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CHAPTER 8

Risk factors for anastomotic leakage and leak-related mortality after colon 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 colon cancer patients. The aim of this study is to identify risk factors for anastomotic leakage (AL) and subsequent mortality in colon cancer surgery.

Methods: Data were retrieved from the Dutch Surgical Colorectal Audit. Patients undergoing a colon cancer resection with creation of an anastomosis between January 2009 to December 2011, were included. Outcomes were AL requiring a re-intervention and post-operative mortality following AL.

Results: AL occurred in 7.5 per cent of a total of 15 667 included patients. Multivariate analyses identified male gender, high ASA 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. In a small group of patients a defunctioning stoma was created, leading to a lower leakage risk. Overall mortality was 4.1 per cent, and mortality was significantly higher in patients with AL compared to patients without leakage (16.4 vs 3.1 per cent P<0.001). Multivariate analyses showed a higher age, high ASA classification, high Charlson score and emergency surgery, as independent risk factors for mortality after AL. Moreover, the adjusted risk of mortality after AL was twice as high in right colectomy compared to left colectomy.

Conclusions: Elderly and patients with comorbidity have higher mortality after anastomotic leakage. Despite a lower adjusted risk of AL after right colectomy compared to left colectomy, the risk of mortality after AL was higher after right colectomies. Of importance is accurate preoperative patient selection, intensive postoperative

surveillance for AL and early and aggressive treatment of AL once suspected, especially in patients undergoing right colectomy.

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 (AL)[1], which is associated with the possible need for reinterventions, increased mortality[2,3] and possibly a worse oncological outcome[4,5]. The reported incidence of AL in colonic anastomosis varies between 3 and 6.4 per cent, depending on patient and tumor characteristics, definition criteria, site of the anastomosis and possibly by case-load per surgeon[6-9]. Several risk factors including co-morbidity, higher American Society of Anesthesiologists (ASA) classification, stage of disease, type of surgery, surgery in emergency setting and intraoperative complications have been associated with AL[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 AL. Although AL has long been subject of debate, the prediction for the risk of AL for the individual patient remains difficult. 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, AL after colorectal resections was appointed as an outcome indicator for surgical quality of care[15]. In rectal cancer surgery, the practice of routine construction of defunctioning stomas 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 AL and related postoperative mortality have not yet been investigated in this particular group. The aim of the present study is to identify risk factors for AL after colon cancer resection and factors influencing mortality associated with AL 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[18]. Data on patient and tumor characteristics, diagnostics, treatment and outcome, were collected. The dataset contained data registered from 92 hospitals with a high concordance on validation against the National Cancer Registry (NKR). In 2009, 89 per cent of the Dutch hospitals participated, increasing to 99 per cent in 2010 and 2011[19]. 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 tumors, 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 AL, defined as clinically significant AL requiring surgical or radiological re-interventions, and mortality after AL, 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 (BMI), Charlson co-morbidity Score[20,21], ASA classification, previous abdominal surgery), tumor factors (tumor stage, tumor location, preoperative tumor 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 performing between 50-100 colon cancer resections annually[22].

Statistical Analysis

Univariate analyses were performed to test the association between the above-mentioned patient, tumor, treatment and hospital factors and the occurrence of AL and mortality after AL, 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. Clinically relevant variables were added to the statistical model. The variables 'timing of surgery (elective/emergency)' and 'preoperative tumor complications' were assumed to indicate the same clinical situation. To check for colinearity when both variables ('timing of surgery (elective/emergency)' and 'preoperative tumor complications') were incorporated in the model, the variance inflation factor was computed. To check our model, we repeated the multivariate analysis with outcome AL, first without the variable 'preoperative tumor complications' and including 'time of surgery'. Thereafter we performed the same analysis conversely (including 'preoperative tumor complications' and without 'timing of surgery'). Results are reported as odds ratios (OR) and 95 per cent confidence intervals (95 per cent c.i.). Analyses were considered to be statistically significant with a 2-sided 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 (Figure 1). After exclusion of 7614 rectal cancer patients and 943 patients with multiple synchronous tumors, 18 702 colon cancer patients were eligible. After excluding another 2581 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 (tables 1-3). From all included patients there were 240 ileocecal resections, 7788 right colectomies, 527 transverse resections, 1601 left colectomies, 5354 sigmoid resections and 157 subtotal colectomies. Surgery was performed in 92 hospitals, with 15.3 per cent of

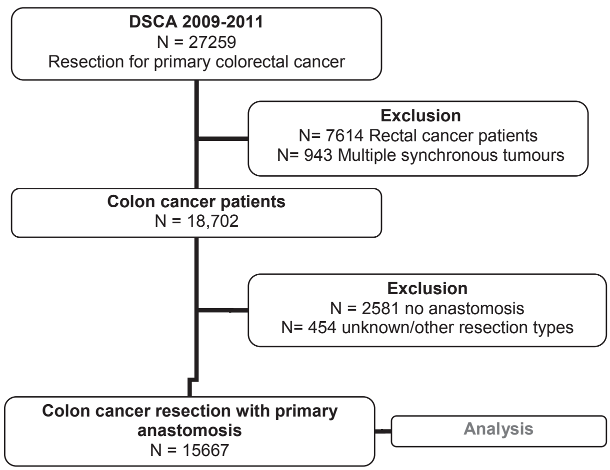

Figure 1: Patient inclusion chart.

Table 1: Patient characteristics of patients operated for colon cancer, and univariate analyses of possible variables associated with anastomotic leakage and with mortality after anastomotic leakage

Patient Characteristics			**Anastomotic Leakage**			**Mortality after AL**		
Patient factors	N	%	N	%	P-Value	N	%	P-Value
	15667		1176	7.5		145	15.7	
Gender								
Female	7605	48.5	477	6.3	<0.001	80	16.8	0.783
Male	8062	51.5	699	8.7		113	16.2	
Age (years)								
<65	4825	30.8	386	8.0	0.284	20	5.2	<0.001
65-80	7616	48.7	551	7.2		101	18.3	
>80	3211	20.5	239	7.4		72	30.1	
BMI								
<20	623	5.0	54	8.5	0.643	11	20.4	0.535
20-25	4922	39.0	366	7.4		59	16.1	
25-30	4986	49.5	389	7.8		54	13.9	
>30	2079	16.5	169	8.1		29	17.2	
ASA								
I -II	11638	74.3	822	7.1	<0.001	94	11.4	<0.001
III-IV	3713	23.7	249	9.2		96	28.2	
Unknown	316	2.0	10	4.4		3	21.4	
Charlson Score								
0	8335	53.2	583	7.0	0.032	56	9.6	<0.001
I	3579	22.8	285	8.0		59	20.7	
≥II	3753	24.0	308	8.2		78	25.3	
Previous abdominal surgery								
Yes	5309	33.9	425	8.0	0.090	81	19.1	0.065
No	10358	66.1	751	7.3		112	14.9	

BMI= Body Mass Index; ASA= American Society of Anesthesiologists

Table 2: Tumour characteristics and univariate analyses of possible variables associated with anastomotic leakage and with mortality after anastomotic leakage

Patient Characteristics			**Anastomotic Leakage**			**Mortality after AL**		
	N	%	N	%	P-Value	N	%	P-Value
Tumour factors								
Preoperative tumour complications								
None	11968	76.4	820	6.9	<0.001	130	15.9	0.100
Perforation	356	2.3	43	12.1		8	18.6	
Obstruction	1557	9.9	175	11.2		30	17.1	
Blood loss	951	6.1	65	6.8		6	9.2	
Other	835	5.3	73	8.7		19	26.0	
TNM Stage								
0	153	1.0	13	8.5	0.176	3	23.1	0.782
1	2811	17.9	180	6.4		31	17.2	
2	5769	36.8	461	8.0		67	14.5	
3	4918	31.4	376	7.6		67	17.8	
4	1784	11.4	131	7.3		23	17.6	
Unknown	232	1.5	15	6.5		2	13.3	
Tumor Location								
Caecum	3513	22.4	216	6.1	<0.001	45	20.8	0.225
Ascending colon	3085	19.7	199	6.5		35	17.6	
Hepatic Flexure	1064	6.8	70	6.6		15	21.4	
Transverse colon	1168	7.5	122	10.4		20	16.4	
Splenic Flexure	448	2.9	54	12.1		9	16.7	
Descending colon	887	5.7	93	10.5		11	11.8	
Sigmoid colon	5502	35.1	422	7.7		58	13.7	

Table 3: Treatment characteristics and univariate analyses of possible variables associated with anastomotic leakage and with mortality after anastomotic leakage. Hospital Volume: low: <50 patients per year, medium: 51-100 patients per year, high: >101 patients per year.

Patient Characteristics			Anastomotic Leakage			Mortality after AL		
	N	%	N	%	P-Value	N	%	P-Value
Treatment factors								
Preoperative surgical procedures								
None	15285	97.6	1133	7.4	0.015	188	16.6	0.383
Stoma formation	118	0.8	15	12.7		3	20.0	
Other	264	1.7	28	10.6		2	7.1	
Surgical Resection								
Right colectomy	7788	1.5	495	6.4	<0.001	101	20.4	0.029
Ileocecal resection	240	49.7	18	7.5		3	16.7	
Transverse resection	527	3.4	57	10.8		10	17.5	
Left colectomy	1601	10.2	172	10.7		20	11.6	
Sigmoid resection	5354	34.2	413	7.7		58	14.0	
Subtotal colectomy	157	1.0	21	13.4		1	4.8	
Time of surgery								
Elective	13139	83.9	925	7.0	<0.001	145	15.7	0.028
Emergency	1625	10.5	159	9.6		37	23.3	
Unknown	869	5.5	92	10.6		11	12.0	
Stoma								
No stoma	15061	96.1	1137	7.5	0.308	187	16.4	0.860
Defuncioning stoma	606	3.9	39	6.4		6	15.4	
Extensive resections								
No	14216	90.7	1025	7.2	<0.001	164	16.0	0.321
Yes	1451	9.3	151	10.4		29	19.2	
Hospital factors								
Hospital Volume								
Low	2680	17.1	180	6.7	0.225	38	21.1	0.162
Medium	8461	54.0	653	7.7		99	15.2	
High	4525	28.9	343	7.6		56	16.3	

the patients being treated in a low-volume center, 55.5 per cent in a medium-volume center and 29.2 per cent in a high-volume center.

Anastomotic leakage

AL leading to re-intervention occurred in 1176 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 AL 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 AL 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 for AL, a secondary stoma was created.

Risk Factors for anastomotic leakage

Tables 1-3 show univariate analyses of possible risk factors for the occurrence of AL. In univariate analyses, patient factors associated with an increased risk of AL were male gender, higher ASA classification and higher Charlson Score. Of the analyzed tumour factors, preoperative tumour complications (mostly tumor perforation or obstruction) and tumor location were associated with an increased risk of AL. Treatment factors associated with a higher risk of AL, were preoperative surgical 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

Table 4: Risk factors for anastomotic leakage; multivariate analyses of all patients who underwent colonic surgery with a primary colonic anastomosis

Characteristics		OR	95% CI	P-value
Gender	Female	Ref		
	Male	1,378	1,219-1,558	<0.001
ASA classification	I-II	Ref		
	III-IV	1,261	1.088-1.449	0.002
	Unknown	0,59	0,343-1,016	0.075
Charlson Score	0	Ref		
	I	1,11	0,954-1,291	0,178
	≥II	1,102	0,944-1,287	0,218
Preoperative surgical procedures	None	Ref		
	Stoma	1,52	0,873-2,647	0,139
	Other	1,209	0,805-1,814	0,361
Surgical Resection	Right colectomy	Ref		
	Ileocecal resection	1,129	0,690-1,848	0,63
	Transverse resection	1,689	1,262-2,261	<0.001
	Left colectomy	1,69	1,404-2,034	<0.001
	Sigmoid resection	1,276	1,109-1,468	0.001
	Subtotal colectomy	2,281	1,421-3,661	0.001
Extensive resection	No	Ref		
	Yes	1,431	1,191-1,720	<0,001
Stoma	No stoma	Ref		
	Defunctioning stoma	0,682	0,486-0,956	0,026
Time of surgery	Elective	Ref		
	Emergency	1,327	1,107-1,592	0,002
	Unknown	1,553	1,232-1,957	<0,001

ASA= American Society of Anesthesiologists a high ASA classification remained independent risk factors for AL (table 4). Treatment factors that remained associated with a higher AL 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 AL in patients with a defunctioning stoma (OR 0.682). In order to check for the presence of colinearity between the two clinical associated variables 'timing of surgery (elective/emergency)' and 'preoperative tumor complications', the variance inflation factor was computed. Results indicated no colinearity 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 AL in patients with preoperative tumor complications as perforation or obstruction (OR 1.684 and 1.629 respectively).

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, AL was diagnosed postoperatively (29.8 %). The mortality in patients with AL was significantly higher than in patients without AL (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 AL (P=0.162).

Risk Factors for mortality after anastomotic leakage

Univariate analyses revealed that patient factors associated with mortality after AL were higher age, high ASA classification and a high

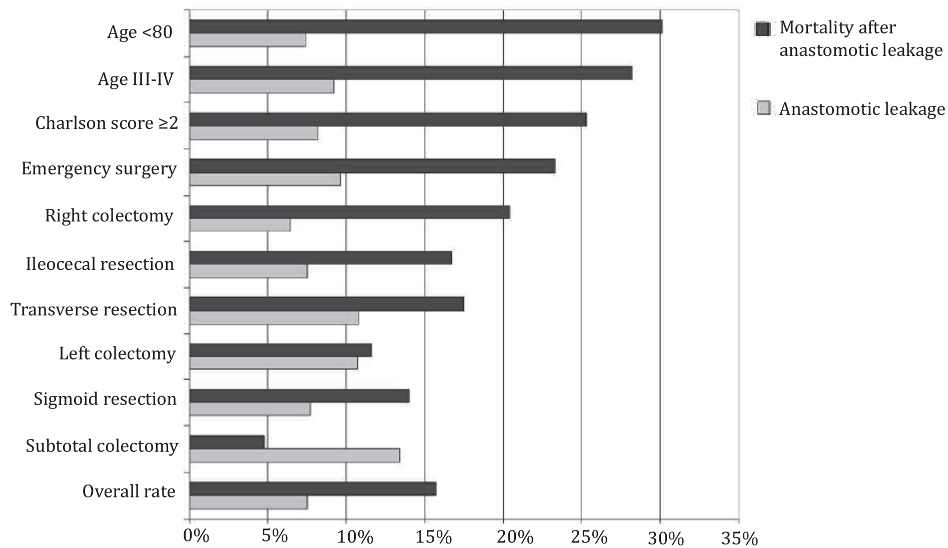

Figure 2: Anastomotic leakage and subsequent mortality rates of the different risk factors for mortality after anastomotic leakage. Results of univariate analysis, with overall rates as a reference.

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 AL (figure 2). After adjustment for possible confounders, multivariate analyses showed that higher age, high ASA classification, higher Charlson score and surgery in an emergency setting were independent risk factors for mortality in patients diagnosed with AL. Multivariate analysis also showed lower mortality associated with AL after left colectomy compared to other surgical resection types (table 5).

Table 5: Risk factors for mortality after anastomotic leakage, multivariate analyses of all patients diagnosed with anastomotic leakage

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

DISCUSSION

The present study on risk factors for anastomotic leakage and mortality following colon cancer resection with an anastomosis showed a 7.5 % leak rate for all patients. There was 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 leak rate found in the present study is higher than the leak 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 leak 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 high ASA classification as independent risk factors for anastomotic leakage, which is consistent with the literature[7,23,24]. Other reported predictors for anastomotic leakage such as previous abdominal surgery[24] or high BMI[3,25], could not be confirmed in our analysis. Another well-known risk factor for anastomotic leakage is co-morbidity[8,11,24], in the present study reflected in the Charlson score and ASA classification. Both scores were associated with anastomotic leakage in univariate analyses and ASA score remained a significant predictor for anastomotic leakage in multivariate 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. The incidence of anastomotic leakage differs per tumour location and subsequent type of surgical resection. Right-sided colectomy is associated with a lower leakage rate compared to left sided colectomy[3,26], and the occurrence of anastomotic leakage is higher after transversectomy[11]. Vascularization of the anastomotic site may be explanatory in this as in a right-sided hemicolectomy a well-vascularized 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[27,28]. 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[26], 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 per cent)[6,29,30]. The 16.4 per cent mortality following AL is high and related to old age and co-morbidity, as is also known from the literature (12.0-18.6 %)[6,11]. The mortality rate after AL is described to be much higher after a colon resection compared to patients undergoing a rectal resection (0.7-4 per cent)[9,31,32]. 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[29,33]. It is of upmost 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 anastomotic leakage[10,34]. 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 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[12,35] and postoperative mortality[12.30,36]. A poor general condition and nutritional state, is associated with higher morbidity and mortality risks in these patients[36,37]. In the present study, emergency surgery was an independent risk factor for both anastomotic leakage and mortality following anastomotic leakage. Our repeated multivariate analysis also confirmed that patients with preoperative complications as tumour perforation and obstruction had a higher odds for postoperative anastomotic leakage occurrence.

Emergency surgery is frequently performed in evening and night shifts. Studies from different medical fields also reported worse postoperative outcome after surgeries performed in late hours[38-40]. Surgical procedures in late hours are sometimes performed by surgeons with a lower disease-specific caseload. Some studies suggested that experience and caseload of the individual surgeon are predictors for postoperative mortality[9,41.] Unfortunately, our database does not contain individual data of surgeons.

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. 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[44], 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. Therefore, it is important to monitor patients postoperatively according to standardized postoperative surveillance, perhaps incorporating colon leakage scores designed for left sided colorectal surgeries[29,33]. 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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