Int Surg 2015;**100**:1332–1339
DOI: 10.9738/INTSURG-D-15-00007.1

Clinical Significance of C-reactive Protein Level After Laparoscopic Gastrectomy: From a Viewpoint of Intra-Abdominal Complications

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In this retrospective study, we investigated whether postoperative intra-abdominal infectious complications (IIC) after laparoscopic gastrectomy (LG) is predictable in an early postoperative period using C-reactive protein (CRP). Intra-abdominal infectious complication after gastrectomy is caused mainly by anastomotic leakage or pancreatic injury associated with peripancreatic lymph node (LN) dissection, which may sometimes result in serious outcomes. C-reactive protein is widely used to evaluate the inflammatory status. However, the relationship between the CRP level and postoperative IIC following LG remains unclear. White blood cell count (WBC), CRP counts, and clinical data were available for 229 consecutive patients undergoing LG with lymphadenectomy. We compared CRP and WBC between patients with (Group A) and without (Group B) IIC to check whether these could be used to predict IIC in an early postoperative period. Using the receiver-operating characteristic (ROC) curve, the diagnostic accuracy was evaluated. On postoperative day 1 (POD1), increased CRP levels were associated with IIC (Group A: 9.6 mg/dL, Group B: 6.0 mg/dL; $P = 0.000048$), while WBC did not differ significantly. On POD3, the difference in CRP between both groups increased (A: 20.2 mg/dL, B: 10.7 mg/dL; $P = 1.6 \times 10^{-8}$). The optimal cutoff value was 14.9 mg/dL on POD3 (sensitivity: 0.79, specificity: 0.78), and the area under the ROC curve was 0.86. Measurements of CRP on POD1 and 3 are helpful for detecting possible IIC after LG, compared with WBC. It is necessary to pay attention to CRP levels for earlier detection of IIC.

Key words: C-reactive protein – Postoperative complication – Laparoscopic gastrectomy

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Laparoscopic gastrectomy (LG) has become recognized as one of the standard surgical options for early gastric cancer, because the safety and feasibility of LG with lymph node (LN) dissection were confirmed by several randomized controlled trials.[1–3] Even though LG was widely accepted as a minimally invasive surgery, the benefits of this minimal invasiveness could be negated if postoperative complications occur after LG. Intra-abdominal infectious complications (IIC) after gastrectomy consist mainly of anastomotic leakage and intra-abdominal abscess formation.[2–4] Intra-abdominal abscesses are usually caused by pancreatic injury associated with peripancreatic LN dissection. To detect IIC in an early postoperative period is difficult because the signs of infectious complications are usually masked by physiological reactions after the operation such as fever, abdominal pain, and the normal elevation of inflammatory markers. The early diagnosis of IIC is of marked importance, because the early initiation of appropriate surgical or conservative treatment could prevent postoperative morbidity and mortality. However, there is presently no reliable diagnostic test for the early detection of IIC following LG.

C-reactive protein (CRP) is employed as a marker of the acute inflammatory response. The measurement of CRP is one of the most commonly available tests in postoperative clinical practice, as well as the white blood cell count (WBC). Recently, several studies demonstrated the usefulness of the CRP level to diagnose infectious complications after colorectal and gastroesophageal surgery in an early postoperative period.[5–11] However, the relationship between the CRP level and postoperative IIC following LG with LN dissection has yet to be reported.

The present study aimed to evaluate the clinical significance of the CRP level after LG for the early detection of postoperative IIC. We also estimated the cutoff value of CRP levels using receiver operating characteristic (ROC) curve analysis. In addition, we evaluated the WBC in the same way, which is also regarded as one of the inflammatory markers, and compared the accuracy of using CRP and WBC to predict IIC.

Patients and Methods

In this retrospective study, clinical data, CRP and WBC of 229 consecutive patients undergoing LG with radical LN dissection from July 2005 to April 2010 in Kyoto University Hospital were reviewed using our prospectively collected database. All patients routinely received prophylactic antibiotics (1000 mg cefazolin IV 30 minutes before surgery and every 3 hours during surgery) according to our institutional guidelines. Neoadjuvant chemotherapy was performed, if necessary, according to the decision of the interdisciplinary tumor board. No postoperative antibiotics were administered to the patients unless inflammatory complications were suspected based on physical examinations, blood tests, and radiological examinations. Patients were given free fluid from POD3 and started a soft diet from POD4.

On the day before the operation, blood samples of all patients were taken for routine laboratory tests, including CRP and WBC. After the operation, all patients underwent daily clinical assessment. Laboratory tests including CRP and WBC were routinely measured on POD1, 3, 5, and 7.

Surgical treatment

Our surgical procedure for LG was described previously.[12] Briefly, radical lymphadenectomy defined as D2 or D1+ LN dissection was performed in almost all patients included in this study. The extent of lymphadenectomy was in accordance with the Japanese Gastric Cancer Treatment Guidelines 2010 (ver. 3)[13] and Japanese Classification of Gastric Carcinoma (3rd English edition).[14] Gastrointestinal continuity was restored intracorporeally by either the Billroth-I[15] or Roux-en-Y[16] method, as described elsewhere.

Definitions of postoperative complications and mortality

Postoperative complications were defined as all adverse events during the first 30 postoperative days. Mortality was defined as any in-hospital death during the postoperative period. Intra-abdominal infectious complication (IIC) was defined as infection occurring inside the abdominal cavity, either diffuse or localized, which included anastomotic leakage, intra-abdominal abscess, and postoperative pancreatic fistula (POPF). Formation of POPF was defined as clinically detectable pancreatic leakage requiring continuous drainage for 10 days or more.[12] Extra-abdominal infections and cardiovascular complications were defined according to the classification by Dindo *et al.*[17] Postoperative morbidity was also rated according to the classification by Dindo *et al*.

CRP and WBC measurements

The serum CRP concentration (normal range, 0.0–0.1 mg/dL) was measured by immunoturbidimetric assay (LABOSPECT 008, Hitachi High-Tech, Tokyo, Japan). We analyzed WBC (reference range, 3.0–9.8 $\times$ 10^9/L) using a hematological blood analyzer (XN9000, Sysmex, Kobe, Japan).

Statistical analysis

Statistical analysis was carried out using statistical software (SPSS Statistics ver. 21.0, IBM Corp, Armonk, New York). All values are presented as the mean $\pm$ SD. Statistical analysis was performed using the χ^2 test for categorical variables and unpaired Student's t-test or Mann-Whitney U test for continuous variables, as appropriate. Two-sided P-values lower than 0.05 were considered significant. Multivariate logistic regression analysis was carried out to identify independent predictors of the development of postoperative IIC.

The diagnostic accuracy of CRP and WBC was evaluated with the area under the curve (AUC) using ROC curve analysis. An ROC curve is obtained by plotting the sensitivity (fraction of true-positives, y-axis) against 1-specificity (fraction of false-negatives, x-axis). The point on the ROC curve closest to the left-upper corner represents the optimal cutoff value. The area under the curve is a direct measure of the diagnostic accuracy of the test. An value of AUC greater than >50% indicates the ability of a test to significantly discriminate between positive and negative cases with regard to the classification variable.

Results

Surgical treatment and postoperative outcomes

Clinical follow-up data for at least 2 months as well as postoperative CRP and WBC on POD1, 3, 5, and 7 were available for all 229 consecutive patients who underwent LG with radical LN dissection for gastric cancer. The clinical characteristics of these 229 patients (144 males and 85 females) are presented in Table 1. Laparoscopic distal gastrectomy (LDG) was performed in 155 patients (68%), with laparoscopic total gastrectomy (LTG) in 74 patients (32%). Regarding LN dissection, almost all patients received radical LN dissection: D1+ or D2 LN dissection was carried out in 119 (52.0%) and 103 (45.0%) patients, respectively. Details of postoperative complications are documented in Table 2. The overall morbidity rate (≥grade 2 in Clavien-Dindo's classification) was 15.7% (36 patients). Intra-abdominal infectious complication was noted in 28 (12.2%) patients. In all IIC cases, there were 7 cases (3.1%) of anastomotic leakage (including 4 of secondary leakage due to abscess formation at the site of anastomoses), 18 cases (7.9%) of intra-abdominal abscess or fluid collection (excluding those directly caused by anastomotic leakage), 3 cases (1.3%) of POPF, 2 cases (0.9%) of panperitonitis due to perforation of the remnant stomach or ileum, and 1 case (0.4%) of acute cholecystitis. Four (1.7%) of the 28 patients with intra-abdominal infections underwent reoperation and 1 (0.4%) received percutaneous drainage or another intervention, while 23 (10.0%) were treated conservatively by the administration of antibiotics. There was one postoperative in-hospital death (0.4%). This patient died of intraluminal bleeding due to aortoenteric fistula formation at the site of esophagojejunal

Table 1 Clinicopathological characteristics and operative outcomes of 229 gastric cancer patients treated by laparoscopic gastrectomy

Parameter	
Age, y	64.2 ± 11.7 (29–91)[a]
Body mass index, kg/m^2	22.2 ± 3.2 (14.5–34.6)[a]
Sex	
Male/female	144/85
Extent of gastrectomy	
Distal/total	155/74
Extent of lymphadenectomy	
≤ D1/D1+/D2	7/103/119
Estimated blood loss, g	164 ± 318 (0–3600)[a]
Operation time, min	313 ± 71 (179–560)[a]
Harvested LNs	46.0 ± 18.6 (1–108)[a]
pStage (UICC the 7th ed.)	
I/II/III/IV	172/27/22/8

[a]Numbers in parentheses represent the range.

Table 2 Postoperative complications after laparoscopic gastrectomy

Complications	n (%)
Total	36 (14.8)
Intra-abdominal infectious complications	28 (12.2)
Intra-abdominal abscess/fluid collection	18
Anastomotic leakage	7
Pancreatic fistula formation	3
Panperitonitis due to perforation	2
Acute cholecystitis	1
Other complications	8 (3.5)
Pneumonia	5
Delayed gastric emptying	1
Cystitis	1
Roux-Y stasis	2
Ileus	1
Intestinal obstruction	2
Reoperation	4 (1.7)
In-hospital death	1 (0.4)

A total does not add up due to overlapping elements.

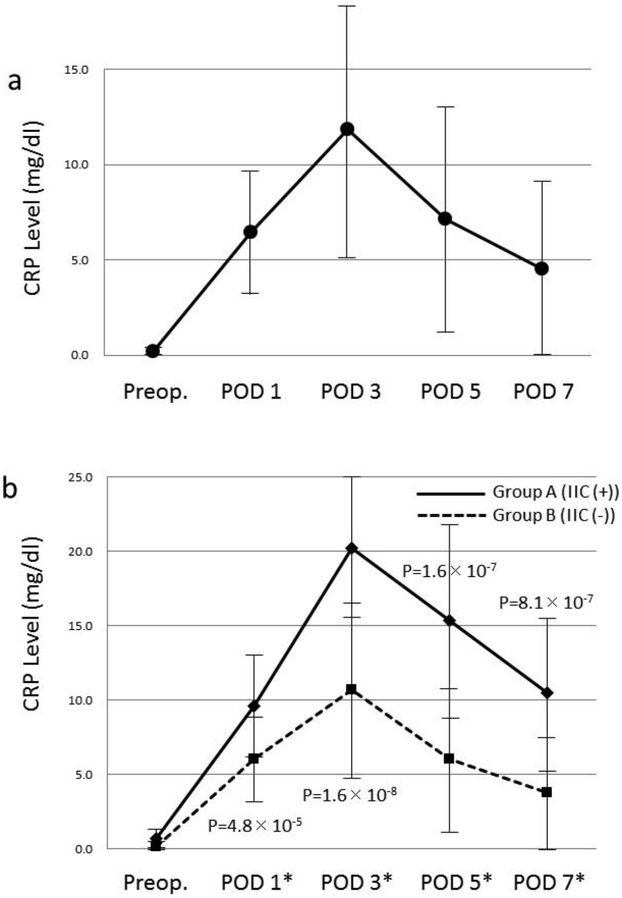

Fig. 1 Perioperative changes in CRP levels in 229 gastric cancer patients undergoing LG with lymph node dissection. Median values with 95% confidence intervals (CI) are presented. (a) Serial measurement of CRP in all 229 patients. C-reactive protein increased in all patients after LG with LN dissection. The peak of the CRP increase was on POD3, followed by its gradual decrease. (b) Comparison of CRP levels between patients with (solid line) and without (dotted line) intra-abdominal infectious complications (IIC). From POD1, the CRP levels differed significantly between the two groups. On POD3, the difference in CRP levels increased between these 2 groups ($P = 1.6 \times 10^{-8}$). $^{*}P < 0.05$.

anastomosis on the 31st day after LTG for stage III gastric cancer. The patient received neoadjuvant chemotherapy with S-1 and cisplatin, although it was uncertain whether this chemotherapy affected the postoperative status of this patient.

Table 3 Multivariate logistic regression analysis of predicting factors for intra-abdominal infectious complications after laparoscopic gastrectomy

Factor	Odds ratio (95% CI)	*P* value
CRP on POD3, mg/dL	1.254 (1.156–1.360)	4.85×10^{-8}
BMI, kg/m^2	0.970 (0.836–1.125)	0.688
Sex, male:female	1.101 (0.366–3.313)	0.865
Diabetes mellitus	1.913 (0.595–6.147)	0.276
Steroid medication	8.614 (1.531–48.46)	0.01455

Postoperative course of CRP levels

The CRP levels on POD1, 3, 5, and 7 are shown in Fig. 1. Overall, an increased CRP level of 11.8 mg/dL was observed on POD3, followed by a gradual decrease (Fig. 1a). We divided these 229 patients into 2 groups: patients with (Group A, n = 28) and without (Group B, n = 201) IIC and compared postoperative CRP levels (Fig. 1b). On POD1, increased CRP levels were already associated with IIC (Group A: 9.6 mg/dL, Group B: 6.0 mg/dL; $P = 4.8 \times 10^{-5}$). On POD3, the difference of CRP between both groups increased (Group A: 20.2 mg/dL, Group B: 10.7 mg/dL; $P = 1.6 \times 10^{-8}$). This difference was even significant on POD5 and 7. The levels of CRP on POD3 were significantly higher in those of the male sex, BMI >25, and LTG. The extent of LN dissection did not significantly affect the CRP levels (data not shown). Multivariate logistic regression analysis was carried out to confirm whether the CRP value on POD3 was an independent factor predicting postoperative IIC after LG. We employed the sex, CRP levels on POD3, BMI, diabetes mellitus, and steroid medication as explanatory valuables. Among these 5 factors, CRP levels on POD3 ($P = 4.8 \times 10^{-8}$) and steroid medication ($P = 0.0146$) were significantly independent factors predicting postoperative IIC (Table 3).

Postoperative course of WBC

White blood cells on POD1, 3, 5, and 7 are shown in Fig. 2. Overall, a physiological increase in WBC (8.9×10^9/L) was observed on POD1, followed by a gradual decrease (Fig. 2a). On POD1, WBC did not differ significantly between Groups A and B. On the contrary, increased WBC levels were associated with IIC on POD3, although the difference was less than that of CRP (Group A: 9.8×10^3/uL; Group B: 7.7×10^3/uL, $P = 0.005$; Fig. 2b).

Diagnostic accuracy of CRP and WBC levels

Using the receiver-operating characteristic (ROC) curve, the diagnostic accuracy of CRP and WBC was evaluated. Based on the AUC, the postoperative

CRP level showed the best diagnostic accuracy for IIC on POD3 (AUC = 0.86), followed by POD1 (AUC = 0.81; Fig. 3a). On the other hand, WBC showed the best diagnostic accuracy on POD3 (AUC = 0.69; Fig. 3b), representing a lower diagnostic accuracy for IIC than CRP. The optimal cutoff value of the CRP level was 14.9 mg/dL on POD3. When we employed this cutoff value, the sensitivity was 0.79 and the specificity was 0.78, respectively.

Discussion

In the present study, postoperative IIC was noted in 12% of patients after LG. We evaluated postoperative inflammatory markers such as the CRP level and WBC to check whether they could be used for the early detection of IIC. Increased levels of CRP on POD3 showed the highest diagnostic accuracy to detect IIC after LG. White blood cell count on POD3 was also associated with the occurrence of IIC, but the difference was less than that of CRP on POD3. These results showed that increased CRP levels on POD3 strongly suggest a high risk of developing IIC during the later postoperative course.

C-reactive protein, a widely employed laboratory marker of the acute inflammatory response, has not been considered as an adequate marker for the early detection of postoperative inflammatory complications. This is because it is difficult to distinguish an inflammatory complication from a normal acute systemic inflammatory response caused by surgical treatment.[9] In addition, the response of the CRP level to inflammation was considered to be delayed compared with that of WBC; during the acute phase response, levels of CRP increase by about 6 hours after acute inflammation, and then reach a peak at 48 hours.[18] However, this study showed that the CRP level on POD1 was already associated with the occurrence of IIC, while WBC on POD1 was not. We speculate that CRP levels are more sensitive reflections of the levels of postoperative intra-abdominal inflammation than WBC, even on POD1. Furthermore, the increased CRP level on POD3 was more strongly associated with the occurrence of IIC than WBC on the same day. Notably, as we showed in multivariate analysis, we confirmed that the CRP level on POD3 was an independent factor predicting the occurrence of IIC. Taken together, postoperative CRP levels might be more useful for the earlier detection of IIC than WBC.

Postoperative intra-abdominal infection after LG is mainly caused by anastomotic leakage and

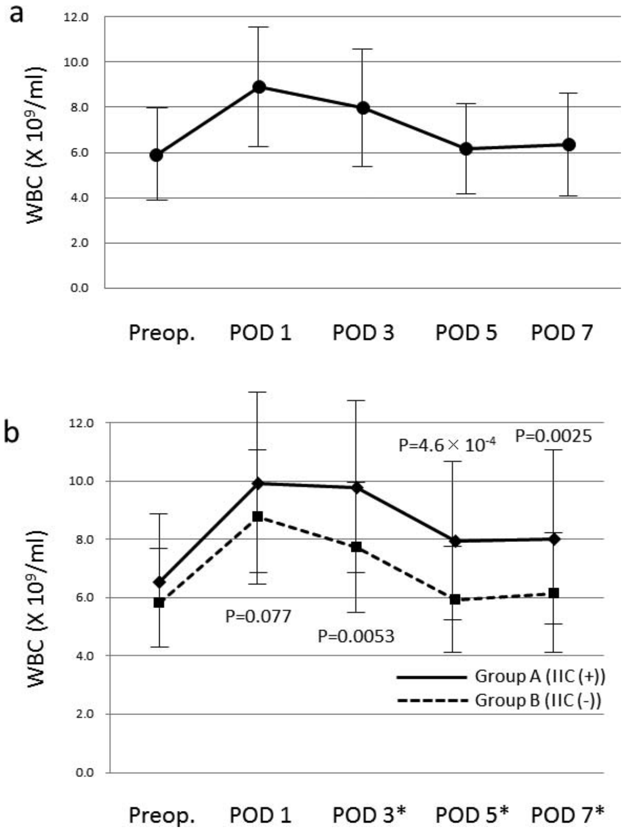

Fig. 2 Perioperative changes in WBCs in 229 gastric cancer patients undergoing LG with LN dissection. Median values with 95% confidence intervals are presented. (a) Serial measurement of WBC in all 229 patients. White blood cell counts increased in all patients after LG with LN dissection. The peak of the WBC increase was on POD1, followed by the gradual decrease of WBC. (b) Comparison of CRP levels between patients with (solid line) and without (dotted line) IIC. Different from CRP measurement, WBC on POD1 did not differ significantly between 2 groups, although the peak WBC increase was on POD1. On POD3, WBC differed significantly between the 2 groups ($P = 0.005$), even though the difference was less than that of CRP. *$P < 0.05$.

pancreatic injury due to peripancreatic LN dissection, which is still a potentially life-threatening condition. Unfortunately, the diagnosis of IIC is often made in a later postoperative period, when many patients present with signs of serious illness or even septic condition. In particular, peripancreatic abscess and POPF are specific complications after peripancreatic LN dissection, which sometimes cause sepsis, pseudoaneurysm, and intra-abdominal bleeding. Thus, a method for the early identification of patients at risk of IIC would be of marked importance, because it is necessary to start antibiotic

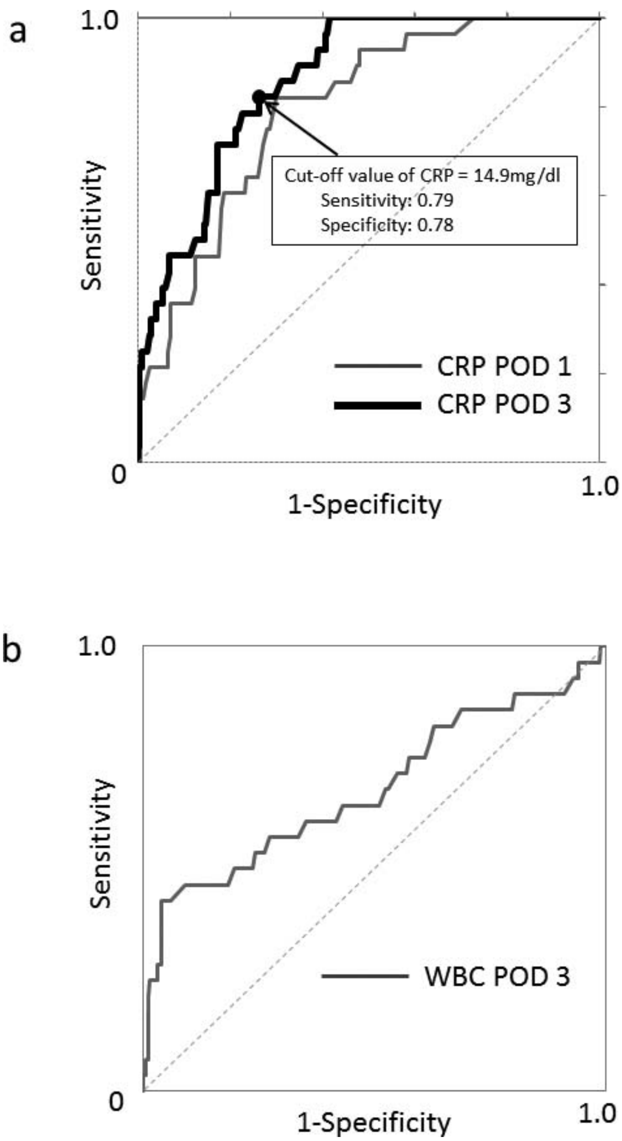

Fig. 3 Receiver operating curves for the diagnostic accuracy of CRP and WBC after LG with LN dissection with regard to IIC detection. (a) CRP on POD3 showed a higher diagnostic accuracy compared with that on POD1, as expressed by AUC values of 0.86 and 0.81, retrospectively. The optimal cutoff value of the CRP level was 14.9 mg/dL on POD3 (arrow). When we employed this cutoff value, the sensitivity was 0.79 and specificity was 0.78, respectively. (b) WBC on POD3 showed a lower diagnostic accuracy compared with the CRP level on POD1 and 3, as expressed by an AUC value of 0.69.

therapy and, if necessary, surgical or interventional drainage as early as possible to avoid a fatal outcome.

To distinguish between patients with IIC and those with a normal postoperative course, we employed ROC curve analysis and determined an optimal CRP cutoff value of 14.9 mg/dL on POD3. The accuracy of this cutoff value was comparable with those of previous reports regarding colorectal or open gastroesophageal surgery.[5,6,9] However, it is undoubtedly difficult to predict IIC solely based on this cutoff value. Elevated CRP levels should be interpreted in a clinical context. When in doubt, in addition to physical examinations, further diagnostic examinations such as chest x-ray, urinalysis, abdominal ultrasonography, computed tomography, and an upper gastrointestinal series with water-soluble contrast media should be considered. Therefore, our present data from ROC curve analysis do not necessarily support the introduction of pre-emptive antibiotic therapy based solely on an elevated CRP level on POD3.

On the other hand, Chromik *et al*[19] demonstrated the clinical usefulness of procalcitonin, an inflammatory marker, in a prospective randomized pilot study. They showed that the pre-emptive antibiotic treatment of patients with elevated serum procalcitonin after colorectal surgery significantly reduced the rate of postoperative infections. However, the superiority of procalcitonin over CRP still remains controversial.[20] Concerning CRP, we should interpret our cutoff value carefully, since CRP is not specific to bacterial infection. Nevertheless, it was advantageous to measure CRP levels: we could use this inflammatory marker more conveniently as a routine screening parameter because of its reasonable price compared with other expensive markers such as procalcitonin. Moreover, significant CRP elevations on POD1 and 3 usually preceded clinical manifestations of postoperative IIC based on our results, which might help surgeons to suspect IIC development in the later postoperative course.

This study has some limitations. First, in interpreting the results, it is important to consider that they are limited to a single center cohort. Second, our data on LG patients were analyzed retrospectively. However, our study included a homogenous and large population of gastric cancer patients who underwent LG. In addition, the data were collected prospectively and the study involved consecutive patients. We believe that our results may be clinically applicable to predict undetected postoperative IIC and select patients for whom further examinations should be provided. Future studies on the validity of additional close examinations (*e.g.*, MDCT) and pre-emptive antibiotic therapy for the patients with high levels of CRP are warranted.

In conclusion, increased levels of CRP on POD3 showed the highest diagnostic accuracy to detect IIC after LG. The optimal cutoff value of the CRP level was 14.9 mg/dL on POD3. The patients with IIC showed increased levels of CRP even on POD1, which may contribute to IIC detection in an earlier period compared to WBC. Thus, for patients with high CRP levels on POD3, IIC should be suspected if the increase of CRP levels is inexplicable based on other conditions of the patients. In gastric cancer patients who have undergone LG with LN dissection, it is necessary for clinicians to pay attention to the CRP levels from an earlier postoperative period to facilitate IIC detection as early as possible.

Acknowledgments

There was no grant support for the research reported, and no potential and real conflicts of interest. Previously presented at the 10th International Gastric Cancer Congress in Verona, Italy (June 21, 2013).

References

1. Huscher CG, Mingoli A, Sgarzini G, Sansonetti A, Di Paola M, Recher A *et al*. Laparoscopic versus open subtotal gastrectomy for distal gastric cancer: Five-year results of a randomized prospective trial. *Ann Surg* 2005;**241**(2):232–237
2. Katai H, Sasako M, Fukuda H, Nakamura K, Hiki N, Saka M *et al*. Safety and feasibility of laparoscopy-assisted distal gastrectomy with suprapancreatic nodal dissection for clinical stage I gastric cancer: A multicenter phase II trial (JCOG 0703). *Gastric Cancer* 2010;**13**(4):238–244
3. Kim HH, Hyung WJ, Cho GS, Kim MC, Han SU, Kim W *et al*. Morbidity and mortality of laparoscopic gastrectomy versus open gastrectomy for gastric cancer: an interim report—a phase III multicenter, prospective, randomized trial (KLASS Trial). *Ann Surg* 2010;**251**(3):417–420
4. Okabe H, Obama K, Tsunoda S, Tanaka E, Sakai Y. Advantage of completely laparoscopic gastrectomy with linear stapled reconstruction. A long-term follow-up study. *Ann Surg* 2014; **259**(1):109–116
5. Krner H, Nielsen HJ, Sreide JA, Nedreb BS, Sreide K, Knapp JC. Diagnostic accuracy of C-reactive protein for intraabdominal infections after colorectal resections. *J Gastrointest Surg* 2009;**13**(9):1599–1606
6. Warschkow R, Tarantino I, Torzewski M, Näf F, Lange J, Steffen T. Diagnostic accuracy of C-reactive protein and white blood cell counts in the early detection of inflammatory complications after open resection of colorectal cancer: a retrospective study of 1,187 patients. *Int J Colorectal Dis* 2011; **26**(11):1405–1413
7. Platt JJ, Ramanathan ML, Crosbie RA, Anderson JH, McKee RF, Horgan PG *et al*. C-reactive protein as a predictor of postoperative infective complications after curative resection in patients with colorectal cancer. *Ann Surg Oncol* 2012;**19**(13): 4168–4177
8. Nason GJ, Barry BD, Obinwa O, McMacken E, Rajaretnam NS, Neary PC. Early rise in C-reactive protein is a marker for infective complications in laparoscopic colorectal surgery. *Surg Laparosc Endosc Percutan Tech* 2014;**24**(1):57–61
9. Warschkow R, Tarantino I, Ukegjini K, Beutner U, Müller SA, Schmied BM *et al*. Diagnostic study and meta-analysis of C-reactive protein as a predictor of postoperative inflammatory complications after gastroesophageal cancer surgery. *Langenbecks Arch Surg* 2012;**397**(5):727–736
10. Noble F, Curtis N, Harris S, Kelly JJ, Bailey IS, Byrne JP *et al*. Risk assessment using a novel score to predict anastomotic leak and major complications after oesophageal resection. *J Gastrointest Surg* 2012;**16**(6):1083–1095
11. Dutta S, Fullarton GM, Forshaw MJ, Horgan PG, McMillan DC. Persistent elevation of C-reactive protein following esophagogastric cancer resection as a predictor of postoperative surgical site infectious complications. *World J Surg* 2011; **35**(5):1017–1025
12. Obama K, Okabe H, Hosogi H, Tanaka E, Itami A, Sakai Y. Feasibility of laparoscopic gastrectomy with radical lymph node dissection for gastric cancer: From a viewpoint of pancreas-related complications. *Surgery* 2011;**149**(1):15–21
13. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer* 2011;**14**(2): 113–123
14. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer* 2011; **14**(2):101–112
15. Kanaya S, Gomi T, Momoi H, Tamaki N, Isobe H, Katayama T *et al*. Delta-shaped anastomosis in totally laparoscopic Billroth I gastrectomy: new technique of intraabdominal gastroduodenostomy. *J Am Coll Surg* 2002;**195**(2):284–287
16. Okabe H, Obama K, Tanaka E, Nomura A, Kawamura J, Nagayama S *et al*. Intracorporeal esophagojejunal anastomosis after laparoscopic total gastrectomy for patients with gastric cancer. *Surg Endosc* 2009;**23**(9):2167–2171
17. 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**(2): 205–213
18. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. *J Clin Invest* 2003;**111**(12):1805–1812

19. Chromik AM, Endter F, Uhl W, Thiede A, Reith HB, Mittelkötter U. Pre-emptive antibiotic treatment vs 'standard' treatment in patients with elevated serum procalcitonin levels after elective colorectal surgery: a prospective randomised pilot study. *Langenbecks Arch Surg* 2006;**391**(3):187–194

20. Lagoutte N, Facy O, Ravoire A, Chalumeau C, Jonval L, Rat P, Ortega-Deballon P. C-reactive protein and procalcitonin for the early detection of anastomotic leakage after elective colorectal surgery: pilot study in 100 patients. *J Visc Surg* 2012;**149**(5):e345–e349