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ORIGINAL ARTICLE

Inflammatory markers as early predictors of infection after colorectal surgery: the same cut-off values in laparoscopy and laparotomy?

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Abstract
Purpose C-reactive protein and procalcitonin are reliable early predictors of infection after colorectal surgery. However, the inflammatory response is lower after laparoscopy as compared to open surgery. This study analyzed whether a different cutoff value of inflammatory markers should be chosen according to the surgical approach.
Methods A prospective, observational study included consecutive patients undergoing elective colorectal surgery in three academic centers. All infections until postoperative day (POD) 30 were recorded. The inflammatory markers were analyzed daily until POD 4. Areas under the ROC curve and diagnostic values were calculated in order to assess their accuracy as a predictor of intra-abdominal infection.
Results Five-hundred-one patients were included. The incidence of intra-abdominal infection was 11.8%. The median levels of C-reactive protein (CRP) and procalcitonin (PCT) were lower in the laparoscopy group at each postoperative day ($p < 0.0001$). In patients without intra-abdominal infection, they were also lower in the laparoscopy group ($p = 0.0036$) but were not different in patients presenting with intra-abdominal infections ($p = 0.3243$). In the laparoscopy group, CRP at POD 4 was the most accurate predictor of overall and intra-abdominal infection (AUC = 0.775). With a cutoff of 100 mg/L, it yielded 95.7% negative predictive value, 75% sensitivity, and 70.3% specificity for the detection of intra-abdominal infection.
Conclusion The impact of infection on inflammatory markers is more important than that of the surgical approach. Defining a specific cutoff value for early discharge according to the surgical approach is not justified. A patient with CRP values lower than 100 mg/L on POD 4 can be safely discharged.

Keywords Diagnostic accuracy · C-reactive protein · Procalcitonin · Anastomotic leak · Intra-abdominal infection · Laparoscopy

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Introduction

Intra-abdominal infections (namely, anastomotic leakage) are a frequent and life-threatening complication after elective colorectal surgery. Their incidence ranges between 5 and 15%, with a short-term mortality around 20% [1–5]. They prolong the in-hospital stay, increase the cost, and worsen the long-term survival in cancer patients [3–5]. An early diagnosis decreases their impact [3, 6–8]. Several studies have analyzed C-reactive protein (CRP) and procalcitonin as early predictors of postoperative infection [9–12]. Two recent meta-analyses confirmed that their best diagnostic accuracies are found on postoperative days (PODs) 3 and 4, without any clear benefit for procalcitonin [13, 14].

Laparoscopy is becoming the standard approach in colorectal surgery because of clear benefit in the postoperative period. Biologically, this approach seems to reduce the inflammatory response as compared to open surgery [15–17]. The thresholds of CRP and procalcitonin (PCT) suggested by several authors to ensure a safe early postoperative discharge after colorectal surgery do not account for the surgical approach [18, 19]. Some authors have suggested a lower cutoff value of CRP in case of laparoscopic approach, while others prefer to use the same threshold [20, 21]. The aim of this study was then to compare the diagnostic accuracy of CRP and PCT after laparoscopic versus after open elective colorectal surgery and to determine if a different cutoff should be used according to the surgical approach.

Methods

Study design

The "Inflammatory Markers After COloRectal Surgery study" (IMACORS) was a prospective observational study conducted in three academic centers (University Hospitals of Dijon and Besançon and Dijon's anticancer center "Georges F. Leclerc", all in France). Its methods have been described in detail elsewhere [10] and was approved by the ethics review board CPP Est 1 and the French National Food and Drug Safety Agency (AFSSAPS).

Briefly, from November 2011 to April 2014, consecutive eligible patients meeting the inclusion criteria in any of the three investigating centers were offered to participate in the study.

Inclusion and exclusion criteria

Patients were eligible for the study if they met all the following criteria: an age of 18 years or older, a scheduled colorectal resection with anastomosis, and if they had a health insurance. Patients with a previous ongoing infection, operated in an emergency setting or with a previously suspected peritoneal carcinomatosis, were excluded. Each participating surgeon was free to choose the surgical approach. When a laparoscopic procedure was converted to open surgery, the patient was included in the laparotomy group as we considered that the inflammatory response would be that of open surgery. Written informed consent was obtained from all patients before inclusion.

Clinical and laboratory assessment and follow-up

Potential patient-specific and intraoperative risk factors were recorded for each patient.

After surgery, blood levels of CRP and PCT were measured daily until POD 4. All complications were recorded until postoperative day 30 and managed according to the surgeon's criteria. All postoperative infections (APIs) were defined according to the Centers for Disease Control and Prevention. Thus, our primary outcome, i.e., intra-abdominal infection (IAI), was considered when at least one of the following criteria was observed: presence of pus or enteric contents within the drains, presence of abdominal or pelvic collection in the area of the anastomosis on postoperative imaging (abdominal scanner), and leakage of contrast through the anastomosis during enema or evident anastomotic dehiscence at reoperation for postoperative peritonitis [22]. All IAIs were considered independently of their clinical significance.

Statistical analysis

Continuous variables were described using means and standard deviations when normally distributed, and using median and interquartile range (IQR) otherwise; they were compared using Student's *t* tests or Mann-Whitney tests when appropriate. Categorical data were expressed using percentage and compared using χ^2 tests. The areas under the ROC curves were calculated for each daily value of CRP and PCT as predictors of IAI and then of API according to the surgical approach. Finally, a cutoff was chosen for each inflammatory marker prioritizing negative predictive value and sensitivity, while requiring a specificity above 50%, A two-sided *P* value below 0.05 was considered to indicate statistical significance. The analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA) and Stata version 12 (StataCorp Inc., College Station, TX).

Results

Description of patients and procedures

Five-hundred-one patients were included in the study. Laparotomy was performed in 352 (70.3%) patients, while 149 (29.7%) patients were operated on by laparoscopy. Their main baseline characteristics and procedures are presented in Table 1.

Inflammatory markers

Inflammatory markers increased as a result of surgery in all patients, with a peak value at POD 2 and a subsequent decrease in the two following days in all (complicated and uncomplicated) patients. The mean values of both inflammatory markers were significantly lower in patients operated on by laparoscopy at each postoperative day (Table 2). This was also the case in the absence of intra-abdominal infection (Table 3).

Table 1 Overall characteristics and potential patient-specific and intraoperative risk factors according to the open or laparoscopic approach (IMACORS study)

All n = 501		Surgical approach		P value
		Open, n = 352 (70.3%)	Laparoscopy, n = 149 (29.7%)	
Demographics				
Age (years), mean ± SD	65.4 ± 14.2	66.7 ± 14.4	62.4 ± 13.5	0.002
Sex, n (%)				
Men	287 (57.3)	210 (59.7)	77 (51.7)	0.099
Women	214 (42.7)	142 (40.3)	72 (48.3)	
BMI (kg/m^2), mean ± SD	26.1 ± 4.9	26.3 ± 5.1	25.5 ± 4.2	0.059
Diabetes (%)	81 (16.2)	64 (18.2)	17 (11.4)	0.060
Neoadjuvant radiotherapy (rectal cancer)	59 (11.8)	50 (14.2)	9 (6.0)	0.010
Surgical characteristics				
Surgical indication, n (%)				
Diverticular disease	58 (11.6)	28 (8.0)	30 (20.1)	<0.001
Neoplasms	348 (69.5)	251 (71.3)	97 (65.1)	0.168
Adenoma	30 (6.0)	16 (4.6)	14 (9.4)	0.037
Chronic inflammatory bowel disease	11 (2.2)	10 (2.8)	1 (0.7)	0.130
Other	58 (11.6)	50 (14.2)	8 (5.4)	0.005
Preoperative bowel cleansing, n (%)	195 (48.4)	148 (52.1)	47 (39.5)	0.021
Type of resection, n (%)				
Colectomy	388 (77.5)	266 (75.6)	122 (81.9)	0.122
Rectal resection	132 (26.4)	102 (29.0)	30 (20.1)	0.040
Reversal of Hartmann's procedure	51 (10.2)	46 (13.1)	5 (3.4)	0.001
Length of operation (min), mean ± SD	231 ± 95	228 ± 100	239 ± 81	0.206
Diverting ileostomy, n (%)	107 (21.4)	88 (25.1)	19 (12.8)	0.002
Drainage of anastomosis, n (%)	301 (60.3)	233 (63.7)	78 (52.4)	0.018
Postoperative data				
Complications, n (%)				
All complications	246 (49.1)	180 (51.1)	66 (44.3)	0.162
Infectious complications	123 (24.6)	88 (25.0)	35 (23.5)	0.720
Intra-abdominal infections	59 (11.8)	43 (12.2)	16 (10.7)	0.639
Length of hospital stay (day), mean ± SD	12.0 ± 9.9	12.8 ± 10	10.3 ± 9.5	<0.0001

Postoperative infections

There were 59 IAIs (11.8%), 48 wound infections (9.7%), 24 urinary-tract infections (4.8%), 6 pneumonias (1.2%), and 9 catheter-related infections (1.8%). Overall, 123 patients (24.6%) presented at least one infectious complication. Among the six patients who died (1.2%), all had an IAI. The median delay between the operation and the diagnosis of IAI was 7 days (interquartile range 5–12 days). The diagnosis was established by imaging in 40 patients (67.8%), clinical features in 13 (22%), and at surgery in the remaining 6 (10.2%). There was no difference in the occurrence of IAI according to the surgical approach, 43 patients operated on by laparotomy (12.2%) versus 16 by laparoscopy (10.7%), $p = 0.64$. The median levels of CRP and PCT in patients with IAI were not different according to the surgical approach at any POD, except for the PCT on the first POD, which was higher in patients operated on by laparotomy (1.34 versus 0.43 mg/L, $p = 0.004$) (Table 4).

For the diagnosis of IAI, the respective areas under the ROC curve for each marker on each postoperative day are presented in Table 5 according to the surgical approach. With a cutoff of 70 mg/L, CRP on POD 4 yielded in the laparoscopic group a 98.5% negative predictive value, a 93.7% sensitivity, and a 50.1% specificity for the detection of IAI. With a cutoff of 100 mg/L, it yielded a 95.7% negative

Table 2 Daily levels (medians and interquarte ranges) of C-reactive protein (CRP) and procalcitonin (PCT) in all patients and according to the surgical approach

All patients, *n* = 501		Surgical approach		*P* value
		Laparotomy, *n* = 325 (70.3%)	Laparoscopy, *n* = 149 (29.7%)	
POD 1				
CRP (mg/L)	105.5 (73.6–137)	111 (82–143)	88 (58–114)	<0.0001
PCT (mg/L)	0.63 (0.2–1.77)	0.87 (0.38–2.08)	0.21 (0.1–0.84)	<0.0001
POD 2				
CRP (mg/L)	161.0 (115–216)	172 (133–225)	130 (88.4–178.5)	<0.0001
PCT (mg/L)	0.72 (0.26–2.18)	0.86 (0.36–2.43)	0.32 (0.14–1.8)	<0.0001
POD 3				
CRP (mg/L)	134.5 (89–178)	143 (99–180)	113 (70–167)	0.0007
PCT (mg/L)	0.53 (0.22–1.64)	0.64 (0.28–1.78)	0.27 (0.11–1.3)	<0.0001
POD 4				
CRP (mg/L)	86.0 (56–133)	90 (63–137)	74.5 (40.5–113)	0.01
PCT (mg/L)	0.38 (0.18–1.12)	0.44 (0.22–1.18)	0.23 (0.1–0.84)	<0.0001

predictive value, a 75% sensitivity, and a 70.3% specificity. In the open group, the same cutoff of CRP on POD 4 yielded a 93.7% negative predictive value, a 70.7% sensitivity, and a 61.3% specificity.

Discussion

The inflammatory response after laparoscopic colorectal surgery is lower than after open surgery [15, 21]. However, this study showed that the onset of IAI in the postoperative period induced a stronger inflammatory response and erased any difference in terms of inflammation between laparoscopy and laparotomy. This is consistent with the results obtained recently by Ramanathan et al. and the meta-analysis by Adamina et al. [20, 21]. Laparoscopy is becoming the standard approach for most patients undergoing a colonic or rectal resection due to a better postoperative recovery leading to an earlier discharge, but the incidence of IAI is not related to the surgical approach [16, 23]. As the length of hospital stay decreases, it is essential to detect IAI early in order to prevent readmissions and the negative impact of a late diagnosis [24–26]. Indeed, it is well known that clinical signs of postoperative infections are rarely apparent before POD 6, with the diagnosis usually established after POD 7, whatever the surgical approach is (even later if the patient has already been discharged) [10,

Table 3 Daily levels (medians and interquartile ranges) of C-reactive protein (CRP) and procalcitonin (PCT) in patients having no intra-abdominal infection and according to the surgical approach

Patients with no intra-abdominal infection, *n* = 442		Surgical approach		*P* value
		Laparotomy, *n* = 309 (87.8%)	Laparoscopy, *n* = 133 (89.3%)	
POD 1				
CRP (mg/L)	103.5 (71.0–135.0)	110 (81–141)	85.5 (57–114)	<0.0001
PCT (mg/L)	0.58 (0.19–1.75)	0.81 (0.34–2.02)	0.21 (0.09–0.78)	<0.0001
POD 2				
CRP (mg/L)	158.0 (108.0–208.0)	172 (129–216)	125.5 (86–166)	<0.0001
PCT (mg/L)	0.62 (0.24–1.86)	0.77 (0.34–2.16)	0.31 (0.12–1.17)	<0.0001
POD 3				
CRP (mg/L)	129.0 (86.9–172.5)	138 (98–177)	105 (65–158)	0.0002
PCT (mg/L)	0.45 (0.21–1.44)	0.6 (0.26–1.62)	0.24 (0.11–1.03)	<0.0001
POD 4				
CRP (mg/L)	80.4 (51.0–120.0)	85 (59.5–127)	69.75 (37.5–106.5)	0.0036
PCT (mg/L)	0.34 (0.17–0.93)	0.41 (0.21–0.98)	0.2 (0.1–0.72)	<0.0001

Table 4 Daily levels (medians and interquartile ranges) of C-reactive protein (CRP) and procalcitonin (PCT) in patients with intra-abdominal infection and according to the surgical approach

Patients with intra-abdominal infections, $n = 59$		Surgical approach		P value
		Laparotomy, $n = 43$ (12.2%)	Laparoscopy, $n = 16$ (10.7%)	
POD 1				
CRP (mg/L)	112 (83–144)	117.5 (89–160)	110 (79.5–119.5)	0.2215
PCT (mg/L)	1.05 (0.48–2.28)	1.34 (0.66–3.28)	0.43 (0.18–1.1)	0.0044
POD 2				
CRP (mg/L)	204 (143–251)	225 (149–257)	184.5 (131.5–240)	0.2178
PCT (mg/L)	1.56 (0.6–4.98)	1.46 (0.69–5.29)	1.81 (0.22–4.41)	0.7189
POD 3				
CRP (mg/L)	168.5 (126–239)	162.5 (143–211)	196 (119.5–248)	0.5012
PCT (mg/L)	1.42 (0.45–4.04)	1.47 (0.48–4.27)	1.39 (0.27–3.08)	0.5507
POD 4				
CRP (mg/L)	157 (100–225)	146 (96–205)	165.5 (103.5–248)	0.3243
PCT (mg/L)	0.97 (0.35–3.03)	1.23 (0.32–2.91)	0.83 (0.38–3.28)	0.9928

20, 27]. Several studies have shown the interest of inflammatory markers to ensure a safe early discharge. According to several prospective studies and meta-analyses, CRP measured on POD 4 reaches its better diagnostic ability, higher than that of PCT [9, 13, 14, 28–30]. In the IMACORS study, a threshold of 100 mg/L of CRP on POD 4 was recommended [10]. The analysis of the laparoscopic group showed results consistent with those reported in open surgery; CRP is more accurate than PCT for the diagnosis of both postoperative and intra-abdominal infections, and POD 4 is the most appropriate timing for this assay. PCT offers no significant added value in this setting [9, 10, 13, 31]. Some authors have claimed a superiority of PCT, particularly in terms of specificity, but its greater dispersion makes it more difficult to use in the clinical setting [11, 12, 32]. *Regarding the costs, a PCT assay is much more expensive than CRP (in France, around 11 euros versus 0.40 euros, thus 25 times more expensive). Therefore, in addition to the fact that PCT brings no further diagnostic information than CRP alone, the surgeon has to keep in mind its high cost.*

Our results are consistent with those of two recent smaller studies having measured inflammatory markers after open and

Table 5 Comparison of the discriminating accuracy of C-reactive protein (CRP) and procalcitonin (PCT) to detect either intra-abdominal infections or any postoperative infections (API) between postoperative days (POD) 2 and 4, according to their respective areas under the ROC curve (AUC)

	Laparoscopy	P value	Open	P value
AUC for intra-abdominal infections (CI 95%)				
POD 2				
CRP	0.713 (0.587–0.838)	0.82	0.645 (0.550–0.740)	0.97
PCT	0.698 (0.566–0.830)		0.643 (0.553–0.733)	
POD 3				
CRP	0.765 (0.638–0.892)	0.32	0.646 (0.553–0.739)	0.73
PCT	0.706 (0.579–0.834)		0.667 (0.577–0.758)	
POD 4				
CRP	0.837 (0.740–0.934)	0.04	0.747 (0.659–0.835)	0.12
PCT	0.745 (0.620–0.871)		0.662 (0.568–0.755)	
AUC for any postoperative infections (CI 95%)				
POD 2				
CRP	0.746 (0.658–0.839)	0.05	0.697 (0.632–0.763)	0.29
PCT	0.656 (0.560–0.751)		0.654 (0.589–0.718)	
POD 3				
CRP	0.787 (0.696–0.879)	0.03	0.700 (0.636–0.764)	0.43
PCT	0.683 (0.592–0.774)		0.666 (0.603–0.729)	
POD 4				
CRP	0.823 (0.748–0.905)	0.003	0.761 (0.702–0.821)	0.02
PCT	0.694 (0.600–0.787)		0.665 (0.600–0.731)	

laparoscopic elective colorectal surgery; laparoscopy induces a lower inflammatory response except in case of IAI, situation in which there is no difference according to the surgical approach [20, 21]. The question in this setting is whether a different threshold in inflammatory markers should be chosen according to the surgical approach as suggested by Adamina et al. The alternative would be to conserve the same threshold accepting that it will have a greater predictive value in the laparoscopy group as suggested by Ramanathan et al.; a patient operated on by laparoscopy having values higher than the cutoff would carry a higher risk of IAI than a patient with the same values operated on by laparotomy. In series analyzing together laparoscopy and laparotomy patients, the cutoff value of CRP at POD 4 ranges between 100 and 130 mg/L for most authors [9, 10, 28, 30, 31]. In our opinion, the sensitivity and the negative predictive value should be prioritized to choose an optimal cutoff, as the consequences of a false negative (discharging a patient with an ongoing infection) are heavier than those of a false positive (keeping the patient under clinical surveillance or performing further imaging). We looked here for a threshold obtaining the highest negative predictive value and sensitivity with a good specificity (over 50% in any case). A cutoff in the CRP concentration at 100 mg/L on POD 4 has the advantage of being accurate in both laparoscopy and laparotomy and easy to remember. Adamina et al. have suggested lower cutoff values for patients operated on by laparoscopy but this was at the price of a lower specificity (49%), while it was much better (75%) in their open group [20]. Seemingly, according to our results, a lower cutoff in CRP on POD 4 (e.g., 70 mg/L) has a much lower specificity and prompts to keep in hospital half of the patients operated on by laparoscopy due to a false positive in too many of them. Thus, we recommend the same threshold whatever the surgical approach is (100 mg/L), because it is also consistent with the physio-pathological fact that the onset of IAI induces a strong inflammatory response erasing the differences due to the surgical approach. Of course, the consequence is that CRP has a better diagnostic ability in the population operated on by laparoscopy (a higher area under the ROC curve), and surgeons must worry particularly about patients with a CRP higher than 100 mg/L if they were operated on by laparoscopy. In this setting, an abdominal CT scan is warranted (with rectal contrast at best), but surgeons should be aware of a high risk of false negative scans [33].

In conclusion, this study confirms a lower inflammatory response after laparoscopic colorectal resection as compared to open procedures, but the onset of intra-abdominal infection suppresses this difference. In the laparoscopic group, CRP measured on POD 4 remains the best inflammatory marker to allow a safe discharge. *Whatever the surgical approach is (laparotomy or laparoscopy), CRP levels lower than 100 mg/L on POD 4 are strongly correlated with the absence of postoperative complications. The measure of procalcitonin showed no added value.*

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Compliance with ethical standards

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