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Research Article

C Reactive Protein: A Reliable Marker for Early Diagnosis of Anastomotic Leakage in Colorectal Surgery?

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Abstract

Background: Anastomotic leakage (AL) related to colorectal surgery is associated with high morbidity and mortality. Predicting AL remains challenging but may improve outcomes significantly. Serum biomarkers, such as C reactive protein (CRP), white blood (WBC) count and platelets could be useful.

Aim: To evaluate the role of CRP, WBC and platelets in postoperative period of colorectal surgery with anastomosis as predictors of AL.

Methods: A prospective database including patients undergoing colorectal surgery was developed during a 16-month period. After applying exclusion criteria, 84 patients were eligible. In the postoperative period, daily blood samples were collected to determine CRP, WBC and platelet count until postoperative day 5 or until discharge.

Results: Eight patients developed AL (50% of which were major). An association between AL and high CRP was demonstrated on postoperative day 2 with a threshold of 223.7 mg/L. CRP presented an area under the receiver operator curve (AUROC) of 0.7993. White blood count (WBC) and platelet count did not demonstrate any significant difference between groups.

Conclusion: CRP is a useful serum biomarker for the early diagnosis of AL after colorectal surgery. Early recognition of AL may lead to better outcomes.

Keywords: *PCR; Anastomosis; Leak; Marker; Colorectal; Surgery*

Introduction

A significant number of surgical procedures carried out within a hospital are related to colorectal pathology, including both benign and malignant diseases. It is usually the Surgery Department that performs the highest number of interventions, which represents 10% of the total procedures in the United States [1].

Most of these surgeries are elective, involving intestinal resection and anastomosis. Despite improvements in surgical technology, the reported incidence of postoperative anastomotic leakages (AL) on multiple studies is reported to be 1 to 40%, depending on the definition used to determine a fistula [2,3]. AL are associated with significant increases in morbidity and mortality, hospital stays, and healthcare-related costs [4-6].

The ability to predict this type of complications would entail a substantial bene-fit for the patient and healthcare systems. Numerous studies have shown that surgeon's diagnostic criteria are not enough to achieve this goal, and in addition to this, the clinical manifestations are usually late [7,8]. Therefore, various scores and serum markers have been studied for the early diagnosis of AL, even though none of these tools have yet been used in daily practice.

C reactive protein (CRP) was identified in 1930 as the first acute phase protein [9]. It is synthesized by the liver and has a short half-life (19 hs). Since its discovery it has been used as an inflammatory marker for various pathologies [10,11]. Some studies have proposed it as a predictor for surgical complication.

Aim of the Study

The aim of the present study was to evaluate the role of serum biomarkers in the postoperative period of colorectal surgery with intestinal anastomosis; CRP, white blood cells (WBC) count and platelet count were evaluated as predictors of AL.

Materials and Methods

Study design and population

A prospective updated surgical database was undertaken at our institution from October 2018 to January 2020, involving all consecutive patients undergoing colorectal surgery. The database was reviewed to identify adult patients who underwent colonic resection, irrespective of extension or location of surgery. A retrospective observational study was undertaken. We excluded patients who were under 18 years old, patients with protective ostomy, resective surgeries without primary anastomosis, or who did not have CRP, WBC, and platelet de-terminations for the first 72 hours after surgical intervention. The study was re-viewed and approved by our local ethics committee.

Perioperative care

Our study was carried out in a teaching hospital at Ciudad Autónoma de Buenos Aires, Argentina.

On elective surgery, performance status and preoperative nutrition was assessed by a group of specialized clinicians and nutritionists. Rectal and left colonic surgery had mechanical bowel preparation 24hs before surgery. Fasting period was applied following the FAAAAR (Federacion Argentina de asociaciones, anestesia, analgesia y reanimación) guidelines [12].

On admission, patients must take a pre surgical bath. All patients were administered antibiotic prophylaxis. Urinary catheter was placed during surgery and was removed on postoperative day 1 (POD1). Laparoscopy and mechanical sutures (circular and lineal staplers) were available either on elective or urgent surgery. Circular staplers were mostly used on rectal and left colonic surgery and lineal on right colonic surgery. Routinely, at least one abdominal drainage was placed.

Postoperatively, patients were examined twice a day to assess the clinical condition (pain, fever, hemodynamic status, abdominal examination, return of bowel function, wounds, and drainages). Medical thromboprophylaxis with low molecular weight heparin was administered from POD1 until discharge. Oral diet was resumed when propulsive bowel sounds were auscultated, considering early feeding important. Given that early mobilization is widely regarded as an important component of enhanced recovery, Physical Therapists and nurses helped the patients since first postoperative hours having exercise routines twice a day.

Aim of the Study

The aim of this original research was to show whether CRP, WBC, or platelet count levels on the first 5 postoperative days could predict AL on patients following colorectal surgery.

Our primary outcome was measured on daily blood samples on the first 5 PODs or until discharge. They were collected to determine CRP, WBC, and platelet counts. CRP concentrations were measured by particle-enhanced immunoturbodimetric method using COBAS c501 automated analyzer, Roche. Both WBC and platelet determinations were measured by Sysmex XT1800 automated hematology analyzer, Roche.

Our secondary outcome measure was the prevalence of postoperative anastomotic leak. AL were diagnosed by means of a contrast study or intraoperatively. These were classified as minor or major: minor leaks were defined as those re-quiring percutaneous treatment and/or antibiotics, whereas major leaks re-quired surgical intervention.

The following variables that could be associated with the risk of an anastomotic leak were also retrieved: age, gender; history of hypertension, diabetes mellitus, dyslipidemia, smoking; body mass index; American Society of Anesthesiologists (ASA) score; reason for referral; location and extension of colonic re-section; procedure status (elective or urgent); type of anastomosis; type of mechanical suture; wound infection.

Statistical analysis

Statistical analysis was performed using Stata software (v11.1, Statacorp, College Station, TX, USA). Numerical variables were described as mean with its standard deviation or, in the case of non-parametric variables (defined by Kolgomorov-Smirnov test), as median with its range. Categorical variables were described as percentages. Chi square test (or Fisher test where applicable) was used for the comparison of categorical variables. For the comparison of numerical variables, Student t-test (or Mann-Whitney test in case of non-parametric variables) was used. A univariate analysis to determine the potential association between the above-mentioned variables and AL. Variables with a p value of less than 0.1 on univariate analysis were included in multivariate analysis, using a logistic regression model.

In addition, diagnostic accuracies of CRP, WBC and platelet counts were estimated by means of receiver operating characteristic (ROC) analysis. Area un-der the curve for each determination was estimated and cut-off values were estimated by optimizing the Youden's index.

Results

During the study period, 106 patients underwent colonic surgery; 84 met eligibility criteria and were finally included for analysis. Figure 1 shows the flow chart explaining the patient-selection process.

Figure 1: *Patient selection process.*

Table 1 shows the main characteristics of included patients. Median age was 64 years and 54.76% were male. The main reason for referral was neoplastic disease (76.19%). Most patients underwent laparoscopic surgery (78.57%).

Age (years)	64 (20-89)
Sex (%M)	54.76 (46/84)
Hypertension	45.24 (38/84)
Diabetes Mellitus	13.10 (11/84)
Dyslipidemia	40.48 (34/84)
Smoking	52.38 (44/84)
Chronic kidney disease	5.95 (5/84)
Obesity	25.40 (16/63)
American Society of Anesthesiologists	
1	8.33 (7/84)
2	66.67 (56/84)
3	23.81 (20/84)
Indication	
Cancer	76.19 (64/84)
Diverticular disease	19.05 (16/84)
Others	4.76 (4/84)
Type of resection	
Left colon	47.62 (40/84)
Right colon	36.90 (31/84)
Rectum	15.48 (13/84)
Emergency surgery	11.90 (10/84)
Surgical approach	
Laparoscopic	78.57 (66/84)
Laparoscopic to open	9.52 (8/84)
Open	11.91 (10/84)
Mechanical suture type	
Lineal	34.52 (29/84)
Circular	65.48 (54/84)
POD 1 CRP	70.30 ± 43.54
POD 1 WBC	12873 ± 3985
POD 1 Platelets	231964 ± 73739

Table 1: *Patients characteristics.*

Overall, AL were identified in 9.52% (8/84) of patients. Table 2 shows the comparative analysis of the characteristics between patients with and without AL. We found a non-significant difference in terms of gender and a significant difference in terms of wound infection prevalence (50% versus 18.42%, p = 0.04).

	Leak (%, n/N)	No Leak (%, n/N)	OR (IC95%)	P
Age	71.5 (28 - 88)	63.5 (20 - 89)		0.58
Sex (%M)	25 (2/8)	57.89 (44/76)	0.24 (0.04 - 1.33)	0.07
Arterial Hypertension	25 (2/8)	47.37 (36/76)	0.37 (0.07 - 2.01)	0.22
Diabetes II	12.5 (1/8)	13.16 (10/76)	0.94 (0.1 - 8.61)	0.95
Dyslipidemia	37.5 (3/8)	40.79 (31/76)	0.87 (0.19 - 3.95)	0.85
Smoking	75 (6/8)	50 (38/76)	3 (0.55 - 16.26)	0.18
Chronic renal failure	0	6.58 (6/76)	N/A	0.45
Obesity	14.29 (1/7)	26.79 (15/56)	0.45 (0.05 - 4.21)	0.47
American Society of Anesthesiologists				
1	0	9.21 (7/76)	N/A	0.37
2	87.5 (7/8)	64.47 (49/76)	3.85 (0.43 - 34.21)	0.19
3	12.5 (1/8)	25 (19/76)	0.43 (0.05 - 3.79)	0.43
Disease				
Cancer	75 (6/8)	67.11(51/76)	0.93 (0.17 - 5.07)	0.93
Digestive bleeding	12.5 (1/8)	0	N/A	0.15
Volvulus	12.5 (1/8)	0	N/A	0.15
Diverticular disease	0	21.05 (16/76)	N/A	0.21
Intestinal reconstruction	0	11.84 (9/76)	N/A	0.54
Type of resection				
Left colon	37.5 (3/8)	48.68 (37/76)	0.63 (0.14 - 2.87)	0.54
Right colon	37.5 (3/8)	36.84 (28/76)	1.02 (0.22 - 4.67)	0.97
Rectum	25 (2/8)	14.47 (11/76)	1.97 (0.34 - 11.22)	0.43
Emergency surgery	25 (2/8)	10.53 (8/76)	2.83 (0.47 - 16.91)	0.23
Open or laparoscopic to open procedures	12.5 (1/8)	22.37 (17/76)	0.49 (0.05 - 4.39)	0.52
Mechanical suture type				
Lineal	25 (2/8)	35.53 (27/76)	0.60 (0.11 - 3.25)	0.55
Circular	75 (6/8)	63.16 (48/76)	1.75 (0.32 - 9.41)	0.51
Surgical site infection	50 (4/8)	18.42 (14/76)	4.42 (1 - 20.89)	0.04

Table 2: *Patients characteristics by outcome.*

CRP determination on the first postoperative day was not significantly different among patients with and without AL. However, CRP on the second postoperative day and onwards was significantly different, as shown in figure 2. We did not find any differences in terms of WBC and platelet counts between patients with or without AL during hospital stay. Figure 3 shows the WBC postoperative trajectory.

On multivariate analysis (Table 3), 48-hour CRP was significantly associated with AL [OR 8.71 (1.03 - 73.33), p = 0.04]. ROC analysis showed that 48-hour CRP determination had an area under the curve of 0.8 (Figure 4). A cutoff value of 223.7 g/L showed a specificity of 94.74%, a sensitivity of 50%, a positive likelihood ratio of 9.5 and a negative likelihood ratio of 0.52.

	OR (IC95%)	z coefficient	p
Sex (M)	0.16 (0.02 - 1.02)	1.87	0.06
CRP > 223.7 on POD 2	8.71 (1.03 - 73.33)	2	0.04
Surgical site infection	3.05 (0.52 - 18.02)	1.23	0.21

Table 3: Multivariate analysis.

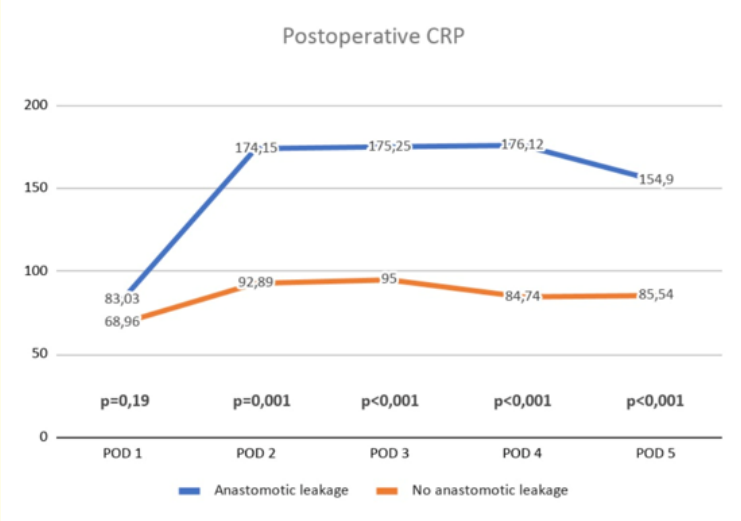

Figure 2: *Postoperative mean CRP trajectory.*

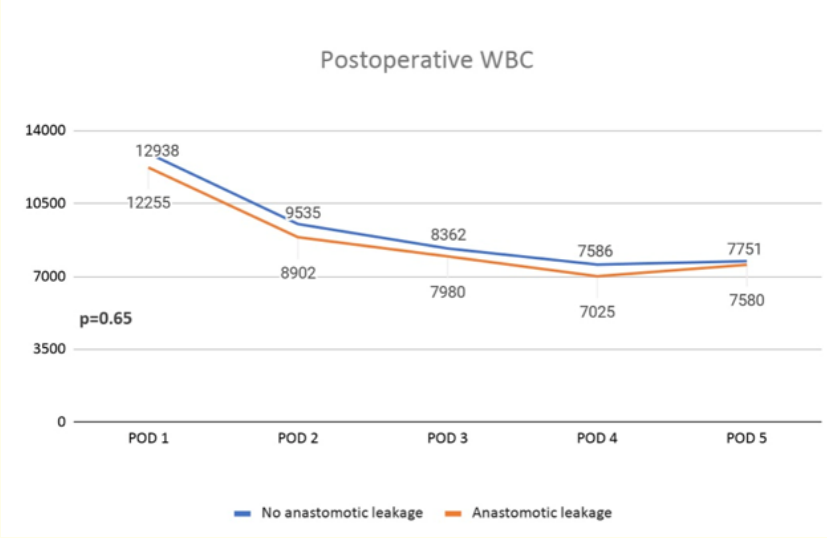

Figure 3: *Postoperative mean WBC trajectory.*

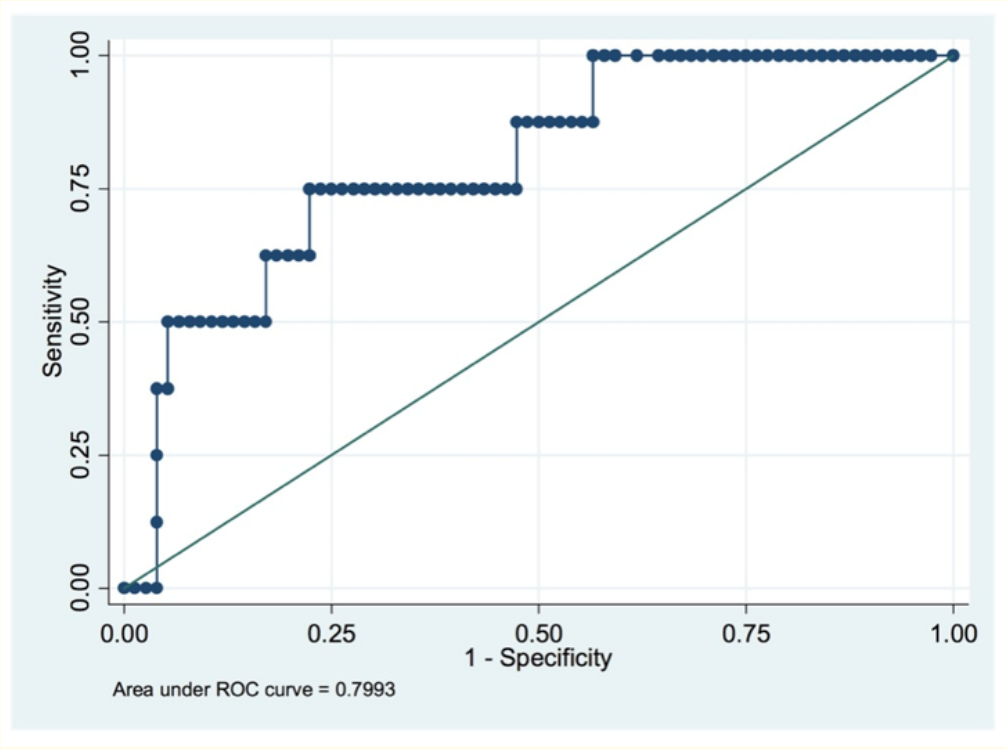

Figure 4: *Postoperative day 2 ROC curve analysis.*

Discussion and Conclusion

Colorectal surgery accounts for most of the surgical procedures performed worldwide. Around 30% of these patients will suffer complications, which are associated with poor outcomes and significantly higher healthcare costs [1,13].

According to several studies, postoperative AL incidence after colorectal surgery ranges from 1 to 30%. Of patients (in our series of patients, it's been of 9.52%). When a patient develops an AL, morbi mortality, length of hospital stays and costs are increased [14-18]. Regarding oncological out-comes, there is controversial evidence. Kingham., *et al*. [14], found that AL after colorectal surgery was a prognostic factor for local recurrence and mortality, having an independent negative association with overall and cancer specific survival. On the other hand, Petersen., *et al*. [17], could only associate AL with increased local recurrence. A recent meta-analysis by Karim A., *et al*. [19], concluded that after AL on rectal surgery and excluding 30-day mortality there was an increased risk of local recurrence (OR 1.50; CI 1.23, 1.82), worse overall survival (OR 0.69; CI 0.60 - 0.81), decreased disease free survival (OR 0.51; CI 0.36 - 0.73) and cancer specific survival (OR 0.71; CI 0.54-0.94). Distant recurrence (OR 1.10; CI 0.89 - 1.37) and overall recurrence (OR 1.33; CI 0.64 - 2.76) were not significantly different between the two groups.

Patients suffering AL usually present overt symptoms such as severe abdominal pain or sepsis on POD 3 or 4. However, some of them just have mild symptoms with insidious signs such as prolonged ileus, isolated fever or abdominal distension, and sometimes patients present symptoms even after dis-charge [20]. In both cases, it is usually very difficult to achieve a timely diagnosis and this delay is associated with worse prognosis [21].

For this reason, different diagnostic methods have been proposed, including clinical scores and serological biomarkers such as white blood count or procalcitonin [22,23]. Martin., *et al*. [22] used the "DULK-score" that takes into account several clinical and laboratory parameters, including CRP value, but some of these parameters are subjective, making it difficult to validate. Smith., *et al*. [23] studied the trajectory of CRP until 5 POD or discharge, concluding it is a useful biomarker for early diagnosis of AL, and that both the cut off value and the daily raise difference are important. However, none of them have been able to reliably anticipate the complication before it becomes clinically evident.

CRP is an acute-phase protein which has been previously suggested as the ideal marker to predict post-operative septic complications, because it has a short plasmatic half-life and tends to acquire normal values soon after surgery. Its usefulness has already been demonstrated in other types of surgery related to the pancreas or esophagus [24,25].

Table 4 analyzes papers published regarding the role of CRP as predictor of anastomotic leakage in colorectal surgery. 15 investigations have been written in 10 years and all of them have been able to conclude that there is a significant relation between the elevation of this biomarker on first POD and patients presenting this complication. These studies have demonstrated that CRP has excellent negative predictive value, with AUROC values ranging from 0.69 to 0.87. In our experience, AUROC value was 0.8.

Reference	Study design	Study Interval	Approach %Conv/%LAP	N	Anastomotic leakage (%)	Infectious complications (%)	Recommended CRP POD	Cut-off value (mg/L)
Kørner., *et al*. (2009)	Retrospective	12 (2004)	96/4	231	18/21 (9)	51/231 (22.1)	3	190
Ortega-Deballon., *et al*. (2010)	Prospective	12 (2007-2008)	88/12	133	21/133 (15.7)	52/133 (39.1)	4	125
Warschkow., *et al*. (2011)	Retrospective	144 (1997-2009)	100/0	1187	89/1115 (8)	347/1887 (29.2)	4	123
Platt., *et al*. (2012)	Retrospective	120 (1997-2007)	100/0	454	26/432 (6)	104/454 (22.9)	3	170
Almeida., *et al*. (2012)	Retrospective	22 (2008-2009)	82/12	173	24/173 (13.9)	n.s	3	140
Lagoutte., *et al*. (2012)	Prospective	14 (2010-2011)	65/35	100	13/100 (13)	32/100 (32)	4	130
Garcia-Granero., *et al*. (2013)	Prospective	17 (2008-2010)	79/21	205	17/205 (8.3)	19/205 (9.3)	3 - 5	POD3 147 POD5 135
Adamina., *et al*. (2014)	Retrospective	153 (1998-2010)	0/100	355	9/355 (2.7)	51/355 (14.4)	4	56
Silvestre., *et al*. (2014)	Prospective	21 (2009-2011)	n.s	50	1/50 (2)	21/50 (42)	6	50
Reisinger., *et al*. (2014)	Prospective	28 (2011-2013)	57/43	84	8/84 (9.5)	n.s	4	99
Zawaszki., *et al*. (2015)	Prospective	18 (2013-2014)	47/53	55	5/55 (9.1)	n.s	3	246

Waterland., *et al*. (2016)	Prospective	36 (2011-2014)	36/64	727	58/727 (7.9)	n.s	2 -3 - 4	LAP: POD2 146,5 Open: POD3 209, POD4 123
Smith., *et al*. (2017)	Prospective	n.s (2011-)	n.s	197	11/197 (5.6)	n.s	First 5PODs	50 mg/l/day increase
Ramos Fernandez., *et al*. (2017)	Prospective	n.s	52/48	168	14/168 (8.3)	33/168 (19.6)	4	Open: 159 LAP: 67,3
Guevara-Morales., *et al*. (2018)	Prospective	41 (2014-2017)	95/5	138	9/138 (6.5)	20/138(14)	3	185
Carrie., *et al*. (2020)	Prospective	16 (2018-2020)	74/10	84	8/84 (9.52)	n.s	2	223.7

Table 4: *Summary of studies.*

A paper presented by Ho., *et al*. [41] presented the use of CRP ratio and routine CT scan in 125 patients with left colon resections, proposing this is a useful algorithm for diagnosis of fistulas.

Other serological markers (platelets, white blood count, among others) have been also suggested and were found less strongly related.

However, there has been no consensus on the CRP cut off value which should be used to differentiate patients who will have an AL from those who will not. Moreover, there is no agreement on which POD this marker should be measured, as some papers have found it to be the third, fourth or even the fifth day.

Interestingly we have found a reliable CRP value as early as the second day after the procedure and have been the first group to find such evidence. We believe that this fact represents a significant finding, as we might be able to predict this complication as soon as 48 hrs after surgery, allowing decision making based on this information.

As previously mentioned, further research should be made to establish the best day and cut-off value of this marker which will allow us to know which patient will suffer an AL and which patient could be discharged early based with low AL risk. However, there is consensus regarding a direct relationship be-tween CRP and this complication. This statement is particularly important, considering that it is not an expensive marker, it is readily available in hospitals and its use is not standardized.

Further research should be conduced to find biomarkers of surgical complications, including AL in colorectal surgery. Larger and multicenter studies are needed before CRP becomes the preferred predictor of AL, but the results shown in the present study are promising.

To conclude, early diagnosis of AL on colorectal surgery is of utmost importance to improve postoperative prognosis. Evidence shows that PO CRP is a crucial serum biomarker to predict it, even though it is not yet standardized on which POD it is most significant and its cutoff value. Our study shows that since POD 2 CRP serum levels are significantly different in patients suffering from AL. This should encourage a higher degree of awareness, further examination of the patient, request imaging studies, and initiate early treatment.

Conflict of Interest

Every author declares that there is no conflict of interest.

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