ORIGINAL CONTRIBUTION

A Practical Predictive Index for Intra-abdominal Septic Complications After Primary Anastomosis for Crohn's Disease: Change in C-Reactive Protein Level Before Surgery

Lugen Zuo, Ph.D. • Yi Li, Ph.D. • Honggang Wang, Ph.D. • Weiming Zhu, M.D., Ph.D.
Wei Zhang, M.D., Ph.D. • Jianfeng Gong, Ph.D. • Ning Li, M.D., Ph.D.
Jieshou Li, M.D., Ph.D.

Department of General Surgery, Jinling Hospital, Medical School of Nanjing University, Nanjing, China

BACKGROUND: Postoperative intra-abdominal septic complications are difficult to manage in Crohn's disease, which makes prevention especially important.

OBJECTIVE: The purpose of this study was to examine the risk factors for intra-abdominal septic complications after primary anastomosis for Crohn's disease and to seek a practical predictive index for intra-abdominal septic complications.

DESIGN: This was a retrospective study.

SETTINGS: The study was conducted in a tertiary referral hospital.

PATIENTS: Based on a computerized database of 344 patients with Crohn's disease who underwent primary anastomosis between 2004 and 2013, the patients were placed into an intra-abdominal septic complications group and a group without intra-abdominal septic complications.

MAIN OUTCOME MEASURES: Univariate and multivariate analyses were performed to identify risk factors, and the predictive accuracy of possible predictors was assessed using receiver operating characteristic curves.

RESULTS: Overall, 39 patients (11.34%) developed intra-abdominal septic complications. Preoperative C-reactive protein level >10 mg/L was found to be an independent risk factor ($p < 0.01$) for intra-abdominal septic complications. For prediction of intra-abdominal septic complications, receiver operating characteristic curve analysis showed that a C-reactive protein cutoff of 14.50 mg/L provided negative and positive predictive values of 96.84% and 34.07%. In addition, the change in C-reactive protein levels over the 2 weeks before surgery was greater in the intra-abdominal septic complications group than the group with no intra-abdominal septic complications ($p < 0.01$), and the directions of change were opposite, upward in the former and downward in the latter. Apart from being a risk factor for intra-abdominal septic complications ($p < 0.01$), receiver operating characteristic curve analysis showed that the change in C-reactive protein levels before surgery had a negative predictive value for intra-abdominal septic complications of 98.66% and a positive predictive value of 76.09%.

LIMITATIONS: This was a retrospective study.

CONCLUSIONS: Changes in C-reactive protein before surgical treatment of Crohn's disease could serve as a practical predictive index for postoperative intra-abdominal septic complications.

KEY WORDS: C-reactive protein; Crohn's disease; Postoperative complications.

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Correspondence: Weiming Zhu, M.D., Ph.D., Department of General Surgery, Jinling Hospital, Medical School of Nanjing University, No. 305 East Zhongshan Rd, Nanjing 210002, China. E-mail: dr_zhuweiming@126.com

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Crohn's disease (CD) is a chronic IBD of unknown etiology. Despite increased use of immunosuppressive and antitumor necrosis factor treatments, ≈75% of patients with CD will require a partial bowel resection at least once during the course of their disease.[1,2] Moreover, the postoperative complication rate after intestinal resection for CD is higher than for other benign diseases, despite the fact that most patients with CD are young and without significant comorbidities.[3] Postoperative intra-abdominal septic complications (IASCs) are defined as anastomotic leaks, enterocutaneous fistulas, or intra-abdominal abscesses,[3,4] the last of which are especially troublesome, with incidences ranging from 5% to 20%.[3,5,6] Patients with a postoperative IASC require more aggressive treatment and longer hospitalizations and have higher surgical recurrence rates than patients without an IASC.[3]

Postoperative IASCs are difficult to manage, which makes their prevention particularly important. However, the risk factors for postoperative IASCs in patients with CD remain controversial. Several publications have reported these risk factors to include preoperative corticosteroid therapy, preoperative serum albumin level <30 g/L, an abscess or fistula at the time of laparotomy, operation time >180 minutes, handsewn anastomosis, blood loss >300 mL, and inflammation-involved histological margins.[4,7,8] In addition, C-reactive protein (CRP) levels at diagnosis are reportedly related to disease severity in patients with IBD, and it has been suggested that CRP levels are predictive of surgical outcome in subgroups of patients with ulcerative colitis or CD.[9,10] Whether a high preoperative CRP level is an independent risk factor for IASCs and whether it can be used as a predictive index for IASCs has not been fully analyzed, however. Furthermore, there is still no practical predictive index for postoperative IASCs that could be used to determine appropriate therapeutic strategies (stoma or anastomose). The purpose of this study was to examine the risk factors for postoperative IASCs after surgery for CD and to develop a practical predictive index for postoperative IASCs that can be used in the clinic.

PATIENTS AND METHODS

Patients

This study was approved by the ethics committee of Jinling Hospital. Information from patients with CD who underwent surgical resection was entered into our prospectively maintained IBD database from 2004 to 2013. All of the data, including medical histories, laboratory reports, and therapeutic procedures, were collected from the patient medical charts, which are permanently recorded in our computer database. We included only elective surgery patients who underwent an intestinal resection with a primary anastomosis. Once enrolled, the patients were divided into IASC and no-IASC groups. None of these patients underwent concomitant strictureplasty or bypass. Patients with active infections were excluded (white blood cell count $>10\times10^9$/L or neutrophil ratio >70%), because preoperative infections can alter preoperative serum CRP levels and the incidence of postoperative IASCs.

Definition of IASCs

Postoperative IASCs were defined as any anastomotic leak, intra-abdominal abscess, or enterocutaneous fistula occurring within 1 month after surgery.[4] A diagnosis of IASC was made based on relaparotomy findings, the presence of infected or fecal material in the percutaneous drainage, and imaging of intra-abdominal abscesses. The diagnosis was ultimately confirmed by percutaneous puncture.

Data Collection

The data collected included age, sex, age at operation, duration of disease before surgery, smoking habits, and disease location and behavior (Montreal classification). Also collected were operative notes, which included operative time, anastomosis type, number of anastomoses, preoperative treatments, occurrence of postoperative IASCs, and hemoglobin, albumin, and CRP levels 1 day before surgery. CRP levels were also determined 2 weeks before surgery, because all of the elective surgery patients received preoperative preparation lasting 2 to 4 weeks in our CD medical center. Blood samples for determining hemoglobin, CRP, and albumin levels 1 day before surgery were collected in the CD surgery center as part of routine preoperative examinations and were analyzed in the clinical laboratory at Jinling Hospital.

Statistical Analysis

All of the data analysis was performed using SPSS version 19.0 (SPSS Inc, Chicago, IL). Continuous normally distributed data are presented as the mean ± SE, whereas nonparametric data are presented as medians, interquartile ranges, or 5% to 95% values, as appropriate. We used unpaired t tests to compare parametric variables and the Mann-Whitney U test for nonparametric data. Binary and categorical data were compared using χ^2 tests for contingency tables (Fisher exact test was performed when there were fewer than 5 patients). Backward Wald multiple regression analysis was performed to identify possible predictors of postoperative IASCs, and predictive accuracy was assessed using receiver operating characteristic (ROC) curve analysis. Values of $p < 0.05$ were considered statistically significant.

RESULTS

Patients

During the 10-year study period, 365 patients underwent enterectomy with a primary anastomosis for CD. Overall, 21 (5.75%) of those patients were excluded from the study because of preoperative infection (4 patients, none with postoperative IASC) or incomplete data (17 patients, 1 patient with postoperative IASC). Ultimately, 344 patients were analyzed in our study. IASCs occurred in 11.34% (39/344) of patients: anastomotic leak occurred in 4.65% (16/344), intra-abdominal abscess in 5.52% (19/344), and enterocutaneous fistula in 1.16% (4/344). Among these IASCs, 27 (69.23%) were treated conservatively, and 12 (30.77%) required a second surgery. There were no postoperative deaths.

Analysis of Possible Risk Factors for IASCs

As shown in Table 1, factors found to be significantly associated with IASCs in a univariate analysis included preoperative albumin level <35 g/L, preoperative CRP level >10 mg/L (1 day before surgery), and preoperative steroid use for ≥3 months. These factors were then inserted into a multivariate analysis model to determine the risk factors independently associated with the development of an IASC. Failure of medical therapy (Montreal classification: B1) was also included because its *p* value in the univariate analysis nearly reached statistical significance. In the multivariate analysis, only preoperative (1-day) CRP level >10 mg/L was found to be an independent risk factor for IASCs. Note, however, that this finding by itself does not indicate whether preoperative CRP can act as a practical predictive index for postoperative IASCs.

Predictive Accuracy of Preoperative CRP for Postoperative IASCs

To assess the predictive value of preoperative (1-day) CRP for postoperative IASCs after 1-stage resection and anastomosis surgery, we performed an ROC curve analysis. The parameters for the ROC curve are shown in Figure 1. The cutoff point was 14.5 mg/L, area under the curve was 0.87, sensitivity was 79.49%, specificity was 80.33%, and the negative predictive value (NPV) was 96.84%. The positive predictive value (PPV), which is used as a practical predictive parameter in the clinic, was only 34.07%. The low PPV indicates that preoperative (1-day) CRP could not serve as a practical index predictive of postoperative IASCs. For example, for a patient with a preoperative (1-day) CRP level <14.5 mg/L, the probability of correctly predicting no IASC would be 96.84%, but when the preoperative CRP is ≥14.5 mg/L, the probability of correctly predicting the occurrence of an IASC would be only 34.07%.

TABLE 1. Univariate analysis of factors associated with IASCs

Group	*No-IASCs*	*IASCs*	*p*
No. of patients	305	39	
Mean age at operation, y	33.33 ± 0.66	35.87 ± 2.45	0.214
Sex			
Men	216 (70.82)	27 (69.23)	0.837
Women	89 (29.18)	12 (30.77)	
Mean disease duration before surgery, y	6.45 ± 0.18	7.34 ± 0.62	0.106
Montreal classification			
Age, y			
A1 (≤16)	49 (16.07)	7 (17.95)	0.764
A2 (17–40)	225 (73.77)	27 (69.23)	0.546
A3 (>40)	31 (10.16)	5 (12.82)	0.581
Location			
L1 (ileal)	125 (40.98)	20 (51.28)	0.220
L2 (colonic)	34 (11.15)	2 (5.13)	0.402
L3 (ileocolonic)	146 (47.87)	17 (43.59)	0.614
L4 (upper gastrointestinal)	33 (10.82)	5 (12.82)	0.785
Behavior			
B1 (inflammatory/ failure of medical therapy)	26 (8.52)	7 (17.95)	0.060*
B2 (stricturing)	167 (54.75)	18 (46.15)	0.310
B3 (penetrating)	112 (36.72)	14 (35.90)	0.920
Perianal disease (P)	58 (19.02)	7 (17.95)	0.873
Operative time <180 min	223 (73.11)	27 (69.23)	0.608
Hemoglobin <12 g/dL	223 (73.11)	30 (76.92)	0.612
Albumin <35 g/L (1 day before surgery)	44 (14.43)	13 (33.33)	0.003*
CRP >10 mg/L (1 day before surgery)	92 (30.16)	33 (84.62)	<0.01*
First time operated	216 (70.82)	25 (64.10)	0.389
Laparoscopic completed cases	38 (12.46)	1 (2.56)	0.102
Smoking status at surgery			
Never smoker	230 (75.41)	28 (71.79)	0.624
Past smoker	67 (21.97)	11 (28.21)	0.381
Active smoker	8 (2.62)	0 (0)	0.604
Anastomosis method, stapled and sutured	305 (100)	39 (100)	NC
Anastomosis type			
Side-to-side anastomosis	264 (86.56)	37 (94.87)	0.198
End-to-end anastomosis	41 (13.44)	2 (5.13)	
No. of anastomoses			
1	293 (96.07)	39 (100.00)	0.374
≥2	12 (3.93)	0 (0)	
Preoperative treatment			
Azathioprine	76 (24.92)	7 (17.95)	0.338
Tripterygium glycosides	35 (11.48)	3 (7.69)	0.597
Infliximab	6 (1.97)	2 (5.13)	0.227
5-ASA	23 (7.54)	2 (5.13)	0.753
Preoperative steroids for ≥3 mo	13 (4.26)	5 (12.82)	0.041*
Enteral nutrition	129 (42.30)	20 (51.28)	0.286
Others	23 (7.54)	0 (0)	0.091

All of the results are presented as number (%) or mean ± SEM.
No-IASCs = no intra-abdominal septic complications; IASCs, intra-abdominal septic complications; CRP = C-reactive protein; NC = not calculated; 5-ASA = 5-aminosalicylate.
*P value is significant.

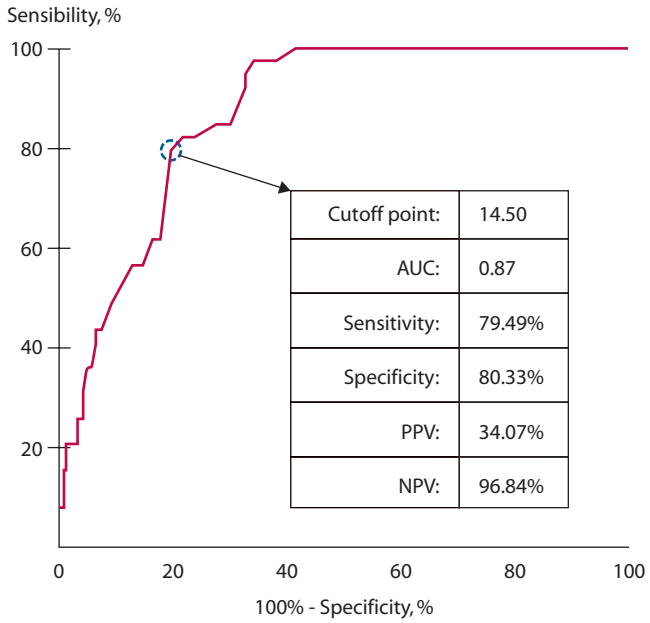

FIGURE 1. ROC curve showing preoperative (1-day) CRP levels predictive of postoperative IASCs. CRP = C-reactive protein; IASCs = intra-abdominal septic complications; ROC = receiver operating characteristic; AUC = area under the curve; PPV = positive predictive value; NPV = negative predictive value.

Opposite Changes in CRP Levels in Patients With and Without IASCs

Although the preoperative (1-day) CRP level proved to be a poor predictor of postoperative IASCs, we reasoned that the change in the CRP level over the 2-week period preceding surgery may be a better predictor of postoperative IASCs. When we evaluated the change in the CRP level over the 2 weeks before the surgery, we found that CRP levels trended downward in patients who did not develop an IASC (Fig. 2A and 2C; $p < 0.01$) and upward in patients who did develop an IASC (Fig. 2B and 2D; $p < 0.01$).

Quantitative Analysis of Preoperative Changes in CRP Levels

To quantitatively assess the changes in CRP levels before surgery and ensure that they could be compared between the IASC and no-IASC groups, we further calculated the percentage change in CRP (ΔCRP) during the 2-week period before surgery using the follows formula: (CRP level 1 day before surgery/CRP level 2 weeks before surgery) × 100%. The data are shown in Figure 3. The IASC group had a higher ΔCRP than the no-IASC group, with a median value well above 100%, which indicates an upward trend in the CRP level. The median value of ΔCRP in the no-IASC group was <100%, indicating a downward trend in the CRP level.

Use of ΔCRP for Prediction of Postoperative IASCs

The abovementioned results indicate that the direction and magnitude of the preoperative change in CRP differs between patients who experienced an IASC and those who did not. We therefore hypothesized that ΔCRP may be a more predictive parameter for IASCs than the preoperative (1-day) CRP level. ROC analysis confirmed this speculation (Fig. 4). A ΔCRP cutoff value of 1.6 (160%) for the prediction of postoperative IASCs provided a sensitivity of 89.74%, specificity of 96.39%, area under the curve of 0.98, NPV of 98.66%, and PPV of 76.09%. This suggests that ΔCRP has potential clinical value for predicting postoperative IASCs. In addition, a ΔCRP >1.6 was confirmed to be an independent risk factor for postoperative IASCs ($p < 0.01$). For clarity, the risk relationship and predictive values for IASCs of the CRP level 1 day and 2 weeks before surgery and the ΔCRP are shown in Table 3.

DISCUSSION

The main findings of our study can be summarized as follows. First, the preoperative (1-day) CRP level is an independent risk factor for postoperative IASCs, but its predictive value for postoperative IASCs is not optimal, because it has a high NPV (96.84%) but a low PPV (34.07%). Second, apart from being a risk factor for IASCs, ΔCRP can also be used as a practical predictive index for postoperative IASCs, with an NPV of 96.39% and a PPV of 76.09%.

In the present study, 39 patients (11.34%) developed IASCs. This IASC rate is comparable to those reported previously, which ranged from 5% to 20%.[3,5,6] Our findings suggest that preoperative CRP >10 mg/L is a risk factor for postoperative IASCs. Previously reported risk factors for postoperative IASCs in patients with CD are controversial. Yamamoto et al[4] reported that low preoperative albumin levels, steroid use, and the presence of an abscess or fistula at the time of laparotomy significantly increased the risk of an IASC after surgery. On the other hand, Kanazawa et al[8] found that operating time >180 minutes, penetration type, and handsewn anastomosis were major risk factors for postoperative IASCs. These 2 investigators addressed the discrepancy between their findings in a recent publication,[11] but it is our view that the risk factors for developing postoperative IASCs remained unknown and required further investigation, particularly through the use of prospective studies.

Our study showed that the NPV of preoperative CRP for postoperative IASCs is 96.83% when the cutoff value is 14.50 mg/L. This means that when preoperative CRP is <14.50 mg/L, it is likely safe to perform primary resection and anastomosis and to expect a low rate of IASCs. In other words, when disease activity is low, 1-stage anastomosis is likely safe. This statement is made based on the finding that CRP is an effective disease activity marker for CD, perhaps better than the CD activity index.[9,10] By contrast, the PPV of

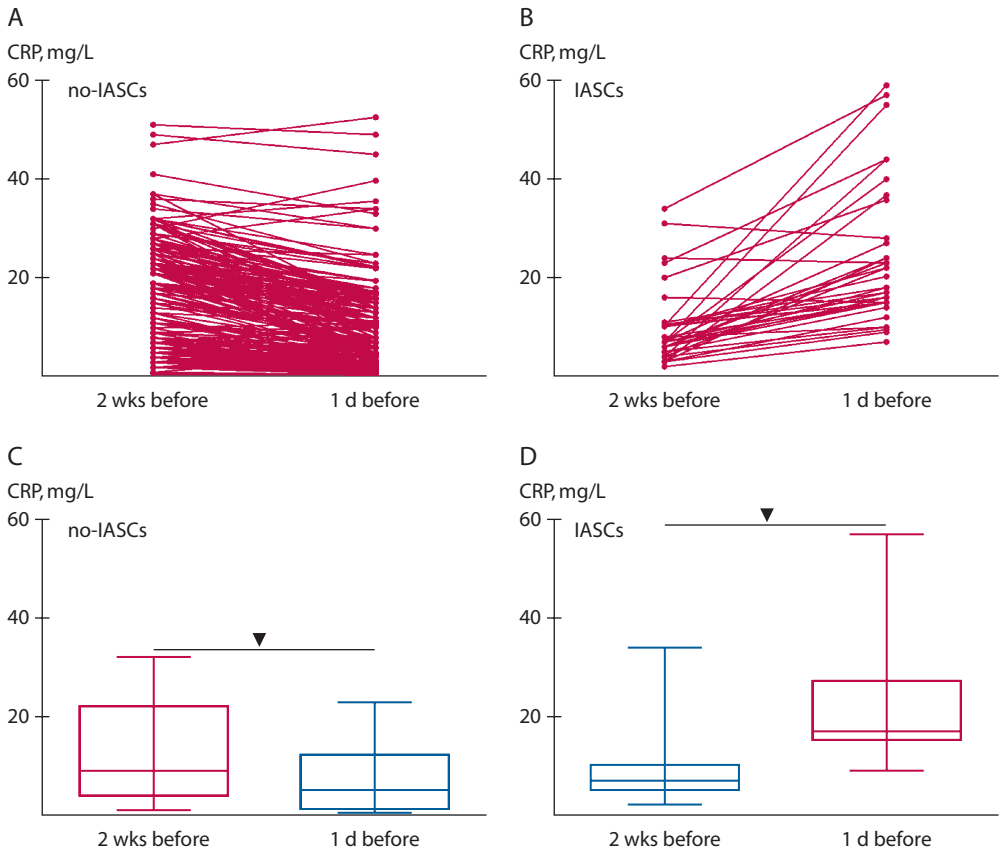

FIGURE 2. Over the 2-week period before surgery, CRP levels in patients in the IASC and no-IASC groups changed in opposite directions. Shown are side-by-side scatter plots with connecting lines illustrating the changes in CRP levels over the period from 2 weeks before to 1 day before surgery for each individual patient in the no-IASC (A) and IASC (B) groups. The same data are represented as box and whisker plots in C and D. The box plots show the median and upper and lower quartiles of the data, whereas the whiskers indicate the 95% CIs of the values. ▾$p < 0.01$ (Mann-Whitney *U* test). No-IASC = no intra-abdominal septic complication; IASC = intra-abdominal septic complication; CRP = C-reactive protein.

preoperative CRP for postoperative IASCs is only 34.07%, which means that there is a 65.93% probability of incorrectly predicting the occurrence of IASCs in patients with preoperative CRP level >14.50 mg/L. This suggests that preoperative CRP alone can only be used as an accurate predictive index for patients who are unlikely to develop an IASC.

The most important finding of the present study was the relative reliability of ΔCRP for the prediction of IASCs, with an NPV of 98.66% and a PPV of 76.09%. This finding derives from our observation that, over the 2 weeks before surgery, CRP levels trended downward in patients without IASCs but upward in patients with IASCs. We suggest that 2 aspects of the ΔCRP should be considered: the direction of change in CRP (below or above 100%) and the magnitude of the change (absolute value). In the context of earlier studies that showed that CRP is a disease activity marker for CD, ΔCPR can be viewed, at least to some extent, as a marker of the direction of disease activity in CD (worsening or toward remission). Furthermore, our findings suggest that 1-stage anastomosis is safe when patient disease exhibits a trend toward remission or no serious disease activity (ΔCRP <1.60). The natural course of CD varies between remission and aggravation,[12,13] and that course can be altered by therapeutic interventions or environmental factors.[14–16] It is our experience that operating

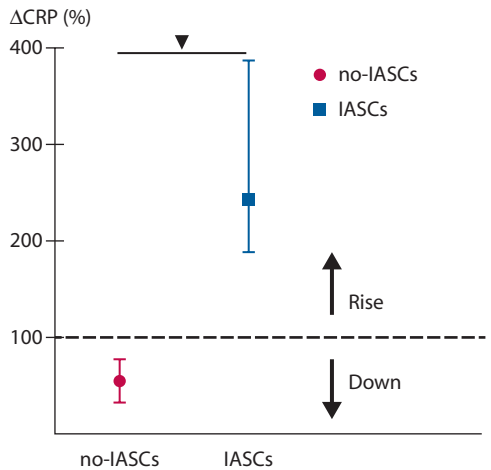

FIGURE 3. Quantitative analysis of preoperative changes in CRP in the no-IASC and IASC groups. The symbols represent the median and interquartile range. ▾$p < 0.01$ (Mann-Whitney *U* test). ΔCRP = (value of CRP 1 day before surgery/value of CRP 2 weeks before surgery) × 100%; no-IASC = no intra-abdominal septic complication; IASC = intra-abdominal septic complication; CRP = C-reactive protein.

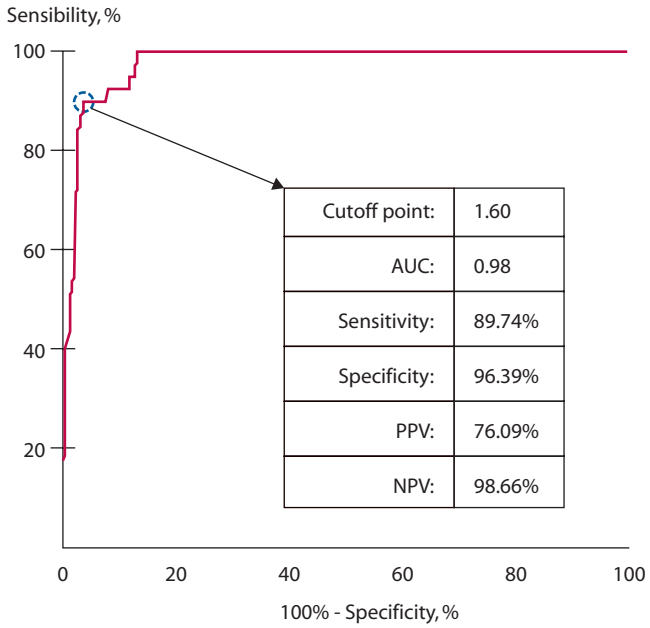

FIGURE 4. ROC curve for ΔCRP values predictive of postoperative IASCs. ΔCRP = (value of CRP 1 day before surgery/value of CRP 2 weeks before surgery) × 100%; IASC = intra-abdominal septic complication; ROC, receiver operating characteristic; AUC = area under the curve; PPV, positive predictive value; NPV, negative predictive value.

on patients with CD while disease activity is high results in high surgical stress, making a poor outcome more likely. Conversely, better outcomes are obtained when operations are performed during a period of remission or when the disease is trending toward remission. This suggests that the concept of damage control surgery may be applicable to CD,[17,18] although the idea that damage control surgery can explain the mechanism by which ΔCRP is predictive of IASCs remains an untested hypothesis that warrants further research.

The limitations of our study include the following. First, this study was a retrospective review, and complete details of postoperative complications other than IASCs or indexes of CD severity other than CRP levels were not available. Second, although this study had a sample size of 344, certainly not a small sample, all of the data were collected from a single center. Consequently, the exact cutoff values in our results may be too narrow to generalize our findings; multicenter studies are needed to rectify this issue. Third, CRP is a marker of disease activity, but it is not a specific indicator. Despite the exclusion of patients with active infections, the presence of unknown factors that could affect CRP levels (eg, medication changes) cannot be completely ruled out. Fourth, the number of patients receiving preoperative antitumor necrosis factor treatment was low, which may have impacted the statistical analysis and applicability of our findings.

TABLE 2. Multivariate analysis of factors associated with IASCs

Risk factor	*OR*	*95% CI*	*p*
CRP level >10 mg/L (1 day before surgery)	8.515	3.361–21.570	<0.01
Albumin level <35 g/L	1.451	0.625–3.369	0.387
Preoperative steroids for ≥3 mo	1.378	0.412–4.603	0.603
Failure of medical therapy	1.269	0.476–3.387	0.634

IASCs = intra-abdominal septic complications; CRP = C-reactive protein.

TABLE 3. Risk relationship and predictive value of CRP levels associated with IASCs

	Risk factors for IASCs		*Predictive value*	
Variable	*Univariate analysis, p*	*Multivariate analysis, p*	*PPV*	*NPV*
CRP level >10 mg/L (1 day before surgery)	<0.01	<0.01	34.07%	96.84%
CRP level >10 mg/L (2 weeks before surgery)	0.174	NC	NC	NC
CR-CRP ratio >1.6	<0.01	<0.01	76.09%	98.66%

IASCs = intra-abdominal septic complications; CRP = C-reactive protein; PPV = positive predictive value; NPV = negative predictive value; NC, not calculated.

CONCLUSION

To the best of our knowledge, this article is the first to report that the direction, and perhaps magnitude, of change in preoperative CRP levels, upward or downward, impacts the likelihood of postoperative IASCs. This information may help us to determine the most appropriate therapeutic strategy (stoma or anastomosis) for each patient. In addition, we found that when preoperative CRP levels are low (≤14.50 mg/L), we should correctly predict the absence of IASC 96.84% of the time. This indicates that preoperative treatment with the aim of reducing CRP levels (ie, inducing remission) may help to lower IASC rates.

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