

**ORIGINAL****Serum C-reactive protein level on first postoperative day can predict occurrence of postoperative pancreatic fistula after laparoscopic gastrectomy**

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**Abstract : Purpose :** Postoperative pancreatic fistula (POPF) is a serious complication after gastrectomy for gastric cancer. The purpose of this study is to identify the risk factor of POPF and evaluate C-reactive protein on postoperative day 1 (POD1) as the predictor for POPF after laparoscopic gastrectomy (LG). **Methods :** Between May 2013 and September 2016, 226 patients who underwent LG for gastric cancer were investigated. Patients were divided into 2 groups; POPF group (n = 17) and control group (n = 209). Clinicopathological factors were compared between 2 groups. **Results :** In POPF group, there are more male patients (p = 0.003) compared with control group. Preoperative factors, such as age, BMI, and prevalence of previous operation and comorbidity showed no significant difference between 2 groups. Regarding tumor factors and perioperative data such as blood loss and operative time, there were also no significant difference between 2 groups. POPF group showed longer postoperative hospital stay, and higher serum CRP level on POD1 (p < 0.0001). Multivariate analysis revealed that high CRP level on POD1 ( $\geq 3\text{mg/dl}$ ) was independent risk factor of POPF. **Conclusions :** High serum CRP level on POD1 can predict the occurrence of POPF. *J. Med. Invest.* 66:285-288, August, 2019

**Keywords :** laparoscopic gastrectomy, postoperative pancreatic fistula, C-reactive protein

**INTRODUCTION**

Laparoscopic gastrectomy (LG) has been reported to be related with reduced intraoperative bleeding, less postoperative pain, and earlier recovery of bowel movements compared with open gastrectomy (1-3). As Japanese gastric cancer treatment guidelines recommend laparoscopic assisted distal gastrectomy (LADG) as well as open distal gastrectomy for the treatment of clinical stage I gastric cancer (4), LG is now widely used, and number of patients who undergo LG may continue to increase, especially in Japan.

Gastrectomy has been performed with lower mortality and morbidity rate recently because of advances in surgical techniques, devices, and perioperative management (5-7). However, intraperitoneal bleeding and abdominal abscess caused by postoperative pancreatic fistula (POPF) is the most serious postoperative complications. Though POPF is usually treated after an abscess has formed, accurate prediction of severe POPF in the early postoperative period would provide a chance to treat appropriately. If POPF could be predicted in early postoperative period, abscess formation might be preventable due to early therapeutic interventions such as administration of appropriate antibiotics and drainage of excess fluid (8). Recent studies have indicated that perioperative systemic inflammatory responses can predict postoperative complications in various types of cancer (9-11). It has been reported that C-reactive protein (CRP) on

postoperative day (POD) 1 might be able to predict the occurrence of POPF after pancreatectomy (12). However, it is unclear that early postoperative inflammatory response, such as CRP on POD1 can predict the occurrence of POPF after LG. We hypothesized that the early inflammatory response might be related to the development of PF after LG. In this study we retrospectively investigated perioperative clinical variables, including CRP on POD1 as predictors of postoperative PF.

**PATIENTS AND METHODS**

Between May 2013 to September 2016, 226 patients underwent laparoscopic gastrectomy for gastric cancer in Ehime Prefectural Central Hospital. Patients underwent preoperative assessments, including gastric endoscopy, computed tomography (CT) scans, and laboratory tests. Clinical stages, D categories indicating the extent of lymph node dissection and other clinicopathological features were classified according to the Japanese Classification of Gastric Carcinoma 3<sup>rd</sup> English edition (13). 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. Pancreatic fistula (PF) was defined according to the ISGPF definition (14) : output via an operatively placed drain of any measurable volume of drainage fluid on or after POD3, with an amylase concentration more than three times higher than the upper normal serum value. It was classified into three categories : transient pancreatic fistula (no clinical impact) (grade A) ; requiring a change in management or adjustment in the clinical pathway (grade B) ; requires a major change in clinical management or deviation from the normal clinical pathway (grade C). In this study, grade B (n = 16) and C (n = 1) are defined as "postoperative

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PF (POPF)". Patients were divided into 2 groups ; POPF group (n = 17) and control group (n = 209), including grade A PF (n = 9). This study was approved by the Institutional Review Board of Ehime Prefectural Central Hospital (No. 30-56).

STATISTICAL ANALYSIS

The chi-squared test for categorical variables and the Mann-Whitney U test for continuous variables were used to compare clinicopathological variables between the two groups. A receiver operating characteristic (ROC) curve was created to identify the best cutoff value of CRP on POD1 for evaluating the risk of POPF. A multivariate logistic regression model was used to detect independent predicting factor for POPF. Variables achieving  $P < 0.05$  in the univariate analysis were included in the multivariate analysis. All statistical analysis was performed using statistical software (JMP 8.0.1., SAS Campus Drive, Cary, NC).  $P < 0.05$  was considered significant.

RESULTS

Table 1 summarizes the univariate analysis with clinicopathological variables of patients in the POPF group and control

Table 1 preoperative data of POPF group and control group with gastric cancer who underwent curative gastrectomy

< Patients' background >	POPF (n=17)	control (n=209)	p-value
Age (years)	72.3 ± 10.9	69.2 ± 11.8	0.29
Gender			0.003
Male	16 (94.1%)	119 (56.9%)	
Female	1 (5.9%)	90 (43.1%)	
BMI (kg/m <sup>2</sup> )	22.9 ± 2.2	22.4 ± 3.4	0.48
Previous operation	2 (11.8%)	64 (30.6%)	0.17
Preoperative complication			
Diabetes Mellitus	3 (17.6%)	29 (13.9%)	0.67
Cardiovascular disease	3 (17.6%)	17 (8.1%)	0.18
CKD with dialysis	0 (0%)	5 (2.4%)	0.52
< Perioperative factor >			
Type of gastrectomy			0.80
Distal	15 (88.2%)	187 (89.5%)	
Total	2 (11.8%)	22 (10.5%)	
Tumor diameter (mm)	40.4 ± 23.5	33.7 ± 20.1	0.19
Histological type			0.36
tub	13 (76.5%)	134 (64.1%)	
por, sig	4 (23.5%)	75 (35.9%)	
pT			0.45
pT1	6 (35.3%)	56 (26.8%)	
pT2-4	11 (64.7%)	153 (73.2%)	
pN			0.16
pN0	2 (11.8%)	57 (27.3%)	
pN1-3	15 (88.2%)	152 (72.7%)	
Lymph node dissection			0.14
D2	8 (47.1%)	63 (30.1%)	
D0, 1, 1+	9 (52.9%)	146 (69.9%)	
Intraoperative bleeding (ml)	78.7 ± 117.7	63.5 ± 94.0	0.53
Operation time (min)	215 ± 49	215 ± 51	0.98
CRP on POD1 (mg/dl)	6.03 ± 4.89	3.31 ± 1.86	<0.0001
Postoperative hospital stay (day)	23 ± 18	13 ± 9	<0.0001

BMI : Body mass index ; CRP : C-reactive protein ; POD : Postoperative day  
The chi-squared test for categorical variables and the Mann-Whitney U test for continuous variables were used to compare clinicopathological variables between the two groups.

group. POPF group had significantly more male patients compared with control group ( $p < 0.05$ ). Other factors including age, BMI, incidence of previous operation, and comorbidities such as diabetes mellitus, cardiopulmonary disease, and chronic renal failure with dialysis showed no significant difference between two groups. Regarding tumor and operative factors, tumor diameter, histological type, T/N factors, extent of lymph node dissection, intraoperative bleeding, and operative time also showed no significant difference between two groups. However, CRP level on POD1 was significantly higher in POPF group compared with control group ( $p < 0.01$ ). To determine the cut off value of CRP for prediction of POPF, ROC curve analysis was performed. (Figure 1), and cut off value of CRP on POD1 was set as 3mg/dl. Area under the curve (AUC) was 0.783. Furthermore, postoperative hospital stay was significantly longer in POPF group compared with control group ( $p < 0.01$ ). Figure 2 showed comparison of CRP level on POD1 among three groups ; no POPF (n = 200), Grade A POPF (n = 9), and Grade B/C POPF (n = 17). Although

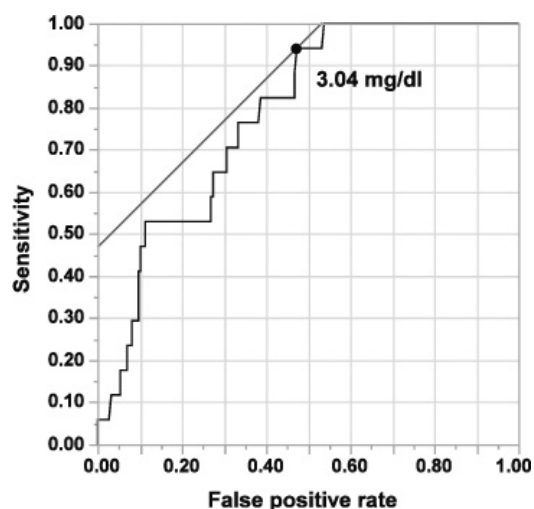


Figure 1. A ROC curve identified the cutoff value of the serum CRP level on POD1 to be 3.04 mg/dl in case with POPF. Area under the curve was 0.783.

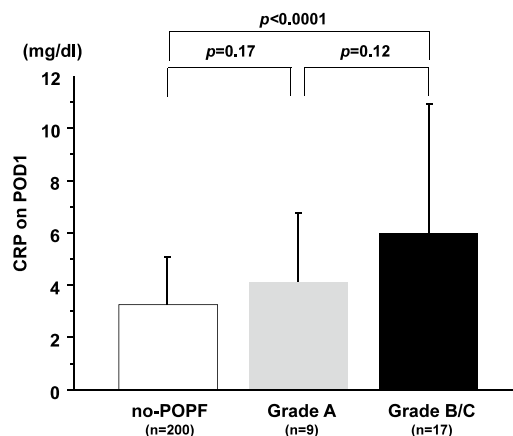


Figure 2. Comparison of CRP level on POD1 among no POPF group, Grade A POPF group, and Grade B/C POPF group. CRP of Grade B/C POPF group was significantly higher than that of no POPF group ( $p < 0.0001$ ). CRP of Grade A tended to be higher compared with that of no PF group ( $p = 0.17$ ), and CRP of Grade B/C tended to be higher compared with that of Grade A ( $p = 0.12$ ). CRP level was compared by Mann-Whitney U test.

there was no significant difference, CRP of Grade A tended to be higher compared with that of no PF group ( $p = 0.17$ ), and CRP of Grade B/C tended to be higher compared with that of Grade A ( $p = 0.12$ ). With factors which were detected in univariate analysis (male gender, CRP on POD1  $\geq 3\text{mg/dl}$ ), multivariate analysis was performed (table 2). High CRP on POD1 ( $\geq 3\text{mg/dl}$ ) was independent predictive factor of POPF ( $p = 0.02$ ). Male gender tended to be independent predictive factor ( $p = 0.08$ ).

**Table 2** Multivariate logistic analysis of risk factors for postoperative pancreatic fistula

Parameters	Odds ratio	95% confidence interval	<i>p</i> value
Gender (male)	6.491	0.818 - 51.474	0.08
CRP on POD1 $\geq 3\text{mg/dl}$	11.596	1.480 - 90.862	0.02

## DISCUSSION

In this study, we have revealed that high CRP level on POD1 ( $\geq 3\text{mg/dl}$ ) was independent risk factor of POPF. CRP on POD1 may be able to predict the occurrence of POPF. Male gender tended to be independent risk factor of POPF. It has been reported that the risk factors for POPF were high BMI, large visceral fat area, extended lymphadenectomy, splenectomy, male sex, and the presence of comorbidities (15-20). Operative factors have been also reported to be important for risk factors of POPF. Ida *et al.* revealed that pancreatic compression by the assistant's forceps can contribute to pancreatic juice leakage using fluorescence imaging in swine model (21). We perform LG in team with fixed member, and shear consciousness that assistants should pay attention to retract the pancreas carefully and gently with gauze. Additionally, ultrasonic coagulating and cutting devices are recently used for supra-pancreatic lymph node dissection in LG. The laparoscopic operation makes the cutting lines for supra-pancreatic lymphadenectomy to be closer to the edge of the pancreas due to the magnified view, which has possibility of heat injury. Operators should pay attention not to cause heat injury to the pancreas when handling ultrasonic coagulating and cutting devices (22, 23).

It is important to detect signs of POPF and its related complication in the early postoperative period and to perform appropriate management because POPF can cause serious complications including intra-abdominal bleeding and severe inflammation with abscess formation. Apparent peripancreatic abscesses due to POPF are related to an increased white blood cell count, neutrophil count, and serum CRP level (24). Because leakage of pancreatic juice occurs during operation, inflammatory response may be enhanced at the early stage of postoperative period when leakage is massive, which correlate with severe PF. It was also reported that CRP on POD1 after pancreatectomy could be independent risk factor for PF (10). Therefore, in this study, we focused on detection of POPF in early postoperative period. Kobayashi *et al.* reported that CRP level on POD 3 after gastrectomy can predict POPF after gastrectomy (25). However, CRP level on POD 1 showed no significant difference between severe POPF patients and other patients. Because their study design included open gastrectomy, CRP level on POD 1 seemed to be higher even in patients without POPF. Matsunaga *et al.* also showed that CRP level on POD3 is predictive indicator of POPF after LG (24). In their study CRP level on POD 1 also showed no significant difference between POPF group and no-POPF group. Longer operation time than our study may relate with relatively

high CRP in no-POPF group. As POPF can be apparently diagnosed on POD3 along with ISGPF definition (14), predictor in earlier postoperative period is necessary to perform appropriate management for POPF. CRP level on POD 1 after LG may enable us to perform more therapeutic postoperative management after gastrectomy, such as observation with lower threshold for CT scan, preservation of drainage tube and prolonged usage of antibiotics. In contrast, patients without elevation of CRP level may be eligible for early removal of drainage tubes from the point of view of enhanced recovery after surgery and avoidance of retrograde infection (25).

To our knowledge, this is the first report which revealed that CRP on POD1 may be a predictive factor for POPF after LG. However, our study has several limitations. First, this study was a retrospective design, and the number of patients with severe POPF was small. Second, there is still no standard definition of severe POPF. Though several studies of pancreatic surgery have used a definition of Grade C PF based on the ISGPF classification (26-28), the number of patients with this severity of gastric surgery is small. Indeed, our study had only one patient with Grade C POPF. So, we defined POPF as Grade B and C PF.

In conclusion, high CRP level on POD1 ( $\geq 3\text{mg/dl}$ ) was independent risk factor of POPF after LG. High serum CRP level on POD1 may be able to predict the occurrence of POPF.

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