Procalcitonin Reveals Early Dehiscence in Colorectal Surgery

The PREDICS Study

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Objectives: We designed a multicentric, observational study to test if Procalcitonin (PCT) might be an early and reliable marker of anastomotic leak (AL) after colorectal surgery (ClinicalTrials.govIdentifier:NCT01817647).

Background: Procalcitonin is a biomarker used to monitor bacterial infections and guide antibiotic therapy. Anastomotic leak after colorectal surgery is a severe complication associated with relevant short and long-term sequelae.

Methods: Between January 2013 and September 2014, 504 patients underwent colorectal surgery, for malignant colorectal diseases, in elective setting. White blood count (WBC), C-reactive protein (CRP) and PCT levels were measured in 3rd and 5th postoperative day (POD). AL and all postoperative complications were recorded.

Results: We registered 28 (5.6%) anastomotic leaks. Specificity and negative predictive value for AL with PCT less than 2.7 and 2.3 ng/mL were, respectively, 91.7% and 96.9% in 3rd POD and 93% and 98.3% in 5th POD. Receiver operating characteristic curve for biomarkers shows that in 3rd POD, PCT and CRP have similar area under the curve (AUC) (0.775 vs 0.772), both better than WBC (0.601); in 5th POD, PCT has a better AUC than CRP and WBC (0.862 vs 0.806 vs 0.611). Measuring together PCT and CRP significantly improves AL diagnosis in 5th POD (AUC: 0.901).

Conclusions: PCT and CRP demonstrated to have a good negative predictive value for AL, both in 3rd and in 5th POD. Low levels of PCT, together with low CRP values, seem to be early and reliable markers of AL after colorectal surgery. These biomarkers might be safely added as additional criteria of discharge protocols after colorectal surgery.

Keywords: anastomotic leak, biomarkers, colorectal cancer, colorectal surgery, procalcitonin

Anastomotic leakage (AL) is the most dreaded surgical complication in patients undergoing colorectal surgery. AL has been described as having great variability, ranging between 2% and 14%, with an increased incidence after anastomosis in the lower rectum.[1,2]

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Anastomotic leak after colorectal surgery has a remarkable impact on patient's outcome, involving higher morbidity and mortality, longer hospital stay, and over all, worse oncological and functional outcomes.[3,4]

Anastomotic leak early diagnosis and treatment, in a latent preclinical phase, are keys to improve outcomes. However, anastomotic leak may be difficult to diagnose in a preclinical phase and is often recognized in the late postoperative period, when the patient presents with sepsis and peritonitis, therefore increasing associated morbidity and mortality.[5]

Moreover, there is nowadays a growing diffusion of the enhanced recovery after surgery protocols, proven to reduce postoperative complications in up to 50% of cases, fasten recovery, and shorten length of stay.[6] Demanding very early patient discharge, these fast-track protocols might be potentially associated with an increased risk of delayed diagnosis and treatment of anastomotic leak, occurring after patient discharge. Consequently, there is an urgent need to find an accurate diagnostic marker of AL to help the surgeon to diagnose it in an early stage, in the aim to decrease its unfavorable sequelae.

Procalcitonin (PCT) is a 116 amino-acids protein produced by C-cells of the thyroid that works as the prohormone of calcitonin. PCT baseline levels are low (<0.1 ng/mL), but increase significantly in generalized bacterial infections, when PCT is produced by all differentiated cells.[7] Therefore, PCT levels are used to monitor the course of systemic bacterial and fungal infections and to tailor the therapeutic interventions more efficiently.[8,9] Considering the good results from our pilot study,[10] we decided to design this multicentric study (http://clinicaltrials.gov/show/NCT01817647) in the aim to confirm the strength of PCT as an early predictor of anastomotic leak and to fix the best cutoff values for an early discharge of patients, according to enhanced recovery after surgery protocols.

METHODS

Study Design

The present study is multicentric, prospective, and observational, based on the results of our previous pilot study, therefore methods have been already published.[10] Our patients underwent either laparoscopic (at least 50%) or laparotomic colorectal surgery, in which an anastomosis was carried out (right colectomy, transverse resection, left colectomy, sigmoid resection, and low anterior resection), in elective setting, for malignant disease. Exclusion criteria were: ongoing infection at surgery, age under 18 years, emergency setting, and benign disease. The protocol was approved by the Ethical Committee of all 3 institutions involved in the study: Sant'Andrea University Hospital in Rome, Monaldi Hospital in Naples, and Ospedali Riuniti in Trieste. All patients included in the study signed a written informed consent, before being included in the protocol.

Recorded Data and Clinical Management

We recorded into a computerized database the following patients' characteristics: sex, age, comorbidities, and renal function. We also included tumor's characteristics (bleeding, stenosing, metastatic...), type of surgical resection (right colectomy, transverse resection, left colectomy, sigmoid resection, and low anterior resection), and intra- and postoperative complications, their treatment, and length of hospital stay. In all patients included in the study, both in 3rd and 5th postoperative day (POD), were performed the following blood tests: white blood cell count (WBC), C-reactive protein (CRP), and PCT levels. We decided not to perform the biomarkers measurement in 1st and 2nd POD because the results of our previous study showed to be useless.[10]

To evaluate patients' clinical conditions, a senior surgeon, jointly with a resident, carried out a twice daily assessment, taking into account vital parameters measured 3 times a day by the nursing staff. Criteria of discharge were: tolerance of oral intake, recovery of lower gastrointestinal function, adequate pain control with oral analgesia, and absence of data suggesting sepsis.[11] In the cases with a clinical suspect of AL, CT scan with hydrosoluble contrast enema was carried out. Wound infections were defined as deposition and multiplication of bacteria in tissue with an associated host reaction. Diagnosis was made in the presence of clear signs of inflammation at the wound margin or purulent discharge from the wound. Pneumonia was diagnosed by the evidence of pulmonary infiltration on chest x-ray or CT-scan, accompanied by clinical symptoms, positive physical examination, and/or laboratory tests. Urinary tract infection was defined by positive urine test, combined with leukocytosis and/or fever.

As follow-up control, we carried out a complete clinical assessment at 1 week, adding blood sampling for laboratory tests 1 month after discharge. According to tumor staging and oncological protocols, total body contrast-enhanced CT scan was carried out at 3 or 6 months or 1 year. At 1-year follow-up, all patients underwent colonoscopy.

Laboratory procedures were the same as in our previous study.[10]

Definition of Anastomotic Leakage

Presence of a fecaloid drain, emission of fecal material from the wound, extravasation of contrast on enema, evidence of postoperative peritonitis at a reintervention and/or the occurrence of fluid, or air in the anastomotic region during a CT scan were considered as definition of anastomotic leakage.[12] We considered as ''major'' ALs those needing reoperation or percutaneous radiologic drainage (Clavien-Dindo grades III), and ''minor'' those in which a conservative medical treatment was appropriate (Clavien-Dindo grades I and II).[13]

Statistical Analysis

Statistical analysis is conducted with the same program and methods as in our previous study.[10]

Using an Excel database, all values were entered as absolute values, means, medians, and percentages, as appropriate. Box plots and Kruskall Wallis test were used to compare biomarkers' distribution between different groups. To compare biomarkers' accuracy as predictors of AL, receiver operating characteristic (ROC) curves and the corresponding area under curve (AUC) were used. A 95% confidence interval (CI) was used to calculate specificity (Sp), sensitivity (Se), positive predictive value (PPV), and negative predictive value (NPV). In the 2-tailed test, a $P < 0.05$ was taken into consideration to indicate statistical significance. The R version 3.1.0 (April 10, 2014) was used for the statistical analysis.

TABLE 1. Clinical Characteristics of the Study Population

Population	Number (504)
Age (yr)	67.6
Sex, n (%)	
Male	294 (58.3%)
Female	210 (41.7%)
Type of surgery, n (%)	
Right colectomy	178 (35.3%)
Transverse resection	11 (2.1%)
Left colectomy	138 (27.4%)
Sigmoid resection	53 (10.5%)
Low anterior resection	124 (24.6%)
Surgical approach, n (%)	
Laparoscopy	378 (75%)
Laparotomy	126 (25%)

RESULTS

From September 2013 to October 2014, a series of 504 patients underwent colorectal surgery, for malignant disease, in elective setting, with primary intestinal anastomosis. More than half of the study population was composed of male (294 male, 58.3% vs 210 female, 41.7%). Mean age was 67.6 years. Three hundred seventy-eight patients (75%) have been operated with laparoscopic approach, 126 with laparotomy. Concerning type of surgery, 178 were right colectomies, 11 transverse resection, 138 left colectomies, 53 sigmoid resections, and 124 low anterior resections. There were more distal than proximal resections (315 vs 188) being carried out in our population. Clinical characteristics of the study population are illustrated in Table 1.

Among patients undergoing low anterior resection (124), 94 went through neoadjuvant chemo-radiation therapy (CRT). Of the remaining 30 patients not undergoing CRT, 4 of them were T1sm3, 20 were T2 and the remaining 6 were advanced cases, 3 presented with bleeding rectal cancer that was not possible to control with conservative therapy and 3 had occluding rectal malignancy undergoing not successful ''bridge to surgery therapy'' with stent implant before CRT. In a total of 124 patients undergoing low anterior resection (LAR), 110 fecal diversions were carried out.

No patients died intraoperatively; 1 died postoperatively (0.19%), in 4th POD, because of myocardial infarction. We registered a total of 92 (18.2%) complications, 28 patients had a clinical anastomotic leak (5.6%). Nine of the latter had also other complications, in particular: 4 wound infection, 2 anemia due to postoperative bleeding, 1 pneumonia, 1 pulmonary embolism, 1 uroperitoneum for ureteral injury, not detected intraoperatively, but diagnosed in 2nd POD and treated with double J stent. Between the 28 patients having AL, most of them (19, 67.8%) underwent distal resections: 10 low anterior resections (35.7%), 6 sigmoid resections (21.4%), and 3 left colectomies (10.7) versus 8 right colectomies (28.5%) and 1 transverse resection (3.5%). AL was diagnosed between POD 2 and 14 (median POD 7).

Moreover, between the 28 cases developing anastomotic leak: 2 of them were on chronic corticosteroidal therapy (1 for polymyalgia rheumatic and 1 for rheumatoid arthritis), 16 of them had multiple comorbidities such as obesity, CHF, hypertension, and type 2 DM (at least 2 of them), 5 had 1 comorbidity and the remaining 5 had no comorbidities at all.

All cases, except 3, were classified as ''major leak.'' All the minor ALs occurred in patients with rectal cancer and fecal diversion. Between the 124 patients undergoing LAR, 10 had AL (12.4%), 7 of them had a major leak, and 3 a minor AL.

In 12 patients, the dehiscence occurred in 7th POD; in 10 patients occurred early between the 2nd and the 5th POD, and in 6 patients the AL occurred late, between the 9th and the 14th POD. Eighteen patients needed reoperation, whereas 10 patients were treated with conservative therapy (percutaneous drain, nothing per os, total parenteral nutrition, and antibiotics). Among these 10 patients, 6 of them presented either in 3rd POD with PCT values greater than 2.7 ng/mL and/or greater than 2.3 ng/mL in 5th POD. Only 9 patients out of 28 had PCT values less than 2.7 ng/mL and/or less than 2.3 ng/mL either in 3rd and 5th POD, respectively. Among them, 4 took immunosuppressant drugs (2 corticosteroids and 2 cyclosporine) and 1 was immunodeficient (affected by AIDS, acquired immunodeficiency syndrome).

Eighty-three patients had a complication other than AL, specifically: bleeding (26), wound infection (21), cardiac problems (13), pneumonia (10), acute kidney injury (3), urinary tract infection (2), deep vein thrombosis (2), and urinary retention (2). The complete list of the postoperative complications is reported in Table 2.

Mean hospital stay was 9 days (range: 4–61 days), 7 days in the uncomplicated group, 12 in the group with complications other than AL and 24 in the AL group, with a statistically significant difference between the uncomplicated group and the AL groups ($P < 0.0001$).

TABLE 2. Postoperative Complications

Postoperative Complication	Number
Anastomotic leak, n (%)	28 (5.6%)
Other than anastomotic leak, n (%)	83 (16.4%)
Bleeding	26
Wound infection	21
Cardiac problems	13
Pneumonia	10
AKI	3
UTI	2
Deep vein thrombosis	2
Urinary retention	2
Respiratory failure	1
Adverse drug reaction	1
Pulmonary embolism	1
Uroperitoneum	1
Total	**92 (18.2%)**

AKI indicates acute kidney injury; UTI, urinary tract infection.

In the AL group, median PCT values in 3rd POD and in 5th POD were respectively 3.6 and 3.2 ng/mL, with a statistically significant difference between this group and the other 2 groups (complication other than AL and no complications group), as seen in Table 3 and Figure 1.

Median CRP values in the AL group were 21.20 mg/dL and 16.10 mg/dL, in 3rd and 5th POD, with a statistically significant difference with the other 2 groups (Table 4 and Fig. 2).

NPV (negative predictive value) for anastomotic leak with PCT less than 2.7 ng/mL in 3rd POD is 96.9%, with a specificity of 91.7%, sensitivity of 59.3%, and positive predictive value(PPV) of 34%. Also in 3rd POD, with CRP less than 16.9 mg/dL, we got a sensitivity of 59.3%, specificity of 81.8%, NPV 96.4%, and PPV 19.5%. In 5th POD, with PCT cutoff less than 2.3 ng/mL, we had a 69.6% sensitivity, 93.0% specificity, 98.3% NPV, and 32.0 PPV. With CRP less than 12.5 mg/dL in 5th POD, we got 73.9%, 86.0%, 98.4%, and 22.1% of sensitivity, specificity, NPV, and PPV (Table 5).

TABLE 3. Median PCT Values in 3rd and 5th POD in the 3 Groups: AL Group, Complications Other Than AL, and No Complications Group

Groups	PCT in 3rd POD (ng/mL, median)	PCT in 5th POD (ng/mL, median)
AL	4.10	3.20
Complications with no AL	1.0	0.90
No complications	0.60	0.32
P	0.001	0.001

TABLE 4. Median CRP Values in 3rd and 5th POD in the 3 Groups: AL Group, Complications Other Than AL, and No Complications Group

Groups	CRP in 3rd POD (mg/dL, median)	CRP in 5th POD (mg/dL, median)
AL	22.00	16.10
Complications with no AL	12.24	7.80
No complications	9.73	4.90
P	0.0001	0.0001

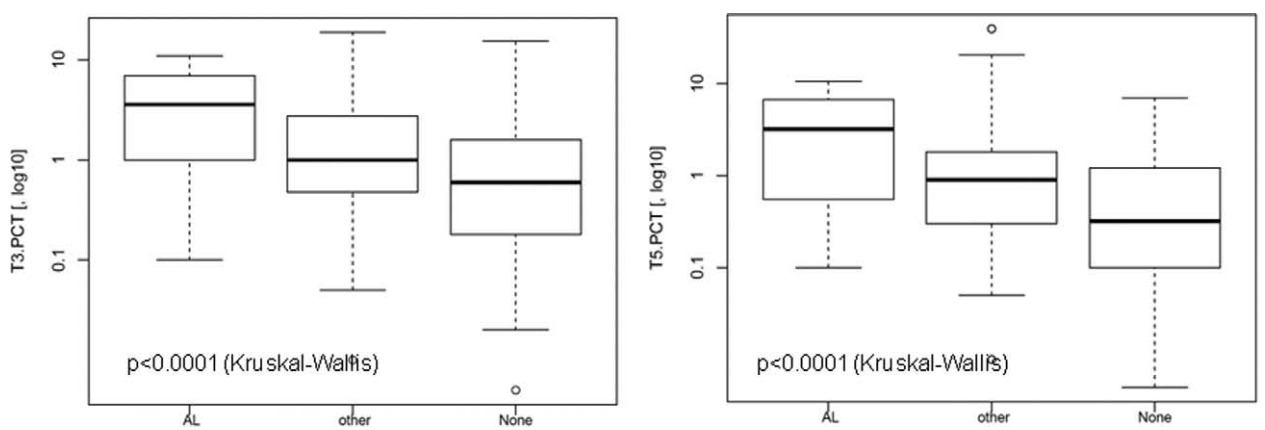

FIGURE 1. There is a statistically significant difference between the AL group and the other 2 groups with regard to median PCT values, both in 3rd and in 5th POD ($P < 0.0001$). None indicates group with no complications; Other, group with complications other than AL.

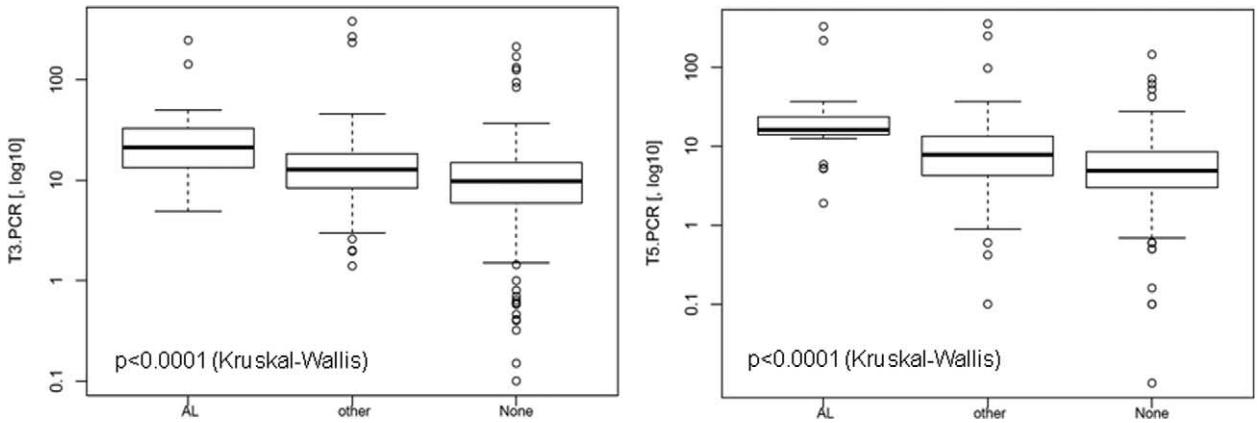

FIGURE 2. There is a statistically significant difference between the AL group and the other 2 groups with regard to median CRP values, both in 3rd and in 5th POD ($P < 0.0001$). None indicates group with no complications; Other, group with complications other than AL.

TABLE 5. Sensibility, Specificity, NPV, and PPV for CRP and PCT in 3rd and 5th POD With Relative Cutoffs

	Cutoff	Sensibility (%)	Specificity (%)	NPV (%)	PPV (%)
PCT (ng/mL)—3rd POD	2.7	59.3	91.7	96.9	34.0
CRP (mg/mL)—3rd POD	16.9	59.3	81.8	96.4	19.5
PCT (ng/mL)—5th POD	2.3	69.6	93.0	98.3	32.0
CRP (mg/mL)—5th POD	12.5	73.9	86.0	98.4	22.1

ROC curve for biomarkers in 3rd POD shows that PCT and CRP have similar area under the curve (AUC), respectively, 0.775 and 0.772; on the contrary, WBC does not improve AL diagnosis (AUC: 0.601) (Fig. 3). In 5th POD, ROC curve shows that PCT has a better AUC compared with CRP (0.862 vs 0.806); both biomarkers are better than WBC (AUC: 0.611) (Fig. 4).

Adding PCT to CRP enhances diagnosis of AL, not significantly in 3rd POD (AUC 0.842) and in a statistically significant way in 5th POD (AUC 0.901), as shown in Figure 5.

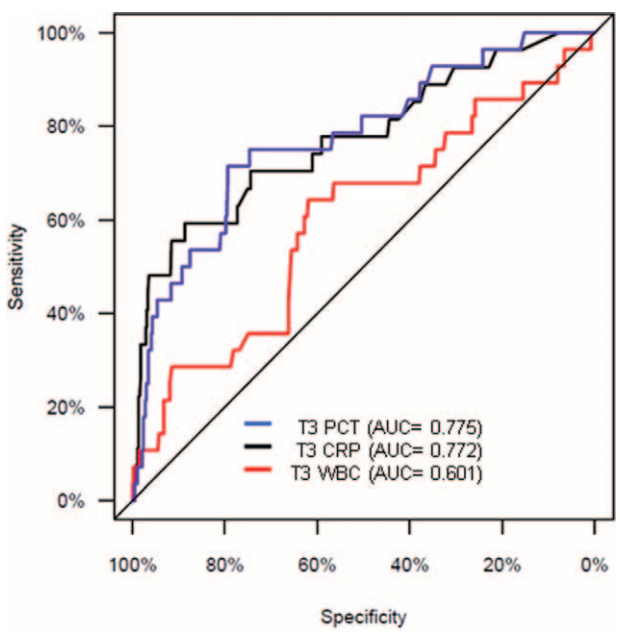

FIGURE 3. ROC curve for biomarkers in 3rd POD. PCT and CRP have comparable AUC (0.775 and 0.772, respectively), both better than WBC (0.601).

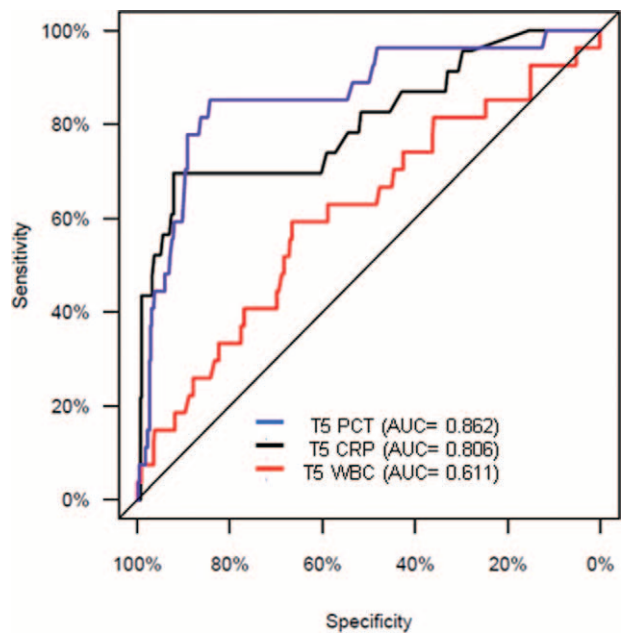

FIGURE 4. ROC curve for biomarkers in 5th POD. PCT has a better AUC than CRP (0.862 and 0.806, respectively), both better than WBC (0.611).

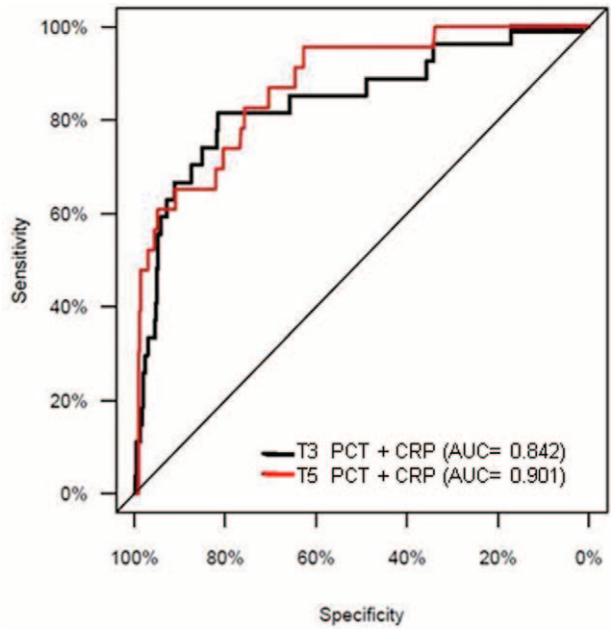

FIGURE 5. Adding PCT to CRP enhances diagnosis of AL, even if not significantly, in 3rd POD (AUC 0.842). Adding PCT to CRP significantly enhances diagnosis of AL in 5th POD (AUC 0.901).POD, postoperative day.

DISCUSSION

Anastomotic leak is one of the most dreaded complications after colorectal surgery. It leads to prolonged hospital stay, increased morbidity, mortality, and medical costs.[4] Early identification of AL after colorectal surgery is a key point to reduce its sequelae.[5] Recently, biomarkers such as CRP and IL-6 (interleukin 6) have been considered as an interesting tool to early diagnose postoperative complications in other surgical fields.[14–16]

CRP seems to be a good predictor of septic complications after elective colorectal surgery, as shown in a recent prospective study on 133 patients from Ortega-Deballon et al.[17] With a cutoff of 125 mg/L in 4th POD, they obtained a sensitivity of 81.8% and a NPV of 95.8%.[17] Moreover, Scepanovic published similar results on 156 patients, getting the best sensitivity and specificity in 3rd POD (73% and 73%, respectively) with a CRP cutoff of 135 mg/L.[18]

Singh carried out a meta-analysis about this topic, including 7 studies with a total of 2483 patients, and concluding that CRP is a useful negative predictive test for AL after colorectal surgery.[19]

Over the last decade, procalcitonin has emerged as a sensitive and specific biomarker for bacterial infection and became widely used in Intensive Care Units to diagnose and monitor sepsis.[7,9] Moreover, a few studies have emphasized the value of PCT measurement for a variety of clinical conditions but little is known about the efficacy of PCT measurements in colorectal surgery.

There are some reports about the usefulness of PCT in the surgical field, like the one from Takakura et al that compared PCT, CRP and WBC as predictors of surgical site infection (SSI) after colorectal cancer surgery, concluding that PCT is the more reliable biomarker to early diagnose SSI.[20] There is also a review investigating the usefulness of PCT for bacterial peritonitis diagnosis in patients with decompensated liver cirrhosis or under peritoneal dialysis.[21] After analyzing the 18 studies published on the field, the authors conclude that PCT is a sensitive and specific test for diagnosis of bacterial peritonitis, with a better predictive capacity than CRP.[15]

Lagoutte et al published the first study comparing PCT and CRP after colorectal surgery.[21] They measured both biomarkers from 1st to 4th POD and concluded that best accuracy for AL diagnosis was given from CRP in 4th POD (AUC 0.869 vs 0.750 for PCT).[21] Oberhofer reported a similar study about 79 patients, achieving similar predictive values on POD 3 for CRP and on POD 2 for PCT (AUC 0.746 and 0.750, respectively) with the best cutoff values of 99.0 mg/L for CRP and 1.34 μg/L for PCT.[22] Garcia-Granero et al[23] published a study on 250 patients, reporting the best accuracy for major AL diagnosis PCT in 5th POD, with a AUC of 0.86, 100% sensitivity, 72% specificity, and 100% NPV with a PCT cutoff of 0.31 ng/mL.

On the contrary, the pilot study recently published by Silvestre et al,[24] where they measured daily PCT and CRP after colorectal surgery, shows the usefulness of CRP but not of PCT, especially in 6th POD.

Considering the results of our previous study and given that in 1st and 2nd POD after intestinal surgery there is a physiological increase of PCT due to transient bacterial contamination during the operation or preparation of intestinal anastomosis, we decided to avoid the measurement of PCT, CPR, and WBC in 1st POD.[10]

In our study, 75% of our patients have been operated on with laparoscopy (VL); we did not register statistically significant differences between the VL and the open group in terms of incidence of AL and biomarkers values.

We registered 5.6% of anastomotic leak, most of them occurring after distal resections (19/28, 67.8%); these data are consistent with the international literature.[1] According to Hyman,[2] also in our study we had some late AL diagnosis; in particular, in 6 patients AL occurred between the 9th and the 14th POD. These data are particularly significant if we consider that, with fast-track protocols, we are supposed to early discharge patients, much before the 9th POD; therefore, a diagnostic tool, like PCT and/or CRP, becomes very important to help the surgeon not to discharge home a patient that will develop a leak.

We did not register intraoperative death, but 1 patient died in the postoperative period (4th POD). He was a 88 years old male patient, with a substenosing sigmoid cancer, obesity (BMI 32 kg/m^2), type 2 diabetes mellitus (DM) requiring insulin therapy, hypertension, and congestive heart failure (CHF) due to coronary heart disease (with previous myocardial infarction undergoing angioplasty 5 years before). Because of the substenosing lesion and notwithstanding multiple patient's comorbidities, we decided—according to patient's willingness—to perform open sigmoidectomy. In 3rd POD, he developed a clinical AL (fecaloid drain without signs of peritonitis), we reoperated him performing colostomy on descending colon and placing multiple drains but unfortunately he died in 4th POD because of massive myocardial infarction. In 3rd POD, his PCT and CRP values were respectively 7.2 ng/mL and 14.33 mg/dL; unfortunately he died before the 5th POD measurements were carried out. It is to note that, although PCT and CRP values were pointing out the AL, WBC values were within normal range (9.96×10^3/mL).

Considering the ROC curve for biomarkers in 3rd POD, PCT and CRP have similar AUC (respectively, 0.775 and 0.772), so this means they both markers help the surgeon to early diagnose AL (Fig. 3). In 5th POD, ROC curve shows that PCT has a better AUC compared with CRP (0.862 vs 0.806). Both biomarkers, in 3rd and in 5th POD, are better than WBC (AUC in 3rd POD 0.601 and in 5th POD 0.611). It is also interesting to note that adding PCT to CRP enhances diagnosis of AL in a statistically significant way in 5th POD (AUC 0.901).

The main limitation of PCT seems to be a lack of sensitivity, for this reason we think that the surgeon should not choose between PCT and CRP, but should use both of them, because they help together to early diagnose AL.

There is no consensus about the most appropriate PCT cutoff level to predict AL after colorectal surgery. We think we should focus to the 3rd POD, because most patients are supposed to be already home in 5th POD, and try to keep both sensitivity and specificity higher than 50%, trying to get the highest NPV. In our study, in 3rd POD with PCT less than 2.7 ng/mL, we had 96.9% NPV, 91.7% specificity, and 59.3% sensitivity. Also in 3rd POD, with CRP less than 16.9 mg/dL, sensitivity, specificity, and NPV are respectively: 59.3%, 81.8%, and 96.4%.

If early discharge was in play (3rd to 4th POD), 4 patients would have been missed (false negatives) and 20 patients would have been kept for observation (false positives). Other postoperative complications like SSI, pulmonary infections, or urinary tract infections, seem not to have a significant statistical effect on false positive rate both in 3rd and 5th POD.

Because renal elimination is the major pathway for PCT clearance, impaired renal function has been reported to affect its measurement.[8] On the contrary, both in our previous[10] and in the present study we showed that renal function did not impair PCT measurement and our results were consistent with Yang study.[15] In our population mean preoperative values of azotemia and creatinine were within the reference range, being respectively 17 and 0.9 mg/dL. Six patients (1.2%) were affected by chronic renal failure (mean azotemia and creatinine being respectively 40 and 2.8 mg/dL), 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. In particular, *P* for the difference between preoperative creatinine and azotemia in the 3 groups (AL, complications other than AL and no complications) was respectively 0.9491 and 0.9626.

CONCLUSIONS

Nowadays, with fast-track protocols demanding very early patients discharge after colorectal surgery, finding a diagnostic tool that easily helps the surgeon to early diagnose anastomotic leak is a key point. Our study shows that PCT is a helpful biomarker for early diagnosis of AL after colorectal surgery. Also CRP seems to be reliable, and using both markers in 5th POD enhances AL diagnosis. The results of furthers studies will tell us if PCT and/or CRP values might be added to discharge criteria after fast-track surgery.

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