

Increased levels of C-reactive protein and leukocyte count are poor predictors of anastomotic leakage following laparoscopic colorectal resection

Torben Pedersen¹, Ole Roikjær^{1, 2} & Per Jess^{1, 2}

ABSTRACT

INTRODUCTION: Laparoscopic procedure and fast-track regimen with short post-operative hospital stay are gaining ground in colorectal surgery. The aim of the present study was to determine whether the levels of C-reactive protein (CRP) and white blood cell counts (WBC) have a role as early predictors of post-operative septic complications including anastomotic leakage in patients operated laparoscopically in a fast-track regimen.

MATERIAL AND METHODS: This was a retrospective analysis of 129 patients who underwent laparoscopic colorectal surgery in a fast-track regimen during a one-year period. The levels of CRP and WBC were measured daily until discharge. The diagnostic accuracy was evaluated using the receiver-operating characteristics methodology.

RESULTS: The median post-operative hospital stay was three days. Septic complications occurred in 32% of cases. Post-operative CRP level was significantly higher in patients with septic complications than in patients without complications, but similar in patients with anastomotic leakage and patients with other septic complications. The best cut-off value for CRP level as a predictor of septic complications was observed on post-operative day (POD) 3, where CRP concentration > 200 mg/l had a sensitivity of 68% and a specificity of 74%. WBC measurements showed the best cut-off value on POD 2, where WBC > 12×10^9 had a sensitivity of 90% and a specificity of 62%.

CONCLUSION: The insufficient diagnostic accuracy of the levels of CRP and WBC made them weak diagnostic markers in prediction of post-operative septic complications, including anastomotic leakage, in the first three post-operative days after laparoscopic colorectal surgery.

FUNDING: not relevant.

TRIAL REGISTRATION: not relevant.

Septic complications after colorectal resections with primary anastomosis are observed in up to 40% of cases [1]. Anastomotic leakage (AL) is the most feared septic complication, causing increased morbidity, increased mortality and prolonged hospital stay [2]. AL is an independent factor of poor prognosis in patients undergoing curative operation for colorectal cancer increasing local recurrence [3] and decreasing survival [4]. The diagnosis

of AL should be made as early as possible in order to reduce its associated morbidity and mortality [5]. Laparoscopic procedure and fast-track regimen with short post-operative hospital stay are gaining ground in colorectal surgery [6]. Therefore, an early, sensitive and specific marker of post-operative septic complications would be of interest to clinicians.

In open surgery, the concentration of C-reactive protein (CRP) has proven useful in predicting post-operative complications on post-operative days (POD) 3-4 [7, 8]. CRP is a liver-derived acute-phase reactant mediated primarily by the cytokines interleukin (IL)-6, IL-1, and tumour necrosis factor (TNF)-alpha. The CRP level reflects the presence and intensity of inflammation [9]. After open colorectal surgery, there is normally a rise in the CRP level on POD 1-3 and then a decline the following days, which makes it difficult to tell whether a post-operative rise in CRP level is pathological or simply caused by the surgical trauma. However, it is recommended that patients with CRP level above 140-145 mg/l on POD 3-4 are examined for septic complications [7, 8].

Equivalent studies with a focus on septic complications do not exist for laparoscopically operated colorectal cancer patients, though it has been shown that the inflammatory response after laparoscopic surgery is in general significantly lower than after conventional surgery [10]. At the Department of Surgery, Roskilde Hospital, patients following a fast-track regimen are discharged median on POD 3 after laparoscopic colorectal resection. The aim of the present study was therefore to determine the role of the levels of CRP and white blood cell counts (WBC) as predictors of AL and other septic complications after laparoscopic fast-track colorectal surgery on POD 1-3.

MATERIAL AND METHODS

Included in the study were a total of 129 consecutive laparoscopically operated patients who had a colorectal resection with primary anastomosis performed at Department of Surgery, Roskilde Hospital in 2009. A retrospective analysis of patient data was performed. The following data were registered: age, sex, type of surgery, length of post-operative hospital stay, post-operative

ORIGINAL ARTICLE

1) Kirurgisk Afdeling, Roskilde Sygehus
2) Det Sundhedsvidenskabelige Fakultet, Københavns Universitet

Dan Med J
2012;59(12):A4552

morbidity including AL and other septic complications (pneumonia, urinary tract infection, wound infection), 30-day mortality and the need for re-admittance after discharge. The levels of CRP and WBC were examined preoperatively and daily post-operatively until discharge. All patients received antibiotic prophylaxis as a single injection at the beginning of the operation. The standard antibiotics were gentamycine and metronidazole.

AL was diagnosed clinically by signs of acute abdomen and fever. In case of suspicious clinical symptoms, a computed tomography of the abdomen with radiographic enema was performed. After clinical or radiological proof of AL, an immediate reoperation was performed in most cases.

Statistical analysis was performed using SPSS version 19. Nonparametric statistics were used. p-values below 0.05 were considered statistically significant. The diagnostic accuracy of CRP and WBC levels were evaluated according to the area under the curve (AUC) using receiver-operating characteristics (ROC) analysis [11].

Trial registration: Not relevant.

Patients, n	129
Patient age, years, median (range)	67 (35-89)
Male/female, n	71/58
<i>Operation type, n (%)</i>	
Right-sided resection	49 (38)
Left-sided resection	51 (40)
Rectum resection	29 (22)
Converted operations	5 (4)
Anastomotic leakage	23 (18)
Other septic complications	18 (14)
Post-operative mortality, n (%)	0 (0)
Post-operative time in hospital, days, median (range)	3 (1-64)

	No septic complication (88 patients)	Septic complication (41 patients)
POD 1	85 (9-215)	106 (12-211)
POD 2	123 (8-316)	223 (35-390)
POD 3	150 (11-316)	249 (48-491)

CRP = C-reactive protein; POD post-operative day.

RESULTS

Patient characteristics and short-term results are shown in **Table 1**. Septic complications occurred in 41 patients (32%), including pneumonia, urinary tract infection, wound infection, infection without known focus and AL. A total of 23 patients (18%) experienced AL. No significant differences in CRP level were found between the patients with AL and those with other septic complications ($p > 0.05$). **Figure 1** shows the post-operative development of CRP level for the patients with and without septic complications. **Table 2** shows wide variations in CRP level in both groups. Nevertheless, the patients had significant elevations in CRP level on POD 1-5 in the group experiencing septic complications ($p = 0.002$, 0.0001 , 0.0001 , 0.003 , and 0.004 , respectively). ROC analysis was used to find the best cut-off value for CRP level as a predictor of septic complications on POD 1-3 (**Figure 2**). The highest diagnostic accuracy was found on POD 3. A CRP concentration over 200 mg/l would then have a sensitivity of 68% and a specificity of 74% in assessing the risk of AL and other septic complications. The highest median value for patients without complications was 150 mg/l on POD 3, but using this value as cut-off would only have yielded a sensitivity of 75% and a specificity of 47%.

Post-operative WBC was significantly higher in patients with septic complications on POD 1-4 ($p = 0.005$, 0.0001 , 0.026 , and 0.049 , respectively) than in patients without septic complications. ROC analysis showed the best cut-off value for WBC as a predictor of septic complications on POD 2, when a value $> 12 \times 10^9$ had a sensitivity of 90% and a specificity of 62%. No significant differences in leucocytes were found when comparing the patients with AL and those with other septic complications ($p > 0.05$).

The median post-operative stay (POS) for patients without septic complication was three days (1-64), while it was six days (3-23) for patients with other septic complications than AL and 16 days (2-62) for patients with AL ($p < 0.0001$). The median time for diagnosis of AL was on POD 7 (POD 1-30). Six of the patients with AL (26%) were discharged before AL was diagnosed and therefore readmitted.

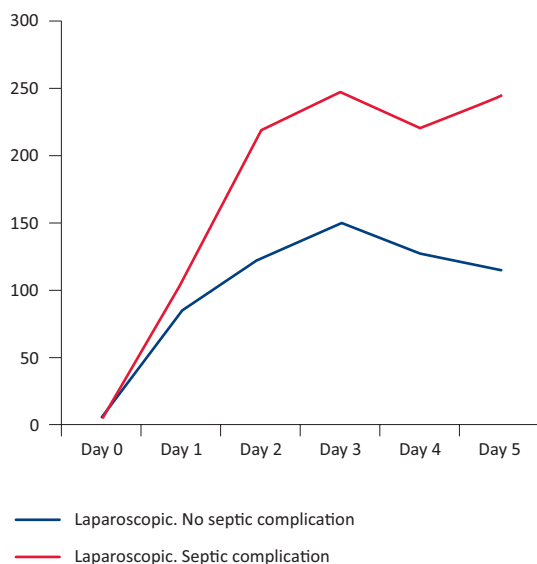
DISCUSSION

Randomized controlled studies have shown that laparoscopic colorectal surgery has equal long-term results, but better short-term results than conventional surgery [12-14]. A result of this is a reduced POS. Similarly, enhanced recovery (fast track) protocols in colorectal surgery have a role in reducing post-operative morbidity and accelerating recovery, which yields further reductions in POS [15]. In the present study, where both laparoscopy and fast-track regimen were used, the median


FIGURE 1

C-reactive protein (CRP) concentration in laparoscopic colorectal surgery in relation to septic complications.

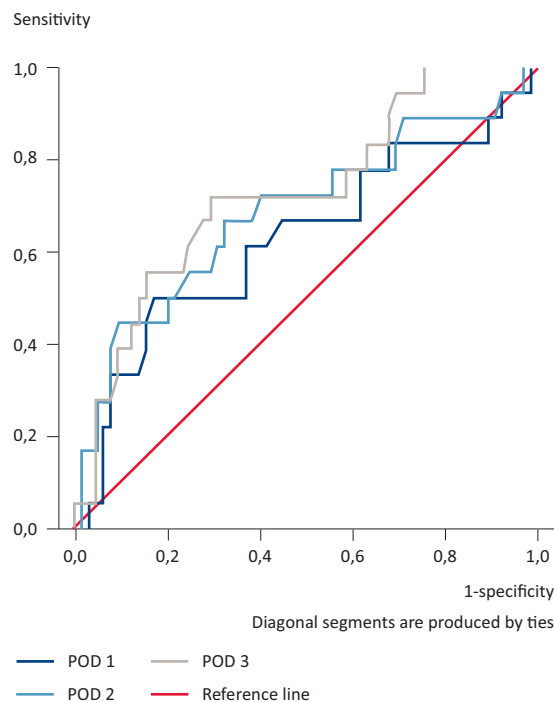
Median CRP concentration, mg/l



POS was three days. However, post-operative morbidity and mortality remain important issues. Especially AL, as previously mentioned, is a serious complication which should be diagnosed as early as possible to reduce its associated morbidity and mortality [5]. CRP concentration has been investigated as an early marker of AL and other septic complications in open colorectal surgery. Measurement of CRP concentration on POD 3-4 is recommended to screen for such complications, and cut-off values of CRP concentration of 123-145 mg/l are claimed to have the highest diagnostic accuracy among clinical and laboratory data with a sensitivity reaching 82% and a specificity reaching 96% [1, 7, 8, 16-18]. It was shown that CRP levels are lower after laparoscopic than after conventional colorectal resections [10]. It could therefore be speculated that a significant difference in CRP level between uncomplicated cases and cases with septic complications would show more quickly and be more pronounced in laparoscopic colorectal surgery than in open surgery. This could be valuable in the modern regimens with a very short POS. The results from the present study, the limitations of which are its retrospective design and a relative small numbers of patients, make this assumption probable as the difference in CRP level between the complicated and uncomplicated cases was significant already from POD 1. Unfortunately, the variations in CRP concentration both in the group with and in the group without septic complications were so wide that the diagnostic accuracy was fairly low. We observed


FIGURE 2

Receiver-operating characteristics curves for C-reactive protein level and septic complication in post-operative days 1, 2, and 3 in laparoscopic colorectal resections.



CRP concentration above 300 mg/l on POD 2 and POD 3 in patients without septic complications. Another possible confounder could be subclinical AL. The optimal cut-off value of 200 mg/l on POD 3 had a sensitivity of 68% and a specificity of 74%. The highest median CRP concentration in the group without complications was 150 mg/l, which was found on POD 3. The sensitivity was 75% and the specificity only 47% when this value was used as cut-off.

In a retrospective study of 1,187 patients, Waeschkow et al [1] found that WBC measurements contributed little to the early detection of inflammatory complications. The diagnostic accuracy of the level of WBC was significantly lower than that of CRP. In the present study, we found significant differences in WBC on POD 1-4 between patients with and without septic complications, but again the diagnostic accuracy was low with a specificity of only 62% on POD 2 and a wide range of values in both groups which makes an interpretation difficult in the individual case. Neither CRP nor WBC can therefore stand alone as predictors of AL and other septic complications. Rather, failure to mobilize the patient "should be considered a red flag sign" [19] in laparoscopic colorectal surgery with an enhanced recovery programme prompting further investigations such as en-

Blood tests are not a short-cut in the diagnosis of anastomotic leakage in colorectal surgery.



doscopy, computed tomography or rectal contrast study [20].

CONCLUSION

The insufficient diagnostic accuracy of the level of CRP and WBC made them weak diagnostic markers in prediction of post-operative septic complications, including AL, in the first three post-operative days after laparoscopic colorectal surgery within a fast-track regimen. Therefore, interpretation of elevated values must be considered in the context of the whole clinical scenario.

CORRESPONDENCE: Per Jess, Kirurgisk Afdeling, Roskilde Hospital, 4000 Roskilde, Denmark. E-mail: pjss@regionsjaelland.dk

ACCEPTED: 15 October 2012

CONFLICTS OF INTEREST: none.

LITERATURE

- Warschlow R, Tarantino I, Torzewski M et al. Diagnostic accuracy of C-reactive protein and white cell counts in the early detection of inflammatory complications after open resection of colorectal cancer: a retrospective study of 1.187 patients. *Int J Colorectal Dis* 2011;26:1405-13.
- Buchs CN, Gervaz P, Secic M et al. Incidence, consequences, and risk factors for anastomotic dehiscence after colorectal surgery: a prospective monocentric study. *Int J Colorectal Dis* 2008;23:265-70.
- Branagan G, Finnis D, Wessex, Colorectal Cancer Audit Working Group. Prognosis after anastomotic leakage in colorectal cancer. *Dis Colon Rectum* 2005;48:1021-6.
- McArdle, McMillan DC, Hole DJ. Impacts of anastomotic leakage on long-term survival of patients undergoing curative resection for colorectal cancer. *Br J Surg* 2005;92:1150-4.
- den Dulk M, Noter SL, Hendriks ER et al. Improved diagnosis and treatment of anastomotic leakage after colorectal surgery. *EJSO* 2009;35:420-6.
- Spanjersberg WR, Reurings J, Keus F et al. Fast track surgery versus conventional recovery strategies for colorectal surgery. *Cochrane Database Syst Rev* 2011;(2):CD007635.
- Almeida AB, Faria G, Moreira H et al. Elevated serum C-reactive protein as a predictive factor for anastomotic leakage in colorectal surgery. *Int J Surg* 2012;10:87-91.
- MacKay GJ, Molloy RG, O'Dwyer. C-reactive protein as predictor of postoperative infective complications following elective colorectal resection. *Colorectal Dis* 2011;13:583-7.
- Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. *N Engl J Med* 1999;340:448-54.
- Schwenk W, Jacobi C, Mansmann U et al. Inflammatory response after laparoscopic and conventional colorectal resections – results of a prospective randomized study. *Langenbeck's Arch Surg* 2000;385:2-9.
- Hanley JA, McNeil BJ. The meaning and use of the area under a Receiver Operating Characteristic (ROC) curve. *Radiology* 1982;143:29-36.
- Nelson H, Sargent D, Wieland HS, Clinical Outcomes of Surgical Therapy Study Group. A comparison of laparoscopically assisted and open colectomy for colon cancer. *N Engl J Med* 2004;350:2050-9.
- Guillou PJ, Quirke P, Thorpe H et al. Short-term endpoints of conventional

versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. *Lancet* 2005;365:1718-26.

- Buunen M, Veldkamp R, Hop WC et al. Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomised clinical trial. *Lancet Oncol* 2009;10:44-52.
- Rawlinson A, Kang P, Evans J et al. A systematic review of enhanced recovery protocols in colorectal surgery. *Ann R Coll Surg Engl* 2012; 93:583-8.
- Welsch T, Müller SA, Ulrich A et al. C-reactive protein as early predictor for infectious postoperative complications in rectal surgery. *Int J Colorectal Dis* 2007;22:1499-507.
- Ortega-Deballon P, Radais F, Facy O et al. C-reactive protein is an early predictor of septic complications after elective colorectal surgery. *World J Surg* 2010;34:808-14.
- Woeste G, Müller C, Bechstein WO et al. Increased serum levels of c-reactive protein precede anastomotic leakage in colorectal surgery. *World J Surg* 2010;34:140-6.
- Boulied CE, Yeo M, Burkill C et al. Factors predicting deviation from an enhanced recovery programme and delayed discharge after laparoscopic colorectal surgery. *Colorectal Dis* 2012;14(3):e103-e110.
- Floodeen H, Hallböök O, Rutegård J et al. Early and late symptomatic anastomotic leakage following low anterior resection of the rectum for cancer: are they different entities? *Colorectal Dis*; 2012 Aug 14 (epub ahead of print).