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ORIGINAL ARTICLE

Diagnostic Accuracy of C-reactive Protein for Intraabdominal Infections After Colorectal Resections

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Abstract

Background Intraabdominal infections are caused mainly by anastomotic leaks and represent a serious complication. Diagnosis is usually made when patients become critically ill. Though inflammatory markers, including C-reactive protein (CRP) and white blood count (WBC), may contribute to an early diagnosis, their clinical roles remain unclear. The diagnostic accuracy of continuous tests depends on the choice of cut-off values. We analyzed the diagnostic accuracy of serial CRP and WBC measurements to detect infectious complications after colorectal resections.

Patients and Methods The CRP and WBC were routinely measured postoperatively in 231 consecutive patients undergoing colorectal resection. Clinical outcome was registered with regard to postoperative complications. The diagnostic accuracy of CRP and WBC was analyzed by receiver operating characteristics (ROC) curve analysis with intra- and extraabdominal infectious complications as the outcome.

Results Increased CRP levels on postoperative day (POD) 3 were associated with intraabdominal infections. The best cut-off value was 190 (sensitivity, 0.82; specificity, 0.73). The area under the ROC curve was 0.82. On POD 5 and 7, the diagnostic accuracy of CRP was similar.

Conclusion Serial CRP measurements are helpful for detecting intraabdominal infections after colorectal resection. Persistently elevated CRP values after POD 3 should be investigated for intraabdominal infection.

Keywords C-reactive protein · Diagnostic accuracy · Receiver operating characteristics curve analysis · Anastomotic leak · Diagnostic accuracy · Intraabdominal infection

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Introduction

Colorectal surgery is associated with overall complication rates of more than 30% and a perioperative mortality of 3–4%.[1–4] Despite the use of preoperative antibiotic prophylaxis, infections still represent the most frequent cause of perioperative morbidity.[5–8] Intraabdominal infections are related primarily to anastomotic leaks and are potentially life-threatening. Anastomotic leaks occur with a frequency of up to 23%.[9–11] In roughly half of patients, anastomotic leaks are clinically silent[11] and may first become evident after a median of 8 days, often when patients have developed critical illness.[12] Consequently, it is important to diagnose infectious complications early in order to initiate either surgical or conservative treatment, preventing serious postoperative morbidity or death. However, there is presently no reliable diagnostic test with sufficient accuracy available to detect anastomotic leaks at an early stage.[11,13]

Several biochemical tests are used to detect inflammatory activity in postoperative patients, including C-reactive protein (CRP), interleukins, and procalcitonin.[14–16] The measurement of CRP in the serum is the most available test and has been used widely in clinical practice to detect infections and monitor their treatment.[17–20] Recently, it was shown that CRP might be useful for diagnosing anastomotic leaks after pancreatic and rectal resections with sensitivities and specificities between 65% and 80%.[21,22] However, CRP levels change considerably during the postoperative course in both uncomplicated and complicated cases, and they are not specific to any one kind of complication.[22] Accordingly, it is important to take into account postoperative changes in CRP levels observed by serial measurements after surgery. In addition, other factors, like the nutritional state of the patient, may influence the response of biochemical tests and make the correct interpretation of test results difficult.[8,23]

C-reactive protein is measured as a continuous variable. The diagnostic accuracy of continuous variables strongly depends on the chosen cut-off value.[24] A correct statistical approach has been to analyze the complete spectrum of observed test results. Receiver operating characteristics curve (ROC) analysis is considered the appropriate statistical method for this purpose.[25]

In our department, CRP measurements are performed on scheduled postoperative days (POD) as a part of the follow-up for patients undergoing colorectal surgery. In this study, we wanted to analyze the diagnostic accuracy of serial CRP measurements after colorectal resections to detect intra-abdominal infections using ROC analysis in a large series of unselected consecutive patients.

Patients and Methods

Our institution offers surgical services as the only hospital for a population of 300,000. Between January and December 2004, 246 consecutive patients underwent colorectal resections at our department. Data regarding diagnoses and procedures, biochemical tests, and radiological procedures were retrieved from the electronic patient registry of our hospital. Patient charts were reviewed retrospectively with regard to the clinical details of postoperative complications or death. Complete data were available for the analysis of 231 (94%) patients.

Preoperative routines included high calorie carbohydrate drinks until 2 h before surgery, subcutaneous low molecular heparin, and antibiotic prophylaxis (400 mg doxycycline i.v. and 1.5 g metronidazole i.v. at least 30 min before surgery). Mechanical bowel preparation was not used routinely. Patients received peroral nutrition immediately after surgery according to their personal preferences and abilities and intravenous Ringer acetate if necessary.

On the day before the surgery, all patients had routine blood tests, including hemoglobin, creatinine, electrolytes, CRP, and white blood count (WBC). Postoperatively, all patients had a daily clinical assessment, and routine blood tests were repeated on POD 1, 3, 5, and 7. Additional investigations, including radiological or endoscopic procedures, were employed as indicated clinically.

Definitions

Postoperative complications were defined as all adverse events encountered during the first 30 days after surgery, which was until the discharge of the patient from the hospital or their readmission to our department or outpatient contact due to complications. Patients were examined for the presence of any infection according to general surgical practice: clinical symptoms, temperature ≥38°C, and/or increased inflammatory biochemical markers (i.e., CRP or WBC). *Intraabdominal infection* was defined as an infection, either diffuse or abscess, within the abdominal cavity or the presence of an anastomotic leak. An *anastomotic leak* was confirmed by radiology (i.e., contrast enhanced multi-detector CT scan or conventional radiology with water soluble contrast enema), endoscopy, or during surgical exploration. *Other infectious complications* were defined as extraabdominal infections, mostly urinary tract infections (i.e., bacteriuria >10,000/ml with or without clinical symptoms) or pneumonia (temperature ≥38°C, clinical findings, and/or pulmonary infiltration at chest X-ray), or *wound infections* (i.e., phlegmonous inflammation or abscess formation in the surgical wound). *Cardiovascular complications* included acute myocardial infarction, stroke, pulmonary thromboembolism, or deep venous thrombosis.

Biochemical Analysis

The WBC (reference range $4–10\times10^9$/L) was analyzed using a hematological blood analyzer (Advia 120, Bayer, or CellDyn, Abbott). The CRP concentration (normal range 0–10 mg/L) was measured by immunoturbidimetric assay (Roche, Switzerland).

Statistics

Data were analyzed using frequency tables for category variables. The median value was used as a measure of the central tendency for continuous variables with non-normal distributions. The chi-square test was used for comparing category variables and the Mann–Whitney *U* test for continuous variables. The diagnostic accuracy of inflammatory tests, CRP or WBC, was assessed by ROC curve analysis.[24–26] This method calculates the sensitivity and specificity of each observed test result with regard to a defined classification variable, identifying the best cut-off value as the test result with the highest sensitivity and specificity. A 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 best cut-off value. The area under the ROC curve (AUC) is a direct measure of the diagnostic accuracy of the test. An AUC value greater than >50% indicates the ability of a test to significantly discriminate between positive and negative cases with regard to the classification variable (e.g., presence or absence of disease). A test with an AUC greater than 0.80 was considered as having a high diagnostic accuracy, which indicates that at least 80% of the patients with the disease were classified correctly.

A P value <0.05 (two-sided tests) was considered significant.

Results

Surgical Treatment

Two hundred and thirty-one patients (125 females, 54%) underwent colorectal resection (Table 1). The median age was 71 years (range, 18–93) in both sexes. Significantly more elderly patients (≥71 years of age) had comorbidities as expressed by ASA class III and IV (47% vs. 30%; P<0.001). The distribution of diagnoses and surgical procedures is

Table 1 Clinical Characteristics of 231 Patients Treated by Colorectal Resection, Including the Distribution of Diagnoses and Surgical Procedures

	Total number	P value[a]	Intraabdominal infection		Extraabdominal infection		P value[b]
			N	(%)	N	(%)	
Sex		0.24					0.45
Male	106		11	(5)	15	(6)	
Female	125		7	(3)	17	(7)	
Age group[c]		1					0.40
≤71	116		9	(4)	12	(5)	
>71	115		9	(4)	20	(9)	
ASA		<0.001					0.14
1	34		2	(1)	2	(1)	
2	107		4	(2)	14	(6)	
3	66		7	(3)	10	(4)	
4	24		3	(1)	6	(3)	
Emergency		<0.001					<0.05
No	176		10	(5)	20	(9)	
Yes	55		7	(3)	10	(5)	
Diagnosis		<0.001					0.14
CRC	146		9	(4)	21	(9)	
IBD	16		0	(0)	2	(1)	
Others	69		9	(4)	9	(4)	
Type of anastomosis		0.4					0.05
Entero-colic	97		4	(2)	16	(7)	
Colo-colic	60		10	(4)	4	(2)	
Pelvic	47		3	(1)	9	(4)	
Ostomy	27		1	(0)	3	(1)	

Other diagnoses included colorectal adenoma, complicated appendicitis, or diverticular disease. The number of infectious complications with regard to intra- and extraabdominal infections (i.e., pneumonia, urinary tract infection, or surgical site infection) are given

[a] P value between groups in category

[b] P value between groups of infection

[c] Age groups defined by median age

shown in Table 1. Most patients (77%) were operated electively. The majority of patients (n=146; 63%) were treated for colorectal cancer (CRC) and 16 (7%) for inflammatory bowel disease (IBD). The remaining patients (n=69; 30%) underwent surgery for various indications (i.e., diverticular disease, bowel obstruction, colorectal adenoma, and complicated appendicitis). Significantly more proximal resections, ileocecal resection and right colectomy, were done as emergency procedures (P=0.007). Resections were performed according to current surgical standards with both hand-sewn or stapled anastomoses. Rectal resections were performed with a triple stapling technique.[27] Most procedures were done by open surgery, and ten (4%) laparoscopy-assisted sigmoid resections were performed. Two hundred and one (87%) of the procedures included an anastomosis, mostly entero-colostomy (P=0.001).

Complications

Complications were encountered in 60 (26%) patients. The majority of complications were extraabdominal infections (n=33, 55%), followed by intraabdominal infections (n=18, 30%). Intraabdominal infections were diagnosed after a median time of 8 days (95% confidence interval, 4–9 days). There were eight cases of cardiovascular complications and two cases of other complications. Eight patients (13% of those with complications; 3% of all patients) died within 30 days after surgery. Seven of these eight postoperative deaths were related to complications, two to intraabdominal sepsis, three to other infections, and two to cardiovascular complications. The clinical characteristics with regard to extra- or intraabdominal infections are shown in Table 1. Complications were encountered significantly more often after emergency operations and were related to the type of anastomosis. Fifteen (83%) of the 18 patients with intraabdominal infections underwent either surgical treatment or percutaneous drainage, and three were treated conservatively.

Inflammatory Markers

The test results for inflammatory markers during the postoperative course and with regard to complications are shown in Table 2. On POD 1, increased CRP levels of approximately 100 Mg/L were observed in all patients. Eventually, CRP decreased in patients with an uncomplicated postoperative course (Fig. 1a). In contrast, CRP eventually increased over the following days when complications occurred. The increase was significantly higher in patients with intraabdominal complications as compared to other sites of infection (median, 257 Mg/L vs. 202 U/mL, P=0.024; Table 2). This difference was even greater on POD 5 and 7. The baseline course of CRP values was similar irrespective of IBD or CRC (Fig. 1b).

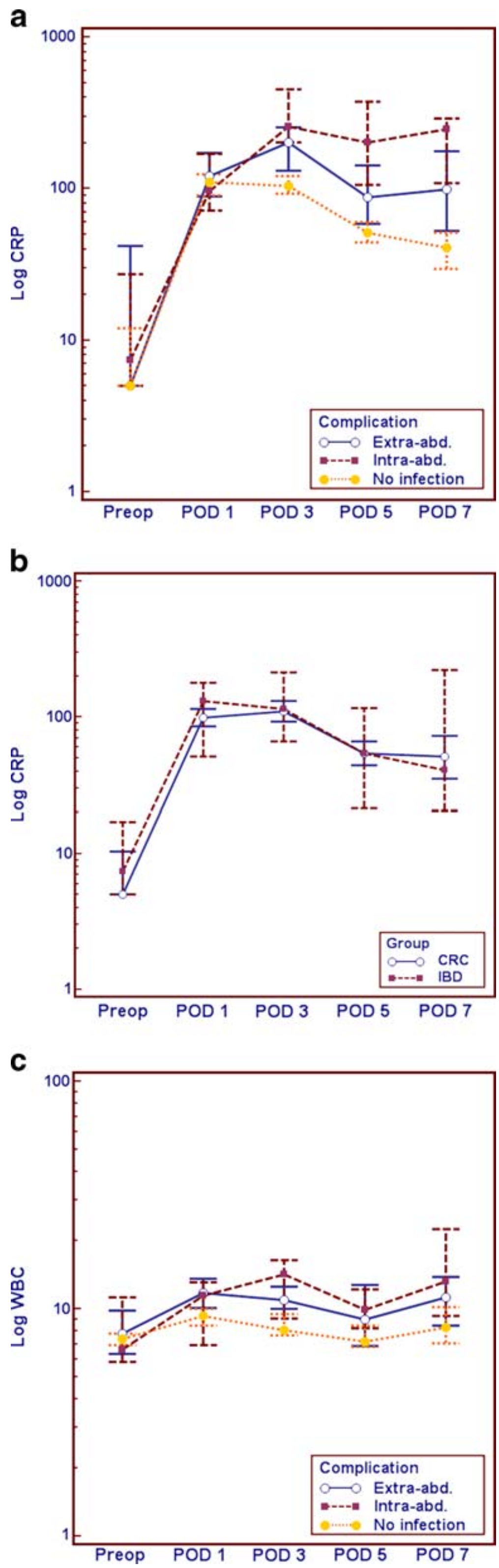
The postoperative WBC levels were less than 10.0 in patients without complications and were only slightly elevated in patients with extraabdominal infections (Fig. 1c). However, in patients with intraabdominal complications, a significantly increased WBC (median 14.2, P=0.02) was encountered on POD 3.

The results of the inflammatory marker ROC analysis with regard to intra- and extraabdominal complications are shown in Table 3. On POD 3, a cut-off value of >190 for CRP was associated with the occurrence of intraabdominal complications, providing a sensitivity of 82%, specificity of 73%, and a high diagnostic accuracy (AUC, 0.82; 95% CI,

Table 2 Test Results for C-reactive Protein (CRP) and White Blood Count (WBC) During the Postoperative Course of 231 Patients who Underwent Colorectal Surgery

	Median (lowest-highest) uncomplicated	Median (lowest-highest) intraabd. sepsis	Median (lowest-highest) other infection	P value
CRP preop.	5 (5–559)	8 (5–211)	5 (5–413)	0.95
CRP day 1	112 (12–462)	96 (35–331)	124 (15–463)	<0.001
CRP day 3	114 (5–548)	257 (74–586)	202 (26–424)	0.024
CRP day 5	54 (5–543)	202 (60–406)	87 (20–342)	0.0014
CRP day 7	48 (5–574)	246 (35–336)	99 (5–333)	0.003
WBC preop.	7.5 (0.6–33.4)	6.6 (2.5–16.5)	7.8 (0.6–14.6)	0.93
WBC day 1	9.5 (0.4–13.8)	11.4 (6.3–15.3)	11.4 (0.4–16.2)	0.31
WBC day 3	9 (0.4–22.7)	14.2 (7.2–18.4)	11.1 (0.5–13.7)	0.02
WBC day 5	7.6 (0.6–23.2)	9.9 (6.9–19.5)	9 (0.3–29.8)	0.36
WBC day 7	9 (0.7–19.4)	13.3 (7.5–24.8)	11.2 (5.4–31.3)	0.13

Tests were taken at postoperative days 1, 3, 5, and 7. The upper normal value of CRP was <10 u/mL and 10.0 for WBC. Median, lowest, and highest values are given for patients without complications, patients with intraabdominal infections, and patients with other infections. The median values for intraabdominal and other infections were compared by the Mann–Whitney U test



◀**Figure 1** Serial measurement of inflammatory markers in 231 patients undergoing colorectal resection. Median values with 95% confidence intervals are given. **a** C-reactive protein (*CRP*) increased in all patients on postoperative day (*POD*) 1. The CRP increase on POD 3 was highest in patients who developed intraabdominal infections, and it persisted on POD 5 and 7 (*red line*). In uncomplicated cases (*yellow line*), CRP decreased after POD 3. In patients with extraabdominal infections (*blue line*), the CRP increase was smaller and decreased after POD 3. **b** WBC changes were limited and showed small differences with regard to complications. **c** CRP values were similar during the postoperative course in patients undergoing surgery for inflammatory bowel disease or colorectal cancer.

0.76–0.87; P=0.0001; Fig. 2). On POD 5 and 7, similar results were found (Fig. 3). Cut-off values for WBC were only slightly increased above the upper normal limit and were associated with lower sensitivity and specificity. The diagnostic accuracy was lower for WBC, as expressed by AUC values <0.80.

The ROC analysis of CRP with regard to other infections resulted in AUC values with significant information on POD 3 and 5 compared to POD 1 for WBC (Table 3). However, the AUC values were less than 0.70. In general, the cut-off values of WBC with the highest diagnostic accuracy were mostly within the normal range or showed a mild increase and had low sensitivity and specificity.

Discussion

In our study, an infectious complication was encountered after colorectal resection in one out of every four patients, and one third of the infectious complications were localized in the abdomen. Intraabdominal infections are mostly caused by anastomotic leaks, which are still a potentially life-threatening condition. Unfortunately, the diagnosis is often made on POD 8 or later, when many patients present with signs of serious illness or even sepsis, which was also true in the present study.[12] Thus, a method for the early identification of patients at risk for intraabdominal infection would be of clinical importance. Inflammatory markers like CRP and WBC are part of the standard repertoire of available biochemical blood tests and have been used in clinical practice for years. However, the surgical literature is sparse with regard to the systematic use of CRP and WBC in this aspect. Recently, the possible role of CRP to detect anastomotic leaks after rectal resection was addressed in two studies.[22,28] Both studies reported persistently increased CRP values after POD 2–4 in patients later diagnosed with an anastomotic leak. Matthiessen et al.[28] prospectively studied several risk factors for anastomotic leaks in 33 patients, and Welsch et al.[22] compared 48 patients with anastomotic leaks to 48 matched patients with an uncomplicated postoperative course from a large database. However, in both studies, the median CRP values were used as cut-offs with their corresponding diagnostic accuracy.

Our study reports on serial postoperative CRP measurements on a routine basis in 231 consecutive patients

Table 3 Receiver Operating Characteristics Curve Analysis of C-reactive Protein (CRP) and White Blood Count (WBC) During the Postoperative Course of 231 Patients After Colorectal Surgery

	Cut-off value	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	*P* value	Cut-off 90% sens.	Cut-off 90% spec.
Intraabdominal infection							
CRP day 1	89	50 (25–75)	61 (53–69)	0.53 (0.46–0.6)	0.66	226	45
CRP day 3	190	82 (56–96)	73 (66–79)	0.82 (0.76–0.87)	<0.001	81	269
CRP day 5	154	75 (48–93)	86 (80–91)	0.87 (0.88–0.92)	<0.001	65	171
CRP day 7	215	75 (48–93)	94 (88–97)	0.86 (0.79–0.91)	0.001	35	–
WBC day 1	10.6	62 (32–86)	63 (54–71)	0.58 (0.49–0.66)	0.38	6.5	–
WBC day 3	13.1	69 (39–91)	82 (74–88)	0.76 (0.68–0.83)	0.002	7.2	14.8
WBC day 5	9.4	80 (44–97)	72 /62–81)	0.72 (0.63–0.81)	0.02	6.9	18.4
WBC day 7	12.5	67 (35–90)	80 (68–89)	0.77 (0.66–0.86)	0.001	7.5	15.1
Extraabdominal infection							
CRP day 1	77	89 (70–97)	31 (24–39)	0.59 (0.51–0.66)	0.17	59	323
CRP day 3	114	78 (60–91)	52 (44–60)	0.66 (0.59–0.72)	0.005	57	270
CRP day 5	65	72 (53–87)	57 (49–65)	0.62 (0.55–0.69)	0.045	29	211
CRP day 7	57	73 (52–88)	56 (46–66)	0.62 (0.53–0.70)	0.07	13	228
WBC day 1	10.2	72 (53–92)	64 (54–72)	0.69 (0.61–0.77)	0.005	8.8	15.3
WBC day 3	9.7	82 (60–95)	60 (50–69)	0.62 (0.53–0.70)	0.09	6.6	–
WBC day 5	8.6	61 (36–73)	62 (51–73)	0.62 (0.52–0.73)	0.12	6.2	13.5
WBC day 7	7.6	94 (71–99)	36 (27–49)	0.62 (0.50–0.73)	0.13	7.5	15.1

Analysis was performed with regard to intraabdominal infections and other infectious complications. The best cut-off value, sensitivity, specificity, area under the ROC curve (AUC), and 95% confidence intervals (95% CI) are given, as well as values for 90% sensitivity and specificity. The *P* value of the AUC indicates the statistical ability to discriminate between positive and negative cases (AUC>0.50)

undergoing colorectal resection. We elaborated the cut-off values with the highest diagnostic accuracy by ROC analysis on each POD with the scheduled blood tests. The advantage of our statistical approach is the possibility to consider the complete spectrum of the observed test results, not only a single value like the median. In our study, the cut-off value with the highest diagnostic accuracy was found to be lower than the median values. Our results clearly support the findings from earlier studies[22,28] showing that increased CRP values on POD 3 strongly indicate a high risk for developing an anastomotic leak

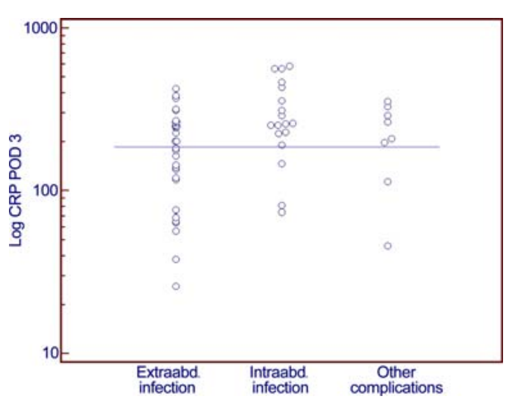


Figure 2 Dot diagram of CRP values on POD 3 of all patients according to type of complication. The *dotted line* indicates the cut-off value with highest sensitivity and specificity as revealed by ROC analysis. CRP values greater than 190 Mg/L were observed in 15 of 18 patients (83%) with intraabdominal infection.

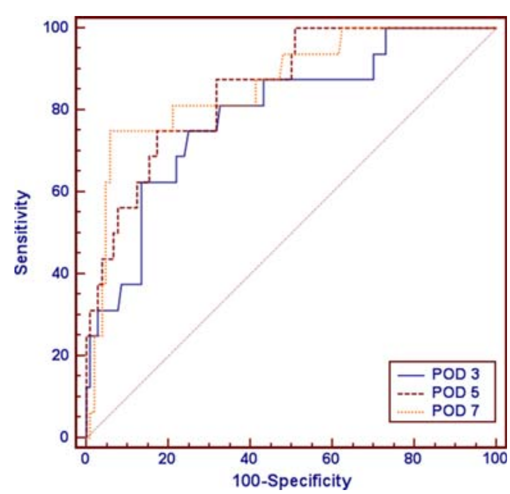


Figure 3 Diagnostic accuracy (DA) of CRP with regard to intra-abdominal infections after colorectal resection as expressed by the ROC curve. Comparison of ROC curves shows that the diagnostic accuracy was similar on POD 3, 5, and 7, as expressed by the AUC values of 0.82, 0.87, and 0.86, respectively.

during the later course. The diagnostic accuracy of CRP on POD 3 was as high as it was on POD 5 and 7. Accordingly, in patients with high CRP levels on POD 3, an undetected anastomotic leak should be suspected if the increased CRP levels are not easily explained by some other obvious diagnosis or condition. This view is challenged by others[29] who analyzed the perioperative use of CRP measurements in 201 patients undergoing elective general surgery. The study did not recommend the routine use of measuring CRP but only when clinically indicated. However, the study focused on perioperative CRP measurements, which were not taken according to a routine schedule. Furthermore, their study did not report on the details of the surgical procedures or complications. However, our results indicate that serial postoperative CRP measurements in patients undergoing colorectal resection after POD 3 may contribute to an earlier diagnosis of an anastomotic leak.

The aforementioned studies[22,28] related their findings to surgically homogenous patient groups undergoing rectal resection. However, CRP is not specific for any organ site or particular procedure. Our study on unselected patients undergoing colorectal resection for the most common indications (CRC, IBD, or common colorectal emergencies) shows that similar findings apply as for rectal resection. Other reports demonstrated similar unfavorable results in patients with a persistent increase in CRP undergoing pancreatic resection[21] or combined pancreas–kidney transplantation.[30]

Our findings are based on a retrospective evaluation of 231 consecutive patients. In line with others, the number of clinical events (18 patients with intraabdominal infections) was rather low, which limits the statistical power of our analyses. Consequently, our findings must be interpreted with caution. Prospective studies are warranted to evaluate the clinical validity and relevance of our findings. However, despite this limitation, our study provides support for the view that serial measurements of CRP after colorectal resection are useful for identifying patients at risk for developing intraabdominal infections. We suggest that, in patients with persisting high, or even increasing, CRP values after POD 3, diagnostic efforts should be considered to exclude any anastomotic leak, particularly when other causes of increased CRP levels are unlikely.

Conclusion

Increased CRP values of 190 Mg/L or more on POD 3 after colorectal resections were associated with anastomotic leak in four of every five patients, particularly when CRP did not decrease the following days. Serial CRP measurements are helpful for detecting intraabdominal infections after colorectal resection. Persistently elevated CRP values after POD 3 should be investigated for intraabdominal infection.

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