Chapter 2

RISK FACTORS FOR ANASTOMOTIC LEAKAGE AND LEAK-RELATED MORTALITY AFTER COLONIC CANCER SURGERY IN A NATIONWIDE AUDIT

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ABSTRACT

BACKGROUND: Surgical resection with restoration of bowel continuity is the cornerstone of treatment for patients with colon cancer. The aim of this retrospective study is to identify risk factors for anastomotic leakage and subsequent mortality.

METHODS: Data were retrieved from the Dutch Surgical Colorectal Audit. Patients with primary colon cancer undergoing a colon resection with creation of an anastomosis in the Netherlands, between January 2009 to December 2011, were included. Outcomes were anastomotic leakage requiring a re-intervention and postoperative mortality following anastomotic leak.

RESULTS: Anastomotic leakage occurred in 7.5% of a total of 15,667 included patients. Multivariate analyses identified male gender, high American Society of Anesthesiologists classification, extensive tumour resection, emergency surgery and surgical resection types as transverse resection, left colectomy and subtotal colectomy, as independent risk factors for anastomotic leakage. Construction of a defunctioning stoma led to a lower leakage risk. There was a 4.1% overall mortality rate. Mortality was significantly higher in patients diagnosed with anastomotic leakage compared to patients without leakage (16.4 vs 3.1% P<0.001). Multivariate analyses showed a higher age, high American Society of Anesthesiologists classification, high Charlson score and emergency surgery, as independent risk factors for mortality after occurrence of anastomotic leakage.

CONCLUSION: Prediction of the development of anastomotic leakage is difficult for the individual patient. In elderly and patients with comorbidity there is a high mortality rate after anastomotic leakage development. This emphasizes the importance of accurate preoperative patient selection, and early leakage detection by close postoperative monitoring.
INTRODUCTION

Surgical resection is the cornerstone of treatment for colon cancer patients. Generally, restoration of bowel continuity with a primary anastomosis is pursued in uncomplicated colon resections. The most serious complication of colonic surgery with restoration of bowel continuity is anastomotic leakage (1), which is associated with the possible need for re-interventions, increased mortality (2,3) and possibly a worse oncological outcome (4,5). The reported incidence of anastomotic leakage in colonic anastomosis varies between 3 and 6.4%, depending on patient and tumour characteristics, definition criteria, site of the anastomosis and possibly by case-load per surgeon (6-9).

From the literature, several risk factors including comorbidity, higher American Society of Anesthesiologists classification, stage of disease, type of surgery, surgery in emergency setting and intraoperative complications, have been associated with anastomotic leakage (7,10-12). Furthermore, concentration of surgery in high-volume centers has been considered as a strategy to improve quality of care, surgical outcomes and mortality (13,14). Therefore, hospital procedural volume could also be a possible risk factor for anastomotic leakage. Although anastomotic leakage has long been subject of debate, the prediction for the risk of postoperative anastomotic leakage for the individual patient remains difficult.

It is relevant to study the occurrence of anastomotic leakage by means of a national database, since many publications are from expert centers not reflecting the incidence on national level. The Dutch Surgical Colorectal Audit (DSCA), a clinical outcome registry in which all Dutch hospitals participate, was initiated in 2009 to monitor and improve outcome of surgical care for colorectal cancer patients. The DSCA facilitates individual hospitals in quality improvement projects but is also used to identify treatment and outcome patterns for different patient groups. In the DSCA, anastomotic leakage after colorectal resections was appointed as an outcome indicator for surgical quality of care (15). In rectal cancer surgery, the practice of routinely defunctioning stoma constructing may play a large role in measuring this outcome and determining risk factors (16). Stoma construction may be of lesser importance in colon cancer resections. Moreover, among all colorectal surgical procedures, patients undergoing colon cancer resections may be considered a specifically vulnerable patient group, being at risk for morbidity and mortality because of advanced age and comorbidity (17). Risk factors for anastomotic leakage and related postoperative mortality have not yet been investigated in this particular group.
Chapter 2

The aim of the present study is to identify risk factors for anastomotic leakage after colon cancer resection and factors influencing mortality associated with anastomotic leakage with patient information from a national audit database.

Methods

Study Population
The dataset was retrieved from the DSCA, a web-based national database, in which all patients undergoing surgical resection for colorectal cancer were entered. Data on patient and tumour characteristics, diagnostics, treatment and outcome, were collected. The dataset contained data registered from 92 hospitals with a nearly 100% concordance on validation against the National Cancer Registry (NKR). In 2009, 89% of the Dutch hospitals participated, increasing to 99% in 2010 and 2011 (18). Medical ethics committee approval was not required for this study as all patients and hospital information in the DSCA was de-identified. Individual patient data was collected in the treating hospital and encrypted transferred to the database of the DSCA.

Inclusion and Exclusion Criteria
All Dutch patients who underwent a colon cancer resection in the Netherlands from January 2009 to December 2011, were included in this study. Rectal cancer patients, patients with multiple synchronous tumours, patients without a primary anastomosis or with an unknown surgical resection type, were excluded from analysis. Surgical resections were categorized in ileocecal resection, right colectomy, transverse resection, left colectomy, sigmoid resection and subtotal colectomy.

Outcome
Primary outcome measures were anastomotic leakage, defined as clinically significant leakage requiring surgical or radiological re-interventions, and mortality after anastomotic leakage, defined as in-hospital mortality or within 30 days after primary surgery.
Potential risk factors for postoperative complications including patient factors (age, gender, body mass index, Charlson comorbidity Score (19,20), American Society of Anesthesiologists classification, previous abdominal surgery), tumour factors (tumour stage, tumour location, preoperative tumour complications) and treatment factors (preoperative surgical procedures (stoma or other), type of surgical resection, emergency surgery, extensive resections, fashioning of a defunctioning stoma) were extracted from the database.
The aim of the present study is to identify risk factors for anastomotic leakage after colon cancer resection and factors influencing mortality associated with anastomotic leakage with patient information from a national audit database.

**METHODS**

**STUDY POPULATION**

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**OUTCOME**

Primary outcome measures were anastomotic leakage, defined as clinically significant leakage requiring surgical or radiological re-interventions, and mortality after anastomotic leakage, defined as in-hospital mortality or within 30 days after primary surgery. Potential risk factors for postoperative complications including patient factors (age, gender, body mass index, Charlson comorbidity Score (19,20), American Society of Anesthesiologists classification, previous abdominal surgery), tumour factors (tumour stage, tumour location, preoperative tumour complications) and treatment factors (preoperative surgical procedures (stoma or other), type of surgical resection, emergency surgery, extensive resections, fashioning of a defunctioning stoma) were extracted from the database.

Hospitals were categorized as low- (< 50), medium- (51 -100) or high-volume (>100) center, based on the number of surgically treated colon cancer patients per year for the years 2010 and 2011 (in 2009 not all hospitals completed registration). These categories reflect the present situation in the Netherlands with 50 percent of the clinics resecting between 50-100 colon cancer patients annually (21).

**STATISTICAL ANALYSIS**

Univariate analyses were performed to test the association between the above-mentioned patient, tumour, treatment and hospital factors and the occurrence of anastomotic leakage and mortality after the occurrence of postoperative anastomotic leakage, with a Chi-square test. Logistic multivariate analyses were performed to correct for possible confounders. A manual stepwise model was used for the variables with a p-value <0.05 in univariate analysis. Irrespective of statistical significance, clinically relevant variables were added to the statistical model. The variables ‘timing of surgery (elective/emergency)’ and ‘preoperative tumour complications’ were assumed to indicate the same clinical situation. To check for collinearity when both variables (‘timing of surgery (elective/emergency)’ and ‘preoperative tumour complications’) were incorporated in the model, the variance inflation factor was computed. To check our model, we repeated the multivariate analysis with outcome anastomotic leakage, first without the variable ‘preoperative tumour complications’ and including ‘time of surgery’. Thereafter we performed the same analysis conversely (including ‘preoperative tumour complications’ and ‘without timing of surgery’).

Results were listed in odds ratios and 95% confidence intervals. Analyses were considered to be statistically significant with a p-value <0.05. All data was analyzed using PASW Statistics, Release 20.0.0.1 (SPSS inc, Chicago, IL).

**RESULTS**

From 2009 to 2011 data from 27,259 patients were included in the database of the DSCA. After exclusion of 7,614 rectal cancer patients and 943 patients with multiple synchronous tumours, 18,702 colon cancer patients were eligible. After excluding another 2,581 patients without a primary anastomosis and 454 patients who underwent another surgical resection (total colectomy or unknown resection type), 15,667 colon cancer patients were included for analysis (Figure 1).
From all included patients there were 240 ileocecal resections, 7,788 right colectomies, 527 transverse resections, 1,601 left colectomies, 5,354 sigmoid resections and 157 subtotal colectomies (Table 1). Surgery was performed in 92 hospitals, with 15.3% of the patients being treated in a low-volume center, 55.5% in a medium-volume center and 29.2% in a high-volume center.

**Table 1. Patient-, tumour- and treatment characteristics of patients operated for colon cancer, and univariate analyses of possible variables associated with anastomotic leakage and with mortality after anastomotic leakage**

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Anastomotic Leakage</th>
<th>Mortality after Anastomotic Leakage</th>
</tr>
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<td>%</td>
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<tr>
<td><strong>Patient factors</strong></td>
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<td>Male</td>
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</tr>
<tr>
<td><strong>Age (years)</strong></td>
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<td>&lt;65</td>
<td>4,825</td>
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<td>65-80</td>
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<td>&gt;80</td>
<td>3,211</td>
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<tr>
<td><strong>Body mass index</strong></td>
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**Figure 1. Patient inclusion chart**
Table 1. Patient factors.

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<thead>
<tr>
<th>Gender</th>
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<th>Female</th>
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<td>80</td>
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<tr>
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ASA

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Charlson Score

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Previous abdominal surgery

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Tumour factors

Preoperative tumour complications

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Tumour Stage

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<td>376</td>
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<tr>
<td>8.5</td>
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<td>7.6</td>
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Tumour Location

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<tr>
<th>Caecum</th>
<th>Ascending colon</th>
<th>Hepatic Flexure</th>
<th>Transverse colon</th>
<th>Splenic Flexure</th>
<th>Descending colon</th>
<th>Sigmoid colon</th>
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<td>1.168</td>
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<td>22.4</td>
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<tr>
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<td>70</td>
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<tr>
<td>6.1</td>
<td>6.5</td>
<td>6.6</td>
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Treatment factors

Preoperative surgical procedures

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<th>Rate</th>
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<th>Rate</th>
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<tr>
<td>Other</td>
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<td>1.7</td>
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Surgical Resection

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<tr>
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<td>7.788</td>
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<td>527</td>
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</tr>
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<td>49.7</td>
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<td>10.2</td>
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Exclusion

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<td>176</td>
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<td>7.5</td>
<td>176</td>
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<tr>
<td>8.7</td>
<td>176</td>
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</tbody>
</table>
Chapter 2

Re-intervention following anastomotic leakage, a secondary stoma was created. In 805 patients (69%) requiring a surgical or radiological intervention, the incidence of anastomotic leakage was significantly higher after resection of the transverse colon, left colectomy and subtotal colectomy compared to right colectomy (mainly transverse resection, left colectomy and subtotal colectomy). There was no difference in leakage rate between the patients with and without defunctioning resections. From all anastomoses created after a sigmoid resection, 8.7% was deviated.

Table 1 shows the univariate analyses of possible risk factors for the occurrence of anastomotic leakage. In univariate analyses, patient factors associated with an increased leakage risk were male gender, higher American Society of Anesthesiologists classification and higher Charlson Score. Of the analyzed tumour factors, preoperative tumour complications (mostly tumour perforation or obstruction) and tumour location were associated with an increased risk of anastomotic leakage. Treatment factors associated with a higher leakage risk, were preoperative surgical interventions (e.g. preoperative construction of a defunctioning stoma), extensive resections (mainly transverse resection, left colectomy and subtotal colectomy) and hospital factors. The risk of anastomotic leakage in patients with extensive resections was 1.684-fold higher compared to right colectomy. Of all anastomoses created after a sigmoid resection, 653 (8.7%) were deviated.

Anastomotic leakage leading to re-intervention occurred in 1,176 patients (7.5%). The re-interventions were laparotomy (82.1%), laparoscopy (2.8%), radiological drainage (8.2%) or other interventions for example wound drainages or wound abscesses (6.9%). During the primary operation a defunctioning stoma was made in 606 patients (3.9%), usually after a sigmoid resection. From all anastomoses created after a sigmoid resection, 8.7% was deviated.

There was no difference in leakage rate between the patients with and without defunctioning stoma, 6.4 vs 7.5% respectively (P=0.308). Compared to the other types of resections, the incidence of anastomotic leakage was significantly higher after resection of the transverse colon, left colectomy and subtotal colectomy. In 805 patients (69%) requiring a surgical or radiological re-intervention following anastomotic leakage, a secondary stoma was created.

Risk factors for anastomotic leakage:

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procedures (e.g. preoperative construction of a defunctioning stoma), extensive resections (resections of other organs during surgery), emergency surgery, and type of resection, especially transverse resection, left colectomy and subtotal colectomy.

Multivariate analyses confirmed that male gender and a high American Society of Anesthesiologists classification remained independent risk factors for anastomotic leakage (table 2). Treatment factors that remained associated with a higher leakage risk were types of resection (mainly transverse resection, left colectomy and subtotal colectomy compared to right colectomy as reference group), extensive resections during surgery and surgery in emergency setting. On clinical grounds, the variable ‘defunctioning stoma’ was added to the model and adjusted data also showed less anastomotic leakage in patients with a defunctioning stoma (OR 0.682). In order to check for the presence of collinearity between the two clinical associated variables ‘timing of surgery (elective/emergency)’ and ‘preoperative tumour complications’, the variance inflation factor was computed. Results indicated no collinearity between these variables.

Repeated analysis of our multivariate model including the variable ‘preoperative complication’ instead of ‘time of surgery’ showed a significant higher risk for anastomotic leakage in patients with preoperative tumour complications as perforation or obstruction (OR 1.684 and 1.629 respectively).

**Table 2: Risk Factors for Anastomotic Leakage; Multivariate Analyses of All Patients Who Underwent Colonic Surgery with a Primary Colonic Anastomosis**

<table>
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<th>Patient Characteristics</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
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<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>Ref</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
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<td>1.219-1.558</td>
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<tr>
<td>I-II</td>
<td>Ref</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>0.805-1.814</td>
<td>0.361</td>
</tr>
<tr>
<td>Surgical Resection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right colectomy</td>
<td>Ref</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ileocecal resection</td>
<td>1.129</td>
<td>0.690-1.848</td>
<td>0.63</td>
</tr>
<tr>
<td>Transverse resection</td>
<td>1.689</td>
<td>1.262-2.261</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left colectomy</td>
<td>1.69</td>
<td>1.404-2.034</td>
<td>&lt;0.001</td>
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<tr>
<td>Sigmoid resection</td>
<td>1.276</td>
<td>1.109-1.468</td>
<td>0.001</td>
</tr>
<tr>
<td>Subtotal colectomy</td>
<td>2.281</td>
<td>1.421-3.661</td>
<td>0.001</td>
</tr>
<tr>
<td>Extensive resection</td>
<td>No</td>
<td>Ref</td>
<td></td>
</tr>
</tbody>
</table>
Mortality

Of all included patients, 648 (4.1%) died within 30 days postoperatively (3.4% after elective surgery vs 7.2% after emergency surgery P<0.001). In 193 of all deceased patients, anastomotic leakage was diagnosed postoperatively (29.8%). The mortality in patients with anastomotic leakage was significantly higher than in patients without clinical leakage (16.4 vs 3.1% P<0.001). There was no significant association between the number of patients treated yearly per hospital and mortality after postoperative anastomotic leakage (P=0.162).

Risk factors for mortality after anastomotic leakage

Univariate analyses revealed that patient factors associated with mortality after anastomotic leakage, were higher age, high American Society of Anesthesiologists classification and a high Charlson score (table 1). Moreover, surgery in emergency setting and type of surgical resection were associated with a higher risk. Especially patients undergoing a right colectomy, transverse resection or ileocecal resection, had high mortality rates after occurrence of anastomotic leakage (Figure 2). After adjustment for possible confounders, multivariate analyses showed that higher age, high American Society of Anesthesiologists classification, higher Charlson score and surgery in an emergency setting were independent risk factors for mortality in patients diagnosed with anastomotic leakage. Multivariate analysis also showed lower mortality associated with postoperative leakage after left colectomy compared to other surgical resection types (table 3).

### Table 1. Risk factors for mortality after anastomotic leakage

<table>
<thead>
<tr>
<th>Factor</th>
<th>Yes</th>
<th>No stoma</th>
<th>Defunctioning stoma</th>
<th>Elective</th>
<th>Emergency</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1,431</td>
<td>1,191-1,720</td>
<td>0,682</td>
<td>0,486-0,956</td>
<td>1,327</td>
<td>1,232-1,957</td>
</tr>
</tbody>
</table>

ASA = American Society of Anesthesiologists
Anastomotic leakage after colonic cancer surgery

Of all included patients, 648 (4.1%) died within 30 days postoperatively (3.4% after elective surgery vs 7.2% after emergency surgery, P<0.001). In 193 of all deceased patients, anastomotic leakage was diagnosed postoperatively (29.8%). The mortality in patients with anastomotic leakage was significantly higher than in patients without clinical leakage (16.4 vs 3.1%, P<0.001). There was no significant association between the number of patients treated yearly per hospital and mortality after postoperative anastomotic leakage (P=0.162).

### RISK FACTORS FOR MORTALITY AFTER ANASTOMOTIC LEAKAGE

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#### FIGURE 2. ANASTOMOTIC LEAKAGE AND SUBSEQUENT MORTALITY RATES OF THE DIFFERENT RISK FACTORS FOR MORTALITY AFTER ANASTOMOTIC LEAKAGE. RESULT OF UNIVARIATE ANALYSIS, WITH OVERALL RATES AS A REFERENCE.

#### TABLE 3. RISK FACTORS FOR MORTALITY AFTER ANASTOMOTIC LEAKAGE, MULTIVARIATE ANALYSES OF ALL PATIENTS DIAGNOSED WITH ANASTOMOTIC LEAKAGE, N=1,176

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>Ref</td>
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<tr>
<td>65-80</td>
<td>3.154</td>
<td>1.887-5.271</td>
<td>&lt;0.001</td>
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<td>&gt;80</td>
<td>5.162</td>
<td>2.976-8.956</td>
<td>&lt;0.001</td>
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<tr>
<td>ASA classification</td>
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<td></td>
</tr>
<tr>
<td>I-II</td>
<td>Ref</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III-IV</td>
<td>1.771</td>
<td>1.244-2.521</td>
<td>0.002</td>
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<tr>
<td>Unknown</td>
<td>1.891</td>
<td>0.479-7.473</td>
<td>0.363</td>
</tr>
<tr>
<td>Charlson Score</td>
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<tr>
<td>0</td>
<td>Ref</td>
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<td></td>
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<tr>
<td>I</td>
<td>1.764</td>
<td>1.156-2.693</td>
<td>0.008</td>
</tr>
<tr>
<td>≥II</td>
<td>2.23</td>
<td>1.474-3.373</td>
<td>&lt;0.001</td>
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<tr>
<td>Surgical resection</td>
<td></td>
<td></td>
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<tr>
<td>Right colectomy</td>
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<td></td>
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</tr>
<tr>
<td>Ileocecal resection</td>
<td>1.002</td>
<td>0.254-3.944</td>
<td>0.998</td>
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<td>Transverse resection</td>
<td>0.802</td>
<td>0.377-1.706</td>
<td>0.566</td>
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<tr>
<td>Left colectomy</td>
<td>0.538</td>
<td>0.313-0.924</td>
<td>0.025</td>
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<tr>
<td>Sigmoid resection</td>
<td>0.745</td>
<td>0.513-1.084</td>
<td>0.124</td>
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<tr>
<td>Subtotal colectomy</td>
<td>0.284</td>
<td>0.036-2.235</td>
<td>0.232</td>
</tr>
<tr>
<td>Time of surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elective</td>
<td>Ref</td>
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<td></td>
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<tr>
<td>Emergency</td>
<td>1.749</td>
<td>1.121-2.730</td>
<td>0.014</td>
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<tr>
<td>Unknown</td>
<td>0.778</td>
<td>0.386-1.568</td>
<td>0.483</td>
</tr>
</tbody>
</table>

ASA = American Society of Anesthesiologists.
DISCUSSION

The present study on risk factors for postoperative anastomotic leakage and mortality following colon resection with an anastomosis for colon cancer, showed a 7.5% leakage rate for all patients and an overall mortality rate of 4.1%, which was significantly higher for patients with anastomotic leakage than in those without (16.4 vs 3.1%).

The anastomotic leakage rate found in the present study is higher than the leakage rate reported in recent literature (3-6.4%) (6-8). This might be attributed to the complete registration in a clinical audit. Reported results from a nationwide study on anastomotic leakage in Denmark also showed a rather high percentage of 6.4% (7). Other publications with lower percentages usually are from dedicated centers. Adjusted data for confounding factors indicated male gender and a high American Society of Anesthesiologists classification as independent risk factors for anastomotic leakage, which is consistent with the literature (7,22,23). Other reported predictors for anastomotic leakage such as previous abdominal surgery (23) or high body mass index (3,24), could not be confirmed in our present analysis. Another well-known risk factor for anastomotic leakage is comorbidity (8,11,23), in the present study reflected in the Charlson score and American Society of Anesthesiologists classification. American Society of Anesthesiologists score remained a significant predictor of postoperative leakage in the present analyses, although both scores were associated with anastomotic leakage in univariate analyses.

Adjusted analysis in the present study indicated that treatment factors such as extensive resections and type of surgical resection were independent risk factors for anastomotic leakage. From the literature it is known that the incidence of leakage differs per tumour location and subsequent type of surgical resection. Right-sided colectomy is mentioned to be associated with a lower leakage rate compared to left-sided colectomy (3,25), and the occurrence of anastomotic leakage is higher after transversectomy (11). Our study confirms these statements. Vascularization of the anastomotic site may be explanatory in this as in a right-sided hemicolecctomy a wellvascularized ileal bowel loop is anastomosed to an adequately vascularized transverse colon loop. While in transverse or left colic resection, where the middle colic artery or inferior mesenteric artery is divided, vascularization of the anastomotic site might be compromised (26,27). Another explanation is the lack of full mobilization of one or both flexures. The poorer outcome after a transverse resection in the present study, emphasize the importance of careful surgical decision-making. In patients requiring a transverse resection, an extended colectomy could be a better alternative than a transverse resection.
Data of other known risk factors as loss of weight (25), intraoperative complications, operative time, blood loss and fecal contamination (8,11), were not available in our database.

The overall mortality of 4.1% in the present analysis is in range with population-based studies in the literature (3.0-7.4%) (6,28,29). The 16.4% mortality following anastomotic leakage is high and related to old age and comorbidity (Charlson and American Society of Anesthesiologists classification) as is also known from the literature (12.0-18.6%) (6,11). The mortality rate after anastomotic leakage was described to be much higher after a colon resection compared to patients undergoing a rectal resection (0.7-4%) (18,30,31). This dissimilarity might be explained by differences in anatomy. Anastomotic leakage after colon resection often results in a generalized peritonitis, compared to more local, extra peritoneal abscess formation after a rectum resection. For early detection of anastomotic leakage after rectal surgery, leakage scores are developed (28,32). It is of utmost interest to validate these scores also for colonic resections, since severity of the consequences of leakage from a colonic anastomosis is underestimated.

To reduce incidence of anastomotic leakage or its clinical sequelae, a defunctioning stoma could be constructed. In rectal anastomoses, temporary defunctioning stomas are made to reduce the clinical consequences of postoperative leakage (10,33). In our series most of the defunctioning stomas were constructed after a sigmoid resection. The present analysis showed no significant decrease of anastomotic leakage in univariate analysis, but after adjustments for patient and tumour characteristics, multivariate analysis showed a protective effect of a defunctioning stoma for postoperative anastomotic leakage. Apparently, there was a good patient selection for fecal diversion, based on the preoperative or intraoperative surgeons’ judgment concerning the risk for anastomotic leakage.

Emergency surgery is also considered as a risk factor for both anastomotic leakage (12,34) and postoperative mortality (12,29,35). A poor general condition and nutritional state, is associated with higher morbidity and mortality risks in these patients (35,36). In the present study, emergency surgery was an independent risk factor for both anastomotic and mortality following anastomotic leakage. The poor state of the patients and the consequences of bowel obstructions and perforations, such as dehydration, electrolyte imbalance, or intra-abdominal sepsis could account for poorer postoperative outcome in these patients (35,36). Our repeated multivariate analysis also confirmed that patients with preoperative complications as tumour perforation and obstruction had a higher odds for postoperative anastomotic leakage.
Furthermore, emergency surgery is frequently performed in evening and night shifts. Studies from different fields also reported worse postoperative outcome after surgeries performed in late hours. For example, it was shown that cesarean sections during night shifts are associated with longer operative time and higher maternal morbidity (37), and a study from orthopedic surgeons showed lower postoperative mortality in patients undergoing hip surgery in daytime (38). Higher mortality rates during the evening and night hours have also been described in coronary artery bypass surgery (39). Surgical procedures in late hours are sometimes performed by surgeons with a lower disease-specific case load. Some studies suggested that experience and caseload of the individual surgeon are predictors for postoperative mortality (9,40). Conflicting evidence exists about the association between hospital volume and postoperative outcomes in colorectal surgery. Some studies report a small, but significant decrease in postoperative mortality rate and an increase in overall and disease free survival after colon cancer resection in high volume centers compared to low volume centers (9,13,40). Others state that there is no difference in the postoperative complication rate (14), cancer recurrence or survival (41), between surgeries performed in high or low volume centers. A Cochrane review from 2012 on workload and surgeon’s specialty for outcome after colorectal cancer surgery showed a significant increase in overall five-year survival for patients operated in high volume centers. However, there was no difference in postoperative mortality after case-mix adjustments (42). The analysis in the present study did not show a significant association between the number of patients treated per center and the occurrence of anastomotic leakage or mortality after anastomotic leakage. This could be due to differences in cutoff points for caseload per hospital. Moreover, we only analyzed operative volume in colon cancer resections and not rectal cancer resections or surgery for benign conditions, which were included in the review. Unfortunately, our database does not contain data on caseload per surgeon.

The strength of this study is that results are based on a complete and large nationwide dataset, which contained registered data from all Dutch hospitals performing colorectal surgery. Validation of the registered data showed a high concordance against the national cancer registry. Therefore a valid analysis of colon cancer surgery in the Netherlands could be made. However, several limitations are worth mentioning. A somewhat heterogeneous study population is included for analysis. All colon cancer patients undergoing resection are included, including patients with stage IV disease, who may represent both curative and palliative resections and operations in emergency setting. Though the analysis of such a complete cohort leads to fair results, the heterogeneity is also accompanied by confounding factors and might lead to bias. In
order to control for bias we also performed a multivariate analysis model stratified for time of surgery (elective and emergency). The main results of the analysis for the subgroups did not differ significantly, compared to the presented results of the total study population (data not shown). Therefore, we used ‘time of surgery’ as possible risk factor for anastomotic leakage and subsequent mortality in our multivariate model. Another limitation of this dataset is that only patients treated for malignancy could be analyzed, while there are also benign indications for colon surgery, like diverticulitis, ulcerative colitis, Crohn’s disease or extensive endometriosis. Furthermore, little intraoperative information is recorded. The dataset contains no data regarding duration of operation, blood loss and surgical techniques. Intraoperative information could be a valuable contribution for the identification of risk factors for anastomotic leakage. The same also applies to information regarding caseload per surgeon.

Colon cancer resections are common surgical procedures. Although for the individual patient the exact mechanism leading to the development of anastomotic leakage is often unknown, and the clinical risk assessment by the operating surgeon is of low predictive value (43), it is important to understand that tumour and treatment factors may play an important role. Mortality rates after the occurrence of anastomotic leakage are high, and mainly determined by patient factors as high age and comorbidity. For all patients it is important to be operated soon after diagnosis, to prevent the occurrence of symptoms necessitating emergency surgery. This is particularly relevant for vulnerable patients with a substantially increased mortality risk. Furthermore, it is important, similar to rectal cancer surgery, to monitor patients postoperatively, according to standardized postoperative surveillance, perhaps incorporating colon leakage scores designed for left sided colorectal surgeries (28,32). Future research projects should be focused on further evaluation of these leakage scores in colon resections, and on continuous monitoring through clinical auditing.
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