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Adequate Timing of Diagnostic CT-Scan in Colorectal Patients Suffering From Anastomotic Leakage Can Improve Survival

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Abstract

Introduction: Anastomotic leakage (AL) is a feared complication of gastrointestinal surgery and has a high morbidity and mortality. Although several studies have investigated risk factors for AL and its diagnosis, little is known about treatment strategies for AL and the relationship between mortality and the time interval between the diagnosis of the AL and its treatment. The aims of this study were to gain insight into the influence of the time between diagnosis and treatment of AL and to investigate what interventions are used.

Methods: Retrospective study of patients surgically treated for AL between January 2008 and December 2012 in our hospital in the Netherlands.

Results: In total 2095 abdominal gastrointestinal surgeries were performed, 120 patients were included in our study (5.7%). Non-survivors were significantly older, had a higher CRP level on the day of reoperation, and had to wait longer for surgery after the diagnostic CT scan. A probit model described mortality risk as a function of age and time to corrective surgery.

Conclusion: Older age and longer delay between diagnostic CT and surgery for AL were associated with an increased mortality. This emphasizes the fact that urgent corrective surgery is necessary to decrease AL mortality, especially in the older patient. We advise to standardize the treatment of AL; this prevents delay and increases chances of survival.

Keywords: Anastomotic leakage; Mortality; Standardisation; Survival

Introduction

Anastomotic leakage (AL) is a feared complication of colorectal surgery and is associated with increased morbidity and mortality. Despite advances in surgical technology, the reported risk of 1–22% is still high [1,2]. AL results in prolonged hospitalization, re-operation, and permanent enterostomy. It also leads to an increased mortality (10–16%) in the immediate postoperative period and a decreased 5-year survival [3,4]. Despite numerous studies investigating the relationship between patient risk factors and AL and different surgical techniques, the pathogenesis of AL remains unclear. Early diagnosis of AL, preferably before it becomes symptomatic, is an important determinant of outcome [2,5]. The level of C-reactive protein (CRP) has been investigated as presymptomatic marker but there is as yet no consensus about its predictive value [6,7] . Clinical signs of a systemic inflammatory response, such as fever, ileus and pain, are common in patients with AL but have a low specificity [8,9].

A delay in managing peritonitis will increase the risk of exacerbation of the inflammatory response [10], but relatively little is known about the most appropriate treatment of AL [5,11]. In a study involving 137 surgeons the most important determinants of treatment for managing colorectal AL, whether to create an enterostomy or a new anastomosis, were the localization and presentation of the leak, and the patient's overall physical condition [12]. The aims of this study were to gain insight into which factors in the diagnosis and management of AL are of influence on mortality in our patient population. This can improve treatment strategies.

Methods

Patients

The medical records were reviewed of all patients who had undergone abdominal gastrointestinal surgery with construction of an anastomosis in the small or large bowel, and who were diagnosed with AL, within 30 days of primary surgery at our institute between January 2008 and December 2012. Only patients who were diagnosed with AL during surgery and who underwent surgical treatment of AL were included in the study. After inclusion, patient characteristics such as age, sex, C-reactive protein (CRP), leucocytes, time between request of CT-scan and the moment the scan was actually made, and the time between CT diagnosis of AL and corrective surgery (CT-time), duration of primary surgery, treatment of AL, American Society of Anesthesiologists (ASA)-score and whether initial surgery was acute or elective, were recorded. Exclusion criteria were; no anastomotic leakage during surgery, and time between CT-scan and corrective surgery >24 hours. We consider duration longer than 24 hours indicates not enough clinical and radiological evidence of AL to perform laparotomy.

Statistical analysis

Data are expressed as means ± standard deviation (SD). Differences between survivors and non-survivors were analyzed by using Students T-test for nominal values and logistics regression when data were binary. A two-tailed $p<0.05$ was considered statistically significant. Statistical analyses were performed using SPSS 21.0 (SPSS Inc., Chicago, IL), the probit analysis was performed using MATLAB R2013b (Mathworks Inc., Illinois, MA).

Probit analysis was used to determine the relationship between mortality and the time between the diagnostic CT scan (CT time) and surgical treatment of AL. Then the effect of age and time to corrective surgery in combination was tested: $Pr(death=1 \mid X) = \varphi(X'\beta)$, where mortality is a dependent variable, X is a matrix containing time from diagnostic CT to corrective surgery (CT time), and/or age, β is a vector containing the coefficients of the variables of interest, and finally φ is the cumulative distribution function. The full model containing CT time and age is: $Y^*=\alpha+\beta 1^*cttime+\beta 2^*age+\varepsilon$.

Results

Patients

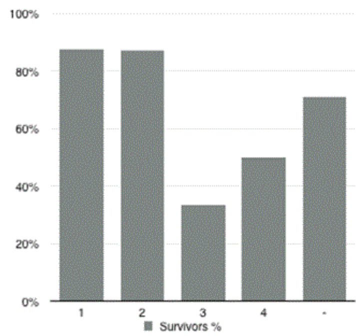
In our study period a total of 2095 gastrointestinal surgeries were performed at the Department of Surgery in our hospital in the Netherlands. Of this number 120 patients (5.7%) suffered from AL and were surgically treated. Patient characteristics are listed in Table 1.

Patients characteristics	**Total group**		**Survivors**		**Non-survivors**		
	n	%	n	%	n	%	
Patients	120	100	90	75	30	25	
Male	71	59.2	49	54	22	73.3	
Female	49	40.8	41	46	8	26.7	
ASA-classification							
1	8	6.7	7	7.8	1	3.3	
2	39	32.5	34	37.8	5	16.7	
3	6	5.0	2	2.2	4	13.3	
4	2	1.7	1	1.1	1	3.3	
unknown	65	54.2	46	51.1	19	63.3	
	Mean	SD	Mean	SD	Mean	SD	p-value
Average age population †	65.8	(± 13.0)	62.8	(± 12.4)	74.8	(± 10.4)	p<0.001
Leucocytes count on day of corrective surgery AL (n=104)	12.7	(± 6.9)	12.7	(± 6.7)	12.4	(± 7.4)	p=0.95
CRP count on day of corrective surgery AL (n=106) †	288	(± 127)	275	(± 130)	326	(± 116)	p=0.06

Table 1: Patient characteristics. Data presented as means and SD of the total patient population, survivors and non-survivors. † = p <0.05.

Thirty patients (25.0%) died within 30 days of primary surgery. The non-survivors were significantly older ($p<0.001$). There was a trend towards higher levels of CRP ($p=0.06$) on the day of reoperation for AL compared to the survivors.

Data on ASA-score was missing in 55% of the patients. More ASA 3 and 4 patients were seen in the deceased group. The percentage of unknown ASA-scores was equal in each subgroup. There was no correlation between ASA-score and mortality. Graph. 1 shows the survival in each ASA-classification subgroup.



Graph 1: Survival in each ASA-score subgroup.

Diagnostic CT scan was performed in 72 of 120 patients. The time between diagnostic CT and corrective surgery was significantly longer among the non-survivors compared to the survivors (465 ± 387 minutes vs. 311 ± 216 minutes, respectively; p<0.05). Time between diagnosis and re-operation could not be determined when AL was diagnosed without CT scan. The preoperative characteristics of patients developing AL are shown in Table 2.

Characteristics	Total group		Survivors		Non-survivors		p-value
	mean	SD	mean	SD	mean	SD	
Time between request CT and CT performed (min) (n=80)	298	(± 182)	313	(± 191)	243	(± 136)	p=0.22
Time between diagnostic CT and corrective surgery for AL (min) (n=72)	341	(± 263)	311	(± 216)	465	(± 387)	p<0.05
Time between request CT and corrective sugery for AL (min) (n=72)	650	(± 302)	634	(± 278)	711	(± 381)	p=0.35
Time between primary surgery and corrective surgery (days)	7	(± 5)	7	(± 5)	7	(± 5)	p=0.75
Duration of primary surgery (min)	104	(± 89)	98	(± 71)	121	(± 128)	p=0.21

Table 2: Surgery-dependent characteristics the total population, survivors and non-survivors. Data presented as means and SD of the total patient population, survivors and non-survivors. † = p <0.05.

Treatment of AL

Table 3 shows the surgical managements that were used for the treatment of AL. Enterostomy was used most often (80.8% of patients); construction of a new anastomosis was performed in 12.5%. There was no significant difference in the treatment of AL between surviving and non-surviving patients, and treatment was not correlated with mortality.

	Total group		Survivors		Non-survivors	
Treatments for AL	n	%	n	%	n	%
Total	120	100	90	75.0	30	25.0
Enterostomy	97	80.8	74	82.2	23	76.7
New anastomosis	15	12.5	11	12.2	4	13.3
Oversewing	7	5.8	4	4.4	3	10.0
Conservative	1	0.8	0	0.0	1	3.3
Drain placed near AL	1	0.8	0	0.0	1	3.3
Endosponge	1	0.8	1	1.1	0	0.0

Table 3: Treatment of anastomotic leakage (AL) of the total population.

In Table 4 the types of initial surgery and indications for surgery are shown. Most patients were treated for colon carcinoma. There were no significant differences in initial surgery and initial disease between survivors and non-survivors.

Type initial surgery	Total group	Survivors		Non-survivors	
		n	%	n	%
Total amount surgeries	120	90	75.0	30	25.0
Right-sided hemicolectomy	30	23	19.2	7	5.8
Left-sided hemicolectomy	19	14	11.7	5	4.2
Ileocaecal resection	7	4	3.3	3	2.5
Low anterior resection	10	7	5.8	3	2.5
Sigmoid resection	25	23	19.2	2	1.7
(Partial) small-bowel resection	14	8	6.7	6	5.0
Partial large resection (unknown location)	7	5	4.2	2	1.7
Continuity restoration after stoma	8	6	5.0	2	1.7
Underlying disease					
Total group	120	90	75.0	30	25.0
Carcinoma	75	59	65.6	16	53.3
Adhesion	5	3	3.3	2	6.7
Ischemia	11	6	6.7	5	16.7
Crohn's disease	2	2	2.2	0	0.0
Adenoma	2	1	1.1	1	3.3
(Perforated) diverticulitis	11	10	11.1	1	3.3
Volvulus	3	2	2.2	1	3.3
Appendicitis/appendectomy	5	4	4.4	1	3.3
No disease, restoring continuity	8	6	6.7	2	6.7

Table 4: Shown are initial surgery and disease where patients were treated for.

Mortality

Univariate and multivariate logistic regression revealed age and time between CT and surgery (CT time) to be significantly associated with mortality (p<0.05) (Table 5).

Variables	Univariate		Multivariate	
	ODDS	CI	ODDS	CI
Age	1.098 *	1.049 - 1.148	1.113 *	1.046 - 1.227
CT-time	1.002 *	1.000 - 1.004	1.003 *	1.000 - 1.005
CRP	1.004 **	1.000 - 1.007	0.999	0.993 - 1.006

Table 5: Univariate and multivariate logistic regression analyses of the relationship between age, delay between diagnostic computed tomography and corrective surgery (CT-time), and level of C-reactive protein (CRP), and mortality. OR = odds ratio, CI = 95 % confidence interval, * = p < 0.05, ** = 0.10 > p > 0.05.

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A probit analysis was performed to investigate the relationship between age and the time between diagnostic CT and surgical treatment of AL on mortality (Figure 1). The relative mortality risk for a 60-year-old patient doubled when surgery was performed 6 hours instead of 2 hours after AL diagnosis. If surgery was performed immediately after AL diagnosis, the mortality risk was twice as high in a 70-year-old patient compared to a 60-year-old patient.

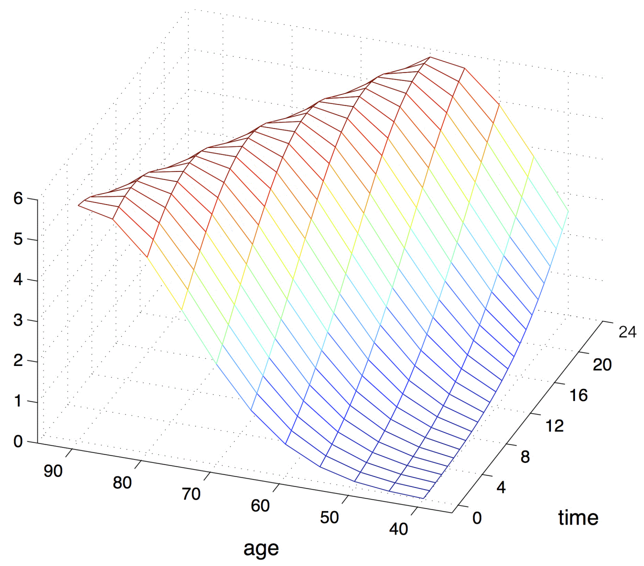

Figure 1: The effect on mortality of age plus delay between diagnostic CT and surgery for AL. Age in 5-year intervals (from 40 to 100) and time between diagnostic CT and corrective surgery in hours (from 0 to 24 hours). The y-axis shows the relative increase on mortality.

Discussion

This study shows that an older age and longer delay between diagnostic CT and surgery for AL are associated with an increased mortality. Therefore, it is of vital importance that surgery to manage AL should be performed as soon as possible after AL diagnosis, especially in older patients. Type of treatment for AL was not associated with mortality, and the mortality rate was similar to other studies [13,14].

This is the first study that endeavors to provide insight into mortality risk and age after AL. In our study, the non-survivors were significantly older than the survivors (p=<0.001). On probit analysis, we found that the mortality risk increased with age, i.e. the mortality risk in an 80-year-old patient was five times higher than in a 60-year-old patient. The association between time to corrective surgery and mortality risk was still present after correction for age.

The association between time to corrective surgery and mortality is probably due to the impact of prolonged exposure to bacterial peritonitis. Barnett et al. showed the effect of inflammation on mortality in mice with bacterial peritonitis. Interestingly, the inflammatory response was disturbed in the mice that died compared with the mice that survived, despite the bacterial count being the same [10]. We found that the non-survivors had a higher CRP level on the day of corrective surgery (p=0.06), which is consistent with the literature and may reflect the above-mentioned disturbed inflammatory response [15-17].

Unlike other studies, our study failed to show a correlation between comorbidity (ASA score >3) and mortality [18, 19]. This was probably due to the fact that the ASA score was lacking in a large amount of patients.

The second goal of this study was to evaluate the various procedures to correct AL. Most surgeons (79%) chose to create an enterostomy. We did not find the choice of treatment to correct AL to be associated to mortality. Even so, initial disease and type of initial surgery were also not associated with mortality. With its retrospective nature, this study was not designed to demonstrate any differences in mortality for different management of AL. Few studies have reported about the different treatment approaches that were used for the management of AL, but the preference for enterostomy is consistent with another study [18]. Fraccalviere et al. found that the creation of a loop stoma and salvage of the anastomosis were accompanied by a lower mortality and morbidity and higher stoma reversal compared with breaking down the initial anastomosis and creating a stoma [20].

Although the decision of treatment for each patient was made by skilled surgeons, the lack of protocol how to treat a patient with (suspected) AL is one of the problems we found. We assume the lack of standardization causes the delay we observed, and thereby the increased risk of mortality. The only protocol in the treatment of the patients in our hospital was post-operative admission to the ICU and intravenously Cefuroxime® and Metronidazole® for five days. The decisions towards surgical treatment are not standardized. Therefore it is hard to assume what steps in the post-operative time are of major influence. For example, as shown by den Dulk et al. standardizing the surveillance after surgery leads to less delay in diagnosis and better outcome after AL [21]. Since we show the effect of delay in the CT-surgery time, we suggest that a system should be developed to indicate the urgency of surgery for specific patients. For example, patients aged 70 years and older should undergo surgery within 2 hours of AL diagnosis, whereas younger patients should undergo surgery within 5 hours, of course taking into account the clinical condition of the individual patient.

One could also consider skipping the CT-scan, especially in patients with high clinical suspicion of AL. This will decrease delay in treatment and improve the chances of survival. The major problem with this approach is the increased chances of negative laparotomy and its negative impact on the patient's already poor condition. More research needs to be done to explore the benefits and risks of this approach.

Conclusion

In conclusion, this study shows no differences in mortality between different treatments of AL. It does show that older age and longer interval between diagnostic CT and corrective surgery for AL are associated with an increased mortality. These results stress the importance of early intervention when patients are diagnosed with or clinically suspected of AL, especially for the elderly patient. We were able to illustrate an exponential increase in mortality when surgery is delayed in older patients. This may help in developing a treatment logarithm for standardizing the management of AL, from the time of diagnosis up to type of surgery, including a maximum waiting time for different patient categories, depending on age, CRP level and comorbidity.

We stress the importance, for the severe complication AL is, to start standardizing treatment from suspicion until the actual intervention. In the future, prospective studies should be done to gain insight into the effects of standardization.

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