

Procalcitonin and C-reactive protein: markers in the early diagnosis of anastomotic leak

Procalcitonina y proteína C reactiva: marcadores en el diagnóstico temprano de fuga anastomótica

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Abstract

Objective: To determine the efficacy of serum procalcitonin (PCT) and C-reactive protein (CRP) in the early diagnosis of anastomotic leak (AL) in patients undergoing colorectal surgery. **Method:** Diagnostic test in a tertiary care hospital. Patients who did not have preoperative measurements of PCT and CRP were excluded. Those with postoperative infection not related to AL were eliminated. The diagnostic efficacy measures were sensitivity (Sn), specificity (Sp), positive (PPV) and negative (NPV) predictive values, positive (LR+) and negative (LR-) likelihood ratios, and area under the receiver operating characteristic curve (AUROC). **Results:** Thirty-nine patients were analyzed; six had AL (15.4%). PCT and CRP increased on the second postoperative day, only in patients with AL. The cut-off points at the second postoperative day were 1.55 ng/mL for PCT and 11.25 mg/L for CRP. The most efficacious test was CRP at second postoperative day (AUROC: 1.00; Sn: 100%; Sp: 96.7%; PPV: 85.7%; NPV: 100%; LR+: 33.0). **Conclusions:** CRP at second postoperative day was the most effective test in the early diagnosis of AL in patients undergoing colorectal surgery, with a cut-off point lower than that reported in the international literature.

Keywords: Anastomotic leak. Sensitivity and specificity. ROC curve. Predictive value of tests. Procalcitonin. C-reactive protein.

Resumen

Objetivo: Determinar la eficacia de la procalcitonina (PCT) y la proteína C reactiva (PCR) séricas en el diagnóstico de fuga anastomótica (FA) en los pacientes sometidos a cirugía colorrectal. **Método:** Prueba diagnóstica en un hospital de tercer nivel. Se excluyeron los pacientes que no tuvieron mediciones preoperatorias de PCT y PCR. Se eliminaron los que cursaron con infección posoperatoria no relacionada con FA. Las medidas de eficacia diagnóstica fueron sensibilidad (S), especificidad (E), valores predictivos positivo (VPP) y negativo (VPN), razones de verosimilitud positiva (RV+) y negativa (RV-), y área bajo la curva característica operativa del receptor (AUROC). **Resultados:** Se analizaron 39 pacientes, de los cuales 6 (15.4%) tuvieron FA. La PCT y la PCR aumentaron al segundo día posoperatorio solo en los pacientes con FA. Los puntos de corte al día 2 fueron 1.55 ng/ml para PCT y 11.25 mg/l para PCR. La prueba más eficaz fue la PCR al día 2 (AUROC: 1.00; S: 100%; E: 96.7%; VPP: 85.7%; VPN: 100%; RV+: 33.0). **Conclusiones:** La PCR en el segundo día posoperatorio fue la prueba más eficaz en el diagnóstico temprano de FA en los pacientes sometidos a cirugía colorrectal, con un punto de corte inferior a lo reportado en la literatura internacional.

Palabras clave: Fuga anastomótica. Sensibilidad y especificidad. Curva ROC. Valor predictivo de las pruebas. Procalcitonina. Proteína C reactiva.

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Introduction

Dehiscence or anastomotic leak (AL) is one of the most serious complications of digestive surgery due to the increased risk of severe complications and death¹. The incidence of AL ranges between 0.3% and 33%²⁻⁷, with associated mortality rates ranging from 0.5% to 45.5%^{2-4,6}. Known risk factors for AL include male sex, arterial hypertension, perioperative transfusions, a Charlson comorbidity index score > 3, distal location of the anastomosis, malnutrition, immunosuppression, diabetes, chronic use of non-steroidal anti-inflammatory drugs, and radiation therapy^{1,4,7,8}.

Early diagnosis of AL is crucial for favorable patient outcomes. However, it is challenging in the early postoperative period in the absence of clinical signs⁹. Therefore, auxiliary laboratory and imaging modalities to enhance diagnostic efficacy are of paramount importance. The decision to perform a computed tomography scan to refine diagnosis is a common thing, which has shown a 69% sensitivity rate⁶. This stresses the need for a faster, accurate, and cost-effective diagnostic tool.

For several years, laboratory parameters measured in venous blood samples in the postoperative period have been used being 2 of these parameters procalcitonin (PCT) and the C-reactive protein (CRP). The former is a peptide prohormone whose precursor—preprocalcitonin—is initially synthesized in thyroid C cells. Under physiological conditions, serum levels are usually very low ($p < 0.05$ ng/ml). However, its extra-thyroidal synthesis increases 100 to 1000 times due to the presence of endotoxins and cytokines such as interleukin-6, tumor necrosis factor- α , and interleukin-1 β ¹⁰. Therefore, PCT has been successfully used in various diagnostic contexts related to bacteremia, such as infectious complications of burns and polytrauma, bacterial meningitis, septicemia, and pancreatitis, among others¹¹. CRP is a pentameric protein synthesized by the liver, and its levels increase in response to inflammation due to its proinflammatory and anti-inflammatory properties¹². CRP has been extensively studied to differentiate bacterial from non-bacterial infections in febrile patients and can be a cost-effective alternative in settings with limited resources as part of the diagnostic algorithm for each particular clinical situation¹³. Therefore, despite extensive research on the diagnostic efficacy of PCT and CRP for AL, the cutoff points for these markers vary ranging from 50 mg/L up to 245 mg/L for CRP¹⁴⁻²⁰, and

0.27 ng/mL up to 5.27 ng/mL for PCT^{15,18,19,21,22}. This variability in the cutoff points complicates the early diagnosis of AL, and no related studies have ever been conducted in the Mexican population. The objective of this study was to determine the effectiveness of serum PCT and CRP in the early diagnosis of AL in patients undergoing colorectal surgery.

Method

This was an ambispective diagnostic test study in patients undergoing elective colorectal surgery at a tertiary referral center that serves patients from north-east Mexico. Using non-probabilistic consecutive case sampling, we included patients who underwent conventional or laparoscopic anastomosis surgery from May through December 2021. Patients without preoperative PCT or CRP determinations and those who, at the time of the preoperative assessment, showed clinical or laboratory evidence of an active infection (which could elevate PCT and CRP levels) were excluded. Patients who developed concurrent postoperative infections unrelated to AL (urinary tract infection and pneumonia) were also excluded.

Procedures

Once the protocol was approved by the hospital research ethics committee, the health records of patients who underwent colorectal anastomosis surgery from May through October 2021 were retrospectively reviewed. Patients were included in the study if they met the selection criteria and had preoperative and postoperative measurements of PCT, CRP, and total leukocyte counts. Subsequently, the prospective inclusion of preoperative patients who met the criteria was considered. These patients were informed about the study objective and then invited to participate by signing an informed consent form. Overall, 4 measurements of each inflammatory marker were taken: the first one the day prior to the surgery and the following 3 on postoperative days 1, 2, and 3, all from venous blood samples. Serum PCT and CRP determinations were performed using the absorbance method with Alinity Hc (Abbott, IL, United States, 2016). Similarly, leukocyte counts were performed using an automatic cell counter with KX-21N (Sysmex Corporation, United States, 2015). To document or rule out the presence of AL, patients were monitored from the 1st postoperative day until discharge. AL was defined by findings made during reoperation, such as fecal drainage from

the wound, contrast extravasation on an enema, or the presence of air or fluid at the anastomotic site visualized by computed tomography. Hospital discharge was left to the treating physician's criterion.

Ethical aspects

The project was submitted to the local research committee 1901 of the Mexican Social Security Institute and later approved with no. R-2021-1901-084. Data confidentiality and patient anonymity were guaranteed at all times. From the moment the protocol was approved onward, the patients who met the inclusion criteria signed a valid informed consent form to participate in the study. Similarly, the health records of patients operated on before the protocol was approved were consulted once the protocol was approved and handled with absolute discretion, respecting their anonymity.

Statistical analysis

Measures of central tendency and dispersion were estimated for quantitative variables, and proportions for categorical ones. The Mann-Whitney U test was used to compare age ranges and hospitalization days between patients with and without AL. Rates of categorical variables were compared using the chi-square test. *P* values < .05 were considered statistically significant.

The efficacy of PCT and CRP tests was evaluated using sensitivity (Sn), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), area under the receiver operating characteristic curve (AUROC), positive likelihood ratio (LR+), and negative likelihood ratio (LR-), all with 95% confidence intervals. The cutoff points for PCT, CRP, and leukocyte count were determined by calculating the Youden index ($S + E - 1$). Estimates of such diagnostic indicators were made using the free statistical package Epidat 3.1²³. Diagnostic efficacy indicators were considered unacceptable, acceptable, or ideal based on the following criteria²⁴⁻²⁷: Sn, PPV, and NPV, ideal $\geq 80\%$, acceptable 60% to 79.9%, and unacceptable < 60%; Sp, ideal $\geq 95\%$, acceptable 90% to 94.9%, and unacceptable < 90%; LR+, ideal ≥ 10 , acceptable 5 to 10, and unacceptable < 5; and AUROC, ideal > 0.90, acceptable 0.70 to 0.90, and unacceptable < 0.70.

Results

Laboratory determinations were conducted on 42 patients, 3 of whom were excluded (without AL)

(2 with pneumonia, and 2 with urinary tract infections on the first after surgery). The 3 patients excluded from the study did not differ from the rest of the sample. Finally, a total of 39 patients were included, with a mean age of 51.9 ± 13.2 years (43.6% were women). The most widely reported comorbidity was arterial hypertension (30.8%). The most common preoperative diagnosis was cancer in 38.5% of the patients, while colorectal anastomosis was the most common type. Among the clinical and surgical variables analyzed, only age and the length of stay were significantly higher in patients with AL ($p < 0.05$ and $p < 0.0001$, respectively) (Table 1).

Postoperative course of PCT, CRP, and leukocyte count

Blood concentrations of PCT and CRP increased on the 2nd and 3rd postoperative days in patients with AL, while in those without AL, these concentrations remained at values similar to preoperative levels (Figs. 1 and 2). Total leukocyte counts increased the 1st day after surgery in patients with and without AL, remaining stable with no inter-group difference being reported on the 2nd and 3rd postoperative days (Fig. 3).

Diagnostic efficacy of PCT, CRP, and total leukocyte counts

In the search for optimal cutoff values, PCT and CRP showed ideal AUROCs, whereas for total leukocyte counts, the AUROC was only acceptable on the 3rd postoperative day. The Sn of all 3 markers was ideal on all 3 postoperative days, while the Sp was optimal only on the 2nd postoperative day for CRP. Furthermore, CRP reached the highest PPV on days 2 and 3 (85.7% and 75%, respectively) and the highest LR+ (33 and 16.5, respectively). PCT showed unacceptable Sp and PPV. All NPVs were optimal. Given the consistent increase in PCT and CRP from the 2nd postoperative day onwards, the cutoff values at that time were 1.55 ng/mL and 11.25 mg/L, respectively. Finally, most diagnostic efficacy indicators for total leukocyte counts were unacceptable (Table 2).

Discussion

In this study, CRP demonstrated superior diagnostic performance vs PCT and total leukocyte counts on the 2nd postoperative day. This result is of paramount

Table 1. Clinical and surgical characteristics of patients treated with intestinal anastomosis

	Total n = 39 (%)	Anastomotic leak Yes, n = 6 (%)	Anastomotic leak No, n = 6 (%)	P
Age, years (mean ± SD)	51.9 ± 13.2	63.7 ± 7.9	49.8 ± 12.8	0.011
Gender				
Woman	17 (43.6)	4 (66.7)	13 (39.4)	0.374
Man	22 (56.4)	2 (33.3)	20 (60.6)	
Comorbidities				
None	12 (30.8)	2 (33.3)	10 (30.3)	0.266
Hypertension	12 (30.8)	1 (16.7)	11 (33.3)	
Diabetes	8 (20.5)	2 (33.3)	6 (18.2)	
Other	7 (17.9)	1 (3.0)	6 (18.2)	
Preoperative diagnoses				
Cancer	15 (38.5)	4 (66.7)	11 (33.3)	0.130
Diverticular disease	7 (17.9)	0 (0)	7 (21.2)	
Intestinal perforation	7 (17.9)	1 (16.7)	6 (18.2)	
Crohn's disease	4 (10.3)	0 (0)	4 (12.1)	
NSUC	4 (10.3)	1 (16.7)	4 (12.1)	
Other	3 (7.7)	0 (0)	4 (12.1)	
Types of anastomoses				
Colon-rectum	22 (56.4)	2 (33.3)	20 (60.6)	0.321
Ileum-rectum	8 (20.5)	1 (16.7)	7 (21.2)	
Ileum-transverse	7 (17.9)	2 (33.3)	5 (15.2)	
Ileum-anus	2 (5.1)	1 (16.7)	1 (3.0)	
Suture type				
Manual	15 (38.5)	2 (33.3)	13 (39.4)	1.000
Mechanical	24 (61.5)	4 (66.7)	20 (60.6)	
Surgical approach				
Laparotomy	18 (46.2)	4 (66.7)	14 (42.4)	0.387
Laparoscopy	21 (53.8)	2 (33.3)	19 (57.6)	
Type of resection				
Right colon	14 (35.9)	2 (33.3)	12 (36.4)	0.520
Sigmoid colon	13 (33.3)	1 (16.7)	11 (33.3)	
Rectum	6 (15.4)	0 (0)	6 (18.2)	
Partial colectomy	4 (10.3)	1 (16.7)	3 (9.1)	
Total colectomy	2 (5.1)	0 (0)	3 (9.1)	
Length of stay, days (mean ± SD)	4.9 ± 1.8	8.5 ± 1.0	4.3 ± 0.9	< 0.0001

NSUC: nonspecific ulcerative colitis; SD: standard deviation.

importance in the in-hospital follow-up of patients, as it may lead to reconsidering the decision for early discharge¹⁹. One important aspect of this study is the cutoff value for the CRP. In this work, it was found to be 11.25 mg/L on day 2, while in international studies, it varies widely, ranging from 44.32 mg/L in Turkey²⁸ up to 245.64 mg/L in Poland.¹⁸ Additionally, the postoperative days on which the best cutoff values were reported are also controversial in the literature, ranging from day 2 in Croatia¹⁵ up to day 6 in Portugal¹⁶. These discrepancies also apply to PCT. For example, this study determined a cutoff value of 1.55 ng/mL on day 2, while levels ranging from 0.24 ng/mL in Poland²¹

up to 5.27 ng/mL in Malaysia²² have been reported. Similarly, the postoperative days for the best cutoff values are also variable ranging from day 3 in Poland and Malaysia^{18,21,22} up to day 5 in Spain²⁹. Therefore, we can see that cutoff values for both inflammatory markers are relatively variable among populations. It is worth considering that no similar studies were found in the Mexican population, making this study necessary to strengthen the scientific evidence available for Mexican surgical practice.

Patients in this study had lower diagnostic levels for both markers vs other populations, suggesting that, with values lower than those internationally published,

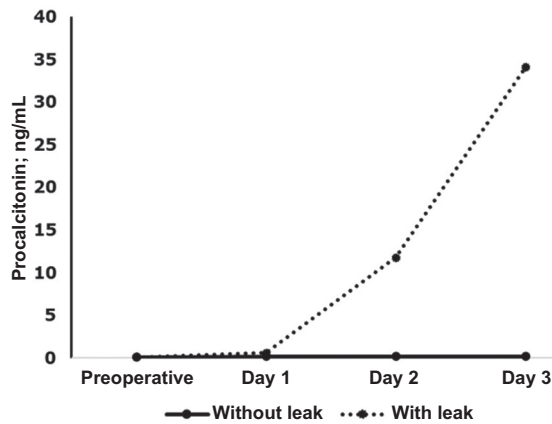


Figure 1. Median preoperative and postoperative concentrations of procalcitonin in 6 patients with anastomotic leak vs 33 patients without anastomotic leak.

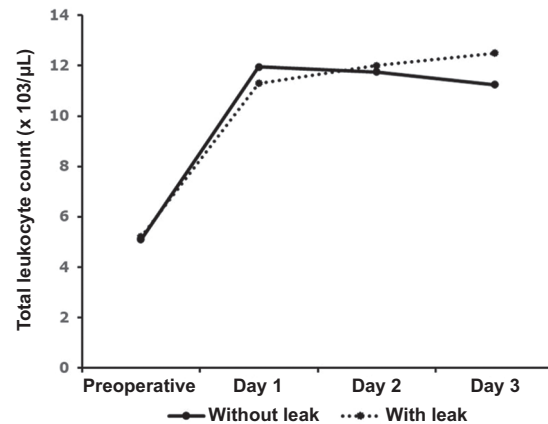


Figure 3. Median preoperative and postoperative total leukocyte count in 6 patients with anastomotic leak vs 33 patients without it.

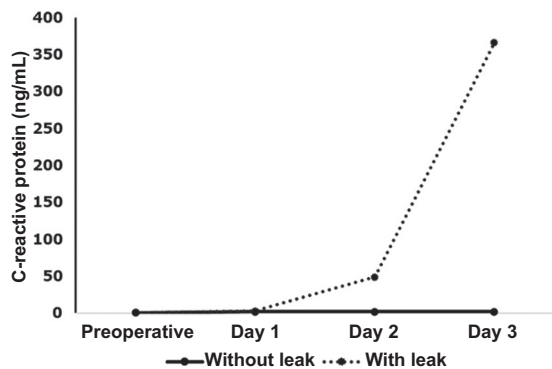


Figure 2. Median preoperative and postoperative C-reactive protein concentrations in 6 patients with anastomotic leak vs 33 patients without it.

a high degree of suspicion of AL can be warranted. Based on this, it seems reasonable to postpone the discharge of a postoperative patient with such CRP values (the inflammatory marker that achieved the highest diagnostic efficacy indices) while the diagnosis is being confirmed. Additionally, this study demonstrated the postoperative progression of circulating concentrations of both inflammatory markers along with the total leukocyte count. On this topic, we should mention that although the leukocyte count is a routine laboratory test, it showed poor diagnostic efficacy compared to CRP and PCT.

Based on the results of this study, it is recommended to monitor CRP or, for the lack of it, PCT levels daily, as they showed a consistent increase from the 2nd postoperative day onwards, at least, in this population. Similarly, we saw that both markers

offered very high Sn but with different Sp. In many of the studies consulted, a lower Sn for CRP vs this study was evident, even with higher diagnostic cutoff values. For example, a study conducted in France by Benoit et al.³⁰ achieved a Sn rate of 63.6%.³⁰ Other studies conducted in Spain²⁹, Portugal¹⁶, and Brazil^{14,20} reported slightly higher results, but none reached rates close to 100%, while 2 studies conducted in Poland found Sn rates of 92%²¹, and 100%¹⁸. The Sp rate of this protein ranged from 66.1% in Turkey²⁸ up to 98% in Poland¹⁸.

For PCT, international variability is even more evident, with Sn rates as low as 69% in Croatia,¹⁵ and up to 100% in Malaysia.²² The Sp rate of this marker also ranged from 68%²¹ up to 100%¹⁸ in Poland. These discrepancies in the diagnostic efficacy of both tests represent a challenge for surgeons using scientific literature, especially in Mexico, where no records of any articles related to these markers were found. Based on these results, we should mention that the role of CRP as a useful and accurate test for the early diagnosis of AL is evident. As previously mentioned in the theoretical framework of this study, the physiological importance of this marker lies in its proinflammatory and anti-inflammatory properties¹². In fact, the CRP may very well become a cost-effective option among the auxiliary diagnostic resources available to surgeons in settings with limited resources¹³.

Limitations

We should acknowledge the small sample size, which is likely due to the limited number of intestinal anastomoses performed, most likely due to the restrictions

Table 2. Diagnostic efficacy of postoperative serum measurements of procalcitonin, C-reactive protein, and total leukocyte counts in the early diagnosis of anastomotic leaks

Marker	AUROC (95%CI)	Cutoff value	Sn (95%CI)	Sp (95%CI)
PCT Day 1	0.94 (0.85-1.00)	0.35 ng/mL	100% (91.7-100)	69.7% (52.5-86.9)
PCT Day 2	1.00 (1.00-1.00)	1.55 ng/mL	100% (91.7-100)	81.8% (67.1-96.5)
PCT Day 3	1.00 (1.00-1.00)	13.4 ng/mL	100% (91.7-100)	84.9% (71.1-98.6)
CRP Day 1	0.83 (0.66-0.99)	2.1 mg/L	100% (91.7-100)	51.5% (33.0-70.1)
CRP Day 2	1.00 (1.00-1.00)	11.25 mg/L	100% (91.7-100)	96.7% (89.6-100)
CRP Day 3	1.00 (1.00-1.00)	63.85 mg/L	100% (91.7-100)	93.9% (84.3-100)
Leukocyte count Day 1	0.43 (0.24-0.63)	10.8 mil/ μ L	100% (91.7-100)	27.3% (10.6-44.0)
Leukocyte count Day 2	0.52 (0.33-0.71)	11.7 mil/ μ L	83.3% (45.2-100)	45.5% (27.0-64.0)
Leukocyte count Day 3	0.86 (0.76-1.00)	11.6 mil/ μ L	100% (91.7-100)	57.6% (39.2-76.0)
Marker	PPV (95% CI)	NPV (95%CI)	LR+ (95%CI)	LR- (95%CI)
PCT Day 1	37.5% (10.7-64.4)	100% (97.8-100)	3.30 (1.97-5.54)	*
PCT Day 2	50.0% (17.5-82.4)	100% (98.2-100)	5.50 (2.67-11.34)	*
PCT Day 3	54.5% (20.6-88.5)	100% (98.2-100)	6.60 (2.94-14.80)	*
CRP Day 1	27.3% (6.4-48.2)	100% (97.1-100)	2.06 (1.45-2.93)	*
CRP Day 2	85.7% (52.7-100)	100% (98.4-100)	33.0 (4.79-227.36)	*
CRP Day 3	75.0% (38.7-100)	100% (98.4-100)	16.50 (4.31-63.22)	*
Leukocyte count Day 1	20.0% (4.0-36.0)	100% (94.4-100)	1.38 (1.12-1.69)	*
Leukocyte count Day 2	21.7% (2.7-40.8)	93.8% (78.8-100)	1.53 (0.95-2.46)	0.37 (0.06-2.28)
Leukocyte count Day 3	30.0% (7.4-52.6)	100% (97.4-100)	1.38 (1.12-1.69)	*

*Impossible to estimate as no false negative results were reported.

95%CI: 95% confidence interval; AUROC: area under the Receiver Operating Characteristic curve; LR-: negative likelihood ratio; LR+: positive likelihood ratio; NPV: negative predictive value; CRP: C-reactive protein; PCT: procalcitonin; PPV: positive predictive value; Sn: sensitivity; Sp: specificity.

imposed by the COVID-19 pandemic. This could have impacted the estimation of diagnostic efficacy indicators, which means that these results should be interpreted with caution and further multicenter studies in the Mexican population should go on. A strength of this study is the inclusion of different measures of diagnostic efficacy, which could provide a comprehensive view of the diagnostic performance of each test.

Conclusions

CRP on the 2nd postoperative day was the test with the highest efficacy in the early diagnosis of AL in patients undergoing colorectal surgery, with a cutoff value lower than the one reported in the international literature. It is recommended to continue this line of research to obtain more precise estimates of both cutoff values and diagnostic efficacy indicators. This

will allow surgeons to have timely evidence to support their clinical decisions, whether for early discharge or closer in-hospital monitoring.

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Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

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

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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