
Accurate Prediction of Anastomotic Leakage after Colorectal Surgery Using Plasma Markers for Intestinal Damage and Inflammation



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BACKGROUND: Anastomotic leakage is a frequent and life-threatening complication after colorectal surgery. Early recognition of anastomotic leakage is critical to reduce mortality. Because early clinical and radiologic signs of anastomotic leakage are often nonspecific, there is an urgent need for accurate biomarkers. Markers of inflammation and gut damage might be suitable, as these are hallmarks of anastomotic leakage.

STUDY DESIGN: In 84 patients undergoing scheduled colorectal surgery with primary anastomosis, plasma samples were collected preoperatively and daily after surgery. Inflammatory markers, C-reactive protein; calprotectin; and interleukin-6, and intestinal damage markers, intestinal fatty acid binding protein; liver fatty acid binding protein; and ileal bile acid binding protein, were measured. Diagnostic accuracy of single markers or combinations of markers was analyzed by receiver operating characteristic curve analysis.

RESULTS: Anastomotic leakage developed in 8 patients, clinically diagnosed at median day 6. Calprotectin had best diagnostic accuracy to detect anastomotic leakage postoperatively. Highest diagnostic accuracy was obtained when C-reactive protein and calprotectin were combined at postoperative day 3, yielding sensitivity of 100%, specificity of 89%, positive likelihood ratio = 9.09 (95% CI, 4.34–16), and negative likelihood ratio = 0.00 (95% CI, 0.00–0.89) ($p < 0.001$). Interestingly, preoperative intestinal fatty acid binding protein levels predicted anastomotic leakage at a cutoff level of 882 pg/mL with sensitivity of 50%, specificity of 100%, positive likelihood ratio = infinite (95% CI, 4.01–infinite), and negative likelihood ratio = 0.50 (95% CI, 0.26–0.98) ($p < 0.0001$).

CONCLUSIONS: Preoperative intestinal fatty acid binding protein measurement can be used for anastomotic leakage risk assessment. In addition, the combination of C-reactive protein and calprotectin has high diagnostic accuracy. Implementation of these markers in daily practice deserves additional investigation. (J Am Coll Surg 2014;219:744–751. © 2014 by the American College of Surgeons)

Anastomotic leakage is a major challenge in patients undergoing colorectal surgery. Of 7,888 registered resections for colorectal cancer in the Netherlands in 2010, six hundred and twenty-four (8%) were complicated by

anastomotic leakage,¹ and in high-risk patients, incidence rates can increase to 18%.² Anastomotic leakage is associated with high morbidity,³ mortality,^{4–6} reoperation,⁷ and duration of hospitalization.⁶ In cancer, anastomotic leakage is related to reduced disease-specific survival and higher recurrence rates.^{7–10}

Delay in recognizing anastomotic leakage after colorectal surgery is associated with increased mortality.^{11,12} Early clinical presentation is heterogeneous and often nonspecific. Anastomotic leakage can present as peritonitis, localized fluid collections, or subclinical leakage detected by contrast radiology. In addition, nonspecific symptoms, including fever, absence of bowel action,

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Abbreviations and Acronyms

| | |
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| AUC | = area under the curve |
| CRP | = C-reactive protein |
| I-FABP | = intestinal fatty acid binding protein |
| L-FABP | = liver fatty acid binding protein |
| LR+ | = positive likelihood ratio |
| LR- | = negative likelihood ratio |
| OR | = odds ratio |
| POD | = postoperative day |
| ROC | = receiver operating characteristic |

and diarrhea, only become apparent on postoperative days (PODs) 4 to 7.¹¹ Abdominal CT scan, the current standard for diagnosis of anastomotic leakage, yields low sensitivity, which can delay the diagnosis and appropriate treatment of anastomotic leakage.¹³ There is an urgent need for accurate diagnostic markers of anastomotic leakage at an early stage after colorectal surgery to decrease delay of diagnosis and its unfavorable sequelae.

In this prospective cohort study, plasma markers of inflammation and intestinal damage in anastomotic leakage diagnosis were investigated. C-reactive protein (CRP) has been proposed to diagnose anastomotic leakage after colorectal surgery in a variety of studies on PODs 2 to 3.¹⁴⁻¹⁹ However, results are not unambiguously persuasive, showing diagnostic accuracy with about 70% to 80% sensitivity and specificity. Calprotectin, a heterodimeric peptide (36 kDa), constitutes about 60% of the cytosol proteins of neutrophils.²⁰ As a marker of neutrophil activation, calprotectin can be an interesting marker for exaggerated inflammation early in anastomotic leakage. The cytokine interleukin-6 is found to be up-regulated in peritoneal fluid during the first 3 postoperative days in patients that have anastomotic leakage develop,²¹ although the diagnostic accuracy of interleukin-6 measurement in plasma is still unknown. Intestinal fatty acid binding protein (I-FABP),²² ileal bile acid binding protein,²³ and liver fatty acid binding protein (L-FABP)²⁴ are proteins expressed in enterocytes and are well-known plasma markers of enterocyte damage. The presence of I-FABP is limited to mature enterocytes of the small and large intestine. Ileal bile acid binding protein is solely expressed in the ileum, and L-FABP is expressed in small and large intestine, liver, and kidney epithelial cells. These intestinal cell damage markers have never been investigated in the context of anastomotic leakage diagnosis.

In this prospective study, the diagnostic accuracy of plasma markers of inflammation and intestinal damage to predict anastomotic leakage after colorectal surgery were investigated.

METHODS**Patients**

Ninety consecutive patients scheduled to undergo colorectal surgery with primary anastomosis were prospectively enrolled at a single teaching hospital (Orbis Medical Center, Sittard, The Netherlands) between April 2011 and July 2013. Patients with inflammatory bowel disease were excluded because this could influence plasma levels of inflammatory biomarkers. None of the enrolled patients received NSAIDs. Nonsteroidal anti-inflammatory drugs have been omitted from routine analgesia in the enrolling hospital because these drugs are associated with increased leak rates.²⁵ In addition, no patients using corticosteroids were included because they could influence marker levels. All patients gave written informed consent and the study was approved by the medical ethical committee of Atrium-Orbis-Zuyd, Heerlen, The Netherlands. The study was conducted according to the revised version of the Declaration of Helsinki (October 2008, Seoul). Patient characteristics (ie, sex, age, BMI, length of hospital stay, and tumor location) and surgical characteristics (ie, approach, type, anastomotic technique, ostomy, operation time, and blood loss) were collected. A fast-track Enhanced Recovery After Surgery protocol was followed in all patients, according to which venous blood was routinely collected at PODs 1 and 3. Both laparoscopic and open resections were performed.

Definition of anastomotic leakage

Clinically relevant anastomotic leakage was defined as extraluminal presence of contrast fluid on contrast-enhanced CT scans and/or leakage when relaparotomy was performed, requiring reintervention. Indications for CT or relaparotomy were based on clinical presentation, including fever, tachycardia, tachypnea, low saturation, low urinary production, abdominal pain, and signs of ileus or gastric retention.

Blood sampling

Venous blood samples were taken at hospital admission (preoperative sample) and daily starting at the first postoperative day until discharge. Blood samples were immediately cooled on ice, centrifuged at 3,500 rotations per minute for 15 minutes, and plasma samples were stored at -80°C until batch analysis. All analyses were performed by one person (AvB) after inclusion of all patients, therefore, the treating clinicians were not aware of the values. The technician was not aware of patient characteristics.

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