ORIGINAL ARTICLE

Increase in C-reactive protein as early predictor of anastomotic leakage in abdominal surgery

Aumento de la proteína C reactiva como predictor precoz de fuga anastomótica en cirugía abdominal

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Abstract

Objectives: *The aim of this study was to evaluate the role of the C-reactive protein (CRP) and white cell count (WC) in the prediction of anastomotic leakage (AL) in major abdominal surgery.* **Methods:** *Multicenter, prospective, and observational study of adult patients who underwent major abdominal surgery. CRP and hemogram were measured after post-operative day (POD) 3 and POD 5. Complications were classified according to the Clavien-Dindo classification. Diagnostic accuracy was evaluated by the area under the receiver operating characteristic curve (AUC).* **Results:** *A total of 97 patients were included in the study. The mean age was 63 ± 12 years and 47 (48%) were male. Colorectal (56%) and gastric cancer (36%) were the most frequent diagnoses. About 23% had post-operative complications, of which 5% had AL. The most significant predictive factor was the increase in CRP ≥ 2.84 mg/L among POD 3 and 5 (AUC, 0.99, sensitivity, 95.6%, specificity, 100%, positive likelihood ratio, 23.0). The accuracy of the other biomarkers was lower, CRP on POD 3 (AUC, 0.55), on POD 5 (AUC, 0.93), WC on POD 3 (AUC, 0.33), and POD 5 (AUC, 0.35).* **Conclusion:** *The increase of CRP among POD 3 and 5 was an early predictor of AL in adult patients with major abdominal surgery.*

Keywords: *C-reactive protein. Predictive value of tests. Anastomotic leak. Digestive system surgical procedures.*

Resumen

Objetivo: *El objetivo de este estudio fue evaluar el papel de la proteína C-reactiva (PCR) y el recuento de glóbulos blancos (RGB) en la predicción de la Fuga Anastomotica (FA) en la cirugía abdominal mayor.* **Método:** *Estudio multicéntrico, prospectivo y observacional de pacientes adultos sometidos a cirugía abdominal mayor. Se midieron la PCR y el hemograma después del día postoperatorio (DPO) 3 y DPO 5. Las complicaciones se categorizaron según la clasificación de Clavien-Dindo y la precisión diagnóstica se evaluó mediante el área bajo la curva (AUC).* **Resultados:** *Se incluyeron un total de 97 pacientes. La edad media era de 63 ± 12 años y 47 (48%) eran hombres. El factor predictivo más significativo fue el aumento de la PCR ≥ 2,84 mg/L entre los DPO 3 y 5 (AUC, 0,99, sensibilidad, 95,6%, especificidad, 100%, ratio de probabilidad positiva, 23,0). La precisión de los demás biomarcadores fue menor, la PCR en el DPO 3 (AUC, 0,55), en el DPO5 (AUC, 0,93), el RGB en*

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el DPO 3 (AUC, 0,33) y en el DPO 5 (AUC, 0,35). **Conclusiones:** *El aumento de la PCR entre los DPO 3 y 5 fue un predictor temprano de FA en pacientes adultos con cirugía abdominal mayor.*

Palabras clave: *Proteína C-Reactiva. Valor Predictivo de las Pruebas. Fuga Anastomótica. Procedimientos Quirúrgicos del Sistema Digestivo.*

Introduction

Anastomotic leakage (AL) is a common and critical complication in gastrointestinal surgery[1]. AL is associated with longer hospital stay, repetitive therapeutic interventions, high mortality, and poor oncological outcomes[2-5]. Besides, AL affects quality of life due to poor functional outcomes with high frequency of stoma formation[6]. The incidence of AL varies between 0.6 and 17.4% depending of the institutions, surgeons, and patient risk factors[7-10]. In Colombia, the incidence of AL has been estimated in 10.8% with a median time to diagnosis of AL of 7 days[11].

AL is defined as clinical signs of peritonitis and/or clinical evidence of free fecal fluid within the abdomen or emerging from the drain site[12], the presentation could be evidenced from some days to few weeks. Early identification and treatment of AL is necessary to timely avoid adverse outcomes[1,4,12]. However, the early diagnosis of AL is difficult due to the wide variety of clinical presentations, from subclinical radiological evidence to generalized fecal peritonitis[1,12]. Standardization of diagnostic approaches is, therefore, challenging. Multiple methods such as clinical assessment, imaging techniques, laboratory biomarkers and endoscopic examination have been identified as possible tools for early diagnosis of AL[12].

Some studies have reported that C-reactive protein (CRP) levels and reduction rate and white cell count (WC) in the 1st post-operative day (POD) would have a role in the prediction of AL and post-operative complications (PC) with some discrepancies[13-17]. Taking into account that CRP is an acute-phase protein that reflects the presence and intensity of inflammation in the body, CRP levels could be used to assess response to treatment and predict prognosis[13]. Furthermore, increase of CRP from normal to highest concentration value over time could be used to more effectively predict patient's prognosis, rather than the highest concentration of the specific POD.

To the best of our knowledge, no previous studies have investigated the increase of CRP concentration over time in the prediction of AL in gastrointestinal surgery. Therefore, the aim of this study was to evaluate the role of the increase of CPR over time, rather than CPR concentration in a given POD in the prediction of AL in major abdominal surgery.

Materials and methods

Patients and design

Multicenter, prospective, and observational study of adult patients who underwent major abdominal surgery from April to November 2018 to November 2019 in the three gastrointestinal surgery reference centers from Colombia. The inclusion criteria were the following: (1) age ≥ 18 years-old, (2) treated by major abdominal surgery (open or laparoscopic approach) in the study period, and (3) complete clinical history including CPR in POD 3 and 5. Patients without gastrointestinal anastomosis were excluded from the study. The study was approved by the Bioethics Committee of Liga Contra el Cancer (Pereira, Colombia) under the category of research without risk. The principles of confidentiality of information established by the Declaration of Helsinki were followed.

Variables

Clinical and sociodemographic relevant data were obtained. Age, sex, patient diagnosis, surgical procedure, PC, management of PC, and reintervention were included in the study. Serum CRP and hemogram were measured after POD 3 and POD 5. Delta (Δ) was defined as the difference among CRP concentration in POD 5 and 3 (CRP on POD 5-POD 3). Complications were classified according to the Clavien-Dindo classification[18,19].

Perioperative management

All patients were allowed to ingest a normal meal until the day before surgery and received pre-operative single antibiotic prophylaxis (2000-mg cefazolin intravenously) before skin incision. Epidural analgesia and NSAIDs were administered for post-operative pain management, avoiding opioid use; intravenous fluids

were administered as needed in each patient. Bladder catheter removal was performed by suspending epidural analgesia. Early walking was promoted since POD 1. In patients with gastrointestinal diversions and subtotal gastrectomy, a nasogastric tube was used, which was removed on the POD 2 and the oral diet with clear water was started between the POD 1 and 2 with progression in three steps (clear liquid, full liquid, and soft diet). Nasogastric tube was not used in patients with colorectal surgery. In patients with esophagectomy, gastrectomy, and multivisceral resections, a nasoenteral tube was used for enteral nutrition, which was started on the POD 1, the oral diet began on POD 4 and 5, and the tube was removed once oral tolerance was identified. In the presence of complications and according to the clinical findings of the patient, medical management, contrast abdominal tomography, or surgery were performed.

Statistical analysis

Continuous variables were summarized through the calculation of mean, standard deviation, median, and interquartile range (IQR), depending on whether the variable followed a normal distribution. Categorical variables were calculated in absolute terms and through proportions. Comparisons between the means of continuous variables were carried out using Student's t-test if they followed a normal distribution according to the Shapiro–Wilk test. Continuous variables with non-normal distribution were compared using the median test. The comparison of proportions was made with the Chi-square test or Fisher's exact test. All comparisons were made at the 5% significance level. Diagnostic accuracy was evaluated by the area under the receiver operating characteristic (ROC) curve (AUC). All statistical analyses were performed using STATA version14.0 (StataCorp, College Station, Texas 77845 USA).

Results

Baseline and PC group versus no-PC group comparison

A total of 97 patients were included in the study. The mean age was 63 ± 12 years, 47 (48%) were male and 50 (52%) were female. The diagnoses of the patients were: colorectal cancer (56%), gastric cancer (36%), diverticular disease (4%), esophageal cancer (2%), and familial adenomatous polyposis (1%). About 23% had post-operative complications, of which 5% had AL. The most performed surgical procedures were: anterior lower resection (20%), subtotal gastrectomy (17%), total gastrectomy (13%), and right hemicolectomy (12%) (Table 1).

There were no significant differences between patients with and without PC in the following variables: age, sex, diagnosis, surgical procedure, and WC; however, the PC group had a significantly higher CRP levels in POD 5 (p = 0.002) and higher rate of reintervention (p = 0.001) (Table 1). Surgical site infection (26%) and AL (22%) were the most common PC. The most frequent Clavien-Dindo classifications were: Grade I (56%), Grade IV (22%), and Grade III (22**%**) (Table 2).

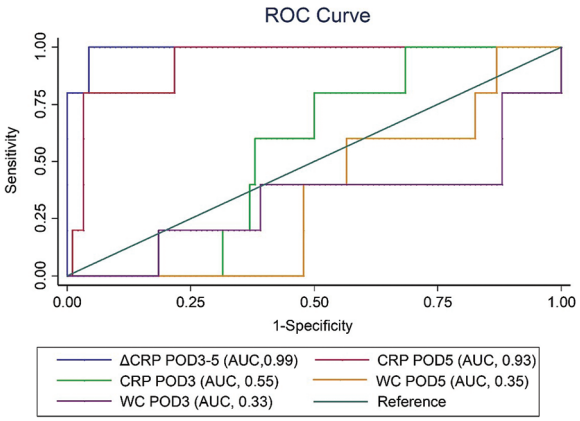

Figure 1. *Receiver operating characteristic (ROC) curves for the diagnostic accuracy of the C-reactive protein (CRP) concentration and White Cell Count (WC) in predicting postoperative AL. AUC, area under the curve.*

Diagnostic accuracy of CRP and WC

The most significant predictive factor was the increase in CRP ≥ 2.84 mg/L among POD 3 and 5 (AUC, 0.99, sensitivity, 95.6%, specificity, 100%, positive likelihood ratio, 23.0). The accuracy of the other biomarkers was lower, CRP on POD 3 (AUC, 0.55), on POD 5 (AUC, 0.93), WC on POD 3 (AUC, 0.33), and POD 5 (AUC, 0.35) (Table 3 and Fig. 1).

Discussion

AL is a common and critical complication in gastrointestinal surgery that increases mortality and reduces quality of life. In this study, we explored the role of

Table 1. Baseline characteristics and clinical outcomes of patients included

Characteristic	Without post-operative complication (n = 74)	With post-operative complication (n = 23)	p-value
Age, mean (SD)	62.4 ± 1.38	66.7 ± 3.11	0.160
Sex, n (%)			
Male	33 (43)	14 (61)	0.154
Female	41 (55)	9 (39)	
Patient Diagnosis, n (%)			
Colorectal cancer	40 (54)	15 (65)	0.345
Gastric cancer	29 (39)	6 (26)	0.253
Diverticular disease	4 (5)	0 (0)	0.255
Esophageal cancer	1 (1)	1 (4)	0.377
Familial adenomatous polyposis	0 (0)	1 (4)	0.237
Surgical procedure, n (%)			
Total gastrectomy	9 (12)	4 (17)	0.520
Multivisceral resection	5 (7)	3 (13)	0.338
Anterior lower resection	16 (22)	4 (17)	0.661
Right hemicolectomy	9 (12)	3 (13)	0.911
Subtotal gastrectomy	15 (20)	2 (9)	0.202
Left hemicolectomy	6 (8)	1 (4)	0.543
Palliative bypass	7 (9)	1 (4)	0.436
Reversal colostomy	3 (4)	1 (4)	0.951
Esophagectomy	1 (1)	1 (4)	0.337
Sigmoidectomy	3 (4)	2 (9)	0.379
Total colectomy	0 (0)	1 (4)	0.237
C-Reactive Protein, median (IQR)			
Post-operative day 3	132.3 (68.6-203.9)	136.9 (97.8-173.0)	0.549
Post-operative day 5	57.0 (29.0-117.7)	142.1 (58.4-189.3)	**0.002**
White Cell Count, median (IQR)			
Post-operative day 3	10,065 (8080-12,900)	11,300 (7350-13,800)	0.932
Post-operative day 5	8415 (6600-9540)	8,540 (6610-10,200)	0.561
Reintervention, n (%)	0 (0)	7 (30)	**0.0001**

All statistically significant associations were highlighted in **bold.**
SD: standard deviation, IQR: interquartile range.

Table 2. Post-operative complications of the patients included

Post-operative complication (n: 23)	n (%)	Grade I	Grade II	Grade III	Grade IV	Management
Surgical site infection	6 (26)	6 (26)	-	-	-	Medical
Anastomotic leakage	5 (22)	-	1 (4)	-	IVa: 3 (13)/IVb: 1 (4)	1 Medical/4 Surgical
Post-operative ileus	4 (17)	4 (17)	-	-	-	Medical
Oral feeding intolerance	3 (13)	3 (13)	-	-	-	Medical
Intra-abdominal abscess	2 (9)	-	-	IIIa: 1 (4)	IVb: 1 (4)	1 Medical/ 1 Percutaneous Drainage
Intra-abdominal hematoma	2 (9)	-	-	IIIb: 2 (9)	-	Surgical
Gastroyeyunal anastomotic stenosis	1 (4)	-	-	IIIa: 1 (4)	-	Endoscopic
Small-bowel obstruction (adhesions)	1 (4)	-	-	IIIb: 1 (4)	-	Surgical

CRP and WC in the prediction of AL in major abdominal surgery. Our main finding was that the increase of CRP among POD 3 and day 5 was an early predictor of AL in adult patients with major abdominal surgery. On the other hand, WC had a poor diagnostic value of AL. To the best of our knowledge, this is the first

Table 3. Diagnostic accuracy and cutoff of CRP and WC for prediction of anastomotic leakage

	Cutoff value	AUC (CI 95%)	Sensitivity (%)	Specificity (%)	Correctly classified (%)	LR+	LR-
Δ CRP POD 3-5	≥ 2.84	0.99 (0.97-1.00)	95.6	100	95.8	23.0	0.0
CRP on POD 3	≥ 151.4	0.55 (0.39-0.70)	60.0	61.9	61.8	1.57	0.64
CRP on POD 5	≥ 154.3	0.93 (0.85-100)	100	78.2	79.3	4.60	0.25
WC on POD 3	≥ 11.580	0.33 (0.01-0.64)	40.0	60.8	59.8	1.02	0.98
WC on POD 5	≥ 8.100	0.35 (0.17-0.54)	60.0	43.4	44.3	1.06	1.38

Δ: delta, POD: Post-operative day, CRP: C-reactive protein, WC: White Cell Count, AUC: Area under the curve, LR: Likelihood ratio, CI: Confidence Interval

study that addressed the use of CRP concentration over time, rather than CPR levels in a given POD in the prediction of AL in major abdominal surgery.

Early diagnosis of AL is a concern for surgeons worldwide as it can reduce mortality, hospital stay, rehospitalization, and increase the quality of life of patients. Furthermore, the early identification of AL will allow enhanced recovery after surgery (ERAS) protocols to be applied effectively. To date, the clinical assessment of patients (body temperature, oral tolerance, normal passage of stool and gas, and discharge acceptance) is the only tool used as a discharge criterion in the ERAS protocols[20,21]. Some studies have evaluated the role of clinical assessment, imaging techniques, laboratory biomarkers, and endoscopic examination as possible tools for early diagnosis of AL[12,22].

CRP has long been considered a primary inflammatory indicator of post-operative complications despite poor specificity[12]. CRP in an acute-phase protein reflects the presence and intensity of inflammation in the body, produced in the liver, with a relatively constant half-life with the advantages that is of low cost, easy measured, and standardized[13]. CRP levels increase in response to trauma or infection, and taking into account that surgery is a planned trauma, CRP levels could be used to assess response to treatment and predict prognosis[13,23].

Some studies have reported the value of the WC and increase or the reduction rate of the CRP as possible predictors of AL in gastrointestinal surgery with some discrepancies[13-17,22]. Matthiessen et al.[22] investigated the role of WC and CRP levels to predict AL after low anterior resection, including 33 patients with rectal carcinoma (n: 32) and severe dysplasia (n: 1) with daily monitoring of these biomarkers until hospital discharge[22]. The authors state that an early rise in serum CRP was a strong indicator of leakage because the serum CRP was increased in patients who leaked from POD 2 onward ($p = 0.004$ on day 2; $p < 0.001$ on day 3-8), by contrast, WC showed no difference between patients with (n: 9) or without AL[22]. Moreover, Dutta et al.[15] analyzed the diagnostic accuracy of PCR and WC levels of 136 patients who underwent surgery for esophageal cancer, the authors identified that the post-operative CRP measurements on PODs 3 (threshold: 180 mg/L, sensitivity: 82% and a specificity of 63%) and 4 (threshold: 180 mg/L, sensitivity: 71% and a specificity of 83%) were clinically useful in predicting AL and WC had no significant differences[15]. Furthermore, the results of Zhang et al.[16] with 278 patients who underwent laparoscopy-assisted gastrectomy showed that CRP concentration on POD 3 and WC count on POD 7 had the highest diagnostic accuracy for major complications with AUC of 0.86 (95% confidence interval [CI], 0.79-0.92] and 0.68 (95% CI, 0.56-0.79), respectively. Those findings were similar to our study results[16].

On the other hand, Pedersen et al.[17] showed evidence of poor diagnostic accuracy of the levels of CRP and WBC in prediction of post-operative septic complications, including AL. They included 129 patients retrospectively analyzed who underwent laparoscopic colorectal surgery and found that the best cutoff value for CRP and WC levels as a predictors of septic complications was observed on POD 3 (threshold > 200 mg/L, sensitivity: 68%, specificity: 74%) and WC on POD 2 (WC > 12 × 10 [9], sensitivity: 90%, specificity of 62%)[17]. Lee et al.[13] explored the role of CRP as an early predictor of PCs in 613 patients who underwent gastrectomy for gastric cancer in Korea, they found that CRP concentration reduction rates between POD 3 and 5 and between POD 2 and 3 were the best combination factors to predict PCs and indicate a safe discharge after gastrectomy for gastric cancer, rather than the use of CRP concentration on

specific POD[13]. These findings generate uncertainty in the usefulness of CPR as an early predictor of AL, but it must be taken into account that they include different populations, interventions, outcomes, and statistical analyzes that could explain these discrepancies.

Our study has some limitations: (1) the inclusion of patients with different etiologies generates a heterogeneous sample and a risk of selection bias, (2) a risk of confounder bias due to the absence of other clinical covariables that were not included in the analysis, and (3) a risk of information bias due to the lack of data on the levels of CRP and WC after POD 5. In contrast, our strengths were: (1) our methodology and analysis were reliable and strong, (2) this was a multicenter and prospective design with some advantages over other study designs, and (3) a standardized and validated definition for AL and complications grades were used. The next step for this study is to evaluate the predictor value of CRP and other biomarkers in a larger sample including possible multiple confounders and validate our findings by replicating the results with other international studies.

Conclusions

The increase of CRP among POD 3 and 5 (AUC, 0.99) was the most significant early predictor of AL in adult patients with major abdominal surgery and the accuracy of the other biomarkers was lower, CRP on POD 3 (AUC, 0.55), on POD 5 (AUC, 0.93), WC on POD 3 (AUC, 0.33), and POD 5 (AUC, 0.35).

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical responsibilities

Protection of humans and animals. The authors declare that no experiments on humans or animals have been performed for this research.

Confidentiality of data. The authors declare that they have followed their center's protocols on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

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