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C-reactive protein is an early predictor of septic complications after elective colorectal surgery

Pablo Ortega-Deballon[1], MD, PhD, François Radais[1], MD, Olivier Facy[1], MD, Philippe d'Athis[2], PhD, David Masson[3], MD, PhD, Pierre E Charles[4], MD, PhD, Nicolas Cheynel[1], MD, PhD, Jean-Pierre Favre[1], MD, FACS, Patrick Rat[1], MD

[1]Department of Digestive, Thoracic and Oncologic Surgery. University Hospital, Dijon, France.

[2] Department of Biostatistics. University Hospital, Dijon, France.

[3] Department of Biochemistry. University Hospital, Dijon, France.

[4] Department of Critical Care. University Hospital, Dijon, France

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Corresponding author and reprints:

Pablo Ortega Deballon, M.D., Ph.D.

Service de Chirurgie Digestive, Thoracique et Cancérologique

Centre Hospitalier Universitaire du Bocage

1, Bd. Jeanne d'Arc

21079 DIJON Cedex, France

e-mail: pablo.ortega-deballon@chu-dijon.fr

Tel. +33 380 29 37 47

Fax. +33 380 29 35 91

Abstract

Background

Nowadays, most patients undergoing colorectal surgery are discharged early. An early predictor of septic complications could avoid readmissions and decrease morbidity. CRP could be a good predictor allowing a safe discharge.

Patients and methods

A prospective, observational study was conducted from November 2007 to October 2008. All patients undergoing elective colorectal surgery were included. Clinical (temperature, pulse, abdominal tenderness, bowel movements) and laboratory data (C-reactive protein, leukocyte count) were recorded and evaluated as early predictors of septic complications (namely anastomotic leaks). All detected leaks were considered as fistulas, independently of their clinical significance. Clinical and inflammatory parameters were analyzed with univariate and multivariate techniques; logistic regression was performed and areas under the receiver operating characteristic curve were compared.

Results

One hundred and thirty-three patients were included. The overall incidence of anastomotic leaks was 15.5% and mortality was 4.5%. C-reactive protein at postoperative days 2 and 4 was a good predictor of anastomotic leak (areas under the curve were 0.715 and 0.845, respectively) and other postoperative septic complications (areas under the curve were 0.804 and 0.787), showing the highest accuracy among clinical and laboratory data. A cutoff of 125 mg/l in the level of C-reactive protein at postoperative day 4 yielded a sensitivity of 81.8% and a negative predictive value of 95.8% for the detection of anastomotic leakage.

Conclusion

C-reactive protein is a simple way to ensure a safe discharge from hospital after elective colorectal surgery. Patients with CRP values higher than 125 mg/l on the 4th postoperative day should not be discharged.

Introduction

Septic complications are responsible for most morbidity after colorectal surgery. Among them, anastomotic leakage results in increased morbidity and mortality and adversely affects duration of stay, cost and cancer recurrence (1). The reported leak rate varies between 1% and 40% depending on the definition (2, 3). There is increased morbidity when there is a delay in treating anastomotic leaks. The early diagnosis of anastomotic leaks is thus warranted, particularly in the era of fast track colorectal surgery in which patients are discharged from hospital more quickly and the diagnosis of anastomotic dehiscence can be delayed.

Surgeons lack predictive accuracy for anastomotic leakage in gastrointestinal surgery (4). Routine imaging is neither reliable nor cost-effective for the detection of leaks and it carries the drawback of radiation. A serum marker would have great advantages provided that it is cost-effective and sensitive enough to allow safe discharge of the patient. C-reactive protein (CRP) has been used for the diagnosis of intra-abdominal surgical infection (5), as a general marker of an unfavorable postoperative course including surgical and nonsurgical complications (6-8), and even as a prognostic factor of survival after the resection of liver metastases (9). Recently, C-reactive protein has been assessed as an early predictor of septic complications following esophageal, pancreatic and rectal resections (10-13).

In the context of fast track surgery, an inflammatory marker with a high negative predictive value could allow safe early discharge from hospital. The aim of this study was to assess the accuracy of C-reactive protein as an early predictor of anastomotic leak after elective colorectal surgery.

Patients and methods

Design

From November 2007 to October 2008, patients undergoing elective colorectal surgery with anastomosis in the Department of Digestive Surgery of the University Hospital of Dijon were included in a prospective database after they had provided written informed consent.

Exclusion criteria

Exclusion criteria for this study were age < 18 years, pregnancy, emergent surgery, ongoing infection prior to surgery and hyperthermic intraperitoneal chemotherapy for carcinomatosis.

Recorded data and follow-up

Potential patient-specific and intraoperative risk factors were recorded: gender, obesity, surgical indication (cancer, polyps, chronic inflammatory bowel disease, diverticular disease) preoperative albuminemia, use of steroids, preoperative leukocytosis and CRP, cardiovascular or respiratory disease, American Society of Anesthesia score, bowel preparation (decision made by operating surgeon), laparoscopy or laparotomy, level of anastomosis and technique (mechanical or hand-sewn), diverting stoma, operative time, presence of drainage, surgeon and perioperative blood transfusion.

During the postoperative period, patients were examined by the attending surgeon daily. Fever (central temperature > 38 °C), pulse, abdominal signs, bowel movements, volume and aspect of drainage (if present) were recorded daily. C-reactive protein and leucocytes were measured in the evening before the operation (in addition to albuminemia) and on postoperative days 2, 4, 6 and 9. CRP levels were determined by immunonephelometry (Dimension Vista® system or Dimension XPand system®, Siemens, Germany). The attending surgeon made the decision for complementary exams and imaging according to his own criteria. During the study period, the policy of our department was to drain most (but not all) colonic anastomosis by leaving in place a low-pressure suction drain. Suction was stopped on the fifth postoperative day and the drain progressively removed in the following days. The rate of septic complications was calculated including all leaks (independently of clinical significance), wound infection, pneumonia, central line infection, urinary tract infection. The surgeons were blinded to the results of the CRP assays. Patients were seen in the outpatient clinic 6 weeks after discharge from the hospital.

Assessment and definition of complications

Anastomotic leakage was defined as one of the following criteria: presence of pus or enteric contents within the drains, presence of abdominal or pelvic collection in the area of the anastomosis on postoperative CT scan (performed at the discretion of the attending surgeon), leakage of contrast through the anastomosis during enema or evident anastomotic dehiscence at reoperation for postoperative peritonitis. Thus, all detected leaks were considered independently of clinical significance. No imaging was performed routinely in order to search for leakage. The management of the patients was not modified from our usual policies. Urinary tract infection was diagnosed on the basis of positive urine culture with bacterial count. Central line infection was diagnosed on the basis of positive blood culture. Superficial and deep incisional infections were diagnosed according to the definitions of the Centers for Disease Control and Prevention and a culture was performed (14). Pneumonia was diagnosed on the basis of clinical symptoms, and physical and radiological examinations.

Statistical analysis

The data were recorded with Excel and the statistical analysis was performed with TRIOMPHE software (designed at the university hospital of Dijon) and STATA software (Stata Corp. College Station, Texas, USA). Quantitative values are expressed as means ± standard deviations and categorical data are expressed with percentage frequencies. Mean values of duration of stay were compared according the presence or absence of fistulas using Student’s two-sided t test (allowing for heterogeneity of variances). Mean values of preoperative CRP levels of patients with undergoing surgery for cancer or for benign diseases were also compared using Student's two-sided t test (allowing for heterogeneity of variances). Univariate analysis (two-sided χ^2 test) and multivariate analysis were performed to assess fever, day of bowel movements, CRP and leukocytes as predictive factors of leaks and overall complications. A stepwise logistic regression was performed using temperature, CRP and leukocytes as predictive factors of every septic complication. The odds ratio (OR) is presented followed by its 95% confidence interval (95% CI). Areas under the receiver-operating characteristics (ROC) curve were calculated. A result with $p < 0.05$ was considered significant.

Results

Description of patients and procedures

One hundred and thirty-three patients (48 women and 85 men), with a mean age of 65 ± 16 years, were included in the study. A description of the operations is given in Table 1. Two patients had 2 anastomoses (ileocolic and high colorectal after right colectomy with associated sigmoidectomy). Eighteen patients were operated on using laparoscopy (13.5%) with two conversions to laparotomy (conversion rate 11.1%).

Table 1. Characteristics of surgery according to the presence or absence of leakage (133 patients, 135 anastomoses).

	No leakage	Leakage	Total
Disease			
• Cancer	70	12 (14.6%)	82
• Diverticular disease	20	6 (23.1%)	26
• Inflammatory bowel disease	5	1 (17%)	6
• Others (*)	17	2 (10.5%)	19
Level of anastomosis			
• Colonic	50	7 (12.3%)	57
• Rectal	64	14 (17.9%)	78
Approach			
• Laparoscopy	13	3 (18.7%)	16
• Laparotomy	99	18 (15.4%)	117
Type of anastomosis			
• Mechanical	52	11 (17.5%)	63
• Hand-sewn	62	10 (13.9%)	72

No one of these factors was significantly related to the risk of leakage.
(*) Including colorectal anastomosis after a previous Hartmann operation (n = 8), adenoma (n = 6), pelvic endometriosis (n = 2), chronic postoperative fistula (n = 1), recurrent sigmoid volvulus (n = 2).

Postoperative period and complications

Six patients died in the 30-day postoperative period (overall mortality 4.5%); 3 with an anastomotic leak and all with at least one septic complication (3 wound infections, 2 cases of pneumonia, 1 urinary tract infection and 1 catheter-related bacteriemia). One patient with a leak and one without anastomotic complication died because of massive pulmonary embolism; the other four deaths were the consequence of multiorgan failure after fistula (n = 2) or pneumonia (n=2). Eight patients out of 127 discharged from hospital were readmitted during the following 30 days (readmission rate 6.3%, all after POD 10); only one of them had an anastomotic leak (a pelvic collection managed with percutaneous drainage). Two of the eight readmitted patients had an elevated leukocyte count on POD 4, while five had a CRP level higher than 125 mg/l on POD 4.

The overall anastomotic leak rate was 15.5% (21 in 135 anastomoses; 14 of them involved rectal anastomoses and 7 involved colonic anastomoses). The median interval from surgery to the onset of the leakage was 6 days (range: 4 to 12). In 16 patients (76.2 %) the diagnosis was based on the aspect of the drainage, in 3 (14.3 %) it was made with the medical imaging and in 2 (9.5 %) at surgery. Four patients required a surgical treatment due to diffuse peritonitis with sepsis and a stoma was performed in all of them.

The overall rate of septic complications was 39.1% (52 patients out of 133 presented at least one infectious complication: anastomotic leaks, wound infection, urinary tract infection, pneumonia and/or central line infection). The overall mean duration of stay was 12.38 ± 6.84 days (range from 6 to 45 days, median: 10 days). It was longer in patients with anastomotic leakage than in those without (21.0 days vs. 10.6 days; $p = 0.015$).

The frequency of leaks or septic complications was not significantly correlated with sex, age, surgeon, perioperative blood transfusion, presence of diverting stoma, preoperative albumin levels, preoperative leukocytes, laparoscopic approach, technique of anastomosis, type of disease (benign or cancer), level of anastomosis and previous respiratory or cardiovascular diseases. Leaks were more frequent in patients with preoperative CRP higher than 7 mg/l (28.1% vs. 11.6%, $p = 0.036$), but the rate of septic complications was not significantly different.

Kinetics of inflammatory markers

The preoperative levels of CRP were not different between patients undergoing surgery for cancer or benign diseases (p = 0.432 at the Student's *t* test). After surgery, CRP peaked on postoperative day (POD) 2 and gradually decreased thereafter (Figure 1), in a more evident way in patients without anastomotic leaks or complications. In cases with complications, the increase in CRP was significantly greater and high levels persisted thereafter (Table 2). Moreover, CRP did not return to normal during the observation period. The kinetics of the white blood cells count were similar but the difference between patients with and without complications was not significant at POD 2 and, although significantly higher at POD 4 and 6 in patients with leaks or septic complications, its absolute values could be considered normal (Table 2, Figure 2).

Table 2. Mean values of C-reactive protein levels (CRP) and leukocytes (WBC) count in patients with and without anastomotic leak and septic complication according to the postoperative day (POD). NS: not significant.

		No leak (n = 112)	**Leak** (n = 21)	**P value**	**No septic complications** (n = 81)	**Septic complications** (n = 52)	**P value**
CRP (mg/l)	**POD 2**	174.1	212.9	0.037	155.9	212.0	<0.001
	POD 4	110.8	174.8	<0.001	83.4	167.3	<0.001
	POD 6	67.9	151.1	<0.001	50.5	120.7	<0.001
WBC count/mm^3	**POD 2**	9929	10839	NS	9627	10631	NS
	POD 4	7830	10074	0.003	7375	9206	0.01
	POD 6	8107	10115	0.01	7771	9312	0.009

Diagnostic accuracy of clinical and laboratory data

The presence of fever on POD days 2, 4 and 9 was not different among patients with or without leaks, but there was a difference on POD 6 (22.2% vs 5%, respectively, p = 0.031). The time to the first bowel movement was not significantly different between patients with and without anastomotic leak (median: 4 days in both groups). The presence of abdominal tenderness at the physical examination was not related to the presence of an anastomotic leak until POD 6 (p = 0.042). Thus, no clinical data could be associated with leakage before POD 6.

The areas under the curve to assess the accuracy of CRP and leukocytes count in both anastomotic leaks and septic complications in POD 2, 4 and 6 are shown in Table 3. CRP was more accurate than the leukocyte count for the detection of leakage or other septic complications in the postoperative setting. Particularly, CRP on POD 4 yielded an accuracy of 80.4% for the detection of postoperative septic complications.

In the multivariate analysis, CRP higher than 125 mg/l at POD 4 was the only predictive factor which remained significant for anastomotic leaks (OR = 18.15; 95% CI [3.89 – 84.74]) and septic complications (OR = 14.27; 95% CI [5.39 – 37.80]). A cutoff of 125mg/l in the CRP value at POD 4 yielded a sensitivity of 81.8%, a specificity of 64.44% and a negative predictive value of 95.8% for the detection of leakage.

Table 3. Diagnostic accuracy of C-reactive protein levels (CRP) and leukocyte count for the diagnosis of anastomotic leak and septic complications (including anastomotic leak) according to the postoperative day (POD).

	Area under the curve for CRP			**Area under the curve for leukocytes**		
	POD 2	**POD 4**	**POD 6**	**POD 2**	**POD 4**	**POD 6**
Anastomotic leak	0.653	0.716	0.845	0.561	0.687	0.701
Septic complications	0.706	0.804	0.788	0.597	0.654	0.638

Discussion

It has been shown that about 40% of clinically significant leaks are diagnosed after discharge from hospital and require readmission for abdominal symptoms (15, 16). This rate is certainly increasing in the era of fast track colorectal surgery with earlier discharges from the hospital (usually as early as the fourth postoperative day). There is increased morbidity when there is a delay in treating anastomotic leaks (3). These facts warrant the need for a simple and reliable method of early detection of anastomotic leaks in order to permit safe and early discharge from hospital (particularly in the context of fast track colorectal surgery).

One of the main problems in the literature dealing with anastomotic leaks is the choice of an adequate definition. The majority of contemporary studies do not include radiological leaks on routine imaging because they are not clinically significant (3). Definitions based exclusively on drainage have been abandoned, as they do not adequately identify early leaks and only a minority of patients with pelvic leaks had pus or enteric contents in the preexisting drains (17). Against the current evidence, during the study period it was the policy in our department to drain most anastomoses in colorectal surgery. This probably increased our leak detection rate as drainage may have revealed some leaks that would otherwise have been undetected as most of them were not clinically significant. Reported rates of anastomotic dehiscence vary between 1% and 30% (usual range of "major" leaks between 3% and 16%), which are consistent with our 15.5% leakage rate, particularly because we considered all leaks and not only those with clinical significance (2-4, 16). Mortality in the present study was 4.5%, which is consistent with the results of the literature (1, 3). Interestingly, an elevated preoperative CRP increased the risk of leakage; this may confirm that an inflammatory environment impairs anastomotic healing. Patients operated on for cancer had not higher CRP levels than those undergoing surgery for benign diseases in the present work (18).

Regarding clinical data, Bellows et al. recently found that pulmonary and neurological events were the earliest clinical predictors of anastomotic leaks; but they appeared later than POD 4 (2). Fever, local tenderness and the absence of bowel activity have also been evaluated in this and other studies, but they also appeared lately (POD 6) or were unreliable (4).

Inflammatory markers have been evaluated as predictors of postoperative surgical and non-surgical complications with heterogeneous results. Procalcitonin has been shown to predict mortality in postoperative sepsis when combined with APACHE II (19). It has also been assessed as an early predictor of postoperative complications after cardiac, vascular and colorectal surgery with promising results (20-22). A prospective randomized pilot study assessed the benefit of early preemptive antibiotic therapy in patients with elevated procalcitonin during the first three days following elective colorectal surgery with positive results (22). It would be interesting to compare the accuracy and the cost-benefit ratio of CRP and procalcitonin, but such a study has not yet been performed. The cost should be considered as in any laboratory test performed in all patients as a routine.

The diagnostic accuracy of CRP on POD 2 and 4 as a predictor of septic complications after elective colorectal surgery (areas under the curve of 0.706 and 0.804, respectively) were only slightly lower than those obtained by Welsch et al. (0.80 and 0.88, respectively) (12). This can be explained by their lower leakage rate (5.7% as compared with 15.5% in the present study) due to the choice of definitions and the different populations (all colorectal surgery vs. rectal surgery for cancer); it has been shown that colectomy for diverticular disease carries a higher risk for leakage (3, 23). It must also be pointed out that they included only clinically significant leaks (detected at radiology or endoscopy in symptomatic patients).

The leukocyte count on POD 4 was significantly higher in patients with septic complications (see table 2), but its accuracy was much lower than for CRP (80.4% vs 65.4%, as reflected by the area under the ROC curve). It is not clear if elevated inflammatory markers on POD 4 reflect an ongoing inflammatory process or if they predict the later occurrence of a leak. Our results show that the leak became clinically significant at POD 6; if they were previously present and unrecognized or if they were organizing with a local inflammatory response can not be concluded with the present results. CRP is a non-specific, systemic, manifestation of an active inflammatory process; but our results show that, in the setting of elective colorectal surgery, its elevation on POD 4 should be considered a powerful signal of alarm to avoid discharging those patients.

Very recently, Korner et al have published a work similar to the present one, including also patients after all types of colorectal surgery. Their methods and their results are close to ours: they showed that CRP at POD 3 had 82% accuracy (we obtained 80.4% at POD 4). They chose a higher cutoff than ours (190 vs 125 mg/l), obtaining a similar sensitivity (82%) for the detection of postoperative complications. It is well known that the peak of CRP happens between POD 2 and 3 and then the values decrease. This may explain that the cutoff value obtained at POD 3 by Korner et al. was higher than ours, obtained at POD 4. They also obtained a similar accuracy in POD 5 and 7, as we did in POD 6. This tallying between both works is a strong argument in favor of the usefulness of the CRP in this setting (24).

Establishing a cutoff value for clinical decision making in general is often a trade-off. For safe early discharge (for example in the setting of fast track surgery), it is more important to detect most complications than to avoid unnecessary further exams. The present work was done in order to define the conditions for a safe discharge prior to start a program of fast-track surgery. We would prefer to decrease morbidity and readmission rates, even at the prize of increasing the duration of hospital stay for a minority of patients due to false positive results. Thus, we preferred to obtain high sensitivity (81.8%) and a high negative predictive value (95.8%). This choice prompted the selection of the cutoff at 125 mg/l on POD 4, also sustained by the high OR obtained in the multivariate analysis. Welsch et al chose a higher cutoff value (140 mg/l), thus obtaining lower sensitivity (54.3%) and a higher specificity (92.3%) at POD 4 (12).

According to our results, measuring CRP on the 4th postoperative day may contribute to a safe discharge from hospital after colorectal surgery. It detects more than 80% of anastomotic leaks and septic complications. Patients with CRP values lower than 125 mg/l on the fourth postoperative day can be safely discharged from hospital. Patients with CRP values higher than 125 mg/l should undergo further imaging (namely CT scan) to search for a surgical site infection.

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Figure 1. Kinetics of C-reactive protein on the day before surgery (-1), postoperative day 2, postoperative day 4, postoperative day 6 and postoperative day 9, in patients with and without anastomotic leaks.

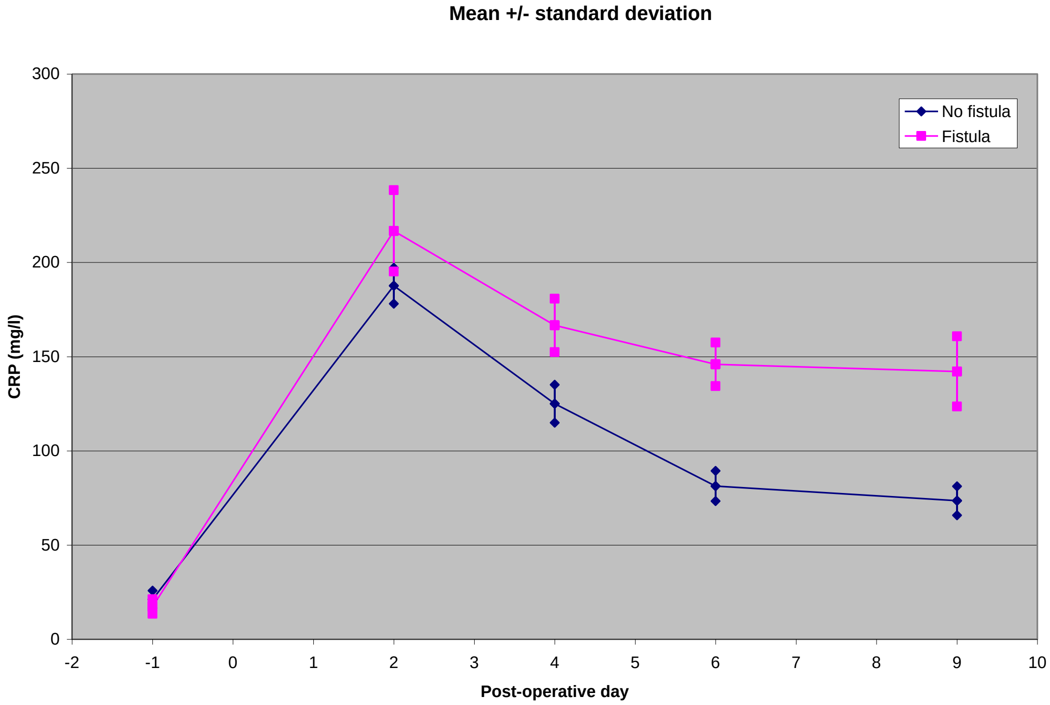

Figure 2. Kinetics of white blood cell count on the day before surgery (-1), postoperative day 2, postoperative day 4, postoperative day 6 and postoperative day 9, in patients with and without anastomotic leak.