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Early prediction of anastomotic leakage after laparoscopic rectal surgery using creactive protein

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Abstract

At present, anterior resection of the rectum or transabdominal rectal resection is the most common surgical technique for rectal cancer. Laparoscopic techniques are popular, and the efficacy and safety of laparoscopic rectal surgery have been confirmed. However, postoperative anastomotic leakage is a common, severe complication that leads to high mortality. Thus, early diagnosis of anastomotic leakage is important for reducing clinical consequences.

The aim of this study was to determine whether C-reactive protein (CRP) is a good predictor of anastomotic leakage in laparoscopic transabdominal rectal resection.

Our retrospective study involved a series of 196 rectal cancer patients who underwent laparoscopic transabdominal rectal resection without ileostomy between May 2013 and April 2015 at the Sir Run Run Shaw Hospital, Zhejiang University College of Medicine. The following patient data were collected: demographic data, manifestations of the complication, CRP levels and neutrophil percentage during the first 7 postoperative days.

Anastomotic leakage was detected in 11 patients (5.6%). Each group showed significant differences ($P < .05$) in CRP levels on postoperative days 3 to 7; compared with other groups, the anastomotic leakage group showed significant differences in CRP levels ($P < .05$) on postoperative day 6. When patients were divided into groups with or without anastomotic leakage, CRP was a reliable predictor on postoperative days 4 to 7 ($P < .05$, area under the curve > 0.800). The best combination was CRP on postoperative day 6 (area under the curve = 0.932) with a cut-off of 76.6 mg/L, resulting in a sensitivity of 83.3%, a specificity of 94.6% and a negative predictive value of 99%.

CRP is a reliable predictor of anastomotic leakage after laparoscopic transabdominal rectal resection surgery. High CRP levels on postoperative days 4 to 7 indicate the need for a more careful patient evaluation.

Abbreviations: AUC = area under the curve, CRP = C-reactive protein, N% = percentage of neutrophils, POD = postoperative day.

Keywords: anastomosis leak, colorectal surgery, C-reactive protein

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This study was approved by the ethics committee of Sir Run Run Shaw Hospital Zhejiang University College of Medicine.

Written consent was obtained from the patient for the patient's personal or clinical details along with any identifying images to be published in this study.

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The datasets generated and/or analyzed during the current study are not publicly available due to protecting individual patient privacy but are available from the corresponding author on reasonable request.

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1. Introduction

According to previous studies, the anastomotic leakage rate after colorectal surgery is between 2.7% and 9%.[1–3] These numbers are particularly shocking given that mortality is noted in approximately 27% of patients.[4] Moreover, patient quality of life is affected, and the length of hospital stay increases, resulting in higher expenses. Although early diagnosis of anastomotic leakage is critical for reducing morbidity and mortality, this condition is often diagnosed late because of misdiagnosis and false-negative radiological examinations.[5] Therefore, identifying a biological marker for the early prediction of anastomotic leakage is a growing need.

Recently, C-reactive protein (CRP) has been reported as an early predictor of infectious complications or postoperative anastomotic leakage after rectal resection in some clinical studies.[5] CRP is a classical acute-phase protein,[6–8] and its plasma concentration increases in response to acute inflammation, infection, tissue damage and cancer. During the acute-phase response, cytokines, predominantly interleukin-6 , originating from the site of pathologic injury, stimulate the synthesis of large quantities of CRP in hepatocytes. CRP levels will typically increase within 6 to 12 hours and peak approximately 48 hours after an inflammatory stimulus.[6–8] The increase is generally proportional to the degree of tissue damage.

Although CRP has been described as a valid parameter to detect postoperative infectious complications or anastomotic

leakage, specific studies should be undertaken to assess the role of CRP as an early predictor of anastomotic leakage.

The aim of our present study was to evaluate whether the plasma concentration of CRP can serve as an early predictor of anastomotic leakage by analyzing postoperative complications after laparoscopic rectal resection in our colorectal unit. CRP concentrations could represent a useful, practical measure for our clinical work.

2. Materials and methods

2.1. Study design

This study was a retrospective, single-center analysis conducted in a 60-bed colorectal unit in the Sir Run Run Shaw Hospital, Zhejiang University College of Medicine, China. The Institutional Review Board of Zhejiang University College of Medicine approved the study, and information about this study was obtained from hospital medical records.

This study was also approved by the Regional Ethics Committee of our hospital, and all patients signed informed consent forms.

2.2. Patient selection

Adults (≥18 years old) who were treated in our unit from May 2013 to April 2015 were screened for inclusion in this study. The exclusion criteria were sigmoid colon resection, abdominal-perineal resection and anterior resection without anastomosis. Metastatic rectal cancer was also excluded. Among the 256 patients who met the criteria, 15 were treated by open surgery and 45 by preventive terminal ileostomy. The remaining 196 patients who underwent laparoscopic anterior resection of the rectum without ileostomy were analyzed in this study.

All patients were administered prophylactic antibiotics, and a standardized anesthetic protocol was used. Abdominal drainage was routinely performed to monitor postoperative complications. All patients were managed by qualified colorectal surgeons.

2.3. Data collection

The following data were obtained from patients' medical records: age, sex and surgical approach. For this study, during the first 7 postoperative days, manifestations of complications, CRP levels and neutrophil percentage were also obtained from patients' medical records. For reference, CRP serum levels for healthy adults are less than 5 mg/L.

2.4. Definition of complications

Complications were recorded for all patients in accordance with previously defined criteria.[5] All anastomotic leakages were confirmed by fecal fluid drainage, digital rectal examination, signs of peritonitis with high fever, computed tomography (CT) scan, endoscopy or operation.[9] Abdominal infections were diagnosed by the manifestations of abdominal pain and distension or a CT scan. Wound infections were diagnosed based on the presence of clear signs of inflammation at the wound margin or purulent drainage from the wound. Pneumonia was diagnosed by pulmonary infiltration on a chest CT scan or chest X-ray accompanied by clinical symptoms of the lower respiratory tract, physical examination or laboratory tests.

2.5. Follow-Up

Patients were reviewed at the hospital or contacted through telephone or mail, every 3 months within the first 2 years after operation, every 6 months for the next 3 years, and annually thereafter in according with the NCCN Guidelines. Patients received a series of follow-up evaluations that included complete serum CEA and CA-199 measurements, and digital rectal examination. Liver color Doppler ultrasound, abdominal and pelvic CT, and chest X-ray were also performed.

2.6. Statistical analysis

Continuous variables are reported as the mean and standard deviation (SD), whereas categorical variables are reported as the number of patients and percentage. A univariate analysis of the differences between groups was performed by Student's *t* test and analysis of variance. Receiver operating characteristic curves and the value of the area under the curve (AUC) were used to analyze the accuracy of different variables as predictors of anastomotic leakage. The cut-off value was selected based on the Youden index (sensitivity + specificity − 1). $P < .05$ was considered to indicate statistical significance (2-tailed test). SPSS package version 17.0 for Windows was used for statistical analysis.

3. Results

A total of 196 patients were included in the present study. The preoperative characteristics of patients and surgical data are shown in Table 1. Details regarding postoperative complications are presented in Table 2. Anastomotic leakage was detected in 11 patients (5.6%). These patients were diagnosed between postoperative days 2 to 12. The median follow-up time was 40 months, during which 19 patients (9.7%) died. There was no significant difference in the 5-year survival rate between the two groups.

The mean CRP level significantly differed ($P < .05$) according to the postoperative outcome on postoperative days 3 to 7. The mean CRP values were significantly different ($P < .05$) between the anastomotic leakage group and other groups on postoperative day

Table 1

Preoperative characteristics of the patients and surgical data.

	Anastomotic leakage group (N = 11)	Nonanastomotic leakage group (N = 185)
Age, mean	58.2	60.8
Sex, n (%)		
Male	8 (72.7%)	118 (63.8%)
Female	3 (27.3%)	67 (36.2%)
Clinical stage*, n (%)		
Stage I	1 (9.1%)	13 (7.0%)
Stage II	4 (36.4%)	56 (30.3%).
Stage III	6 (54.5%)	116 (62.7%)
Differentiation, n(%)		
High-Moderate	9 (81.8%)	147 (79.5%)
Low-Mucinous	2 (18.2%)	38 (20.5%)
Tumor location from anal margin (0–15 cm), n(%)		
≤5cm	6 (54.5%)	55 (29.7%).
5–10cm	4 (36.4%)	66 (35.7%).
≥10cm	1 (9.1%)	64 (34.6%).

* TNM Classification, 8th edition.

Table 2

Postoperative morbidity.

	Patients N = 196 (%)
No complications	151 (77.0)
Anastomotic leakage*	11 (5.6)
Respiratory tract infectious complications	4 (2.0)
Wound infectious complications	2 (1.0)
Abdominal infectious complications	5 (2.6)
Other infectious complications	5 (2.6)
Noninfectious complications	18 (9.2)

* According to International Study Group of Rectal Cancer (ISREC) grading recommendations, there were 5 patients in B level and 6 in C level

6 based on the least significant difference test or Bonferroni multiple comparisons test (Table 3).

The mean values of CRP increased immediately after surgery. CRP decreased in patients without anastomotic leakage between postoperative days 4 to 7 and reached normal values. By contrast, CRP values peaked on postoperative day 3 and remained elevated in patients with anastomotic leakage. The neutrophil percentage did not exhibit such trends (Fig. 1).

When patients were divided into groups with or without anastomotic leakage, the AUC was > 0.800 for CRP on postoperative days 4 to 7 and reached its maximum value on postoperative day 6. The AUC was > 0.800 for the neutrophil percentage on postoperative days 3, 5, and 6 and reached its maximum value on postoperative day 3 (Table 4; Fig. 2).

The best combination was CRP on postoperative day 6 (AUC = 0.932), with a cut-off of 76.6 mg/L, resulting in a sensitivity of 83.3%, a specificity of 94.6% and a negative predictive value of 99% (Table 5). We analyzed 11 patients with anastomotic leakage; the average time of anastomotic leakage diagnosis was 7.34 days after surgery. Seven patients were diagnosed with anastomotic leakage after the 7th postoperative day by a physical examination or an imaging method.

4. Discussion

Anastomotic leakage is one of the most serious postoperative complications of a rectal operation. Although the early diagnosis of anastomotic leakage is critical in reducing morbidity and mortality, the condition is often diagnosed late due to misdiagnosis and false-negative radiological examinations.[5] Therefore, the aim of the present study was to identify a sensitive, specific, convenient biological marker for the early prediction of anastomotic leakage for laparoscopic transabdominal rectal resection surgery. In the present study, the incidence of anastomotic leakage was 5.6%, which is similar to that reported by international colleagues.

CRP is a classical acute-phase protein.[6–8] The plasma concentration of CRP increases in response to acute inflammation, infection, tissue damage, and cancer. During the acute-phase response, cytokines, predominantly interleukin-6, originating from the site of pathologic injury, stimulate the synthesis of large quantities of CRP in hepatocytes. CRP levels typically increase within 6 to 12 hours and peak approximately 48 hours after an inflammatory stimulus.[6–8] This increase is generally proportional to the degree of tissue damage. In the present study, CRP levels increased after surgery in all groups. Due to reduced tissue damage or the use of anti-infective drugs, CRP decreased in patients without anastomotic leakage, including those with infectious complications, after postoperative day 3. Therefore, the curves of infectious complications and no infectious complications in Figure 1A are almost the same. However, anastomotic leakage is a serious tissue injury that results in severe pathophysiologic reactions. Accordingly, CRP levels peaked on postoperative day 3 and remained high in patients with anastomotic leakage. In contrast, the neutrophil percentage did not exhibit a similar trend.

Bacterial contamination during anastomotic suture[10,11] is a major cause of anastomotic leakage, which leads to increased CRP levels. In addition, chronic infection of the anastomosis may lead to leakage. Thus, CRP levels increase before the clinical diagnosis of anastomotic leakage. In contrast, in other infectious complications, CRP levels increase simultaneously with infections without anastomotic leakage. Other factors such as increased white blood cell count or high body temperature also indicate inflammation, such as lung infection, urinary tract infection, incision infection, etc. However, they are not as specific as CRP, which can be used as an indicator of anastomotic leakage.

Through further comparison, the mean CRP level was significantly different ($P < .05$) according to the postoperative outcome on postoperative days 3 to 7. The mean CRP values significantly differed ($P < .05$) between the anastomotic leakage group and other groups on postoperative day 6. Thus, we can monitor postoperative CRP levels to reduce the morbidity and mortality caused by late diagnosis of anastomotic leakage.[12,13]

Table 3

CRP mean values and analysis of variance *P* values during the first 7 postoperative days between different complication groups.

	POD1	POD2	POD3	POD4	POD5	POD6	POD7
Anastomotic leakage	60.3	96.0	142.8	92.5	85.6	99.1	77.8
N = 11	(20.7)	(72.5)	(74.4)	(23.6)	(11.5)	(47.7)	(43.0)
Infectious complication	66.3	75.9	92.1	100.1	44.2	25.5	23.6
N = 16	(34.7)	(39.2)	(62.7)	(0.4)	(30.4)	(19.1)	(13.2)
Noninfectious complication	46.6	70.8	76.2	84.0	45.8	31.4	28.3
N = 18	(23.7)	(18.9)	(31.6)	(39.6)	(26.0)	(17.1)	(17.3)
No complications	49.7	79.6	76.0	47.5	36.7	32.0	27.4
N = 151	(26.9)	(28.8)	(43.8)	(30.8)	(25.0)	(27.5)	(25.6)
P	.186	.775	.018	.009	.035	<.001	.02

Data are expressed as the mean (SD), mg/L, or *P* value.

The mean CRP was significantly different ($P < .05$) between the anastomotic leakage group and other groups on postoperative day 6 by least significant difference (LSD) or Bonferroni multiple comparison.

CRP = C-reactive protein, POD = postoperative day.

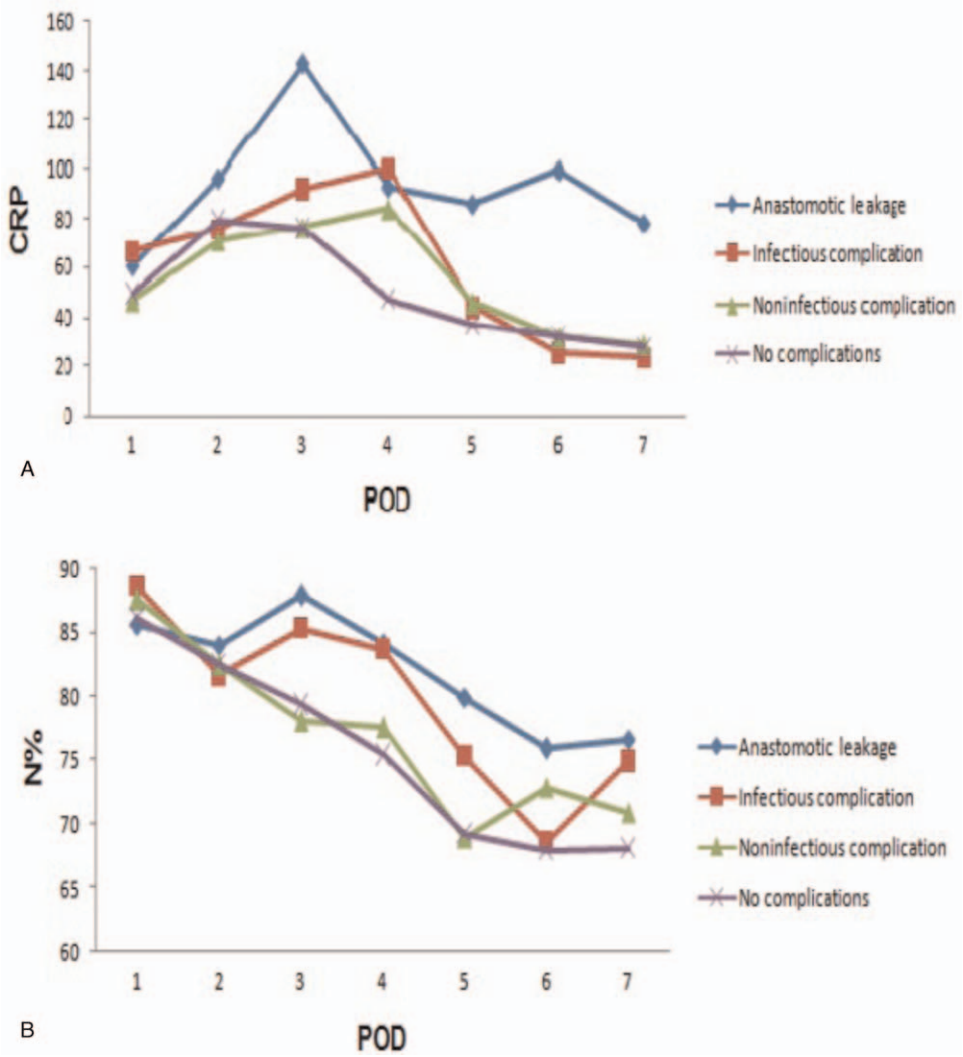

Figure 1. (A) Mean C-reactive protein values expressed in milligrams per liter according to the postoperative outcome. (B) Mean percentage of neutrophil values expressed according to the postoperative outcome.

Table 4

CRP and percentage of neutrophil mean values of patients with or without anastomotic leakage during the first 7 postoperative days.

	POD	Non-anastomotic leakage group (N = 185)	Anastomotic leakage group (N = 11)	*P*	AUC
CRP, mg/L	1	50.9 (27.6)	60.3 (20.7)	.38	0.625
	2	78.4 (28.8)	96.0 (72.5)	.36	0.622
	3	78.2 (45.1)	142.8 (74.4)	.002	0.766
	4	53.3 (33.6)	92.5 (23.6)	.05	0.856
	5	39.2 (25.9)	85.6 (11.5)	.004	0.922
	6	31.2 (25.4)	99.1 (41.7)	< .001	0.932
	7	27.3 (22.0)	77.8 (43.0)	.001	0.875
N%	1	86.4 (4.3)	85.5 (3.1)	.51	0.420
	2	82.3 (4.6)	84.0 (4.6)	.40	0.605
	3	80.0 (5.9)	87.8 (3.2)	.001	0.885
	4	76.0 (7.8)	84.1 (6.9)	.03	0.770
	5	70.1 (8.4)	79.9 (7.8)	.02	0.805
	6	68.4 (8.3)	75.9 (4.6)	.01	0.817
	7	69.6 (7.7)	76.6 (11.0)	.09	0.696

Data are expressed as the mean (SD), *P* value, or area under the curve.

N% = percentage of neutrophils, AUC = area under the curve, CRP = C-reactive protein, POD = postoperative.

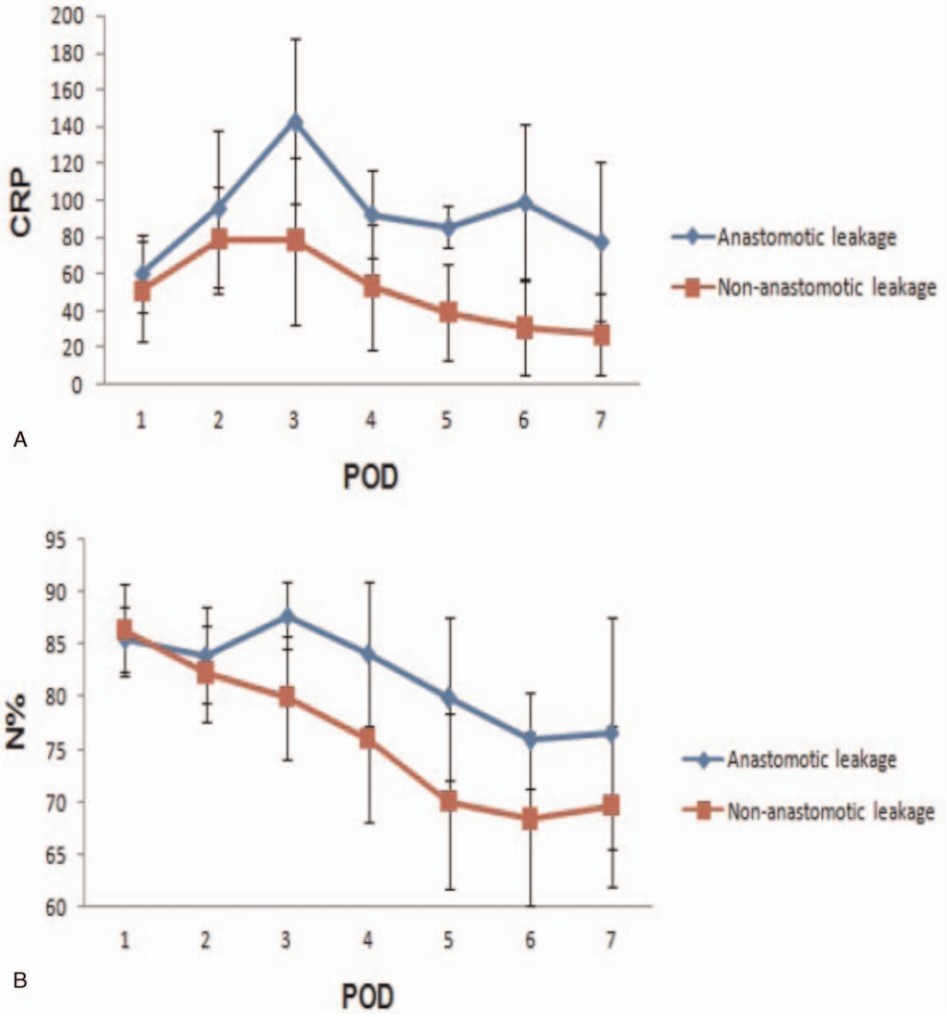

Figure 2. (A) Mean C-reactive protein values expressed in milligrams per liter according to the postoperative outcome. (B) Mean percentage of neutrophil values expressed according to the postoperative outcome.

The present study shows that CRP is a useful predictor for anastomotic leakage, with a high negative predictive value on postoperative days 4 to 7 and a maximum AUC of 0.932 on postoperative day 6 (with a cut-off value of 76.6 mg/L and a negative predictive value of 99%). We analyzed 11 patients with anastomotic leakage and found that the average time of anastomotic leakage diagnosis was 7.34 days after surgery. After the 7th postoperative day, 7 patients were diagnosed with anastomotic leakage by a physical examination or an imaging method. The other 4 cases of anastomotic leakage occurred on

Table 5

Best cutoff for predicting anastomotic leakage with C-reactive protein, percentage of neutrophils on postoperative days 3 to 7 and the relative sensitivity, specificity, and positive and negative predictive values.

	POD	AUC	Cutoff	Sensitivity at cutoff, %	Specificity at cutoff, %	PPV, %	NPV, %
CRP, mg/L	3	0.766	103.15	66.7	83.6	19	98
	4	0.856	64.35	100	75.7	20	100
	5	0.922	72.15	100	88.2	33	100
	6	0.932	76.6	83.3	94.6	68	99
	7	0.875	56.55	75	90.9	33	98
N%	3	0.885	82.25	100	65.3	14	100
	4	0.770	87.1	60	97.7	61	98
	5	0.805	79	80	82.5	21	99
	6	0.817	71.85	88.9	75.6	18	99
	7	0.696	72.35	80	66.7	12	98

AUC = area under the curve, CRP = C-reactive protein, N% = percentage of neutrophils, NPV = negative predictive value, POD = postoperative, PPV = positive predictive value.

the 3rd (2 cases), 4th and 5th day after operation respectively. The CRP of these patients was higher than the normal value on the third day after operation.

Currently, the treatment of anastomotic leakage after rectal surgery is mainly conservative treatment, including antibiotics, nutritional support and drainage, and reoperation. In addition, patients with acute diffuse peritonitis or septic shock require reoperation as soon as possible. In the present study, 6 patients required reoperation, and 2 of these patients were diagnosed with anastomotic leakage prior to postoperative day 6.

The International Study Group of Rectal Cancer (ISREC) in 2010 recommended that postoperative anastomotic leakage after rectal surgery could be defined as the lack of intestinal wall integrity at colon-rectal anastomosis or colon-anal anastomosis. The study group also recommended that the anastomotic leakage could be divided into three grades according to the effect of anastomotic leakage on clinical decision making. A: asymptomatic anastomotic leakage; B: obvious clinical symptoms; C: need surgical intervention again. In our study, there were 11 patients with complication of anastomotic leakage. According to ISREC grading recommendations, there were 5 patients in B level and 6 in C level.

The usefulness of CRP as a marker for infectious complications after colorectal surgery has been previously demonstrated by other authors.[14,15] Similarly, many authors have shown that the CRP serum concentration significantly increases immediately after surgery and tends to normalize on postoperative day 3 in patients without complications. According to Matthiessen et al,[14] persistent increases in CRP after rectal resection suggest anastomotic leakage, and its evaluation in the postoperative period could be useful for early anastomotic leakage detection. However, in their study, a cut-off value was not established. In another study, MacKay et al[16] recently demonstrated that CRP is a good marker for infectious complications after elective colorectal surgery with a cut-off value of 145 mg/L, but they did not specifically analyze its usefulness for anastomotic leakage prediction. According to a Spanish study,[5] CRP is a good predictor for major anastomotic leakage on postoperative days 3, 4 and 5, with a maximum AUC of 0.85 on postoperative day 5 (with a cut-off value of 135 mg/L and a negative predictive value of 98%).

CRP had a low positive predictive value on postoperative days 4 to 7 in our present study. A potential reason is that some severe infections and anastomotic leakage events could not be identified by the increased CRP value, which is more prone to false positive results. However, the CRP value as an early predictor of anastomotic leakage remains meaningful. In the present study, the best combination was CRP on postoperative day 6 (AUC = 0.932), with a 99% negative predictive value. We also found that the average time of anastomotic leakage diagnosis was 7.34 days after surgery, and 7 patients were diagnosed with anastomotic leakage after the 7th postoperative day by a physical examination or an imaging method in our study. In addition, this study has clinical significance because we determined that CRP is a good predictor of anastomotic leakage in laparoscopic transabdominal rectal resection; CRP can enable clinicians to intervene as soon as possible to reduce morbidity and mortality.[1,17–22] We did not identify another gold standard for anastomotic leakage diagnosis. Therefore, increased CRP values should indicate further imaging explorations, that is, CT scan,[23,24] to exclude the presence of anastomotic leakage. CRP is a sensitive inflammatory biomarker. When postoperative CRP levels are persistently elevated or remain high, which likely suggests the existence of anastomotic leakage, the time of diagnosis should be reduced. Moreover, an antibiotic treatment strategy or even reoperation should be implemented to reduce morbidity and mortality.[5,25]

Several limitations in our study require consideration. For example, this study was retrospective, involved a single center and included a limited number of patients with heterogeneous backgrounds. More international multi-institutional data are necessary because our study included only 11 patients with anastomotic leakage, which may lead to the statistical bias of the results. However, the anastomotic leakage incidence of 5.6% is the same as that reported by international colleagues. Thus, we believe that our study also provides important information. After more international multi-institutional data are collected, we can perform relevant prospective studies in the future.

5. Conclusion

CRP is a reliable predictor of anastomotic leakage after laparoscopic transabdominal rectal resection surgery. Therefore, we can monitor postoperative CRP levels in our clinical work to properly prevent and address the complication of anastomotic leakage.

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