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ORIGINAL ARTICLE

C-reactive protein (CRP) trajectory as a predictor of anastomotic leakage after rectal cancer resection: A multicentre cohort study

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Abstract

Aim: This study aimed to identify whether CRP-trajectory measurement, including increase in CRP-level of 50 mg/l per day, is an accurate predictor of anastomotic leakage (AL) in patients undergoing resection for rectal cancer.

Methods: A prospective multicentre database was used. CRP was recorded on the first three postoperative days. Sensitivity, specificity, positive and negative predictive values, and area under the receiver operator characteristic (ROC) curve were used to analyse performances of CRP-trajectory measurements between postoperative day (POD) 1–2, 2–3, 1–3 and between any two days.

Results: A total of 271 patients were included in the study. AL was observed in 12.5% (34/271). Increase in CRP-level of 50 mg/l between POD 1–2 had a negative predictive value of 0.92, specificity of 0.71 and sensitivity of 0.57. Changes in CRP-levels between POD 2–3 were associated with a negative predictive value, specificity and sensitivity of 0.89, 0.93 and 0.26, respectively. Changes in CRP-levels between POD 1–3 showed a negative predictive value of 0.94, specificity of 0.76 and sensitivity of 0.65. In addition, 50 mg/l changes between any two days showed a negative predictive value of 0.92, specificity of 0.66 and sensitivity of 0.62. The area under the ROC curve for all CRP-trajectory measurements ranged from 0.593–0.700.

Conclusion: The present study showed that CRP-trajectory between postoperative days lacks predictive value to singularly rule out AL. Early and safe discharge in patients undergoing rectal surgery for adenocarcinoma cannot be guaranteed based on this parameter. High negative predictive values are mainly caused by the relatively low prevalence of AL.

KEYWORDS
anastomotic leakage, C-reactive protein, rectal surgery

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INTRODUCTION

Anastomotic leakage (AL) is one of the most severe complications after rectal resection. Leakage rates are still up to 19% and have not reduced over the last decade, despite improvement in surgical techniques [1–4]. Early detection of AL is crucial to reduce morbidity, mortality and to allow early and safe discharge. Nonetheless, the mean time to diagnose AL is still between six and 15 days after surgery, possibly caused by the lack of a valid diagnostic test to detect AL in early postoperative course [5, 6]. As a result, 20% of AL becomes clinically apparent after discharge [5, 6]. This delay in diagnosis is associated with prolonged hospital stay and increased mortality [7, 8].

C-reactive protein (CRP) is a well-known biomarker used clinically to detect infective complications during the postoperative course. Previous studies observed that CRP cutoff levels of 159 mg/l at postoperative day (POD) 3 or 132 mg/l at POD 4 could be useful in the diagnostic process [9–12]. However, the downside of these individual measured CRP levels is that these do not consider patient- and surgical characteristics, that is, BMI and extent of operative trauma which is associated with higher CRP release in general [13, 14]. To overcome these variations, some studies focused on day-to-day elevation of 50 mg/l in individual CRP levels postoperatively as so-called CRP trajectory measurement analysis. These trajectory measurements showed excellent predictive validity and negative predictive values for colorectal anastomotic leakage [15, 16].

Therefore, this study aimed to identify whether CRP-trajectory is an accurate predictor of AL on postoperative day 1, 2 and 3 in patients undergoing resection for rectal adenocarcinoma.

What does this paper add to the literature?

In contrast to previous literature, the present study showed that CRP-trajectory (increase in CRP level of 50 mg/l per day) measurement between postoperative days lacks predictive value to singularly rule out anastomotic leakage (AL). Early and safe discharge in patients undergoing rectal surgery for adenocarcinoma cannot be guaranteed based on this parameter. High negative predictive values are mainly caused by the relatively low prevalence of AL.

MATERIALS AND METHODS

Study design and participants

The present study was performed on an international, multicentre, prospectively collected database. A total of 10 hospitals in the Netherlands and Belgium participated. Patients who underwent a rectal resection between August 2015 and October 2017 were eligible for inclusion.

Patients more than 18 years of age who underwent an elective partial mesorectal excision (PME) or total mesorectal excision (TME) were included. In addition, a colorectal or coloanal anastomosis had to be constructed to be eligible. Pregnant women and patients with indications other than adenocarcinoma were excluded. Patients in whom serum CRP was not collected on more than two of three days after surgery were also excluded. The database followed-up until the first outpatient clinic visit after hospital discharge.

Data collection

Baseline patient characteristics (age, gender, body mass, bowel preparation, medication use, smoking, alcohol, previous abdominal surgery, American Society of Anaesthesiologists (ASA) score, indication for surgery, preoperative radiotherapy, preoperative chemotherapy, location of lesion) and surgical characteristics (surgical procedure, surgical technique, conversion, construction of anastomosis, configuration of anastomosis, diverting ileostomy) were prospectively collected. Registration of creation of anastomosis included “stapler” or “manual”. A hand-sewn technique with interrupted coloanal sutures was used to perform a manual anastomosis. Transanal TME was defined as part of a TME that was performed with transanal assistance, including a down-to-up TME using semi-rigid platforms with rigid instruments. Registered postoperative characteristics included CRP levels up to day three after operation, time to discharge, postoperative complications with their respective treatment strategies, readmission, reoperation, elective stoma reversal and mortality.

Anastomotic leakage

To optimize the comparison with previous studies a similar definition of AL was used [15, 16]. AL was defined as a clinically manifest insufficiency of the constructed anastomosis leading to a clinical state requiring reoperation or reintervention [15–17]. This included (percutaneous) drainage, lavage, endosponge therapy, transanal closure, resuturing of the anastomosis, an anastomosis re-do, disconnection of the anastomosis with construction of an end-colostomy, and construction of a protective stoma. Elective stoma reversal was not registered as reoperation. Patients treated with antibiotics only were included in the non-AL group. AL was confirmed by endoscopy, computed tomography (CT) scan with/without contrast enema or reoperation. Presacral abscesses (extravasation of colonic contrast visible on radiological imaging) and fistulas (only when communicating with anastomosis on CT scan) were also defined as AL.

CRP trajectory

The CRP trajectory included an increase in CRP-level of 50 mg/l per day as defined in previous studies [15, 16]. CRP was measured on the

first three postoperative days, and peripheral blood samples were analysed at the hospitals' clinical laboratories. Furthermore, the predictive value of individual CRP-levels was assessed.

A secondary analysis to assess predictive value of CRP trajectory was performed. Patients who developed AL and required antibiotics only were added to the AL group. This makes the definition of AL differ from the primary analysis which included those who required reoperation or reintervention only. The definition of AL in the secondary analysis could be defined as grade B and C by the Rahbari classification, which is a more commonly used definition [17].

Statistical analysis

Categorical data were presented as numbers with percentages. For comparison, the Pearson Chi-square test was used, and if group counts were <5 the Fisher's exact test was applied. Continuous variables are presented as mean (standard deviation) or median (interquartile range) depending on distribution. If normally distributed, the *t*-test was applied to compare means. If not, the nonparametric Mann-Whitney U test was used to compare medians. A two-sided *p*-value of <0.05 was considered as statistically significant.

Sensitivity, specificity, positive (PPV) and negative predictive values (NPV), and positive and negative diagnostic likelihood ratios were used to analyse performances of CRP-trajectory measurements between POD 1–2, 2–3,1–3 and between any two days.

The area under the receiver operating characteristic (ROC) curve was used to measure diagnostic accuracy of CRP-trajectory and CRP-levels. An area under the ROC curve of 1.0 indicates a perfect association and predictor for the outcome of interest. No association is considered when an area under the ROC curve of ≤0.5 is found. An area under the ROC curve of ≥0.75 is defined as clinically useful [18]. For CRP-levels, no predefined cutoff point was used and daily continuous variables of CRP were analysed. Statistical analyses were performed in SPSS v. (IBM Corp.).

RESULTS

Study population

Initially, a total of 292 patients were included in the database. 21 patients were excluded because CRP data was unavailable. In the end, 271 patients could be included for analysis.

Baseline and surgical characteristics

Baseline and surgical characteristics are provided in Table 1. Median time of follow-up was 27.0 days (IQR 16.0–34.0). Overall, 34 of 271 patients (12.5%) patients suffered from AL. Patients developing AL had a prolonged hospital stay (AL 21.0 [IQR 10.5–29.0] versus No-AL 6.0 [IQR 5.0–10.0] days, $p < 0.001$). In addition, 41 of 271 (15%) patients were readmitted to hospital and 38 of 271 (14%) patients underwent reoperation. Two patients died: one of AL and cause of death was unknown in the other patient.

Anastomotic leakage

The median time to diagnosis was 6.0 days (IQR 6.0–14.8). No major differences in patient or surgical characteristics were observed between those with and without AL (Table 1). Construction of a diverting ileostomy did not interfere with the prevalence of AL (AL 47.1% vs. non-AL 53.2%, $p = 0.505$). Neither did preoperative radiotherapy (AL 47.1% vs. non-AL 52.5%, $p = 0.550$) or the distance of lesion from the anal verge (AL 9.0 cm vs. non-AL 10.0 cm, $p = 0.293$). In four patients, AL was treated with antibiotics and in three patients no additional treatment was required.

CRP trajectory

An increase of CRP by 50 mg/l between POD 1 and POD 2 after surgery had a negative predictive value of 0.92, a specificity of 0.71 and sensitivity of 0.57. The changes in CRP-levels by 50 mg/l between POD 2 and POD 3 were associated with a negative predictive value, specificity and sensitivity of 0.89, 0.93 and 0.26, respectively. Changes in CRP-levels by 50 mg/l between POD 1 and 3 showed a negative predictive value of 0.94, specificity of 0.76 and sensitivity of 0.65. In addition, 50 mg/l changes between any two days showed a negative predictive value of 0.92, specificity of 0.66 and sensitivity of 0.62 (Tables 2a, 2b, 2c and 2d). Area under the ROC curve values for all CRP-trajectory measurements ranged from 0.593–0.700 (Table 3).

For secondary analyses, four patients in whom AL was managed with antibiotics only were added to the AL-group. The results in terms of sensitivity, specificity and negative predictive value minimally differed from primary analyses (Table 4).

The area under the ROC curve was assessed for daily CRP levels which improved from 0.562 on POD 1 to 0.790 on POD 3.

DISCUSSION

This international, multicentre, prospectively collected cohort study assessed the predictive value of 50 mg/l increase of CRP between postoperative days. It was found that sensitivity rates lacked adequacy, besides seemingly high negative predictive values which are mainly caused by the relatively low prevalence rates of AL. Furthermore, CRP trajectory measurement showed inadequate area under the curve and specificity rates and should not be used to either detect AL in an early stage or rule out AL to allow an early and safe discharge.

TABLE 1 Baseline characteristics

	Overall $n = 271$	Anastomotic leakage $n = 34$ (12.5%)	No anastomotic leakage $n = 237$ (87.5%)	Missing	*p*-value
Patient characteristics					
Age (years)	63.0 (57–0–70.0)	60.0 (53.75–67.75)	63.0 (57.0–71.0)	0	0.133
BMI	25.9 (23.5–28.8)	25.5 (24.1–29.2)	26.1 (23.4–28.8)	1	0.893
Gender				0	0.760
male	177 (65.3)	23 (67.6)	154 (65.0)		
Female	94 (34.7)	11 (32.4)	83 (35.0)		
ASA score				2	0.497
I	43 (16.0)	7 (20.6)	36 (15.3)		
II	169 (62.8)	23 (67.6)	146 (62.1)		
III	55 (20.4)	4 (11.8)	51 (21.7)		
IV	2 (0.7)	0 (0.0)	2 (0.9)		
Corticosteroids	16 (5.9)	3 (8.8)	13 (5.5)	1	0.435
NSAIDs	6 (2.2)	1 (2.9)	5 (2.1)	1	0.558
Bowel preparation	225 (91.1)	31 (91.2)	194 (91.1)	24	1.000
Smoking	36 (13.8)	7 (21.2)	29 (12.7)	10	0.184
Alcohol abuse	36 (13.8)	6 (17.6)	30 (13.2)	10	0.435
Previous abdominal surgery	92 (34.1)	10 (29.4)	82 (34.7)	1	
Clinical tumour stage				41	0.961
T1	12 (5.2)	1 (3.3)	11 (5.5)		
T2	69 (30.0)	9 (30.0)	60 (30.0)		
T3	132 (57.4)	19 (63.3)	113 (56.5)		
T4	17 (6.1)	1 (3.3)	16 (8.0)		
Clinical nodal stage				51	0.806
N0	94 (42.7)	13 (44.8)	81 (42.4)		
N1	76 (34.5)	8 (27.6)	68 (35.6)		
N2	49 (22.3)	8 (27.6)	41 (21.5)		
N3	0 (0.0)	0 (0.0)	1 (0.5)		
Preoperative/neoadjuvant radiotherapy	140 (51.9)	16 (47.1)	124 (52.5)	1	0.550
Type of radiotherapy				5	
Short course	56 (41.5)	6 (42.9)	50 (41.3)		
Long course	79 (58.5)	8 (57.1)	71 (58.7)		
Preoperative chemotherapy	91 (33.7)	12 (35.3)	79 (33.5)	1	0.834
Location of lesion from anal verge (cm)	10.0 (6.0–13.0)	9.0 (5.5–12.0)	10.0 (6.0–14.0)	15	0.293
Surgical characteristics					
Procedure				0	0.056
PME	58 (21.4)	3 (8.8)	55 (23.2)		
TME	213 (78.6)	31 (91.2)	182 (76.8)		
Surgical technique				0	0.782
Open	10 (3.7)	1 (2.9)	9 (3.8)		
Laparoscopic	156 (57.6)	18 (52.9)	138 (58.2)		
Transanal + laparoscopic	105 (38.7)	15 (44.1)	90 (38.0)		
Conversion	7 (4.5)	0 (0.0)	7 (5.1)	116	1.000
Construction of anastomosis				2	0.033

(Continues)

TABLE 1 (Continued)

	Overall $n = 271$	Anastomotic leakage $n = 34$ (12.5%)	No anastomotic leakage $n = 237$ (87.5%)	Missing	*p*-value
Manual	41 (15.2)	1 (2.9)	40 (17.0)		
Stapler	228 (84.8)	33 (97.1)	195 (83.0)		
Configuration of anastomosis				30	0.708
Side-to-side	4 (1.7)	0 (0.0)	4 (1.9)		
Side-to-end	163 (67.6)	25 (78.1)	138 (66.0)		
End-to-end	69 (28.6)	7 (21.9)	62 (29.7)		
End-to-side	5 (2.1)	0 (0.0)	5 (2.4)		
Diverting Ileostomy	142 (52.4)	16 (47.1)	126 (53.2)	0	0.505

Note: Data are mean (SD), n (%), or median (IQR); The American Society of Anaesthesiologists (ASA); Body mass index (BMI)

TABLE 2A Increase of >50 mg/l from postoperative day 1–2 for patients with and without AL

C-reactive protein trajectory increase >50 mg/l	Anastomotic leakage	No anastomotic leakage	Total
Yes	17	60	77
No	13	148	161
Total	30	208	238

Note: Sensitivity = 0.57; Specificity = 0.71; positive likelihood ratio = 2.00; negative likelihood ratio = 0.61; positive predictive value = 0.22; negative predictive value = 0.92; Missing data 33 (12.2) patients.

TABLE 2B Increase of >50 mg/l from postoperative day 2–3 for patients with and without AL

C-reactive protein trajectory increase >50 mg/l	Anastomotic leakage	No anastomotic leakage	Total
Yes	8	14	22
No	15	190	205
Total	23	204	227

Note: Sensitivity = 0.26; Specificity =0.93; positive likelihood ratio = 3.71; negative likelihood ratio = 0.80; positive predictive value = 0.36; negative predictive value = 0.89; Missing data 44 (16.2) patients.

TABLE 2C Increase of >50 mg/l from postoperative day 1–3 for patients with and without AL

C-reactive protein trajectory increase >50 mg/l	Anastomotic leakage	No anastomotic leakage	Total
Yes	15	56	71
No	9	159	168
Total	24	215	239

Note: Sensitivity = 0.65; Specificity = 0.76; positive likelihood ratio = 2.71; negative likelihood ratio = 0.46; positive predictive value = 0.28; negative predictive value = 0.94; Missing data 32 (11.8) patients.

TABLE 2D Increase of >50 mg/l between any 2 days for patients with and without AL

C-reactive protein trajectory increase >50 mg/l	Anastomotic leakage	No anastomotic leakage	Total
Yes	21	80	101
No	13	157	170
Total	34	237	271

Note: Sensitivity = 0.62; Specificity = 0.66; positive likelihood ratio = 1.84; negative likelihood ratio = 0.58; positive predictive value = 0.21; negative predictive value = 0.92; Missing data 0 patients.

Our data showed that if CRP levels did not increase 50 mg/l from POD 1 to POD 2 the chance of not developing AL is 92% (NPV 0.92). Question remains towards added value since leakage rate was 13%, which means that the chance of not developing leakage only went from 87% to 92% when 50 mg/l elevation of CRP was not observed.

In addition, a sensitivity of 0.57 means that in 13 of 30 (43%) patients still developed AL despite CRP not increasing 50 mg/l. Therefore, focusing on the negative predictive value only is not recommended and to rule out a potentially dangerous complication, sensitivity of a test is of utmost importance since the primary objective would be to identify all patients with anastomotic leakage.

Furthermore, an increase of 50 mg/l should not be used as a predictor for AL after rectal resection either as the predictive value was not sufficient with an area under the ROC curve of <0.75 and sensitivity/specificity varying from 0.26–0.93.

CRP is an acute phase protein and used as a biological marker for detecting inflammation. In most of the European hospitals, containing CRP levels for multiple postoperative days has become standard procedure in the rehabilitation process after surgery [19].

The value of CRP levels in abdominal surgery was investigated and cutoff points have been established over the last decade [11, 12]. However, these cutoff point have some limitations. It has been shown that the level of CRP production varies between patients depending on extent of trauma, blood loss, BMI and duration of

TABLE 3 Secondary analysis, diagnostic indices for ability of CRP trajectory >50 mg/l to predict anastomotic leakage including those treated with antibiotics

Postoperative day, increase of CRP by 50 > mg/L	Sensitivity	Specificity	PLR	NLR	PPV	NPV	Total patients	Missing
From day 1 to day 2	0.56	0.72	2.00	0.61	0.25	0.91	238	33 (12.2)
From day 2 to day 3	0.26	0.93	3.71	0.80	0.41	0.87	227	44 (16.2)
Between day 1 and day 3	0.63	0.76	2.63	0.49	0.31	0.92	239	32 (11.8)
Between any 2 days	0.61	0.67	1.82	0.91	0.22	0.91	271	0 (0)

Abbreviations: CRP, C-reactive protein; NPR, negative likelihood ratio; NPV, negative predictive value; PLR, positive likelihood ratio; PPV, positive predictive value.

TABLE 4 Predictive accuracy of daily CRP levels and CRP trajectory >50 mg/l

CRP-levels daily	AUC	95% CI	Total patients	Missing
Day 1	0.562	(0.487–0.703)	260	11 (4.1)
Day 2	0.700	(0.600–0.800)	247	24 (8.9)
Day 3	0.790	(0.710–0.870)	250	21 (7.7)
Postoperative day, increase of CRP by 50 > mg/l				
From day 1 to day 2	0.639	(0.529–0.749)	215 vs. 23	33 (12.2)
From day 2 to day 3	0.593	(0.476–0.711)	204 vs. 23	44 (16.2)
Between day 1 and day 3	0.700	(0.596–0.804)	215 vs. 24	32 (11.8)
Between any 2 days	0.642	(0.541–0.743)	237 vs. 34	0 (0)

Abbreviations: AUC, area under the ROC curve; CRP, C-reactive protein.

surgery [11, 20–22]. Therefore, one should be careful in generalizing these cutoff points without considering patient and surgical characteristics.

The main advantage of CRP trajectory measurement is the opportunity to analyse day-to-day elevation based on a patient specific baseline measurement set on POD 1 [13, 14].

Notably, it is of importance that patients with relatively high CRP levels over several days should be observed with caution despite absence of 50 mg/l elevation.

Furthermore, clinical evaluation of the attending doctor should not be underestimated and combining clinical assessment with CRP trajectory might further increase predictive value [10].

A leakage rate of 12.9% was observed, which is a representative number in rectal surgery [1–4]. To optimize the comparison to previous literature, we defined AL similar to previous studies [15, 16]. To broaden the outcomes a secondary analysis was performed considering patients who developed AL as defined initially in the present study and adding those who suffered a subclinical leakage only requiring therapeutic management. The outcomes were almost identical as the primary outcome. The secondary outcomes considers patients with AL defined as grade B and C by the Rhabari classification which is a more commonly used definition for AL after colorectal surgery [17]. The present study showed that CRP-trajectory theory could also be applied to this classification.

Previous studies analysing CRP-trajectory focused on colorectal surgery without differentiation between colon and rectum [15, 16]. Therefore, this is the first study that assesses predictive values of CRP-trajectory after rectal surgery. For the first three days after surgery our study found a NPV ranging from 0.89–0.94 compared to 0.96–0.97 and 0.99 for previous studies [15, 16]. The discrepancy in NPV is mainly caused by the difference in leakage rates that is, 5.6 and 4.9% for the previous studies compared to 12.5% in the present study [15, 16]. It should be considered that a prevalence of 4.9% of AL will lead to a NPV of 0.95 minimally as most patients did not develop anastomotic leakage. Smith et al. showed a sensitivity of 0.91 (POD 1–2) and Stephensen et al. found a sensitivity ranging from 0.17 (POD 4–5) to 0.85 (between any two days of 5 days) [15, 16]. The question remains whether a sensitivity of 0.85 is sufficient to allow safe discharge. Because this implicates that in the best case scenario, considering CRP analyses for five consecutive days, 15% of patients with anastomotic leakage would be missed [16].

Hence, high sensitivity rates are of importance to prevent discharge of patient with an increased risk of developing AL.

The strength of this study includes the prospectively collected database. Furthermore, only rectum resections for adenocarcinoma were included. This minimizes the heterogeneity which is inevitable when colon and rectum surgery is included in one cohort.

Despite the prospectively collected database, methodological design was in a retrospective way. A potential limitation of this study was that selection bias might be introduced by excluding patients with insufficient CRP measurements. In addition, CRP data collection was limited up to POD 3. Potentially, sensitivity might increase slightly by including POD 4 and 5. However, Stephensen et al. did not show adequate sensitivity rates between POD 3–4 and POD 4–5 with 0.20–0.17, respectively. Nonetheless, the present study showed that up to POD 3 substantial number of false negatives were identified and cautiousness in ruling out AL based on absence of 50 mg/l CRP elevation is warranted.

The present study showed that 50 mg/l increase of CRP between postoperative days lacks adequate sensitivity rates, besides seemingly high negative predictive values which are mainly caused by the relatively low prevalence rates of AL. Therefore, CRP-trajectory cannot be used singularly in ruling out AL and an early and safe discharge in patients undergoing rectum surgery for adenocarcinoma cannot be guaranteed in this cohort.

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CONFLICT OF INTEREST

Nothing to disclose.

AUTHOR CONTRIBUTIONS

Conceptualization and design: V.T. Hoek, C.L. Sparreboom, A. M. Wolthuis, A.G. Menon, G.J. Kleinrensink, A. D'Hoore, N. Komen, J.F. Lange. Methodology: V.T. Hoek, C.L. Sparreboom, A. M. Wolthuis, A.G. Menon, G.J. Kleinrensink, A. D'Hoore, N. Komen, J.F. Lange. Formal analysis: V.T. Hoek. Validation: C.L. Sparreboom, N. Komen. Writing - original draft: V.T. Hoek, C.L. Sparreboom. Writing - review & editing: A. M. Wolthuis, A.G. Menon, G.J. Kleinrensink, A. D'Hoore, N. Komen, J.F. Lange. All authors agree to be accountable for all aspects of the work and approve the final version submitted.

ETHICS STATEMENT

The initial APPEAL II study was approved by the medical ethics committee of the Erasmus MC University Medical Center in The Netherlands and of the University Hospital Leuven in Belgium and was registered a at www.ISRCTN.org (Study ID: 84052649). The Declaration of Helsinki guidelines were followed.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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