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## International Journal of Surgery

journal homepage: [www.theijs.com](http://www.theijs.com)

## Original research

## Elevated serum C-reactive protein as a predictive factor for anastomotic leakage in colorectal surgery

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## ARTICLE INFO

## Article history:

Received 11 September 2011

Received in revised form

9 November 2011

Accepted 21 December 2011

Available online 28 December 2011

## Keywords:

Colorectal surgery

Anastomotic leakage

C-reactive protein

## ABSTRACT

**Background:** C-reactive protein (CRP) has been used as an indicator of postoperative complications in abdominal surgery. Its short half-life makes it a reliable marker of the systemic inflammatory response secondary to a surgical procedure or to the appearance of complications, rapidly returning to normal values with the recovery of the patient.

**Aim:** To demonstrate the value of sequential serum determinations of postoperative C-reactive protein (CRP) and white blood cell counts (WBC) in the identification of increased risk of anastomotic leakage after colorectal surgery.

**Methods:** We reviewed the daily postoperative serum CRP and white blood cell counts in 173 patients who underwent surgery for colorectal disease with anastomosis, between January 2008 and October 2009. Patients with anastomotic leakage (Group A,  $n = 24$ ) were compared to patients without leakage (Group B,  $n = 149$ ). Patients with ongoing infections before surgery or with acquired postoperative infections other than leakage were excluded. Mean pre- and postoperative values of CRP and WBC were compared.

**Results:** The diagnosis of anastomotic leakage was made between the 4th and 11th postoperative day (POD; mean 7th POD). The daily average values of serum CRP were significantly higher in group A starting at the 2nd POD and remained significantly elevated until the diagnosis of leakage ( $p = 0.003$ ). The cut-off value of 140 mg/L on the 3rd POD maximized the sensitivity (78%) and specificity (86%) of serum CRP in assessing the risk of leakage. Comparison of postoperative serum WBC values did not show any significant differences between the two groups until the 6th POD.

**Conclusion:** According to these results, an early and persistent elevation of CRP after colorectal surgery with anastomosis, is a marker of anastomotic leakage. A cut-off value  $> 140$  mg/L on POD3 maximizes sensitivity and specificity.

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## 1. Introduction

Anastomotic leakage is a serious complication after colorectal surgery, associated with increased postoperative morbidity and mortality, longer length of hospital stay and higher costs related to caregiving.<sup>1–4</sup> This complication is also an independent factor of poor prognosis in patients undergoing curative resection for colorectal cancer, contributing to local recurrence and decreased survival in these patients.<sup>5–8</sup>

There are multiple risk factors associated with anastomotic leakage, yet it is difficult to predict this complication in individual patients.<sup>9</sup>

Despite the increased understanding about risk factors for anastomotic leakage and improvement in surgical technique, anastomotic leakage remains an important complication and occurs without obvious cause in some patients with no known risk factors.<sup>9</sup>

The diagnosis of anastomotic leakage should be as early as possible in order to reduce its associated morbidity and mortality.<sup>10</sup> C-reactive protein (CRP), an acute phase protein synthesized by the liver, has been used as an indicator of postoperative complications in abdominal surgery.<sup>9,11–13</sup> Due to its short half-life (19 h), CRP is a reliable marker of systemic inflammatory response secondary to the surgical procedure or even a marker of complications, tending to normalize rapidly with the patient's recovery.<sup>13,14</sup> Recently, this

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**Table 1**

Characteristics of patients submitted to colorectal resection with primary anastomosis: Group A – with leakage;  $n = 24$ ; Group B – without leakage;  $n = 149$ .

	Group A	Group B	P
Mean age (years)	69.5	65.5	0.77
Gender			0.82
Male	13 (54.2%)	75 (50.3%)	
Female	11 (45.8%)	74 (49.7%)	
Disease			0.65
Cancer	17 (70.8%)	112 (75.2%)	
Inflammatory bowel disease	2 (8.3%)	6 (4.0%)	
Diverticular disease	0 (0.0%)	4 (2.7%)	
Other pathologies	5 (20.9%)	27 (18.1%)	
Surgical planning			0.36
Elective	22 (91.7%)	142 (95.3%)	
Emergency	2 (8.3%)	7 (4.7%)	
Surgical approach			0.08
Laparotomy	23 (95.8%)	119 (79.9%)	
Laparoscopy	1 (4.2%)	30 (20.1%)	
Type of resection			0.25
Right colon	6 (25.0%)	62 (41.6%)	
Left colon	12 (50.0%)	56 (37.6%)	
Rectum	4 (16.7%)	31 (20.8%)	
Total colectomy	2 (8.3%)	0 (0.0%)	
Average hospital stay (days)	29.5	11.7	<0.001
Postoperative mortality (%)	12.5	2.7	0.02

one of two groups according to the presence or absence of anastomotic leakage: with anastomotic leakage (Group A,  $n = 24$ ), without anastomotic leakage (Group B,  $n = 149$ ). Exclusion criteria for this study were age younger than 18 years, presence of a defunctioning stoma, ongoing infection before surgery or an acquired infection in the postoperative period other than leakage. Only patients with more than three postoperative determinations of CRP and serum WBC were included in this study. The two groups were compared according to the following characteristics: gender and average age of patients, underlying pathology, planning of intervention (elective vs. urgent), surgical approach (laparotomy vs. laparoscopy), type of resection, mean hospital stay, postoperative mortality, and mean values of serum CRP and WBC in the pre- and postoperative period. Serum CRP <3 mg/L and serum WBC < $11 \times 10^9/L$  were considered normal values.

Anastomotic leakage was diagnosed on the clinical signs of peritonitis and/or clinical evidence of free faecal fluid within the abdomen or emerging from the drain site. On clinical suspicion and whenever deemed necessary, the diagnosis was confirmed by abdominal and pelvic CT scan, using intravenous and anorectal contrast.

Differences between groups were evaluated based on the chi-square test for the dichotomic variables and on the Mann–Whitney test for the continuous variables.  $p$  Values < 0.05 were considered significant. The ROC (receiver operator characteristic) curves of CRP were used to determine the best cut-off values for anastomotic leakage. The ROC curves are a plot of the sensitivity (true positives) of the test against 1-specificity (false positives), for each threshold of the test (each CRP level). Each point on the ROC curve represents a particular pair of sensitivity and (1-) specificity for each determined threshold.

### 3. Results

There was no significant difference between the two groups regarding gender ( $p = 0.82$ ) and mean age ( $p = 0.77$ ) of patients, underlying disease ( $p = 0.65$ ), planning of intervention (elective vs. urgent,  $p = 0.36$ ), surgical approach (laparotomy vs. laparoscopy,  $p = 0.08$ ) and type of resection ( $p = 0.25$ ). Mean hospital stay was significantly higher in group A (29.5 vs. 11.7 days,  $p < 0.001$ ). Postoperative mortality was significantly higher in group A (12.5% vs. 2.7%,  $p = 0.02$ ) (Table 1).

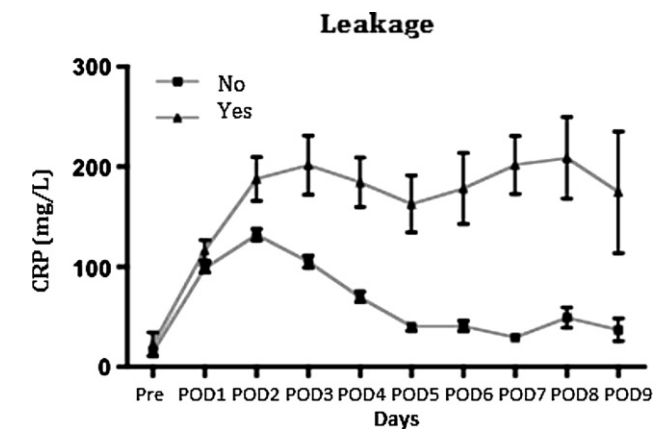
The diagnosis of anastomotic leakage was performed between the 4th and 11th POD (mean 7 days). The therapeutic options in patients with anastomotic leakage were: defunctioning stoma ( $n = 17$ ), drainage of abdominal and/or pelvic abscess ( $n = 4$ ) and medical treatment with intravenous antibiotics ( $n = 3$ ).

Mean preoperative values of serum CRP were not significantly different between patients operated for cancer and for benign colorectal disease.

There was no statistically significant difference in preoperative CRP between the two groups. In the postoperative period, however, it was clearly observed that from POD 2 onwards, the values of serum CRP were significantly higher in group A (Table 2). In group B, mean serum CRP reached a peak on POD 2, followed by a rapid decline thereafter (Fig. 1).

On POD 2, mean serum CRP was 187 mg/L in group A and 132 mg/L in group B ( $p = 0.001$ ). On POD 3, those values were 201 mg/L in group A and 105 mg/L in group B ( $p < 0.001$ ) (Table 2). Based on the evaluation of the ROC curves (Fig. 2), a cut-off value of 140 mg/L on POD 3 maximized the sensitivity (78%) and specificity (86%) of serum CRP in predicting the risk of leakage (Table 3).

The comparison of postoperative serum WBC values did not reveal any significant differences between groups until the POD 6 (Table 4, Fig. 3).



**Fig. 1.** Evolution of serum CRP in the pre- and postoperative period in patients with and without anastomotic leakage ( $p = 0.003$ ).

protein has been identified as an early predictor of abdominal septic complications after esophageal, pancreatic and rectal resection.<sup>9,13,15,16</sup>

This study aimed to evaluate the utility of sequential postoperative serum determinations of CRP and white blood cell counts (WBC) in the identification of the increased likelihood of anastomotic leakage after colorectal surgery.

## 2. Methods

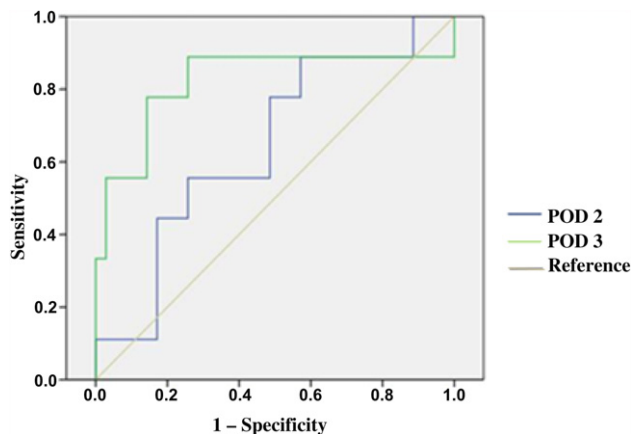
173 consecutive patients who underwent surgery for colorectal disease with primary anastomosis between January 2008 and October 2009, were assigned to

**Table 2**

Mean values of CRP in the pre- and postoperative periods (Group A – with leakage; Group B – without leakage).

	CRP (mg/L)									
	Pre	POD1	POD2	POD3	POD4	POD5	POD6	POD7	POD8	POD9
Group A	22	116	187	201	184	162	178	201	209	174
Group B	15	98	132	105	69	40	40	29	49	36
$p$	0.55	0.13	0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

POD: postoperative day.



**Fig. 2.** Receiver operator characteristic (ROC) curve for cut-off analysis of serum CRP on POD 2 and 3 in patients with anastomotic leakage.

**Table 3**

Sensitivity and specificity of serum CRP used as a cut-off in the identification of anastomotic leakage, calculated on postoperative days 2 and 3 (ROC analysis).

CRP (mg/L)	D2		D3	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
70	100	9	92	9
100	89	23	89	54
120	89	34	89	69
130	78	43	78	77
140	67	51	78	86
160	56	63	56	86

POD: postoperative day.

#### 4. Discussion

The incidence of anastomotic leakage after colorectal surgery varies between 1% and 40%, depending on the definition of leakage and on the type of resection performed,<sup>17,18</sup> being higher in extraperitoneal anastomosis.<sup>2</sup> This complication is associated with high mortality (4%–15%),<sup>19</sup> accounting for more than a third of hospital deaths after colorectal surgery.<sup>20</sup> In our study, the mortality observed in group A was 12.5% (3/24).

Therefore, the necessity of an early diagnosis of anastomotic leakage becomes clear. However, this diagnosis is not always easy in the early postoperative period because of the few clinical manifestations present at that time, which contributes to increased morbidity and mortality. The presence of respiratory, neurologic or abdominal symptoms, such as pain and bloating does not allow an early diagnosis of leakage, as these symptoms usually occur after POD 4.<sup>17,21</sup> However, according to some studies, these may be regarded as complications that precede by several days the

diagnosis of anastomotic leakage.<sup>17</sup> The presence of fever and abdominal hypersensitivity, as well as the time it takes to recover bowel function, do not specifically identify patients with anastomotic leakage.<sup>17,21</sup>

According to Alves et al.,<sup>1</sup> the delayed diagnosis (after POD 5) of anastomotic leakage is associated with a mortality rate of 18%, but minimal morbidity if diagnosed and treated before POD 5. Early detection of this complication is essential for timely institution of treatment, making early distinctive markers useful.

CRP is a protein synthesized almost exclusively by the hepatocytes as part of the acute phase response, stimulated by IL-6,  $\alpha$ -TNF and IL-1 $\beta$  originating at the site of inflammation.<sup>13</sup> This protein acts at the endothelial cells and on complement, thereby participating in the inflammatory cascade. Its short half-life (approximately 19 h), makes CRP a valuable marker for detecting disease activity, inflammatory response and postoperative recovery or the appearance of postoperative complications.<sup>13</sup>

Elevated preoperative CRP was considered an independent predictor of poor prognosis in patients with hepatocellular, pancreatic and colon cancer.<sup>13</sup> This inflammatory marker was also used in detecting pancreatic necrosis and in monitoring the severity of patients with acute pancreatitis.<sup>13</sup> Together with clinical signs and other inflammatory markers, CRP has been evaluated as an indicator of an unfavorable postoperative course, including surgical and non-surgical complications.<sup>13,21</sup> Recently, this protein was identified as an early predictor of septic complications after esophageal, pancreatic and rectal resection.<sup>21</sup> Given the potential complications associated with anastomotic leakage in colorectal surgery, particular emphasis has also been given to this marker in this area.

In this series, we observed that from the second postoperative day onwards, mean serum CRP was significantly higher in the group who developed leakage, and this marker remained elevated until the diagnosis of the complication. These results are consistent with others recently published<sup>9,13,21,22</sup> and seem to suggest that the early and sustained elevation of postoperative serum CRP may be used as a predictor of anastomotic leakage in patients in whom other infectious complications (respiratory, urinary tract and surgical wound infections) could be excluded.

The changes observed in postoperative CRP levels in patients who developed leakage demonstrate the presence of an inflammatory process and the activation of hepatic synthesis of CRP immediately after the surgical procedure (and before the occurrence of clinical manifestations). As the synthesis of this inflammatory marker is dependent only on the liver function and not compromised by any other organ failure, the rate of CRP production actually reflects the intensity of the inflammatory process.<sup>13</sup>

Tissue ischemia at the suture line of a leaking anastomosis seems to be responsible for the appearance of an intense and early inflammatory response, with subsequent increased synthesis of CRP.<sup>13</sup> The theory stating that poor tissue perfusion increases the risk of anastomotic complications could be demonstrated in several studies.<sup>23–27</sup> In a few animal and human models, the decrease in

**Table 4**

Mean values of white blood cells (WBC) in the pre- and postoperative periods (Group A – with leakage; Group B – without leakage).

	WBC ( $\times 10^9/L$ )									
	Pre	POD1	POD2	POD3	POD4	POD5	POD6	POD7	POD8	POD9
Group A	7.5	12.5	10.2	8.9	6.9	7.3	8.8	10.9	12.3	15.4
Group B	7.4	10.9	10.6	9.1	8.3	7.4	7.9	7.9	8.5	10.9
p	0.85	0.30	0.62	0.84	0.07	0.81	0.47	0.016	0.021	0.13

POD: postoperative day.

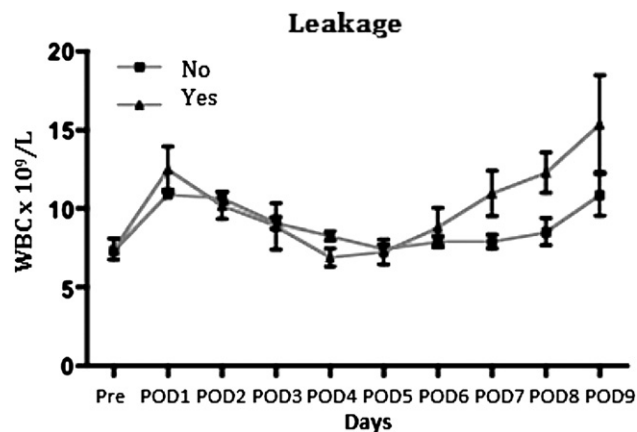


Fig. 3. Evolution of serum WBC count in the pre- and postoperative period in patients with and without anastomotic leakage ( $p = 0.4$ ).

anastomotic tissue oxygen tension that causes changes in the healing process could be demonstrated.<sup>24–26</sup> The decrease in anastomotic intramucosal pH level in the first 24 h after surgery is significantly associated with increased risk of dehiscence<sup>23</sup> and supports the theory that poor tissue perfusion of an anastomosis starts early and increases the risk of complications.

In patients undergoing anterior rectal resection, Welsh et al. concluded that serum CRP levels above 140 mg/L on POD 3 had a sensitivity of 80%, specificity of 81% and positive predictive value of 85.7% in the prediction of postoperative complications.<sup>13</sup> In our study, using the same cut-off on POD 3, we observed a sensitivity of 78% and a specificity of 86%.

Regarding the course of postoperative serum leukocytes, the mean values were significantly different between the two groups only on POD 7. Interestingly, POD 7 was also the median day for the diagnosis of leakage, so the white blood cell count is not as useful as the serum CRP which rises much earlier. Our findings are similar to those reported in several other studies.<sup>9,13,21</sup>

Recently procalcitonin has been studied as an even earlier marker of inflammatory changes than CRP, but tends to reflect the magnitude of the systemic inflammatory response in the first postoperative 12 h, particularly after extensive surgery, and has to be interpreted with caution.<sup>13</sup>

It is possible that some patients in group B might have had a subclinical anastomotic leakage. However, these patients usually do not require therapeutic intervention and our primary goal was to achieve an early identification of clinically significant complications, associated with increased morbidity and mortality, and that might benefit from earlier treatment.

## 5. Conclusion

According to the results of this study, early and persistent elevation of serum CRP (in particular a value exceeding 140 mg/L on POD 3) after colorectal surgery had a significant association with anastomotic leakage. Daily postoperative CRP measurements may therefore be useful in identifying those patients requiring careful clinical reassessment and possibly imaging to confirm or exclude anastomotic leakage, especially if other sources of infection (such as the wound, chest or urinary tract) can be exonerated.

## Conflict of interest statement

Nothing to declare.

## Sources of funding

Nothing to declare.

## Ethical approval

Nothing to declare.

## Author contribution

Please specify the contribution of each author to the paper, e.g. study design, data collections, data analysis, writing. Others, who have contributed in other ways should be listed as contributors.

Ana Beatriz Almeida – data collection, writing

Gil Faria – data analysis

Herculano Moreira – conception and study design, writing

João Pinto de Sousa – writing and review of the article

Pedro Correia da Silva – review of the article

José Costa Maia – review of the article

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