



The Value of Acute Phase Reactants in the Early Diagnosis of Complications following Colorectal Resection

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Abstract

Background: The aim was to investigate the rise of acute phase reactants; CRP, WBC, thrombocytes and cortisol, in patients with postoperative anastomotic leakage compared to patients with other infectious and noninfectious complications.

Methods: Prospectively collected data from two clinical trials, including 318 patients undergoing colorectal surgery, were analyzed. Blood was sampled every day until discharge or postoperative day (POD) 7 and complications were registered every day during admission and with 30 days of follow-up.

Results: Of 318 patients, 12 (3.7%) developed AL (anastomotic leakage) and 72 (22.6%) developed other infectious complications. No differences in basic characteristics were seen. CRP levels were significantly higher in patients with AL on POD 5 when compared to those who developed urinary tract infection and no complications. Patients with pneumonia had a significantly higher cortisol level at POD 3 compared to patients without complications. No significant difference was seen in the postoperative level of WBC and thrombocytes.

Conclusion: Based on the level of CRP and cortisol, it is possible at POD 5 and 3 to detect whether a patient is at risk of developing an infectious complication. With the possible exception of UTI, there is, however, no significant difference in the CRP level between AL and other infectious complications. The level of cortisol was significantly higher at POD 3 for the patients developing pneumonia compared to the uncomplicated group, but this showed to be of a low diagnostic accuracy and of no use to diagnose neither pneumonia nor AL.

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Introduction

Any surgical procedure is accompanied by the risk of postoperative complications, such as haemorrhage or infection. Anastomotic leakage (AL) following bowel resection is associated with increased postoperative morbidity and mortality, longer hospital stay and higher cost [1]. Following surgery on the colon or the rectum the prevalence varies from 1% up to 39% [2], and the variation is due to both a lack of standardized definitions, but also the site of the resection. Right sided colonic anastomoses have a lower risk of leakage than left sided anastomosis, with the highest risk of leakage when anastomosis is involving the rectum [3].

AL causes sepsis with possible fatal consequences for the patient. Early identification of patients with leakage is therefore of the highest priority. Multiple risk factors are associated with AL, such as male gender and low anastomosis [3,4] but the complication continues to occur without obvious reason in patients without known risk factors [1].

In the early stages AL have vague clinical symptoms and signs, and the diagnosis is therefore delayed - where the sepsis may be severe. The symptoms are abdominal pain and tenderness, continuing need for analgesia, intestinal paralysis, fever and if the patient has an intraabdominal drain, it may function with intestinal content [5] but at this point the patient will already be critical ill [6] and in serious need of surgical intervention.

Several studies have identified different factors that may help the surgeon in the early diagnosis of AL. It appears that the amplitude of the acute phase proteins, especially C-reactive protein (CRP), in the postoperative period, may be useful [1,2,4,6-14]. CRP is a nonspecific inflammatory biomarker with a short half-life (19h) and is valuable in the diagnosis of inflammation, infection, tissue damage

Table 1: Clinical characteristics of study population.

| Parameter | | With infectious complications N=84 | Without infectious complications N=234 | P value |
|---------------------------|---|---------------------------------------|---|---------|
| Sex | Women Men | 37 (44.1%) 47 (55.9%) | 108 (46.2%) 126 (53.8%) | 0.899 |
| Age, years | | 67.8 (65.4-70.3) | 65.9 (64.7-70.9) | 0.222 |
| Body Mass Index | | 25.8 (24.6-27.0) | 25.0 (24.4-27.8) | 0.276 |
| ASA | | 1.7 (1.6-1.8) | 1.7 (1.6-1.9) | 0.626 |
| Daily smoking (yes or no) | | 23(27.4%) | 68 (29.1%) | 0.718 |
| Alcohol (units/week) | | 6.5 (4.8-7.9) | 6.2 (5.2-8.8) | 0.286 |
| Diagnosis | Malign | 73 (86,9%) | 213 (91.1%) | 0.341 |
| Specific diagnosis | | | | 0.108 |
| | Duke's A | 11 (13.1%) | 26 (11.1%) | |
| | Duke's B | 32 (38.1%) | 81 (34.6%) | |
| | Duke's C | 25 (29.7%) | 57 (24.4%) | |
| | Duke's D | 0 (0.00%) | 17 (7.3%) | |
| | Other | 16 (19.1%) | 53 (22.6%) | |
| Surgery technique | | | | 0.168 |
| | Laparoscopic | 14 (16.7%) | 56 (23.9%) | |
| | Open | 70 (83.3%) | 178 (76.1%) | |
| Anastomosis | Ileo-colo or colo-colo/ Ileo-rectal or colo-rectal | 36 (42.9%) 26 (30.9%) | 119 (50.1%) 74 (31.6%) | 0.238 |
| Comorbidities | | | | 0.483 |
| | None | 33 (39.3%) | 102 (43,6%) | |
| | One comorbidities | 33 (39.3%) | 86 (36.8%) | |
| | Two comorbidities | 12 (14.3%) | 34 (14.5%) | |
| | Three or more comorbidities | 6 (7.1%) | 12 (5.1%) | |

and malignant tumors because it increases rapidly [14] and tends to normalize quickly after the patients recovery [1]. However, only a little is known about the ability for CRP to discriminate between AL and other postoperative infectious complications [7,8].

White blood cell level (WBC) may also be valuable, but has been a less convincing specific marker for AL in previous trials [1,8]. No previous studies have analyzed the relationship between postoperative serum cortisol or thrombocytes and the development of AL.

The aim of this study is to investigate whether the rise of acute phase reactants, CRP, WBC, thrombocytes and cortisol can be used to diagnose AL and other infectious complications early in the postoperative period, and if they can distinguish between AL and other infectious complications.

Materials and Methods

We did a cohort trial of prospectively collected data originating from two clinical randomized multi center trials with a total of 318 consecutive included patients, who had all undergone elective colorectal resection [15,16]. Both trials were approved by the ethic committees representing the participating hospitals ref. nr. KF-01-227/98 [15] and H-C-2007-0030 [16].

All the patients enrolled were ASA 1-3 and had no mental disorders, language problems, renal insufficiency, allergy towards Hydroxyethyl starch (HES), severe bleeding disorders disseminated cancer or other non-radically treated malignancies. Alcohol consumption was less than 35 drinks/week, they were adult and not pregnant or lactating women [15,16].

The patients had a resection of the colon or the rectum by either open [15,16] or laparoscopic [16] technique in accordance with good clinical practice. Antibiotic prophylaxis was given to all patients, and followed the routine of the department. The anesthesia and analgesic drugs were standardized to all patients. The basic characteristics of the patients were recorded.

Venous blood samples were collected from every patient preoperative and thereafter for 5 [16] or 7 [15] days postoperative or until discharge. Blood samples were analyzed with equivalent methods in each centre.

The two trials were both randomized trials testing the effect on different fluid regimens on the development of postoperative complications the primary outcome. However, no difference between the randomization groups was found for the level of CRP, WBC, thrombocytes or the serum cortisol. Also, patients were operated with two different techniques; open and laparoscopic, but no significant difference was seen within the postoperative level of the acute phase reactants. The data can therefore be pooled.

All complications were registered, not only the first appearing or the most severe.

The postoperative complications were in both trials defined by the same diagnostic criteria. AL was defined as presence of symptomatic leakage requiring reoperation and leakage of the rectum by blowout of the rectum with drainage of an abscess. Pneumonia was defined by clinical symptoms of the lower respiratory tract with crepitation and confirmed by pulmonary infiltration at chest radiography, urinary tract infections (UTI) by positive urine sediment analysis, wound

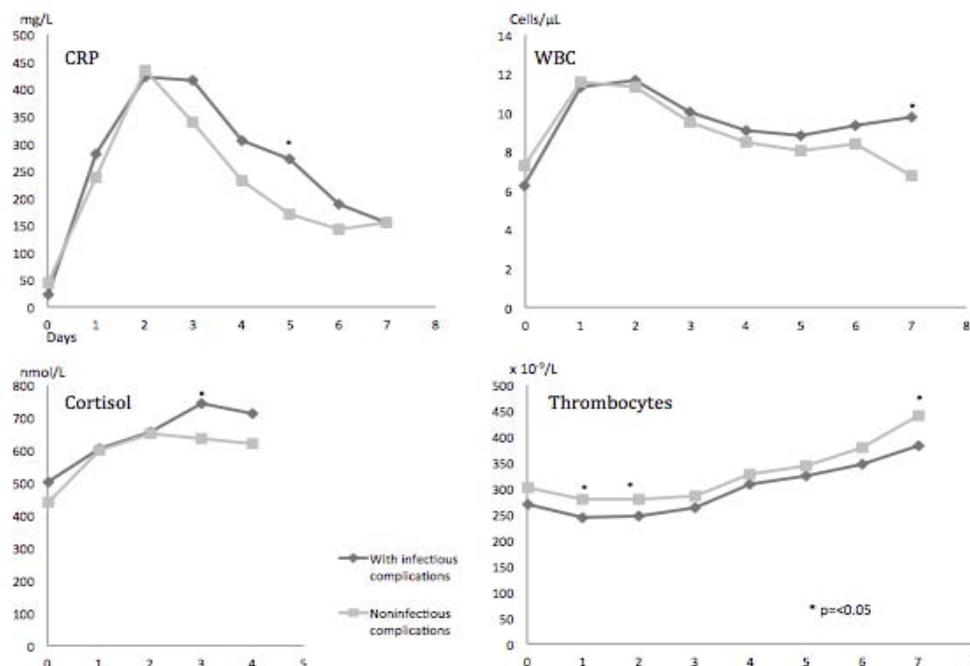


Figure 1: Distribution of acute phase reactants throughout the postoperative period for patients with infectious complications and noninfectious complications.

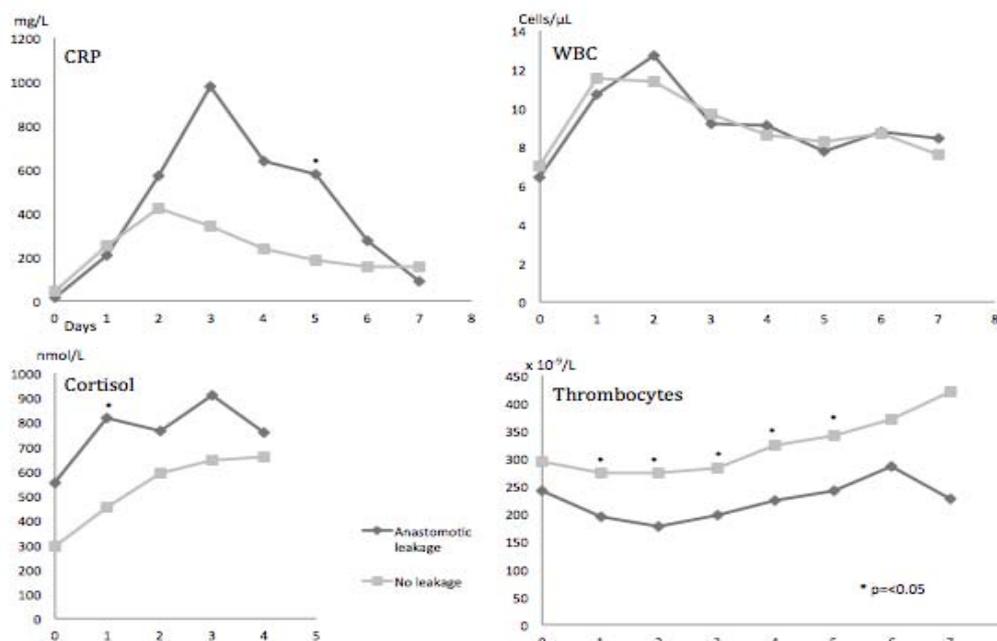


Figure 2: Distribution of acute phase reactants throughout the postoperative period for patients with anastomotic leakage and the remaining population.

infections (WI) by the presence of redness, warmth, swelling and pain and need of treatment with cleavage of the wound and dehiscence was pooled with the group of wound infections and defined by spontaneous rupture with or without emptying of pus [15,16]. Follow-up were 30 days.

To perform statistical analysis patients were divided into groups according to the presence or the absence of postoperative complications. Patients with infectious complications were grouped after above mentioned definitions, patients with noninfectious complications; cardiopulmonary, CNS-symptoms, renal involvement etc. were grouped together and patients with no complications were

put into one group.

Statistics

Statistical analyses were performed with SPSS 22.0 software. The mean value was used as a measure of the central tendency for continuous variables. Parametric statistics were used and data that did not meet the assumptions of parametric data was transformed using Log10. Independent samples t-test and One Way-ANOVA for each postoperative day was performed.

Power was calculated using univariate One-Way ANOVA for each postoperative day and a strong test was defined when >0.8 .

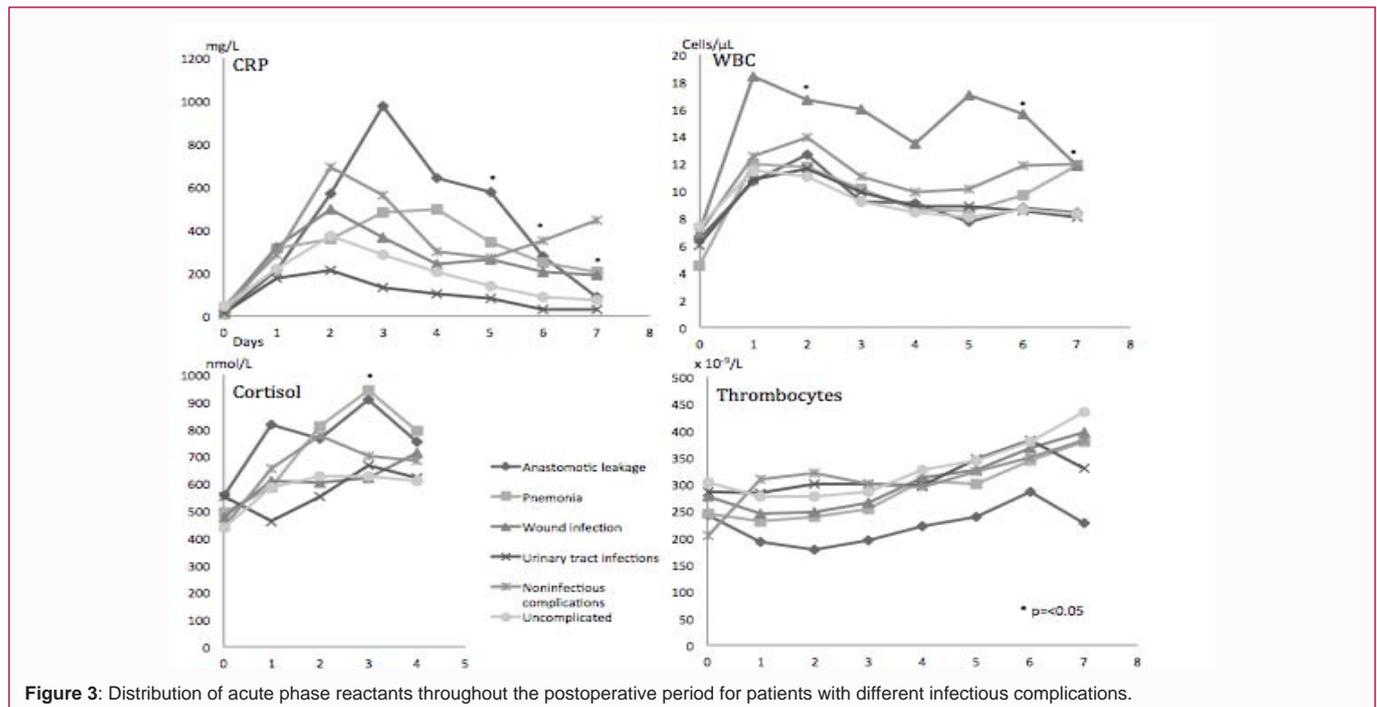


Figure 3: Distribution of acute phase reactants throughout the postoperative period for patients with different infectious complications.

Results reported is confirmed by Bonferroni's procedure controlling for Type I Error, and further confirmed by Hochberg's GT2 test, which is more powerful, when the sample sizes are different and homogeneity of variance is assumed [17].

Pearson's chi square test was used for comparing category variables and independent samples t-test for comparing continuous variables.

Line graphs were used to present CRP, WBC, thrombocytes and cortisol distribution throughout the postoperative period.

Positive predictive values (PPV), negative predictive value (NPV), sensitivity, specificity were calculated and the area under the curve was estimated using Receiver Operation Characteristic Curve calculated by non-parametric method.

Two-sided P-values were always computed and an effect was considered statistically significant at P-value = 0.05.

Results

Baseline, exclusion criteria and outcomes

318 patients were included in the trial, and underwent colorectal resection, 248 (78.0%) by open procedure and 70 (22.0%) by laparoscopic procedure. The vast majority 249 (78.3%) patients had colorectal cancer, classified after Dukes type A-D, and the remaining patients had other gastrointestinal diseases.

Clinical characteristics of the study population are shown in Table 1. Of the 318 patients included in the current study 84 (26.4%) developed infectious complications and 234 (73.6%) developed noninfectious complications or no complications within the postoperative period.

In the subgroup of patients who developed an infectious complication, AL was found in 12 (14.3%). Diagnosis of AL was clinically confirmed at a median of postoperative day (POD) 8 (median range 3-23). 12 (14.3%) patients developed pneumonia, 17 (20.2%) UTI and 40 (47.6%) WI postoperatively.

Six patients died within the 30 days follow up: four patients had noninfectious complications (AMI, ARDS, pulmonary emboli), one was diagnosed with AL and one was diagnosed with pneumonia postoperatively.

Postoperative course of CRP, WBC cortisol and thrombocytes

The relationship between circulating concentrations of the acute phase reactants and the development of infectious complications is shown in Figure 1-3. The following results have a mean observed power of >0.8 (0.795-0.928).

The distribution of the acute phase reactants in the group with infectious complications compared to the group with noninfectious complications is shown in Figure 1. A significant higher level of CRP was seen at POD 5 and the infectious group showed a significant higher level of cortisol preoperatively at POD 3. Thrombocytes were significantly lower until POD 2 and at POD 7. WBC showed no significant difference within the groups.

In Figure 2 the patients with AL is compared to the remaining patients with no leakage. The level of CRP for patients who developed AL peaked at POD 3 with a mean of 974.38 mg/l and decreased hereafter without normalizing within the observation period. Cortisol peaked, for the patients who developed AL, at POD 3 with 909.29 nmol/l. When comparing AL to the remaining study population, a significant higher level of CRP was seen at POD 5 (p=0.006) and a higher level of cortisol at POD 1 (p=0.004). Thrombocytes showed surprisingly to be lower until POD 5 (p< 0.05) and WBC showed no difference within the groups.

In Figure 3 the population is divided into groups according to their postoperative course and the distribution of the acute phase reactants is visualized. Comparing the level of CRP in AL to the other groups one by one, a significantly lower level was seen in the uncomplicated group at POD 5 (p=0.032) and in the group with UTI at POD 5 (p=0.049). No significant difference in the level of CRP was seen when comparing the other groups to each other one by one.

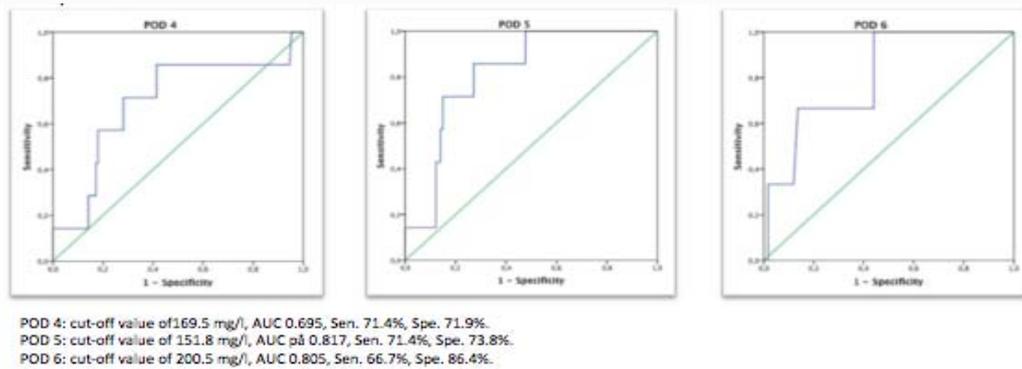


Figure 4: Diagnostic accuracy of CRP with regard to development of anastomotic leakage compared to no leakage after colorectal resection expressed by the ROC curve. Comparison of ROC curves for POD 4, POD 5 and POD 6 with respective area under the curve values of 0.690, 0.800 and 0.767.

Cortisol showed no significant difference within the groups. Only one significant difference was seen; between the patients who developed pneumonia and the uncomplicated cases at POD 3 ($p=0.027$).

For patients who developed AL WBC peaked at POD 4 with $9,14 \times 10^9/\mu\text{L}$, but showed no significant difference from the other complications. A higher level was seen in the patients who developed wound infection throughout the period, but this was insignificant. A significant difference was seen when comparing the noninfectious group to the uncomplicated at POD 2 ($p=0.004$), 6 ($p=0.002$) and 7 ($p < 0.001$). A significant difference was also seen between pneumonia and the uncomplicated group at POD 2 ($p=0.002$).

When comparing the level of thrombocytes in the patients with AL to other complications one by one no significant difference was found.

Diagnostic accuracy of CRP, WBC and cortisol

The diagnostic accuracy of CRP in order to distinguish AL from no leakage is represented by ROC curves, Figure 4. POD 5 showed to be most appropriate as a cut-off day, depending on the area under the curve, and a cut-off value of 191.5 mg/l was found. This cut-off value was associated with development of AL compared to no leakage and represented by an AUC of 0.800 (95%CI 0.662-0.915, $p=0.010$), PPV of 12%, NPV of 98% sensitivity of 71.4% and a specificity of 80.1%.

When comparing AL to the group without complications a cut-off value of 151.5 mg/l POD 5 was found. The cut-off value showed a PPV of 14%, NPV of 98%, sensitivity of 71.4% and specificity of 73.8% and a diagnostic accuracy of AUC of 0.817 (95%CI 0.699-0.935, $p=0.005$). The cut-off value at POD 5, associated with developing of AL compared to UTI, was found at a lower level at 109.0 mg/l, represented by a PPV of 67%, NPV of 91%, sensitivity of 85.7%, specificity of 76.9% and an AUC of 0.890 (95%CI 0.744-1.00, $p=0.005$).

ROC curves for cortisol showed that a cut-off value of 641.5 nmol/l on POD 3 was associated with development of pneumonia compared to the uncomplicated group. The cut-off value provided a PPV of 17%, NPV of 97%, sensitivity of 75.0% and specificity of 57.3% with a diagnostic accuracy of AUC 0.745 (95%CI 0.570-0.920, $p=0.005$). The ROC curves for WBC showed no diagnostic accuracy of use at any POD.

Discussion

Anastomotic leakage is one of the most severe complications

in gastrointestinal surgery. Postoperative mortality due to AL is as high as 22% and estimated to account for one third of all deaths after colorectal surgery [7]. In the literature, reported leaks occurred between the 4th and 28th postoperative day [14,18,19].

The aim of this study was to detect the diagnostic value of the acute phase reactants in early diagnostic of AL and other postoperative infectious complications, and their ability to distinguish between postoperative infectious complications.

CRP tends to increase spontaneously on second postoperative day when undergoing a surgical procedure and decrease hereafter if the postoperative period is uneventful [1,4,7,11], and has been suggested as a marker of AL, if other infectious complications (pneumonia, urinary tract infection and wound infections) can be excluded [1] It has been proposed, that CRP might be less useful for monitoring patients with the aim of detecting infectious complications before POD 3 [3], but after POD 3 it has been reported as a valuable negative predictive test [12,13]. This was confirmed by our study with a peak on POD 2 followed by a decline and a low CRP thereafter, when the patient had an uncomplicated course.

Previous studies have found WBC a less valuable diagnostic marker in gastrointestinal surgery, and little is known about the diagnostic accuracy of thrombocytes. It is known, that the hypothalamic-pituitary axis plays an important role in moderating the systemic inflammatory response to tissue injury, but no correlation between the level of cortisol and the clinical infections in patients after colorectal surgery has been reported in modern time [20].

In this study a higher mean level of CRP was seen in the uncomplicated cases compared to previous reports [1,7]. This could be explained by the surgical trauma and the blood loss, since CRP is known to be more than a marker of infection [21]. In addition CRP might play an important role in modulating the postoperative immune function in patients with colorectal cancer, and the presence of an elevated systemic inflammatory response in cancer patients has previously been described [20].

Several trials have been conducted with the aim of analyzing the value of the acute phase reactants, especially CRP, in the early phase of diagnosing AL. Previous studies have reported a significant correlation between postoperative increased CRP and the risk of developing AL compared to no leakage [1,2,4,14] and to other infectious complications [6–11].

The postoperative days that seem most appropriate for analysis

have been shown to be POD 3 [1,6,7,9,14] and POD 4 [8,10,11]. To add, the different trials have suggested very different cut-off values, varying from 123 mg/L to 200 mg/l [1,2,4,6–11,14]. None of the above mentioned trials found significant correlation between the level of white blood cell count and the risk of AL [1,2,8,9,15].

Only two of the above mentioned trials [2,7] focused on the other infectious complications. No significant difference between the complications was found. For all complications POD 3 and 4 were found to be most appropriate for analysis of CRP [7]. Thrombocytes were not significantly different in the complicated and uncomplicated groups, and WBC did not show any significant difference before POD 7 [7].

Previous trials have weaknesses such as heterogenic study populations, the CRP and WBC were analysed only every second day [10] and their designs were retrospective. In addition, there was no consensus in how to diagnose AL; one study defined AL as clinical presence of enteric contents within the drain [14], other studies accepted a diagnose based on imaging [1,4,10] while the remaining studies required reoperation with positive findings [2,6–9,11].

Strengths of present study are the cohort size and homogeneity of the population 78.3% of the patients were diagnosed with colorectal cancer classified by Duke's A-D stages preoperatively. The prospectively collected data, classification of postoperative complications by standardized definitions and 30 days of follow-up increase the strength of this study.

Weaknesses are the unequal number of patients in the subgroups and also not all blood samples were registered for every postoperative day - because some patients were discharged before the 7th postoperative day. Low and unequal rates of complications often limit statistical analysis, which is even more aggravated if not all parameters are available a measurement bias can therefore not be excluded. Besides this, some of the patients had multiple complications, which may have influenced their inflammatory response. The randomization of the different fluid regimes and the different operative techniques may represent a bias, though no significant differences were seen in level of the acute phase reactants within the groups.

The results of the present study are consistent with previous studies in case of increased postoperative level of CRP and the lack of diagnostic value of WBC In our study we clinically confirmed AL at a median of 8 days, which is consistent with previous reported leaks [14]. This study finds a cut-off day for CRP later in the postoperative period than earlier reported [1,2,4,6–11,14]. This difference could be accounted to a larger cohort size, varying thresholds for diagnosis of infectious complications and a higher mean level of CRP in the uncomplicated group, than what has been reported previously [1,7].

The ability of CRP and cortisol levels to distinguish between different infectious postoperative complications is not convincing, and our study shows that neither WBC nor thrombocytes were able to distinguish between the postoperative complications.

Conclusion

The results of the current study support the role of the acute phase reactants as a tool in the clinical assessment of postoperative patients: when a patient develops an infectious complication CRP, WBC, cortisol tends to rise, while the thrombocytes tend to be low. A significant difference in the level of CRP within patients who developed AL compared to patients who developed no leakage was

seen on POD 5. This supports the importance of clinical examination of the patient and intensive search for infectious complications if no postoperative reduction in CRP is seen. Our study finds no use of the acute phase reactants in discriminating between AL and other postoperative infectious complications. Cortisol tends to rise in patients developing pneumonia, but did not show significant diagnostic value.

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