Surgical Endoscopy
https://doi.org/10.1007/s00464-018-6144-x

Procalcitonin and C-reactive protein as early markers of anastomotic leak after laparoscopic colorectal surgery within an enhanced recovery after surgery (ERAS) program

José Luis Muñoz[1] · María Oliva Alvarez[2] · Vicent Cuquerella[1] · Elena Miranda[1] · Carlos Picó[1] · Raquel Flores[1] · Marta Resalt-Pereira[1] · Pedro Moya[3] · Ana Pérez[1] · Antonio Arroyo[3]

Received: 11 January 2018 / Accepted: 6 March 2018

Abstract

Background C-reactive protein (CRP) and procalcitonin (PCT) have been described as good predictors of anastomotic leak after colorectal surgery, obtaining the highest diagnostic accuracy on the 5th postoperative day. However, if an enhanced recovery after surgery (ERAS) program is performed, early predictors are needed in order to ensure a safe and early discharge. The aim of this study was to investigate the efficacy of CRP, PCT, and white blood cell (WBC) count determined on first postoperative days, in predicting septic complications, especially anastomotic leak, after laparoscopic colorectal surgery performed within an ERAS program.

Methods We conducted a prospective study including 134 patients who underwent laparoscopic colorectal surgery within an ERAS program between 2015 and 2017. The primary endpoint investigated was anastomotic leak. CRP, PCT, and WBC count were determined in the blood sample extracted on postoperative day 1 (POD 1), POD 2 and POD 3.

Results Anastomotic leak (AL) was detected in 6 patients (4.5%). Serum levels of CRP and PCT, but not WBC, determined on POD 1, POD 2, and POD 3 were significantly higher in patients who had AL in the postoperative course. Using ROC analysis, the best AUC of the CRP and PCT levels was on POD 3 (0.837 and 0.947, respectively). A CRP cutoff level at 163 mg/l yielded 85% sensitivity, 80% specificity, and 99% negative predictive value (NPV). A PCT cutoff level at 2.5 ng/ml achieved 85% sensitivity, 95% specificity, 44% positive predictive value, and 99% NPV.

Conclusions CRP and PCT are relevant markers for detecting postoperative AL after laparoscopic colorectal surgery. Furthermore, they can ensure an early discharge with a low probability of AL when an ERAS program is performed.

Keywords Laparoscopic colorectal surgery · C-reactive protein · Procalcitonin

Enhanced recovery after surgery (ERAS) programs integrate multimodal perioperative interventions which include the use of minimal invasive surgical techniques such as laparoscopic approach, the introduction of short-acting anesthetic agents, optimal pain and antiemetic control, and aggressive postoperative rehabilitation, including early oral nutrition and wandering. These programs are designed to reduce physiological stress, facilitate early return of bodily function, and reduce healthcare costs by shortening hospital stay [1].

Laparoscopic colorectal surgery results in a faster return of gastrointestinal function, with a reduction in postoperative pain, hospital stays, complications and readmission rates, and a lower total healthcare use, when compared with open surgery [2].

Although the minimally invasive approach attenuates the risk of global complications, postoperative infections, especially anastomotic leak, remain among the major complications that follow colorectal surgery. It is difficult to anticipate when such complications will occur, however, an early diagnosis is essential to improve the prognosis.

✉ José Luis Muñoz
jlmunyoz@gmail.com

[1] Department of Anaesthesia, General University Hospital Elche, Camí de l´Almazara 11, CP 03203 Elche, Alicante, Spain

[2] Department of Pathology, General University Hospital Elche, Alicante, Spain

[3] Department of Surgery, General University Hospital Elche, Alicante, Spain

Published online: 08 March 2018

Several studies in colorectal surgery corroborate the connection between an increase in CRP and the development of postoperative infectious complications such as anastomotic leak or intra-abdominal abscesses [3–8]. Different meta-analyses [9–11] have shown a low positive predictive value and a high negative predictive value for CRP.

Procalcitonin (PCT) is widely used in emergency services and critical care units both for the diagnosis of septic patients and to assess their prognosis. Recently, several studies [12–14] have described PCT as a good predictor of anastomotic leak after colorectal surgery.

The highest diagnostic accuracy for both CRP and PCT has been proven to occur on the 5th postoperative day [15]. However, if an ERAS program is performed, we need these predictors to be useful in the previous days too, so we can ensure a safe and early discharge.

The aim of this study was to investigate the efficacy of CRP, PCT, and white blood cell (WBC) count determined on first postoperative days, in predicting septic complications, especially anastomotic leak, after laparoscopic colorectal surgery performed within an ERAS program.

Materials and methods

The study was conducted at the Colorectal Unit of the General University Hospital Elche (Alicante-Spain). A prospective study in patients who underwent elective laparoscopic colorectal cancer resection within an ERAS program, between February 2015 and October 2017, was performed.

Inclusion criteria

All patients were required to be at least 18 years old to be scheduled for colorectal cancer surgery with a laparoscopic approach, within an ERAS program, and to provide written consent.

Exclusion criteria

All patients who did not meet the inclusion criteria were excluded. Other exclusion criteria were the need for emergency surgery, an American Society of Anesthesiologists (ASA) physical status of IV, renal failure defined by hemodialysis, the impossibility of normal oral food intake (dysphagia, esophageal stricture, and pyloric stenosis), psychiatric disorders, human immunodeficiency virus (HIV), pregnancy, bowel obstruction, undergoing colostomy or ileostomy and uncontrolled infection.

Enhanced recovery after surgery (ERAS) protocol

All patients were treated according to an ERAS program based on previously published protocols [16–19]. During the preoperative period, patients were given advice and received intravenous iron supplements in case of anemia. Colon preparation was not performed; only low fiber diet and enemas were given before surgery. It was also required that patients received four carbohydrate-rich drinks (800 ml) 1 day prior to surgery and two additional drinks (400 ml each) on the morning of surgery. During surgery, goal-directed fluids were administered using esophageal Doppler monitoring or pulse contour analysis device; hypothermia and drainages were avoided. A multimodal analgesia approach was used. After surgery, nasogastric tubes were not used. Instead, measures as early mobilization, opioid-free pain control and nausea and vomiting prophylaxis were applied, and oral fluids intake was reestablished early. Patients were discharged when all the following criteria were satisfied: oral intake tolerance, recovery of lower gastrointestinal function, adequate pain control with oral analgesia, and absence of sepsis-suggesting data.

Variables

The primary endpoint investigated was the appearance of anastomotic leak in the postoperative course.

C-reactive protein (CRP), procalcitonin (PCT), and white blood cell (WBC) count were determined in the blood sample extracted 24 h (POD 1), 48 h (POD 2), and 72 h (POD 3) after surgery.

Patient characteristics (age, gender, ASA status, and major comorbidities), surgical procedure, surgical time, length of stay, and mortality were recorded, as well as the 30-day postoperative complications.

Definitions

Complications were defined as any deviation from the normal postoperative course and were divided into minor and major. Minor complications included minor risk events, such as wound infections at the bedside, urinary tract infections, and postoperative ileus (Clavien-Dindo I–II) [20]. Major complications included potentially life-threatening complications and those requiring surgical, endoscopic, or radiological intervention, such as anastomotic leakage, abdominal abscess or pneumonia (Clavien-Dindo III–IV) [20].

Surgical site infection (SSI) was defined as superficial or deep incisional SSI and intra-abdominal abscesses (organ/space SSI).

Incisional SSI was defined as a purulent discharge from a surgical incision, as determined by a surgical nurse, and confirmed with microbiologic culture. Intra-abdominal abscess was defined as a fluid collection identified by computed tomography distal to the anastomosis in a symptomatic patient who presented with fever, abdominal pain, prolonged postoperative ileus, or sepsis. The diagnosis of intra-abdominal abscess was made by a radiologist.

Anastomotic leak (AL) was defined as a find at reoperation, fecaloid drain, fecal material from the wound, extravasation of contrast on enema, or the presence of air or fluid in the anastomotic region visualized by computed tomographic (CT) scan [21].

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. Urinary tract infection was defined by positive urine sediment test combined with leukocytosis and/or fever.

Hemorrhage was defined as blood output through drainage tubes (intra-peritoneal hemorrhage), or the appearance of postoperative hematemesis, melena, or a continuous decrease of hemoglobin levels in postoperative blood samples.

Ileus was defined as a temporary delay in gastrointestinal motility after surgery, presented by nausea, vomiting, abdominal distention, abdominal tenderness, or delayed passage of flatus and stool [22].

Statistical analysis

All statistical analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL). Gaussian distribution of the variables was analyzed using the Kolmogorov-Smirnoff test; p values > 0.05 were considered as Gaussian distribution. Quantitative variables following a normal distribution were defined by mean and standard deviation (SD); non-gaussian variables were defined by median and range. Qualitative variables were defined by number of cases and percentages. Comparisons of variables were performed with Student's t and Pearson's correlation methods for quantitative variables following Gaussian distribution and Mann–Whitney method for non-gaussian distributions. Comparison of qualitative variables was performed with the χ^2 method. A p value < 0.05 was considered statistically significant. Furthermore, receiver operating characteristic (ROC) curve analysis was performed, and the respective areas under the curve (AUC) were calculated to evaluate the predictive value for the diagnosis of AL, only for variables with statistically significant differences at the univariate analysis. The sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) of these parameters were calculated.

Results

A total of 134 patients were included in the study. Patients characteristics, ASA score, and comorbidities are shown in Table 1. Surgical data and postoperative complications are illustrated in Table 2. Infectious complications were observed in 14 patients (10.4%). Five patients (3.7%) presented with incisional SSI in the first 30 days post surgery. Intra-abdominal abscesses were observed in 3 patients (2.2%), two patients during hospital stay and one patient after discharge on 15th postoperative day. Anastomotic leak was detected in 6 patients (4.5%). Five patients required a second surgery, all due to AL: 1 patient on POD 4; 1 patient on POD 5; 2 patients on POD 7 and 1 patient on POD 8 during the hospital stay. One patient was re-admitted after discharge on the 12th postoperative day with fever and abdominal pain. The CT scan showed small anastomotic collections that were treated conservatively with antibiotic therapy. Six patients (4.5%) presented with postoperative hemorrhage, 4 of them required a reoperation (all at POD 2). Nine patients (6.7%) presented ileus in the postoperative course.

Mean postoperative hospital stay in patients with major complications (Clavien-Dindo III–IV) was 19 days (range 5–50 days), compared with 9.5 (range 4–15 days) in patients with minor complications (Clavien-Dindo I–II) and 5.5 days (range 4–11 days) in no complications group. No patient died during the hospital stay or following discharge.

Serum levels of CRP and PCT, but not WBC, determined on POD 1, POD 2, and POD 3 after surgery were significantly higher in patients who had AL in the postoperative course (Table 3). Higher levels of CRP and PCT were also observed in patients who developed a major septic

Table 1 Patients characteristics and comorbidities $n = 134$

Age (years)	66.5 SD 11.2
Sex	
Male	73 (54.5%)
Female	61 (45.5%)
BMI (kg/m^2)	27.4 SD 4.5
ASA score	
I	23 (17.2%)
II	65 (48.5%)
III	46 (34.3%)
Comorbidities	
Diabetes mellitus	28 (20.9%)
Hypertension	62 (46.3%)
Dyslipidemia	43 (32.1%)
Heart disease	15 (11.2%)
Respiratory disease	9 (6.7%)
Smokers	23 (17.2%)

complications (anastomotic leak or intra-abdominal abscess) (Table 4).

Receiver operating characteristic curve analysis (ROC) for the diagnosis of anastomotic leak was summarized on Table 5. Using ROC analysis on POD 1 (Fig. 1) (Table 5), the area under the curve (AUC) of the CRP level was 0.700 ($p = 0.133$), and a cutoff level at 60 mg/l for predicting AL achieved 80% sensitivity, 55% specificity, 99% negative predictive value (NPV), and 8% positive predictive value (PPV), whereas the AUC of the PCT level was 0.862 ($p = 0.007$),

Table 2 Surgical data and postoperative complications

	Total $n = 134$	Right colectomy $n = 31$	Left colectomy $n = 75$	Rectal resection $n = 28$	Length of stay
Without complications	105 (78.4%)	21 (67.8%)	65 (86.7%)	19 (67.8%)	5.5 SD 1.4
Clavien-Dindo I–II	14 (10.4%)	4 (12.8%)	4 (5.3%)	6 (21.4%)	9.5 SD 3.4
Incisional SSI	5 (3.7%)	2 (6.4%)	1 (1.3%)	2 (7.1%)	6.2 SD 2.1
Ileus	9 (6.7%)	2 (6.4%)	3 (4%)	4 (14.3%)	11.3 SD 2.5
Urinary tract infection	(0%)				
Clavien-Dindo III–IV	15 (11.2%)	6 (19.4%)	6 (8%)	3 (10.8%)	19 SD 12.3
Anastomotic leak	6 (4.5%)	3 (9.7%)	3 (4%)	0	22 SD 15.6
Intra-abdominal abscess	3 (2.2%)	1 (3.2%)	0	2 (7.1%)	18 SD 13.5
Hemorrhage	6 (4.5%)	2 (6.5%)	3 (4%)	1 (3.7%)	16.5 SD 9.5
Pneumonia	0 (0%)				
Postoperative mortality	0 (0%)				
Surgical time (min)	172.2 SD 69.3	126.2 SD 49.6	176.4 SD 68.5	211.7 SD 64.6	

SD standard deviation

Table 3 Postoperative analytical data for anastomotic leak

	POD	No AL	AL	*p*
C-reactive protein (mg/l)	1	56.2 SD 39.9	111.5 SD 109.5	0.004
	2	97.1 SD 102.7	216.7 SD 96.1	0.007
	3	91.4 SD 74.8	254.7 SD 138.4	< 0.001
Procalcitonin (ng/ml)	1	0.40 SD 0.9	3.18 SD 4.54	< 0.001
	2	0.50 SD 1.1	6.84 SD 6.12	< 0.001
	3	0.36 SD 0.66	16.45 SD 20.15	< 0.001
White blood cell count (mm^3)	1	9680 SD 3285	11,011 SD 4076	0.23
	2	8376 SD 2905	9684 SD 2962	0.175
	3	7955 SD 7445	8340 SD 3126	0.872

Mean +/− SD standard deviation

AL anastomotic leak

Table 4 Postoperative analytical data for major septic complications

	POD	No MSC	MSC	*p*
C-Reactive protein (mg/l)	1	58.5 SD 37.3	109.3 SD 93.2	0.002
	2	97.8 SD 95.5	227.6 SD 80.5	< 0.001
	3	96.1 SD 74.7	256.8 SD 124.4	< 0.001
Procalcitonin (ng/ml)	1	0.46 SD 0.9	2.4 SD 3.96	< 0.001
	2	0.52 SD 1.1	5.93 SD 6.09	< 0.001
	3	0.40 SD 0.65	14.13 SD 17.05	< 0.001
White blood cell count (mm^3)	1	9283 SD 3176	11,670 SD 3904	0.108
	2	8059 SD 2858	9164 SD 3095	0.18
	3	7865 SD 7468	8891 SD 3516	0.684

Mean +/− SD standard deviation

MSC major septic complications

Table 5 Receiver operating characteristic (ROC) analysis for the diagnosis of anastomotic leak

	POD	AUC	*p*	95% CI	Cutoff value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
C-reactive protein (mg/l)	1	0.700	0.133	0.482–0.918	60	80	55	8	99
	2	0.837	0.006	0.673–1.00	130	85	80	17	99
	3	0.837	0.006	0.649–1.00	163	85	80	17	99
Procalcitonin (ng/ml)	1	0.862	0.007	0.748–0.976	0.36	80	80	15	99
	2	0.904	0.001	0.791–1.00	1.05	70	90	24	98.5
	3	0.947	< 0.001	0.870–1.00	2.5	85	95	44	99

AUC area under the curve, *CI* confidence interval, *PPV* positive predictive value, *NPV* negative predictive value

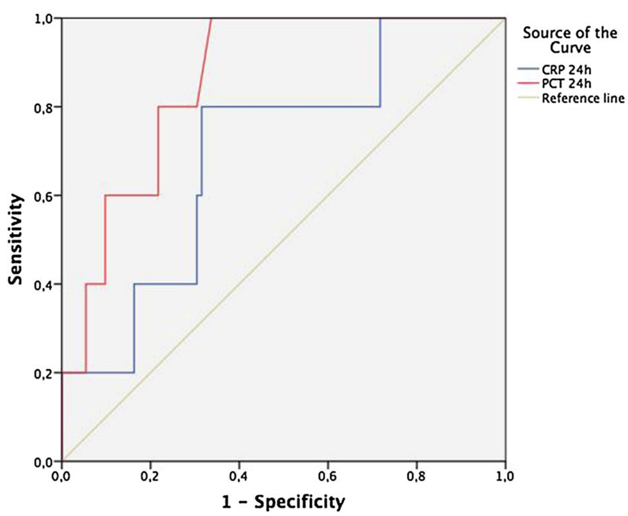

Fig. 1 Plot of the receiver operating characteristic (ROC) curve of the C-reactive protein (CRP) level and procalcitonin (PCT) level for the diagnosis of AL on POD 1 after laparoscopic colorectal surgery. (Color figure online)

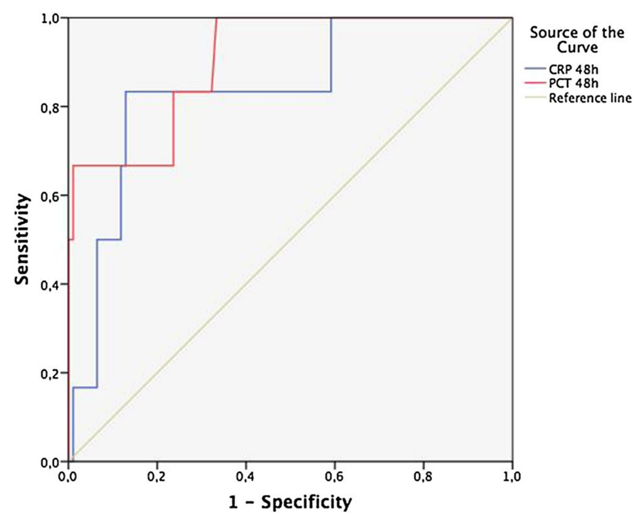

Fig. 2 Plot of the receiver operating characteristic (ROC) curve of the C-reactive protein (CRP) level and procalcitonin (PCT) level for the diagnosis of AL on POD 2 after laparoscopic colorectal surgery. (Color figure online)

and a cutoff level at 0.36 ng/ml achieved 80% sensitivity, 80% specificity, 99% NVP, and 15% PPV.

Using ROC analysis on POD 2 (Fig. 2) (Table 5), the AUC of the CRP level was 0.837 ($p = 0.006$), and a cutoff level at 130 mg/l for predicting AL achieved 85% sensitivity, 80% specificity, 99% NVP, and 17% PPV, whereas the AUC of the PCT level was 0.904 ($p = 0.001$), and a cutoff level at 1.05 ng/ml achieved 70% sensitivity, 90% specificity, 98.5% NVP, and 24% PPV.

As shown in Fig. 3 (Table 5), the AUC of the CRP levels on POD 3 was 0.837 ($p = 0.006$), and a cutoff level at 163 mg/l yielded 85% sensitivity, 80% specificity, 99% NVP, and 17% PPV. The AUC of the PCT on POD 3 was 0.947 ($p < 0.001$), and a cutoff level at 2.5 ng/ml achieved 85% sensitivity, 95% specificity, 99% NVP, and 44% PPV.

Receiver operating characteristic curve analysis (ROC) for the diagnosis of major septic complications (anastomotic leak and intra-abdominal abscesses) was also calculated (Table 6).

Discussion

Anastomotic leak (AL) after colorectal surgery has a remarkable impact on patient's outcome, involving higher morbidity, mortality and longer hospital stay [23–25]. Early diagnosis of infectious complications remains a challenge for surgeons, and it is essential to enhance patients' outcome. Furthermore, this is more important when the patient is scheduled to undergo an early discharge as part of an ERAS program. In these cases, providing a marker that may alert the surgeon about the development of a septic complication, like anastomotic leak, before it is clinically evident, would be essential to decide whether the patient can leave the hospital or should remain hospitalized for further investigations in order to discard a postoperative complication [23–27]. In the present study, the appearance of complications in postoperative course, especially anastomotic leak (AL), led to a considerable increase in hospital stay (5.5–20 days).

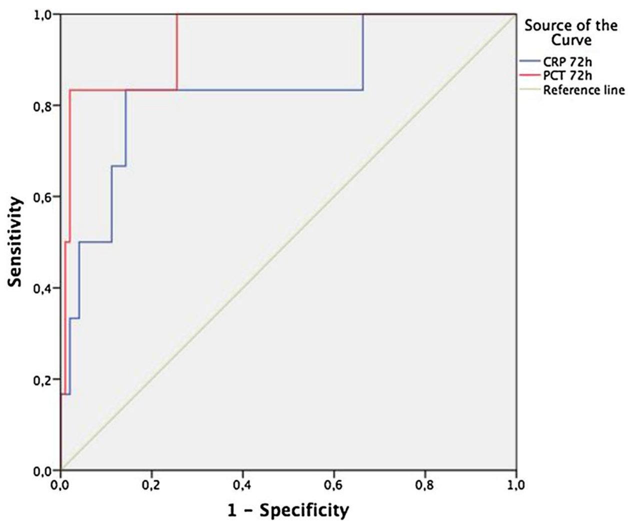

Fig. 3 Plot of the receiver operating characteristic (ROC) curve of the C-reactive protein (CRP) level and procalcitonin (PCT) level for the diagnosis of AL on POD 3 after laparoscopic colorectal surgery. (Color figure online)

Several studies in colorectal surgery corroborate the connection between an increase in CRP and the development of postoperative infectious complications such as anastomotic leak or intra-abdominal abscesses [3–8]. All these studies attempt to establish a cutoff level for CRP as a predictor of such complications. Different meta-analyses [8–10] have shown a low positive predictive value for CRP.

An isolate increase in CRP values is not enough for the diagnosis of major complications, as many patients who do not develop an anastomotic leak can also exhibit a severe systemic inflammatory response or elevated CRP levels for a prolonged period, due to other factors such as surgical trauma, blood loss, and length of the surgery. Despite this, some authors support the idea that CRP measurement should be part of postoperative laboratory routine at least at POD 3 and 4, as its high negative predictive value dismiss the possibility of a septic complication, in order to ensure a safe early discharge [27–29]. This is important when an ERAS program is performed. The implementation of multimodal rehabilitation programs and laparoscopic surgery attenuate the patient's systemic inflammatory response to surgery [30–33] and this could even improve the sensitivity and specificity of CRP to detect infectious complications in the previous days. In our study, CRP levels in patients who did not develop AL were very low (mean < 100 mg/dl in all days) with a peak in POD 2 due to the pharmacokinetics of CRP. That is the reason way CRP on POD 2 and POD 3 proved to be a good predictor for AL with a maximum AUC on POD 3 (0.837). These findings could be explained because all patients followed a multimodal rehabilitation program (ERAS), and the percentage of laparoscopic approach (100%) was higher than in previous studies [12–14, 29]. These results suggest that the measurement of CRP in POD 2 and 3 could be useful in the early detection of complications, especially anastomotic leak, when an ERAS program is performed, including laparoscopic approach. Furthermore, CRP showed a high negative predictive value (NPV 99%) in our study; this would allow us to rule out the appearance of complications and ensure a safer discharge.

Procalcitonin (PCT) concentration increases during bacterial reactions but not in non-infectious inflammatory reactions, so it seems to be more useful than CRP as an early biomarker of colorectal anastomotic leak [9–11]. Several studies [13, 14] have demonstrated that PCT is a good marker in the early prediction of major anastomotic leak at postoperative days 3 to 5. A meta-analysis performed by Cousin et al. [15] confirms that PCT, measured on POD 5, is a helpful biomarker for early diagnosis of intra-abdominal infection, including AL, after colorectal surgery. However, we thought we should focus on the POD 3 because, within an ERAS program, most patients are supposed to be already at home in POD 5. In our study, PCT levels in patients without AL remained low (< 0.6 ng/dL) in the first postoperative days. PCT proved to be better predictor of AL than PCR, especially in POD 3, with a AUC of 0.947 (a PCT cutoff level at 2.5 ng/ml achieved 85% sensitivity, 95% specificity, 99% NPV, and 44% PPV). As with the CRP measurement, the implementation of

Table 6 Receiver operating characteristic (ROC) analysis for the diagnosis of Major septic complications

	POD	AUC	*p*	95% CI	Cutoff value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
C-reactive protein (mg/l)	1	0.724	0.036	0.566–0.881	60	87	55	12	98
	2	0.875	0.001	0.749–1.00	130	85	80	23	99
	3	0.879	0.001	0.733–1.00	163	85	80	23	99
Procalcitonin (ng/ml)	1	0.851	0.004	0.749–0.953	0.36	80	80	22	98
	2	0.863	0.003	0.744–0.982	1.05	60	90	30	97
	3	0.922	0.001	0.826–1.00	2.5	70	95	50	97

AUC area under the curve, *CI* confidence interval, *PPV* positive predictive value, *NPV* negative predictive value all items of an ERAS program, including a laparoscopic approach, is fundamental to improve the accuracy of the PCT to predict AL in the first postoperative days. Our study agrees with previously published results, especially by Giaccaglia et al. [14] in the PREDICS study, which includes more than 500 patients and a high percentage of laparoscopic approach (75%).

If we consider the major septic complications (anastomotic leak and intra-abdominal abscesses), CRP and PCT continued to maintain a high negative predictive value (99% and 97%, respectively, on POD3), in addition, PCT in POD3 also proved to be more accurate than CRP in the diagnosis of major septic complication (50% PPV). This fact is important within the ERAS programs in order to ensure a safe and early discharge.

To our knowledge, no other study has measured CRP and procalcitonin level in the first postoperative days within an ERAS program to evaluate their predictive value for detecting anastomotic leak after laparoscopic colorectal surgery. The main limitation of this study is the small sample size and a single center study. Future studies with a higher number of patients are required to confirm the results we obtained.

Finally, the routine measurement of CRP and PCT plays an important role in order to ensure a safe discharge within an ERAS program in laparoscopic colorectal surgery. When both are in the normal range on POD 3 the patient can be discharged early with a low probability of AL. On the other hand, if these markers are increased, even in an asymptomatic patient, an early discharge should be avoided and other tests, e.g., CT scan, should be evaluated to exclude an AL.

Conclusions

Our study supports the role of CRP and PCT as relevant markers for detecting postoperative anastomotic leak after laparoscopic colorectal surgery. Furthermore, they can ensure an early discharge with a low probability of AL when an ERAS program is performed.

Compliance with ethical standards

Disclosures José Luis Muñoz, María Oliva Alvarez, Vicent Cuquerella, Elena Miranda, Carlos Picó, Raquel Flores, Marta Resalt-Pereira, Pedro Moya, Ana Pérez, and Antonio Arroyo have no conflicts of interest or financial ties to disclose.

Ethical approval This study was approved by the local ethics committee.

Informal consent All patients signed an informed consent form for the ERAS program and for inclusion in the study.

References

1. Gustafsson UO, Scott MJ, Schwenk W et al (2013) Guidelines for perioperative care in elective colonic surgery/enhanced recovery after surgery (ERAS) society recommendations. World J Surg 37:259e284
2. Zhuang CL, Huang DD, Chen FF, Zhou CJ, Zheng BS, Chen BC et al (2015) Laparoscopic versus open colorectal surgery within enhanced recovery after surgery programs: a systematic review and meta-analysis of randomized controlled trials. Surg Endosc 29:2091–2100
3. Welsch T, Müller SA, Ulrich A, Kischlat A, Hinz U, Kienle P et al (2007) C-reactive protein as early predictor for infectious postoperative complications in rectal surgery. Int J Colorectal Dis 22:1499–1507
4. Mackay GJ, Molloy RG, O'Dwyer PJ (2011) C-reactive protein as a predictor of postoperative infective complications following elective colorectal resection. Colorectal Dis 13:583–587
5. Platt J, Ramanathan M, Crosbie R, Anderson JH, McKee RF, Horgan PG et al (2012) C-reactive protein as a predictor of postoperative infective complications after curative resection in patients with colorectal cancer. Ann Surg Oncol 19:4168–4177
6. Ortega-Deballon P, Radais F, Facy O, dÁthis P, Masson D, Charles PE et al (2010) C-reactive protein is an early predictor of septic complications after elective colorectal surgery. World J Surg 34:808–814
7. Kørner H, Nielsen HJ, Søreide JA, Nedrebø BS, Søreide K, Knapp JC (2009) Diagnostic accuracy of C-reactive protein for intra-abdominal infections after colorectal resections. J Gastrointest Surg 13:1599–1606
8. Almeida AB, Faria G, Moreira H, Pinto-de-Sousa J, Correia-da-Silva P, Maia JC (2012) Elevated serum C-reactive protein as a predictive factor for anastomotic leakage in colorectal surgery. Int J Surg 10:87–91
9. Warschkow R, Beutner U, Steffen T, Müller SA, Schmied BM, Güller U et al (2012) Safe and early discharge after colorectal surgery due to C-reactive protein. Ann Surg 256:245–250
10. Singh PP, Zeng IS, Srinivasa S, Lemanu DP, Connolly AB, Hill AG (2014) Systematic review and meta-analysis of use of serum C-reactive protein levels to predict anastomotic leak after colorectal surgery. Br J Surg 101:339–346
11. Straatman J, Harmsen AMK, Cuesta MA, Berkhof J, Jansma EP, van der Peet DL (2015) Predictive value of C-reactive protein for major complications after major abdominal surgery: a systematic review and pooled-analysis. PLoS ONE 10(7):e0132995
12. Takakura Y, Hinoi T, Egi H, Shimomura M, Adachi T, Saito Y et al (2013) Procalcitonin as a predictive marker for surgical site infection in elective colorectal cancer surgery. Langenbecks Arch Surg 398:833–839
13. Garcia-Granero A, Frasson M, Flor-Lorente B, Blanco F, Puga R, Carratalá A et al (2013) Procalcitonin and C-reactive protein as early predictors of anastomotic leak in colorectal surgery: a prospective observational study. Dis Colon Rectum 56:475–483
14. Giaccaglia V, Salvi PF, Antonelli MS, Nigri G, Pirozzi F, Casagranda B et al (2016) Procalcitonin reveals early dehiscence in colorectal surgery: the PREDICS study. Ann Surg 263:967–972
15. Cousin F, Ortega-Deballon P, Bourredjem A, Doussot A, Giaccaglia V, Fournel I (2016) Diagnostic accuracy of procalcitonin and C-reactive protein for the early diagnosis of intra-abdominal infection after elective colorectal surgery: a meta-analysis. Ann Surg 264(2):252–256
16. Ramírez JM, Blasco JA, Roig JV, Maeso-Martínez S, Casal JE, Esteban F, Spanish working group on fast track surgery (2011) Enhanced recovery in colorectal surgery: a multicentre study. BMC Surg 11:9

17. Arroyo A, Ramirez JM, Callejo D, Viñas X, Maeso S, Cabezali R, Miranda E, Spanish Working Group in Fast Track Surgery (GERM) (2012) Influence of size and complexity of the hospitals in an enhanced recovery programme for colorectal resection. Int J Colorectal Dis 27:1637–1644
18. Esteban F, Cerdan FJ, Garcia-Alonso M, Sanz-Lopez R, Arroyo A, Ramirez JM et al (2014) A multicentre comparison of a fast track or conventional postoperative protocol following laparoscopic or open elective surgery for colorectal cancer surgery. Colorectal Dis 16:134–140
19. Moya P, Miranda E, Soriano-Irigaray L, Arroyo A, Aguilar MD, Bellón M, Muñoz JL, Candela F, Calpena R (2016) Perioperative immunonutrition in normo-nourished patients undergoing laparoscopic colorectal resection. Surg Endosc 30:4946–4953
20. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD et al (2009) The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 250:187–196
21. Adams K, Papagrigoriadis S (2013) Little consensus in either definition or diagnosis of lower gastro-intestinal anastomotic leak amongst colorectal surgeons. Int J Colorectal Dis 28:967–971
22. Holte K, Kehlet H (2002) Postoperative ileus: progress towards effective management. Drugs 62:2603–2615
23. Woeste G, Muller C, Bechstein Wo Wullstein C (2010) Increased serum levels of C-reactive protein precede anastomotic leakage in colorectal surgery. World J Surg 34:140–146
24. Reisinger KW, Poeze M, Hulsewé KW, van Acker BA, van Bijnen AA, Hoofwijk AG et al (2014) Accurate prediction of anastomotic leakage after colorectal surgery using plasma markers for intestinal damage and inflammation. J Am Coll Surg 219:744–751
25. Mirnezami A, Mirnezami R, Chandrakumaran K, Sasapu K, Sagar P, Finan P (2011) Increased local recurrence and reduced survival from colorectal cancer following anastomotic leak: systematic review and meta-analysis. Ann Surg 253:890–899
26. Pompilio E, Casigliani R, Sommariva S, Saggese MP (1989) Acute phase proteins as markers of septic risk in surgical patients. Minerva Chir 44:2185–2190
27. Daams F, Wu Z, Lahaye MJ, Jeekel J, Lange JF (2014) Prediction and diagnosis of colorectal anastomotic leakage: a systematic review of literature. World J Gastrointest Surg 6:14–26
28. Giaccaglia V, Salvi PF, Cunsolo GV, Sparagna A, Antonelli MS, Nigri G et al (2014) Procalcitonin, as an early biomarker of colorectal anastomotic leak, facilitates enhanced recovery after surgery. J Crit Care 29:528–532
29. Domínguez-Comesaña E, Estevez-Fernández SM, López-Gómez V, Ballinas-Miranda J, Domínguez-Fernández R (2017) Procalcitonin and C-reactive protein as early markers of postoperative intra-abdominal infection in patients operated on colorectal cancer. Int J Colorectal Dis 32:1771–1774
30. Lane JC, Wright S, Burch J, Kennedy RH, Jenkins JT (2013) Early prediction of adverse events in enhanced recovery based upon the host systemic inflammatory response. Colorectal Dis 15:224–230
31. Ramanathan M, MacKay G, Platt J, Horgan PG, McMillan DC (2013) Impact of day 2 C-reactive protein on day 3 and 4 thresholds associated with infective complications following curative surgery for colorectal cancer. World J Surg 37:2705–2710
32. Veenhof AA, Vlug MS, van der Pas MH, Sietses C, van der Peet DL, de Lange-de Klerk ES et al (2012) Surgical stress response and postoperative immune function after laparoscopy or open surgery with fast track or standard perioperative care: a randomized trial. Ann Surg 255:216–221
33. Facy O, Paquette B, Orry D, Santucci N, Rat P, Rat P, Binquet C, Ortega-Deballon P (2017) Inflammatory markers as early predictors of infection after colorectal surgery: the same cut-off values in laparoscopy and laparotomy? Int J Colorectal Dis 32:857–863