations (SD) or median. Statistical analysis was performed using the Mann–Whitney U test for continuous variables and the Chi-square test for categorical variables as appropriate. Variables with a P value < 0.05 in the univariate analysis were subsequently introduced in the multivariate analysis. The receiver operating characteristic (ROC) curve of AVD on POD 3 was used to identify an appropriate cutoff level to detect POPF. All data were analyzed by SPSS version 13.0 (SPSS, Chicago, IL). P values < 0.05 were considered statistically significant and all tests were two-sided.

RESULTS

Patient background is shown in Table 1. In this study, 8 patients developed sPOPF (5.3%). High BMI (≥ 25 kg/m²) were predisposing factors for POPF. There were no significant differences in sex, age, and presence of diabetes mellitus between the two groups.
Type of operation and grade of POPF are shown in Table 2. There were 59 patients (39%) underwent open gastrectomy, and none of this group had sPOPF ($P = 0.023$). No patients underwent splenectomy. The number of patients who developed grade II, IIIa, IIIb, and IV sPOPF were 3, 3, 1, and 1, respectively. Level of lymphadenectomy was not a significant factor ($P = 0.410$). The median volume of drainage fluid on POD3 was 61 ml (interquartile range, 2–636 ml).

Figure 1 shows AVD and the amylase concentration ratio on POD 3 stratified by whether or not sPOPF was observed during the postoperative course. It was found that AVD and amylase concentration ratio on POD 3 was significantly correlated with occurrence of sPOPF ($P = 0.000$ vs. $0.001$). ROC curves analysis revealed that AVD was slightly better than the conventional amylase concentration ratio (area under the curve, 0.876 [95% CI, 0.748–1.000] vs. 0.844 [95% CI 0.671–1.000]) in prediction of sPOPF after gastrectomy (Figure 2).

The best cut-off values on POD3 were estimated as 48.2 IU for the AVD and 3.8 for the amylase concentration ratio, respectively. Table 3 shows comparison of diagnostic values for the determined cut-off values on POD 3 for AVD and amylase concentration ratio, and conventional definition of POPF (i.e., amylase concentration ratio of 3.0). Among the three measures, AVD at POD 3 showed the highest diagnostic value with a sensitivity of 62.5%,
specificity of 97.9%, and positive predictive value of 62.5%.

DISCUSSION

In the present study, we proposed a new drainage measure AVD, and compared the predictive power with the conventional amylase concentration ratio for clinically important POPF. As a result, AVD at POD 3 had a better AUC value (0.876 [95% CI, 0.748–1.000]).

POPF is a major postoperative complication after gastrectomy, with a reported incidence of 1.7–18% [8-10, 13, 14, 29]. Timely diagnosis and treatment are crucial for sPOPF because it might lead to a life-threatening condition such as pseudoaneurysm or hemorrhage [16]. However, grade I POPF sometimes resolve spontaneously. Therefore, early prediction of patients who are at risk of developing sPOPF is clinically important.

Molinari et al. reported that the amylase concentration in drains on POD 1 was a significant predictive factor for sPOPF after pancreatic resection, and inferred that the drainage volume would less predictive [23]. However, as shown in the present study, the actual median volume of the drained fluid varies considerably among patients, ranging from 2 to 636 ml/day, and the volume of the fluid might modify the “concentration” of amylase. In fact, the present study demonstrated that the AUC of AVD on POD 3 was better than the amylase concentration ratio on POD 3, and comparison of the predictive value of sPOPF
including the conventional definition of amylase concentration ratio of 3 showed that AVD on POD 3 had the best positive predictive value for development of sPOPF.

The novelty of using this AVD factor as an alternative predictive measure for sPOPF may be summarized in two points. First, AVD reflects the net amount of leakage of pancreatic juice excluding the masking effect of massive ascites especially in patients with latent major pancreatic leakage which could be missed with the conventional amylase concentration ratio. Second, AVD is an easy measure, calculated by just multiplying the amylase concentration ratio with the drainage fluid volume.

Limitations of this study include its retrospective nature and lack of external validation. However, this is the first report to clarify that the risk of development of sPOPF may be better correlated with the net amount of pancreatic leakage than the conventional measure of the amylase concentration ratio. A prospective validation study would be needed to confirm the better predictive value of AVD for sPOPF after gastrectomy.

In conclusion, AVD on POD 3 may have better predictive value for the development of sPOPF than the conventional amylase concentration ratio after gastrectomy with radical lymphadenectomy. A prospective validation study is needed to confirm the clinical relevance of the net amount of pancreatic leakage as an alternative predictive
measure for the risk of sPOPF.

CONFLICTS OF INTEREST

All authors declare no conflicts of interest. There was no financial support for this study.
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1. **Fig 1.** AVD (a) and the amylase concentration ratio (b) on postoperative day 3.

2. AVD total amylase value in drains

3. *sPOPF group* patients with a postoperative pancreatic fistula > grade B;

4. **Fig 2.** ROC curve based on AVD and amylase concentration ratio on postoperative day 3.

5. AVD: area under the curve, 0.876; \( P = 0.000 \); 95% CI, 0.748–1.000.

6. Amylase concentration ratio: area under the curve, 0.844; \( P = 0.001 \); 95% CI, 0.671–1.000.

7. AVD total amylase value in drains
### TABLE 1. Patient characteristics

|                          | sPOPF (n=8) | Non-sPOPF (n=143) | P    |
|--------------------------|-------------|-------------------|------|
| Male/female              | 8/0         | 91/52             | 0.051|
| Age (years)              |             |                   |      |
| Median                   | 67 (37 – 88)| 65 (53 – 74)      | 0.372|
| (range)                  |             |                   |      |
| < 65 years               | 4           | 60                | 0.723|
| ≥ 65 years               | 4           | 83                |      |
| BMI (kg/m2)              | 26.4 ± 2.1  | 22.4 ± 0.5        | 0.000|
| < 25                     | 2           | 115               | 0.002|
| ≥ 25                     | 6           | 28                |      |
| Diabetes                 | 2           | 22                | 0.614|

*sPOPF group* patients with a postoperative pancreatic fistula > grade B; *BMI* body mass index

Data are means ± standard deviations or numbers of patients unless otherwise indicated.
### TABLE 2. Data related with POPF

|                         | sPOPF (n=8) | Non-sPOPF (n=143) | P    |
|-------------------------|-------------|-------------------|------|
| Surgical procedure      |             |                   | 0.023|
| Open                    | 0           | 59                |      |
| Laparoscopic            | 8           | 84                |      |
| Type                    |             |                   | 0.705|
| Distal gastrectomy      | 5           | 59                |      |
| Total gastrectomy       | 3           | 26                |      |
| Level of lymphadenectomy<sup>a</sup> |             |                   | 0.410|
| D1                      | 0           | 11                |      |
| D1+                     | 7           | 83                |      |
| D2                      | 1           | 49                |      |
| Grade of POPF<sup>b</sup> |             |                   |      |
| 0                       |             | 122               |      |
| I                       |             | 21                |      |
| II                      | 3           |                   |      |
| IIIa                    | 3           |                   |      |
| IIIb                    | 1           |                   |      |
| IVb                     | 1           |                   |      |
| pT stage<sup>c</sup> (1-2/2-4) | 8/0        | 124/19            |      |
| pN stage<sup>c</sup> (0/1-3) | 7/1        | 106/37            |      |

**POPF** postoperative pancreatic fistula

**sPOPF group** patients with a postoperative pancreatic fistula > grade B;

<sup>a</sup> Level of lymphadenectomy was defined according to the Japanese gastric cancer treatment guidelines 2010

<sup>b</sup> Postoperative pancreatic fistula was defined according to the Clavien–Dindo classification.
Pathological stage was classified according to the Japanese Classification of Gastric Carcinoma, third English edition

Data are numbers unless otherwise indicated.
### TABLE 3. Power to predict sPOPF

| Parameter on POD 3 (cutoff value) | Sensitivity | Specificity | PPV % | NPV % |
|----------------------------------|-------------|-------------|-------|-------|
| AVD (48.2IU)                     | 62.5        | 97.9        | 62.5  | 97.9  |
| Amylase content ratio (3.0)      | 75.0        | 86.0        | 23.1  | 98.4  |
| Amylase content ratio (3.8)      | 75.0        | 90.9        | 31.6  | 98.5  |

*PPV positive predictive value; NPV negative predictive value; AVD total amylase value in drains; POD postoperative day*
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