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Procalcitonin, as an early biomarker of colorectal anastomotic leak, facilitates enhanced recovery after surgery

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ABSTRACT

Purpose: Procalcitonin (PCT) is a biomarker used to help sepsis diagnosing and monitoring and guide antibiotic therapy. Anastomotic leak (AL) after colorectal surgery is a severe complication associated with relevant short- and long-term sequelae. The aim of our study is to assess the predictive value of PCT levels to early diagnose AL after colorectal surgery.

Methods: Between September 2011 and September 2012, a series of 99 patients underwent colorectal surgery in our institution. In all cases, white blood cell (WBC) count, C-reactive protein (CRP), and PCT levels were measured in first, third, and fifth postoperative day (POD). Anastomotic leaks and all other postoperative complications were recorded.

Results: We registered 7 ALs (7.1%). Decreased PCT levels had a significant negative predictive value (NPV) for AL in third and fifth POD (96.7% and 96.7%, respectively), compared with CRP and WBC. The best diagnostic performance was obtained with the combination of PCT and CRP measurements in third and fifth POD (area under the curve, 0.87 and 0.94, respectively). In 5th POD, PCT improves diagnosis, but not in a statistically significant way (area under the curve, 0.86).

Conclusions: Compared with more established biochemical values such as CRP and WBC, PCT is an earlier, more sensitive, and reliable marker of AL. Increased PCT levels in early PODs after colorectal surgery may provide a more effective way to detect AL, before clinical symptoms appear. Moreover, normal PCT values might be also a useful marker to facilitate a safe and early discharge of selected patients after colorectal surgery.

1. Introduction

Anastomotic leak (AL) after colorectal surgery represents a major clinical problem observed in a range from 2% to 7% of patients, increasing up to 8% to 14% in low colorectal resections and even to 26% in some older reports [1–4]. Enhanced recovery after surgery (ERAS) programs are suggested to reduce postoperative complications in up to 50% of cases, fasten recovery, and shorten length of stay [5,6]. These fast-track protocols demand very early patient discharge, but this might be potentially associated with an increased risk of delayed diagnosis and treatment of AL, occurring after patient discharge. Hence, there is a strong need of an additional tool to help early diagnosing of AL, prior patient discharge. Serum procalcitonin (PCT) is a 116-amino acid protein produced by C-cells of the thyroid gland. Procalcitonin baseline levels are low (<0.1 ng/mL) but increase significantly in patients with severe bacterial infections and sepsis. Therefore, PCT levels can be used to monitor the course and prognosis of systemic bacterial infections and to tailor the therapeutic interventions more efficiently [7,8]. Furthermore, PCT could serve as an early predictive marker for the clinical course of septic complications after abdominal surgery [9,10].

The aim of our study is to demonstrate if PCT is a more sensible, specific, and reliable biomarker of AL than C-reactive protein (CRP) and white blood cell (WBC) count and if low levels of PCT (<5 ng/mL in third postoperative day [POD] and/or <2.0 ng/mL in fifth POD) might be safely added as an additional criteria of early discharge in ERAS protocols.

2. Materials and methods

Between September 2011 and September 2012, a series of 99 patients underwent elective colorectal surgery in our institution. Colorectal surgery includes a wide number of procedures, in this article—because we are studying a biomarker supposed to early detect AL, we analyze only the procedures where an anastomosis is performed, which are the following: right colectomy, transverse resection, left colectomy, sigmoid resection, and low anterior resection.

Our inclusion criteria were as follows: patients undergoing various kinds of laparotomic or laparoscopic colorectal surgery (from right colectomies to low anterior resection, as explained above), in elective

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setting, either for cancer or benign disease (eg, diverticular disease) with an anastomosis being performed (ileo-colic, colo-colic, colo-rectal, or colo-anal). Exclusion criteria were as follows: age younger than 18 years, pregnancy status, patients undergoing abdomino-perineal resection or other kinds of colorectal-surgery without an anastomosis being performed (eg, Hartmann procedures), operations performed in emergency setting.

Patients' characteristics (age, sex, renal function, comorbidities); type of surgical resections, intraoperative and postoperative complications (hemorrhagic, cardiovascular, pulmonary, infective…); and their management, reinterventions, and length of hospital stay were recorded. In all cases, WBC, CRP, and PCT levels were measured in first, third, and fifth POD.

Between surgeons, there is not clear consensus about the definition of AL. We adopted the description of AL recently published by Adams and Papagrigoriadis [11], as one of the following: postoperative peritonitis found 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. Anastomotic leaks were classified as "major" (need of reoperation or percutaneous radiologic drainage, Clavien-Dindo grades III) and "minor" (conservative medical treatment, Clavien-Dindo grades I and II) [12].

Written informed consent was obtained from all patients. The study was approved by our institution's ethical committee.

2.1. Technique

Whole blood from EDTA-anticoagulated tubes was used to test for WBC. White blood cells were counted by flow cytometry and peroxidase staining on ADVIA Hematology System (Siemens, Erlangen, Germany). C-reactive protein was measured by immunonephelometry on an automated Dimension Vista analyzer (Siemens). Measurement of procalcitonin can be performed either in venous or arterial blood samples. Procalcitonin is a relatively stable protein, and it does not require special attentions for laboratory management [7]. It is determined by homogeneous phase sandwich enzyme-linked immunosorbent assay analysis (Kryptor; BRAHMS, Hennigsdorf, Germany).

Patients were examined at least twice daily from a senior surgeon together with a resident to assess clinical conditions; vital parameters (blood pressure, heart rate, body temperature, urine, and drain output) were measured 3 times a day by the nurses. Patients were discharged when all the following criteria were satisfied: tolerance of oral intake, recovery of lower gastrointestinal function, adequate pain control with oral analgesia, and absence of data suggesting sepsis [13]. All ALs were confirmed by enema with hydrosoluble contrast performed with either with x-ray or CT scan. Wound infections were diagnosed in the presence of clear signs of inflammation at the wound margin or purulent drainage from the wound. Pneumonia was diagnosed by the evidence of pulmonary infiltration on a chest x-ray accompanied by clinical symptoms of the lower respiratory tract, physical examination, or laboratory tests.

Follow-up consisted of complete clinic evaluation at 1 week and clinical evaluation and blood sampling for laboratory tests 1 month after discharge. Total body contrast-enhanced CT scan was performed at 3 or 6 months or 1 year, depending on tumor staging and pertaining oncological protocols. Colonoscopy was planned to be performed in all patients at 1-year follow-up.

2.2. Statistical analysis

All data were collected prospectively and entered in a computerized database. Analysis included the following variables: age, sex, renal function, comorbidities, tumor localization, type of operation, postoperative complications (included AL), and length of hospital stay. Values are expressed as means and SDs, medians and interquartile ranges, or counts and percentages as appropriate. Box plots and Kruskal-Wallis test were used to compare biomarker distributions in groups. Logistic regression was used to evaluate biomarkers for the diagnosis of AL in both univariable and multivariable analysis. Receiver operating characteristic (ROC) curves were constructed to assess the sensitivity and specificity of biomarker measurements obtained at 3 and 5 POD to compare their ability to diagnose AL. Sensitivity, specificity, negative predictive value, and positive predictive value were calculated with 95% confidence intervals as usual. To demonstrate independence of PCT, the added value of PCT on top of CRP was evaluated based on the likelihood ratio χ^2 test for nested models. All statistical tests were 2 tailed, and a 2-sided P value of .05 was considered for significance. The statistical analyses were performed using R version 2.5.1 (http://www.r-project.org, library Design, Hmisc, ROCR).

3. Results

A total of 99 patients were enrolled in this study, 56 were male (56.56%) and 43 female (43.43%); mean age was 68 years. Thirty-six patients (36.36%) had at least 1 comorbidity, 23 were affected by cardiovascular disease (hypertension, coronary artery disease, heart failure…), 9 chronic obstructive pulmonary disease, 6 diabetes mellitus, and 3 chronic renal failure. Patients' characteristics are summarized in Table 1. In all cases, surgical resections were performed in an elective regimen, most of them with a laparotomy (89 vs 12 laparoscopic resections) and for neoplastic disease (92 vs 7 for benign disease), as shown in Table 1. Because impaired renal function can affect PCT measurement, we preoperatively measured in all patients blood azotemia and creatinine. In our population, mean values of azotemia and creatinine were within the reference range, being 17 and 0.9 mg/dL, respectively. Only 3 patients (3%) were affected by chronic renal failure (mean azotemia and creatinine, 40 and 2.8 mg/dL, respectively), but we did not register statistically significant differences in the PCT values and incidence of AL between the chronic renal failure group and the patients with normal values of kidneys function.

Most of our patients underwent distal colic resections (58 cases), with 13 left colectomies, 22 sigmoid resections, and 23 low anterior resections being performed. Types of surgical resections, due to the localization of the lesions, are illustrated in Table 2.

No patients died either intraoperatively or postoperatively. Mean hospital stay of our population was 11 days. Twenty-five cases (24.7%) developed postoperative complications, which are summarized in Table 3. Seven of these (7.1%) had AL, one of them associated with wound infection; in the remaining 16 cases, we registered complications other than AL such as wound infection, bleeding, pneumonia, and acute renal failure (Table 3). Mean hospital stay of the latter patients, with complications other than AL, was 12 days, compared with 32 days of the AL group and 8 days in the no complications group. Between the 7 patients developing AL (7.1%), 4 cases occurred after low anterior resection (57.1%), 2 after sigmoid resection (28.6%), and 1 after right colectomy (14.3%), as shown in Table 4. Therefore, almost

Table 1
Patient's characteristics

Characteristics	n (101)
Sex: male/female	56/45
Mean age (y)	68.2
Blood azotemia (mean, mg/dL)	17
Blood creatinine (mean, mg/dL)	0.9
Comorbidities (total)	38 (37.6%)
Cardiovascular	23 (22.7%)
COPD	9 (8.9%)
Diabetes mellitus	6 (5.9%)
Chronic renal failure	3 (2.9%)
Laparotomy/laparoscopy	89/12
Tumor/benign disease	93/8

COPD indicates chronic obstructive pulmonary disease.

Table 2
Type of surgical resection

Operation	n (101)
Right colectomy	40 (39.6%)
Transverse resection	1 (0.9%)
Left colectomy	13 (12.8%)
Sigmoid resection	23 (22.7%)
Low anterior resection	24 (23.7%)

all the ALs (85.7%) occurred after distal resections, involving sigmoid or rectum. On the other hand, complications other than AL occurred in 65% of distal resections compared with 35% of proximal resections (Table 4). All cases of AL were classified as "major leak"; in 2 patients, the dehiscence occurred in seventh POD; in 3 patients, it occurred early between the second and the fifth POD, and in 2 patients, the AL occurred late rather between the 9th and the 14th POD. Four patients needed reoperation, whereas 3 patients were treated with conservative therapy (percutaneous drain, nothing per os and antibiotics). Among these 7 patients, all of them presented either in third POD PCT values greater than 5 ng/mL and/or greater than 2 ng/mL in fifth POD. In first POD, we did not observe statistically significant differences in PCT levels between the AL group (mean, 3.42 ng/mL), the group with complications other than AL (mean, 2.86 ng/mL), and the no complications group (mean, 2.36 ng/mL; $P = .478$), as shown in Table 5. Procalcitonin levels in third POD where significantly higher in patients with AL (mean, 4.97 ng/mL) than in the other complications group (mean, 2.27 ng/mL) or no complications group (mean, 1.12 ng/mL; $P = .007$; Table 5). Negative predictive value for AL with PCT less than 5 ng/mL in third POD is 96.7%, with a specificity of 95.7%. Receiving operating characteristic curve for biomarkers in third POD shows that PCT has better area under the curve than CRP (0.884 and 0.767, respectively; Fig. 1). In fifth POD, as shown in Table 5, PCT levels were higher in patients who developed AL (mean, 3.17 ng/mL) and in patients with other complications (mean, 2.58 ng/mL) than in those with no complications (mean, 0.47 ng/mL; $P = .0005$). Test for AL with PCT less than 2.0 ng/mL at fifth POD shows an NPV of 96.7% and specificity of 94.6%. Receiving operating characteristic curve for biomarkers in fifth POD shows that adding PCT to CRP enhances diagnosis of AL, even if not significantly (area under the curve, 0.942).

4. Discussion

In patients undergoing colorectal surgery, AL is the most serious postoperative infective complication; it can be catastrophic for the patient, both in short- and long-term outcomes. In fact, symptomatic fistula leads to abscess and/or peritonitis, reoperation, higher morbidity and mortality, longer hospital stay, increased costs, and worse long-term oncological outcomes [14–17]. Its early diagnosis and treatment, in a latent preclinical phase, are keys to improve outcomes [18]. However, AL may be difficult to diagnose and is often recognized in the late postoperative period, when the patient is already critically ill [19]. For example, Hyman et al [20] showed that diagnosis of AL was made a mean of 12.7 days postoperatively, including 4 beyond 30 days (12.1%). Clearly, if these patients could be identified earlier, subsequent leak of feces into the peritoneal cavity and resultant sepsis may be avoided or reduced. Moreover, the diffusion of laparoscopic colorectal resections and ERAS protocols means earlier patients discharge but might increase the risk of late AL diagnosis [5,6].

Procalcitonin works as the prohormone of calcitonin; under normal metabolic conditions, its levels in the circulation are very low (<0.05 ng/mL). Bacterial infections induce a generalized release of PCT from all differentiated cell types throughout the body, so that significant concentrations of PCT can be detected in the serum of patients. Procalcitonin increases quickly, normally after 2 to 3 hours following induction, and may rise up to 700 ng/mL in severe sepsis and septic shock [7,8,21]. Therefore, a value of less than 0.5 ng/mL represents a low risk of severe sepsis; meanwhile, a value of greater than 2 ng/mL shows a high risk of severe sepsis and septic shock. In contrast to CRP, PCT levels do not rise following inflammation of noninfectious origin, as shown by Meisner et al [22]. The interesting characteristic of PCT is that its levels increase before clinical signs present, therefore becoming an ideal tool for early diagnosis of AL after colorectal surgery. Compared with CRP, PCT has been demonstrated to be the best marker for differentiating patients with sepsis from those with systemic inflammatory reaction not related to infectious cause and is widely used in intensive care units [23,24]. Moreover, intraabdominal infections, especially ALs, have been associated with higher postoperative CRP levels than extraabdominal infections [25–27]. Receiver operating characteristic curve analysis showed that diagnostic accuracy of CRP for intraabdominal infections and other septic complications was as high on POD 3 as it was on POD 4 [28,26,29]. Taking this into consideration, together with faster kinetics of PCT, we decided to determine CRP and PCT concentrations on PODs 1, 3, and 5. About cutoffs, Lagoutte et al [30], in a study about PCT and AL after colorectal surgery, found that with a threshold of 0.068 mg/dL, PCT had a sensitivity and specificity of 70%. More recently, in the article written by Garcia Granero et al [31], a PCT cutoff of 0.31 ng/mL in fifth POD resulted in 100% sensitivity, 72% specificity, 100% NPV, and 17% positive predictive value. In our study, mean PCT values in the group with no AL and no other complications in third and fifth POD were 1.09 and 0.47 ng/mL, respectively. For this reason, we could not use the previous published cutoffs and decided to adopt 5 and 2 ng/mL for third and fifth POD, respectively.

Table 3
Postoperative complications

Complications	n
AL	9 (8.9%)
Wound infection	7 (6.9%)
Bleeding	4 (2.9%)
Pneumonia	2 (1.9%)
Acute renal failure	2 (1.9%)
Myocardial infarction	2 (1.9%)
Ileal perforation	1
Entero-cutaneous fistula	1
Fever and diarrhea	1

Table 4
Type of surgery and complications divided in AL, complications with no AL, and no complications

Type of surgery	n (101)	AL (9)	Complic no AL (20)	No Complic (72)
Low anterior resection	24 (23.7%)	5 (55.5%)	4 (20%)	15 (20.8%)
Sigmoid resection	23 (22.7%)	3 (33.3%)	5 (25%)	15 (20.8%)
Right colectomy	40 (39.6%)	1 (11.1%)	7 (35%)	32 (44.4%)
Left colectomy	13 (12.8%)	0	4 (20%)	9 (12.5%)
Transverse resection	1 (0.9%)	0	0	1 (1.3%)

Complic indicates complications.

Table 5
Mean PCT values in first, third, and fifth POD in the AL, complications with no AL, and no complications groups

Groups	PCT in first POD (ng/mL, mean)	PCT in third POD (ng/mL, mean)	PCT in fifth POD (ng/mL, mean)
AL	3.42	4.97	3.17
Complic with no AL	2.86	2.27	2.77
No Complic	2.36	1.12	0.47
P	NS	.007	.0005

NS indicates nonsignificant.

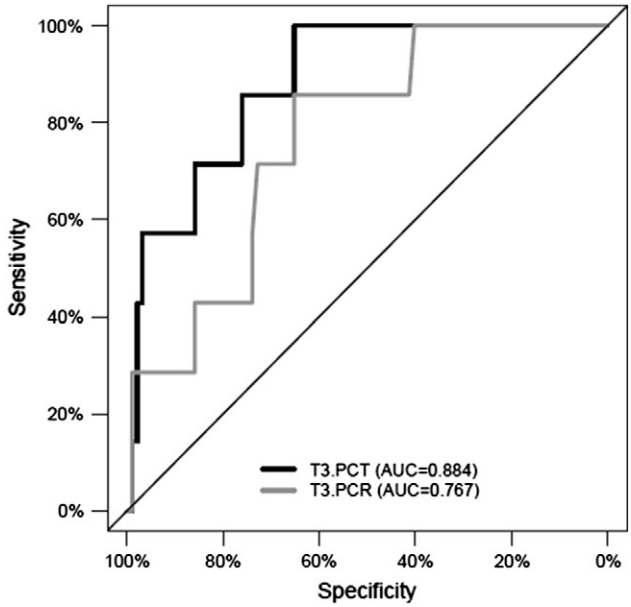

Fig. 1. Receiver operating characteristic curve for biomarkers in third POD.

In our study, we registered 7 ALs (7.1%), almost all of them after distal colorectal resections (85.7%). Both findings are in agreement with the current literature that shows similar results [3,4].

In first POD, we did not observe statistically significant differences in WBC, CRP, and PCT levels between the AL and no-AL group. Meisner et al [32] showed that, in first and second POD after intestinal surgery, there is a physiological increase of PCT due to transient bacterial contamination during the operation or preparation of intestinal anastomosis. So, in our experience, WBC, CRP, and PCT measurement in the first POD after colorectal surgery showed to be not necessary and might be avoided. On the other hand, in third POD, PCT levels were significantly higher in patients with AL, than in the ones having complications other than AL or no complications at all. In addition, PCT values less than 5 ng/mL have a good NPV for AL. Also in fifth POD, mean PCT levels were significantly higher in patients with AL than in other patients, with good NPV for AL when PCT less than 5 ng/mL. In this case, using PCT to CRP levels together enhances AL diagnosis but not in a statistically significant way.

Renal elimination is thought to be one of the major pathways for the elimination of PCT. Previous studies showed that urine levels of PCT were reduced in patients with severe renal dysfunction [33]. On the other hand, Lu et al [34] showed that PCT diagnostic accuracy is similar between normal patients and subjects with severe impairment of renal function. In our study, we did not register statistically significant differences in PCT values and incidence of AL between the chronic renal failure group and the patients with normal values of kidneys function.

In the literature, there are different studies about PCT and sepsis, but only a few about PCT and postoperative abdominal infections after colorectal surgery. In 1998, Reith et al [10] published a prospective study on 70 patients undergoing elective surgery, 35 colorectal and 35 aortal surgeries, measuring CRP and PCT levels preoperatively, from first to fifth and in 7th and 10th POD to test its inflammatory prognostic value. They found a statistically significant increase of PCT but not of CRP in the complicated colorectal surgery group concluding that PCT, compared with CRP, seems to be a better biomarker of early prediction of infective complications when high postoperative levels are found [10]. In 2002, Di Filippo et al [35] measured PCT at T1 preoperative, T2 6 hours after the operation, T3 and T4, respectively, 24 and 48 hours after surgery in 33 patients undergoing major abdominal surgery with an intestinal resection. They found a statistically significant increase of PCT at T3 in patients having infectious complications, including AL, than in the noncomplicated group [35]. In 2005, Sarbinowski et al [36] assessed CRP, PCT, WBC, interleukin 6, and complement 3a on 50 patients undergoing colorectal surgery, focusing their attention on systemic inflammatory response syndrome (SIRS) development. Only PCT and complement 3a concentrations were statistically significant higher in the SIRS group compared with the non-SIRS group [36]. More recently, Montagnana et al [37] published a study on 18 patients with gastrointestinal cancer, 12 of them undergoing colorectal resections, and 18 controls, measuring CRP and PCT. Preoperatively CRP but not PCT levels were significantly higher in patients with neoplasia. They also found that PCT is a more useful marker than CRP to early diagnose infectious complications after surgery for gastrointestinal malignancies [37]. In 2012, Lagoutte et al [30] conducted a prospective study on 100 patients undergoing colorectal surgery, measuring CRP and PCT the day before surgery and on first, second, third, and fourth POD. They found that CRP, especially in the third or fourth POD, is the most appropriate predictive biomarker of infectious complications, with a better NPV compared with PCT (87% vs 75%) [30].

In 2012, Oberhofer et al [38] conducted a prospective observational study on 79 patients undergoing elective colorectal surgery, measuring WBC, CRP, and PCT preoperatively and on PODs 1, 2, 3, and 5. They showed that CRP and PCT concentrations, respectively, on POD 3 and 2, had similar predictive values for the development of infectious complications with the best cutoff values of 99.0 mg/L for CRP and 1.34 μg/L for PCT. They also stated that serial postoperative PCT measurements do not offer an advantage over CRP measurements for prediction of infectious complications following colorectal surgery [38].

In 2013, Garcia Granero et al [31] conducted a prospective observational study enrolling 205 patients undergoing elective colorectal surgery, measuring WBC, PCT, CRP, and platelets. Anastomotic leak was detected in 17 patients; 11 of them had a major AL. None of the variables evaluated were shown to be reliable in early detection of AL, considering both major and minor AL; in contrast, when considering only major AL, PCT, and CRP were reliable predictors on PODs 3 to 5, with a cutoff of 0.31 ng/mL, resulting in 100% sensitivity, 72% specificity, 100% NPV, and 17% PPV [31].

Our study has some weaknesses. First of all, it included a limited number of patients ($n = 101$). To overcome this bias, we designed a multicentric study called Procalcitonin Reveals Early Dehiscence in Colorectal Surgery that is currently recruiting patients and aiming to enroll 600 subjects in 3 different high-volume colorectal units in Italy (ClinicalTrials.gov Identifier: NCT01817647). Moreover, in our population, there is only a limited number of patients undergoing colorectal resection with laparoscopic technique (12 vs 87) that should facilitate earlier discharge and lessen inflammatory response after the operation. Another limitation of our article is that we did not measure preoperative PCT values, which may vary between patients. We are aiming to overcome both limitations in the Procalcitonin Reveals Early Dehiscence in Colorectal Surgery study, recruiting at least 50% of patients undergoing colorectal surgery and measuring PCT preoperatively and in third and fifth POD.

5. Conclusions

White blood cell, CRP, and PCT measurement in first POD after colorectal surgery showed to be not necessary and might be avoided. Procalcitonin demonstrated to have a good NPV for AL both in third and in fifth POD. The best diagnostic performance is obtained in third POD with PCT. Low levels of PCT (<5 ng/mL in third POD and/or <2.0 ng/mL in fifth POD), together with low CRP values in third POD, might be safely added as an additional criteria of discharge protocols after colorectal surgery.

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