

Original Article



Optimal Timing to Assess Drain Amylase Concentration after Elective Gastrectomy

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

ABSTRACT

Purpose: While the amylase concentration of the drainage fluid (dAmy) has been reported to be a predictor of postoperative pancreas-related complications (PPRC), the optimal timing for its measurement has not been fully investigated.

Materials and Methods: The clinicopathological data of 387 patients who underwent elective gastrectomy for gastric cancer were reviewed. Laboratory data, including dAmy on postoperative days 1 (dAmy1) and 3 (dAmy3), and serum C-reactive protein (sCRP) concentrations on postoperative days 1 (sCRP1) and 3 (sCRP3) were compared between patients with PPRC and without PPRC.

Results: Nineteen of the 387 patients (4.9%) developed PPRC. The optimal cutoff values of dAmy1, dAmy3, sCRP1, and sCRP3 were 1514 IU/L, 761 IU/L, 8.32 mg/dL, and 15.15 mg/dL, respectively. The area under the curve of dAmy1 was greater than that of dAmy3 (0.915 vs. 0.826), and that of sCRP3 was greater than that of sCRP1 (0.820 vs. 0.659). In the multivariate analysis, dAmy1 ($P < 0.001$) and sCRP3 ($P = 0.004$) were significant predictors of PPRC, while dAmy3 ($P = 0.069$) and sCRP1 ($P = 0.831$) were not. Thirteen (41.9%) of 31 patients with both dAmy1 $\geq 1,545$ IU/L and sCRP3 ≥ 15.15 mg/dL had PPRC \geq Clavien-Dindo II. In contrast, among 260 patients with both dAmy1 $< 1,545$ IU/L and sCRP3 < 15.15 mg/dL, none developed PPRC.

Conclusions: dAmy1 was more useful than dAmy3 in predicting PPRC. The combination of dAmy1 and sCRP3 may be a useful criterion for the removal of drains on postoperative day 3.

Keywords: Gastrectomy; Pancreatic fistula; Amylases; C-reactive protein; Predictor

INTRODUCTION

Radical gastrectomy with D2 lymph node dissection remains the mainstay of treatment for gastric cancer [1,2]. However, lymph node dissection around the pancreas can cause minute trauma or burn the surface of the pancreas, leading to postoperative pancreas-related complications (PPRC). Since pancreatic fistula may cause critical conditions, including sepsis or intra-abdominal bleeding, it is important to identify patients who are at a high risk of developing clinically significant PPRC early in the postoperative period.

The International Study Group on Pancreatic Surgery (ISGPS) defined pancreatic fistula as an abnormal communication between the pancreatic ductal system and another epithelial

surface containing pancreas-derived enzyme-rich fluid, which presents as drain fluid with amylase activity increased to >3 times the upper limit of institutional normal serum amylase on or after postoperative day 3. When this condition leads to clinical relevance, it is referred to as a pancreatic fistula [3]. This definition is based on the experience of pancreatic resection, in which drains are usually placed near the cut end of the pancreas. In gastric cancer surgery, however, drain tubes are not always placed at the site of pancreatic injury because it is not always easy to know where the pancreas is injured by heat or trauma.

Although the amylase concentration of the drainage fluid (dAmy) [4-7] and serum C-reactive protein level (sCRP) [8-10] have been reported to predict PPRC, the optimal timing to assess these parameters has not been fully investigated.

This study aimed to assess the diagnostic value of dAmy and sCRP and to determine the optimal day on which to measure these parameters to detect clinically relevant PPRC, including pancreatic fistula and intraabdominal abscess, requiring medical, radiological, or surgical intervention. by reviewing the clinicopathological data of patients who underwent elective gastrectomy for gastric cancer.

MATERIALS AND METHODS

A total of 404 consecutive patients underwent elective surgery for primary gastric cancer at Yodogawa Christian Hospital between January 2012 and December 2018. Among them, 17 patients were excluded from the analysis, including 5 who underwent pancreatoduodenectomy due to duodenal invasion, comorbid pancreatic cancer, or cholangial cancer, 10 who underwent gastrectomy for remnant stomach cancer, and 2 who underwent palliative partial gastrectomy. The remaining 387 patients were included in this study. The clinicopathological data of these patients were retrospectively obtained by reviewing their medical records and operative reports.

The stages of gastric cancers were recorded according to the Japanese Classification of Gastric Carcinoma, 3rd English edition [11]. The surgical procedure and the extent of lymph node dissection were defined according to the 2014 Japanese gastric cancer treatment guidelines (ver. 4) [12]. In this study, cases of total gastrectomy, D2 lymph node dissection without splenectomy or dissection of the 10 lymph nodes were classified as D2.

This study defined PPRC as a postoperative complication of \geq grade II according to the Clavien-Dindo (CD) classification system [13] in patients with increased dAmy on postoperative day 1 (dAmy1) or day 3 (dAmy3) to >3 times the upper limit of normal serum amylase level (>125 IU/L $\times 3$) whose drain fluid became purulent or clinical imaging showed intraabdominal abscess, peripancreatic fluid, or intraabdominal bleeding. We compared laboratory data, including sCRP and dAmy, between patients with and without PPRC to identify factors predictive of complications.

The protocol was approved by the Institutional Ethical Committee on human experimentation (No. 2019-051) and was in accordance with the principles of the Declaration of Helsinki of 1964 and later versions. Informed consent or its substitute was obtained from all patients before their inclusion in the study.

Statistics

Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cutoff values, which were identified based on the Youden index or maximum (sensitivity + specificity - 1) [14]. ROC curves were also used to calculate the area under the curve (AUC). Differences in the proportions or frequencies between the two groups were compared using Fisher's exact or χ^2 tests. Variables with $P < 0.10$ in the univariate analysis were included in the multivariate logistic regression analysis to identify factors predictive of PPRC. All statistical analyses were performed using JMP software 12.2.0 (SAS Institute Inc., Cary, NC, USA).

RESULTS

The patient characteristics are listed in **Table 1**. Among these 387 patients, 254 (65.6%) and 102 (26.4%) had high dAmy1 and dAmy3 (>375 IU/L), respectively. Nineteen patients had PPRC according to our definition.

The ROC curves of dAmy1, dAmy3, sCRP1, and sCRP3 were drawn to compare their predictive values for PPRC and calculate the appropriate cutoff values for each parameter (**Fig. 1**). The AUCs of dAmy1, dAmy3, sCRP1, and sCRP3 were 0.915, 0.826, 0.659, and 0.820,

Table 1. Patient characteristics (n=387)

Variables	Values
Age (yr)	70 (25–92)
Sex	
Male	255 (65.9%)
Female	132 (34.1%)
BMI (kg/m ²)*	22.5 (15.6–35.2)
Comorbidity	
(+)	288 (74.4%)
(-)	99 (25.6%)
Laboratory data	
eGFR (mL/min/1.73 m ²)	68.9±18.5
Albumin (g/dL) [†]	3.9±0.6
Lymphocytes (cells/ μ L)	1,661±632
Type of gastrectomy	
DG	266 (68.7%)
PG	8 (2.1%)
PPG	13 (3.4%)
TG	100 (25.8%)
Splenectomy	
(+)	25 (6.5%)
(-)	362 (93.5%)
Lymph node dissection	
D0	9 (2.3%)
D1	16 (4.1%)
D1+	153 (39.5%)
D2	205 (53.0%)
D2+	4 (1.0%)
Approach	
Open	252 (65.1%)
Laparoscopy	135 (34.9%)
Blood loss (mL)	104 (0–2,899)

Values are presented as median (range), mean±standard deviation, number of patients (%).

BMI = body mass index; eGFR = estimated glomerular filtration rate; DG = distal gastrectomy; PPG = pylorus-preserving gastrectomy; PG = proximal gastrectomy; TG = total gastrectomy.

*BMI data are missing for 1 patient; [†]Serum albumin level data are missing for 1 patient.

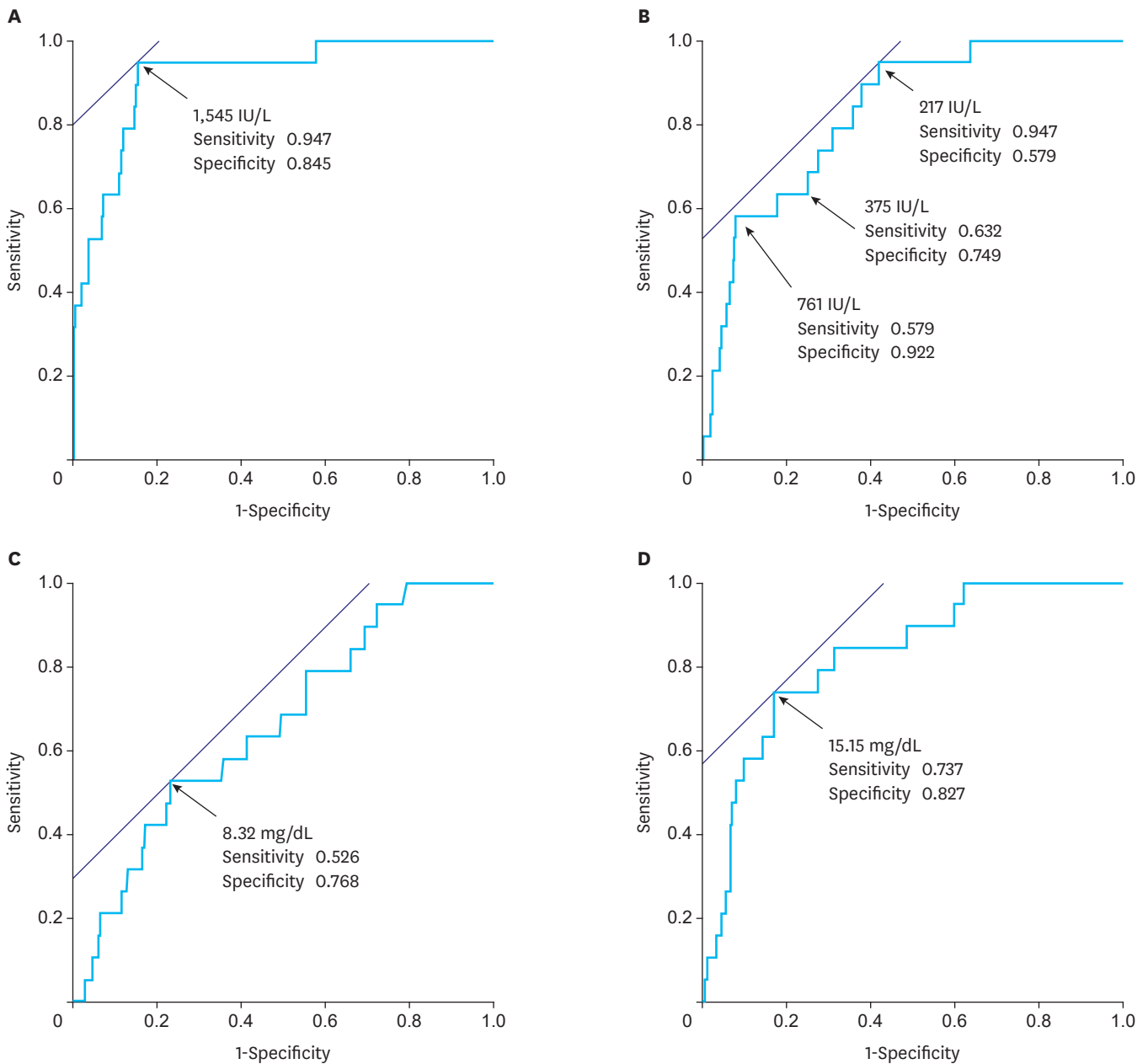


Fig. 1. Receiver operating characteristic curves of the amylase (A, B) and serum C-reactive protein (C, D) concentrations in the drainage fluid on postoperative days 1 and day 3, respectively, for predicting postoperative pancreas-related complications. The arrow indicates the optimal cutoff point. The optimal cutoff values and areas under the curve are (A) 1,514 and 0.915 IU/L, (B) 761 and 0.826 IU/L, (C) 8.32 and 0.659 mg/dL, and (D) 15.15 and 0.820 mg/dL, respectively.

respectively. The AUC of dAmy1 was greater than that of dAmy3, while that of sCRP3 was greater than that of sCRP1. The optimal cutoff values of dAmy1, dAmy3, sCRP1, and sCRP3 for PPRC identified according to the Youden indexes were 1545 IU/L, 217 IU/L, 8.32 mg/dL, and 15.15 mg/dL, respectively. However, 217 IU/L as a cutoff value for dAmy3 was lower than 375 IU/L, which was three times the upper limit of normal serum amylase level in our institution; thus, we calculated based on a cutoff value of 375 IU/L or larger with maximum (sensitivity + specificity - 1) within the range to establish 761 IU/L as a more appropriate dAmy3 cutoff (**Fig. 1B**).

Drain Amylase Level after Gastrectomy

Table 2. Univariate and multivariate analysis of the relationships between dAmy and sCRP, and postoperative pancreas-related complications

Variables	Pancreas-related complications		P-value	Multivariate analysis		
	(+) (n=19)	(-) (n=368)		OR	95% CI	P-value
dAmy1 (IU/L) [†]			<0.001*			< 0.001*
≥1,545	18 (94.7%)	56 (15.5%)		43.865	7.796–826.887	
<1,545	1 (5.3%)	305 (84.5%)		1		
dAmy3 (IU/L) [‡]			<0.001*			0.069
≥761	11 (57.9%)	28 (7.8%)		2.929	0.920–9.666	
<761	8 (42.1%)	331 (92.2%)		1		
sCRP1 (mg/dL) [§]			0.004*			0.831
≥8.32	10 (52.6%)	85 (23.2%)		0.872	0.234–3.018	
<8.32	9 (47.4%)	281 (76.8%)		1		
sCRP3 (mg/dL)			<0.001*			0.004*
≥15.15	14 (73.7%)	63 (17.3%)		6.225	1.775–24.986	
<15.15	5 (26.3%)	302 (82.7%)		1		

dAmy1 = amylase level in drain fluid on postoperative day 1; dAmy3 = amylase level in drain fluid on postoperative day 3; sCRP1 = serum C-reactive protein level on postoperative day 1; sCRP3 = serum C-reactive protein level on postoperative day 3.

*Statistically significant; [†]dAmy1 data are missing for 7 patients in the no complication group; [‡]dAmy3 data are missing for 9 patients in the no complication group; [§]sCRP1 data are missing for 2 patients in the no complication group; ^{||}sCRP3 data are missing for 3 patients in the no complication group.

Using these cutoff values, the relationships between these variables and PPRC were investigated. In the univariate analysis, all 4 variables, dAmy1 ($P < 0.001$), dAmy3 ($P < 0.001$), sCRP1 ($P = 0.004$), and sCRP3 ($P < 0.001$) were correlated with PPRC (**Table 2**). Among the 19 patients with PPRC according to our definition, 8 had dAmy3 < 761 IU/L (**Table 2**). Of these 8 patients, 7 had dAmy3 < 375 IU/L (3 times the upper limit of the normal serum amylase level). In all 8 patients, the dAmy1 was $\geq 1,545$ IU/L. Of the 19 patients with PPRC, 11 had dAmy3 ≥ 761 IU/L (**Table 2**). Only one of these 11 patients had dAmy1 $< 1,545$ IU/L; however, the sCRP3 in this case was ≥ 15.15 mg/dL. The correlation between dAmy1 and dAmy3 was not strong (**Fig. 2**). In the multivariate analysis, dAmy1 ($P < 0.001$) and sCRP3 ($P = 0.004$) were significant predictors of PPRC, while dAmy3 ($P = 0.069$) and sCRP1 ($P = 0.831$) were not (**Table 2**).

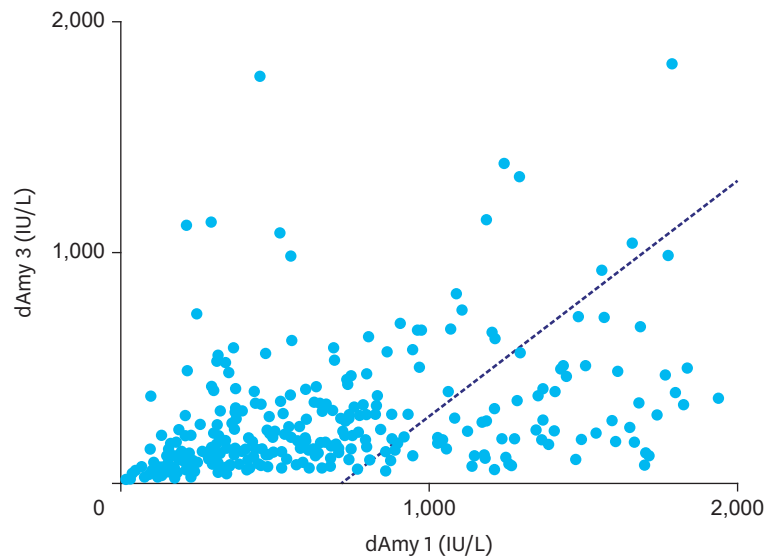


Fig. 2. Correlations between dAmy1 and dAmy3. The correlation coefficient was 0.786. $dAmy3 = -731.059 + 1.017 dAmy1$.

dAmy1 = amylase concentration of the drainage fluid on postoperative day 1; dAmy3 = amylase concentration of the drainage fluid on postoperative day 3.

Table 3. Correlation between the combination of dAmy1 and sCRP3 and pancreas-related complications

dAmy1 (IU/L)	sCRP3 (mg/dL)			
	<15.15		≥15.15	
≥1,545	n=43		n=31	
	CD ≥II	5 (11.6%)	CD ≥II	13 (41.9%)
	CD ≥III	2 (4.7%)	CD ≥III	10 (32.3%)
<1,545	n=260		n=45	
	CD ≥II	0 (0.0%)	CD ≥II	1 (2.2%)
	CD ≥III	0 (0.0%)	CD ≥III	0 (0.0%)

CD = Clavien-Dindo classification; dAmy1 = amylase level in drain fluid on postoperative day 1; sCRP3 = serum C-reactive protein level on postoperative day 3.

When dAmy1 alone was used as a predictor for PPRC, 18 (24.3%) of 74 patients with dAmy1 ≥1,545 IU/L had a PPRC of CD ≥II and 12 (16.2%) required more aggressive treatment including image-guided reposition of operatively placed drains or angiography for pseudoaneurysms (**Tables 2 and 3**). When sCRP3 alone was used, 14 (18.2%) of 77 patients with sCRP3 ≥15.15 mg/dL had PPRC of CD ≥II and 10 (13.0%) had CD ≥III (**Tables 2 and 3**).

The combination of these two parameters increased the accuracy of predicting PPRC (**Table 3**). Among 31 patients with both dAmy1 and sCRP3 above the cutoff values, 13 (41.9%) had CD ≥II and 10 (32.3%) had CD ≥III. In contrast, among 260 patients with both parameters below the cutoff values, none developed PPRC (**Table 3**).

DISCUSSION

According to the ISGPS, the diagnosis of pancreatic fistula requires any measurable volume of drain fluid on or after postoperative day 3 with an amylase level >3 times the upper limit of normal amylase at a specific institution. When this condition leads to clinical relevance, it is referred to as a pancreatic fistula [3]. However, some authors [5,10,15] reported generally lower dAmy3 than dAmy1, even in patients with pancreatic fistula.

In 7 of 19 patients with PPRC in the present study, dAmy3 was <375 IU/L on postoperative day 3, but higher than that on day 1 (range: 1,545–28,650 IU/L). Their drain fluid became purulent or the clinical images demonstrated intra-abdominal abscess, peripancreatic fluid, or intra-abdominal bleeding requiring treatment including repositioning of the operatively placed drain, image-guided drainage, or administration of antibiotics.

Two possibilities should be considered in patients with dAmy3 values not high enough to fulfill the ISGPS criteria while dAmy1 was high. One is a pancreatic fistula itself in remission and the other is the insufficient drainage of peripancreatic fluid. Inappropriate localization of operatively-placed drain tubes or fibrin formation around the drain tubes may cause insufficient drainage, resulting in low dAmy3. In contrast, dAmy1 may reflect the concentration of amylase in the fluid collected from a wide area around the surgical site because there is less adhesion in the peritoneal cavity; thus, dAmy1 may be more reliable in predicting PPRC in cases of gastric cancer surgery where the location of the pancreatic injury is not always recognizable. In one patient with a dAmy3 of 367 IU/L, the drain fluid became purulent. Computed tomography revealed peripancreatic fluid. After repositioning the draining tube, the dAmy on postoperative day 14 was 626 IU/L. In this case, the dAmy1 was 1,941 IU/L. In another patient with a dAmy3 of 484 IU/L, the amylase concentration in the fluid acquired from the left subphrenic region using computed tomography-guided drainage

was 15,740 IU/L. In this case, the dAmy1 was 1,615 IU/L. The reasons for the low dAmy3 included the formation of fibrin around the draining tubes or adhesion to surrounding organs, forcing drainage away from the site of pancreatic injury. Therefore, dAmy1 is more useful than dAmy3 in detecting PPRC. Other authors reporting on PPRC after gastric cancer surgery indicated that dAmy1 is a useful predictor of PPRC [5-7,9]. Therefore, the definition provided by ISGPS may not be appropriate for gastric cancer surgery.

sCRP3 was also strongly correlated with PPRC ($P=0.004$). Even in patients with insufficient drainage in whom dAmy did not increase, increased sCRP reflected a local inflammatory reaction caused by intra-abdominal fluid, including pancreatic juice. Thus, sCRP3 is helpful to identify “occult” PPRC, as we previously reported [16].

The results of this study demonstrated that the combination of dAmy1 and sCRP3 better predicted PPRC than either alone. Thirteen (41.9%) of 31 patients with both dAmy1 $\geq 1,545$ IU/L and sCRP3 ≥ 15.15 mg/dL had PPRC \geq CD II. In contrast, among 260 patients with both dAmy1 $< 1,545$ IU/L and sCRP3 < 15.15 mg/dL, none developed PPRC. Thus, in these patients, drainage tubes can be safely removed on postoperative day 3. Although a high dAmy3 is necessary to diagnose a pancreatic fistula according to the ISGPS definition, dAmy1 is more important in identifying patients who may develop PPRC during gastric cancer surgery. In addition, the combination of dAmy1 and sCRP3 may be a useful criterion for the removal of surgically placed drains on postoperative day 3.

This study has several limitations. First, this was a retrospective study, and 7 (1.9%), 9 (2.4%), 2 (0.5%), and 3 patients (0.8%) without PPRC had missing dAmy1, dAmy3, sCRP1, and sCRP3 values, respectively. Missing dAmy or sCRP values higher than the respective cutoff values, might have affected the conclusions of this study. Second, the sample size was small and only 19 patients (4.9%) developed PPRC with CD \geq II. Thus, the study may lack statistical power.

In conclusion, dAmy1 was more useful than dAmy3 in detecting patients who developed PPRC. Moreover, the combination of dAmy1 and sCRP3 may be a useful criterion for the removal of surgically placed drains on postoperative day 3.

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