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ORIGINAL ARTICLE

Amylase concentration in drainage fluid as a predictive factor for severe postoperative pancreatic fistula in patients with gastric cancer

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Abstract
Purpose Postoperative pancreatic fistula (PPF) sometimes occurs after gastrectomy. We examined the risk factors for severe PPF and evaluated the predictive value of amylase concentration in drainage fluid.
Methods We retrospectively reviewed 591 patients who underwent curative gastrectomy for gastric cancer. A multivariate analysis was conducted to identify the risk factors for severe PPF. Receiver operating characteristic curves were used to identify the appropriate amylase cut-off value to predict severe PPF.
Results Severe PPF occurred in 23 (3.9%) cases. The multivariate analysis indicated that splenectomy ($P=0.009$) was the only significant risk factor. The area under the curve of amylase in drainage fluid for predicting severe PPF on postoperative day (POD) 3 was much greater than that on POD 1 (0.972 vs. 0.894). When the cut-off values for amylase were determined to be 2900 U/L on POD 1 and 2100 U/L on POD 3, the risk ratio for severe PPF on POD 3 was higher than that on POD 1 (99.2 vs. 30.2).
Conclusions Splenectomy was an independent risk factor for severe PPF. An amylase level of 2100 U/L on POD 3 may be a reliable cut-off value for the early diagnosis of patients at high risk of severe PPF.

Keywords Pancreatic fistula · Gastric cancer · Amylase concentration

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Introduction

Gastric cancer has increased in prevalence and is now the fifth-most common cancer worldwide as well as the third leading cause of cancer-related deaths [1]. Gastrectomy with radical D2 lymph node dissection has been considered the standard treatment for resectable gastric cancer and is performed in many countries [2, 3]. However, postoperative pancreatic fistula (PPF) is still a major complication after gastrectomy, even in high-volume hospitals, because D2 gastrectomy requires extended lymph node dissection around the pancreas. In a Japanese, randomized controlled trial (JCOG9501) comparing D2 and D2 plus para-aortic node dissection for resectable gastric cancer, PPF was the most frequent complication [4, 5]. Once PPF develops, it may lead to other major complications, such as bleeding, anastomotic leakage, and intra-abdominal abscess, all of which usually require prolongation of hospitalization [6, 7]. Although several previous studies identified risk factors for PPF after open gastrectomy, few have determined the PPF risk factors following laparoscopic gastrectomy. As laparoscopic gastrectomy has recently become widespread worldwide, it is important to evaluate the risk factors for PPF after both gastrectomy approaches.

The insertion of drainage tubes during surgery may be useful for both the prediction and management of PPF, but these drains should be removed as soon as possible to prevent retrograde infection and other complications. A few retrospective studies have shown that the amylase concentration in drainage fluid on postoperative day (POD) 1 was a significant predictive factor of PPF and that it was useful in the early detection of PPF [8, 9]. However, even if the amylase concentration is elevated on POD 1 it can decrease rapidly thereafter; therefore, whether or not POD 1 is the best time point at which to evaluate amylase in drainage

fluid is controversial. Indeed, the amylase concentration on POD 3 is used in the PPF definition of the International Study Group on Pancreatic Fistula (ISGPF) [10].

We, therefore, investigated the risk factors for severe PPF and the predictive value of amylase concentrations on POD 1 and POD 3 in a population of patients who underwent gastrectomy.

Methods

We retrospectively collected data on 591 consecutive patients who underwent curative gastrectomy for histologically confirmed gastric cancer at Osaka University Hospital between January 2009 and December 2014. Patients underwent preoperative assessments, including gastric endoscopy, computed tomography (CT) scans, and laboratory tests. We used the 14th edition of the Japanese Classification of Gastric Carcinoma to establish pT and pN stages [11]. During gastrectomy, we inserted a drainage tube above the pancreas or behind the anastomosis. The amylase concentration in the drainage fluid was measured on POD 1 and POD 3. PPF was defined according to the ISGPF definition: output via an operatively placed drain of any measurable volume of drainage fluid on or after POD 3, with an amylase concentration more than three times higher than the upper normal serum value, and classified into Grade I (no need for pharmacological, surgical, endoscopic, or radiological interventions), Grade II (treated with antibiotics, protease inhibitor, somatostatin analogue, total parenteral nutrition), Grade III (treated with percutaneous catheter drainage or reoperation for PPF), or Grade IV (life-threatening complication requiring intensive-care management) based on the Clavien–Dindo classification [12, 13]. In this study, severe PPF was defined as PPF of Grade II–IV requiring hospitalization for more than 30 days after surgery. This study was approved by the institutional review board of Osaka University Hospital.

We evaluated the association between the clinicopathological factors and the occurrence of severe PPF using the chi-squared test for categorical variables and the Mann–Whitney *U* test for continuous variables. A multivariate logistic regression model was used to adjust for confounding factors. Variables achieving $P<0.10$ in the univariate analysis were included in the multivariate analysis. The receiver operating characteristic (ROC) curves of amylase concentrations on POD 1 and POD 3 were used to identify the appropriate cut-off value to predict severe PPF. The cumulative rate of hospital discharge was estimated using the Kaplan–Meier method. $P<0.05$ was considered significant. All statistical analyses were performed with the SPSS statistics software package, version 22 (IBM Corp., Armonk, NY, USA).

Table 1 Patients' characteristics

	Patients ($n=591$)
Age (years)	
Median (range)	67 (29–98)
Sex	
Male	414 (70.1%)
Female	177 (29.9%)
Body mass index (kg/m^2)	
Median (range)	22.0 (13.9–37.1)
Surgical approach	
Open	193 (32.7%)
Laparoscopy	398 (67.3%)
Type of gastrectomy	
Total	166 (28.1%)
Distal or proximal	425 (71.9%)
Lymph node dissection	
<D2	375 (63.5%)
≥D2	216 (36.5%)
Splenectomy	
Yes	35 (5.9%)
No	556 (94.1%)
Operation time (min)	
Median (range)	228 (90–750)
pT	
pT1	327 (55.3%)
pT2	71 (12.0%)
pT3–4	193 (32.7%)
pN	
pN0	405 (68.5%)
pN1	74 (12.5%)
pN2–3	112 (19.0%)

Results

The background characteristics of all eligible patients are shown in Table 1. Of the 591 patients, 398 (67.3%) underwent laparoscopic gastrectomy. Although total gastrectomy was performed in 166 (28.1%) of 591 patients, the proportion of patients who underwent splenectomy was only 5.9%. Approximately, half of the patients had pT1 tumors.

Of the 591 eligible patients, 151 (25.5%) experienced any grade of PPF (Grade I in 115, Grade II in 26, and Grade III in 10), and 23 (63.9%) of 36 patients with ≥Grade II PPF were classified as having severe PPF that required hospitalization for more than 30 days after surgery. In the univariate analysis between the clinicopathological factors and the occurrence of severe PPF, total gastrectomy ($P=0.032$), splenectomy ($P<0.001$), and operation time ($P=0.005$) were significant risk factors for severe PPF (Table 2). When we investigated the risk factors for severe PPF according to the surgical approach, male gender ($P=0.037$), body mass

Table 2 Associations between clinicopathological factors and severe postoperative pancreatic fistula

	Without severe PPF ($n=568$)	With severe PPF ($n=23$)	*P* value
Age (years)			
Median (range)	67 (29–98)	67 (47–87)	0.485
Sex			
Male	394 (69.4%)	20 (87.0%)	0.071
Female	174 (30.6%)	3 (13.0%)	
Body mass index (kg/m^2)			
Median (range)	22.0 (13.9–37.1)	22.2 (18.1–28.0)	0.229
Surgical approach			
Open	185 (32.6%)	8 (34.8%)	0.824
Laparoscopy	383 (67.4%)	15 (65.2%)	
Type of gastrectomy			
Total	155 (27.3%)	11 (47.8%)	0.032
Distal or proximal	413 (72.7%)	12 (52.2%)	
Lymph node dissection			
<D2	360 (63.4%)	15 (65.2%)	0.858
≥D2	208 (36.6%)	8 (34.8%)	
Splenectomy			
Yes	29 (5.1%)	6 (26.1%)	<0.001
No	539 (94.9%)	17 (73.9%)	
Operation time (min)			
Median (range)	227 (90–750)	260 (196–635)	0.005
pT			
pT1	318 (56.0%)	9 (39.1%)	0.190
pT2	66 (11.6%)	5 (21.7%)	
pT3–4	184 (32.4%)	9 (39.1%)	
pN			
pN0	392 (69.0%)	13 (56.5%)	0.337
pN1	71 (12.5%)	3 (13.0%)	
pN2–3	105 (18.5%)	7 (30.4%)	

PPF postoperative pancreatic fistula

Table 3 A multivariate logistic analysis of the risk factors for severe postoperative pancreatic fistula

Variables	Odds ratio (95% CI)	*P* value
Male	2.83 (0.82–9.80)	0.100
Total gastrectomy	1.40 (0.53–3.66)	0.497
Splenectomy	4.58 (1.47–14.30)	0.009
Operation time ≥228 min	2.20 (0.83–5.84)	0.115

CI confidence interval

index ($P=0.046$), splenectomy ($P=0.003$), and operation time ($P=0.014$) showed statistical significance in the laparoscopic gastrectomy group, while only splenectomy ($P=0.002$) was a significant factor in the open gastrectomy group. In the multivariate logistic analysis using the four covariables with $P<0.10$ in the univariate analysis, splenectomy ($P=0.009$) was the only significant risk factor for severe PPF (Table 3).

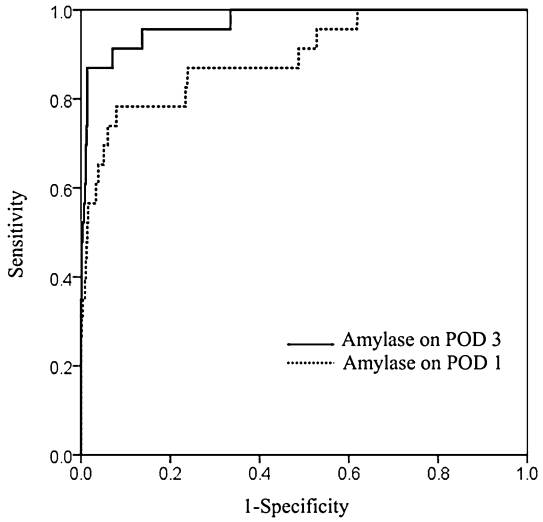

Fig. 1 Receiver operating characteristic curves of amylase concentrations in drainage fluid on POD 1 and POD 3 for predicting severe postoperative pancreatic fistula

Table 4 Associations between the amylase concentration in drainage fluid and severe postoperative pancreatic fistula

	Without severe PPF ($n=568$)	With severe PPF ($n=23$)
Amylase in drainage fluid on POD 1		
<2900 U/L	523 (92.1%)	5 (21.7%)
≥2900 U/L	45 (7.9%)	18 (78.3%)
Amylase in drainage fluid on POD 3		
<2100 U/L	560 (98.6%)	4 (17.4%)
≥2100 U/L	8 (1.4%)	19 (82.6%)

PPF postoperative pancreatic fistula, *POD* postoperative day

The median amylase concentrations in cases with severe PPF were 11,449 U/L (range 474–290,340 U/L) on POD 1 and 3642 U/L (range 318–196,100 U/L) on POD 3. ROC curves based on amylase concentrations in drainage fluid on POD 1 and POD 3 were used to compare the predictive value of severe PPF (Fig. 1). The area under the curve (AUC) on POD 3 (0.972) was much greater than that on POD 1 (0.894) or those of white blood cell count (0.774) or serum C-reactive protein levels (0.883) on POD 3. Based on an ROC curve analysis, the cut-off value for the amylase concentration on POD 1 was determined to be 2900 U/L, yielding a sensitivity and specificity of 0.78 and 0.92, respectively (Table 4). In contrast, the cut-off value on POD 3 was determined to be 2100 U/L, resulting in increased sensitivity and specificity values of 0.83 and

0.99, respectively (Table 4). The risk ratio for severe PPF on POD 3 was also higher than that on POD 1 (99.2 vs. 30.2).

Regarding the cumulative rate of hospital discharge, the median durations of postoperative hospitalization were 17 days in the POD 1 non-high amylase (<2900 U/L) group and 26 days in the POD 1 high amylase (≥2900 U/L) group (Fig. 2a), compared to 17 days in the POD 3 non-high amylase (<2100 U/L) group and 43 days in the POD 3 high amylase (≥2100 U/L) group (Fig. 2b). The difference between the median durations of postoperative hospitalization in the non-high and high amylase groups was much greater on POD 3 than on POD 1 (26 vs. 9 days).

Discussion

In the present study, a multivariate analysis showed that splenectomy was the only independent risk factor for severe PPF in a patient population in which the majority of individuals underwent laparoscopic gastrectomy. Although the amylase concentration in drainage fluid increased on POD 1 and POD 3 in patients with severe PPF, the amylase concentration on POD 3 showed higher sensitivity and specificity for predicting severe PPF than that on POD 1. Furthermore, the amylase concentration in the drainage fluid on POD 3 reflected the duration of postoperative hospitalization more accurately than that on POD 1.

PPF is known to be a major complication after open gastrectomy in patients with gastric cancer, with a reported frequency ranging from 4.7 to 22.1% [4, 8, 14–16]. However, some cases of PPF are cured rapidly, making it important to evaluate only severe PPF that leads to a prolonged hospital stay. Indeed, 23 (64%) of 36 patients with Grade II–IV PPF in our study required hospitalization for more than 30 days after surgery. Although several previous studies have revealed that male gender, old age, high body mass index, total gastrectomy, and combined resection of the pancreas or spleen were risk factors for PPF after open gastrectomy [15–19], they did not consider the prolongation of hospital stay. Furthermore, little is known about the risk factors for this complication after laparoscopic gastrectomy [20, 21]. In our study, over two-thirds of patients underwent laparoscopic gastrectomy, and splenectomy was found to be the only independent risk factor for severe PPF that led to the prolongation of hospital stay. Our study indicates that even in laparoscopic gastrectomy, dissection of the lymph nodes along the splenic hilum is still a surgical challenge for ensuring local control without injuring the pancreas.

It is important to achieve an early and accurate diagnosis of severe PPF. In patients at high risk, this will accelerate the provision of intensive care to prevent deterioration of the PPF, while in non-high-risk patients, it will allow for relief from troublesome consequences, such as retrograde infection. Miki et al. reported that an amylase concentration of ≥3398 U/L in the drainage fluid on POD 1 was useful for predicting PPF [8]. Iwata et al. reported that an amylase concentration of ≥1000 U/L in the drainage fluid on POD 1 was a significant predictor of pancreas-related complications [9]. However, Molinari et al. reported that the amylase concentration in the drainage fluid tended to decrease from POD 1 to POD 4, both in patients with and without PPF [22]. In our study, 24 (44%) of the 54 patients with an amylase concentration of ≥3398 U/L in the drainage fluid on POD 1 showed a rapid decrease in the concentration to <1000 U/L on POD 3. We believe the main reason for this

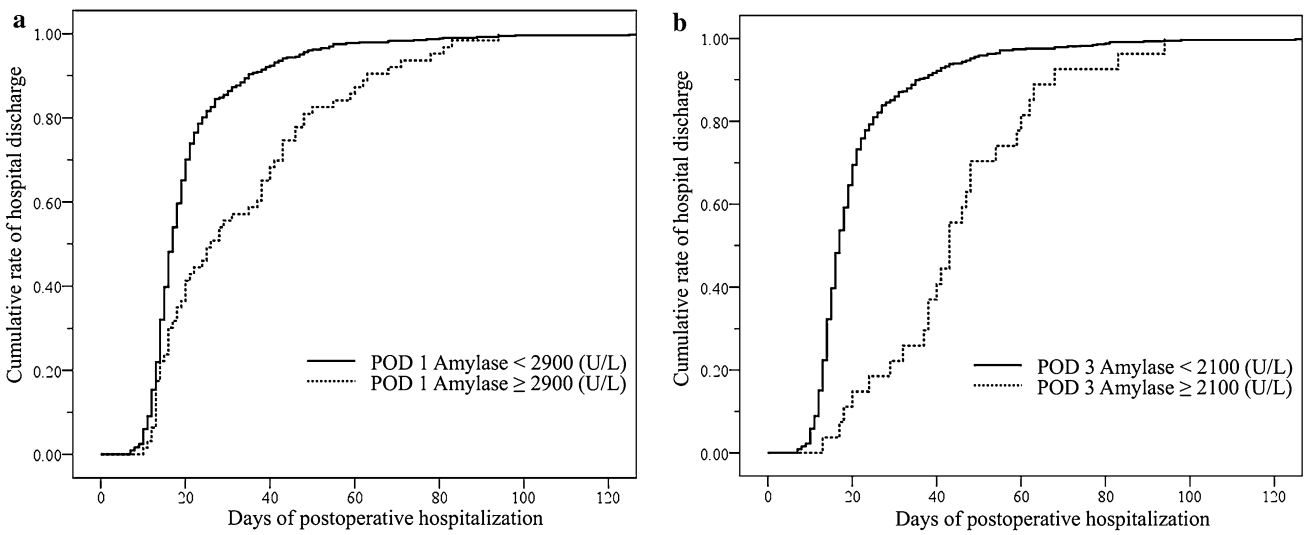

Fig. 2 The cumulative rate of hospital discharge between the non-high and high amylase concentration groups on POD 1 (**a**) and POD 3 (**b**)

event is that the amount of pancreatic juice secreted into the duodenum increases gradually with recovery of the bowel movement. Our findings suggest that drainage tubes can be removed in cases where the amylase concentration is <2100 U/L on POD 3 after confirming that the drainage tube is placed in an appropriate position. However, careful and intensive management of PPF is needed if the amylase concentration in the drainage fluid is >2100 U/L on POD 3.

Several limitations associated with the present study warrant mention. First, it used a retrospective design, and the number of patients with severe PPF was small. Prospective large-scale studies are therefore warranted to validate our findings. Second, there is still no standard definition of severe PPF. Although several studies in the field of pancreatic surgery have used a definition of Grade C PPF based on the ISGPF classification [23–26], the number of patients with disease of this severity in the field of gastric surgery is usually extremely small. Indeed, our study had only one patient (0.2%) with Grade C PPF, while approximately 30% of the Grade A/B PPF patients required hospitalization for more than 30 days after surgery (data not shown). We, therefore, defined severe PPF as that requiring hospitalization for more than 30 days after surgery, as several previous studies have treated complications that occurred within 30 days after surgery as short-term conditions [27, 28].

In conclusion, splenectomy was an independent risk factor for severe PPF. Our study also showed that the amylase concentration in the drainage fluid on POD 3 was more useful than that on POD 1 in terms of predicting severe PPF. An amylase level of 2100 U/L on POD 3 may be a reliable threshold for determining whether clinicians should remove drainage tubes or pursue careful and intensive management of PPF.

Compliance with ethical standards

Conflict of interest There are no conflicts of interest to declare regarding this manuscript.

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