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Trends in risk factors of anastomotic leakage after colorectal cancer surgery (2011–2019): A Dutch population-based study

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Abstract

Aim: Anastomotic leakage (AL) after colon cancer (CC) and rectal cancer (RC) surgery often requires reintervention. Prevalence and morbidity may change over time with evolutions in treatment strategies and changes in patient characteristics. This nationwide study aimed to evaluate changes in the incidence, risk factors and mortality from AL during the past nine years.

Methods: Data of CC and RC resections with primary anastomosis were extracted from the Dutch Colorectal Audit (2011–2019). AL was registered if requiring reintervention. Three consecutive cohorts were compared using logistic regression analysis.

Results: Incidence of AL after CC surgery decreased from 6.6% in 2011–2013 to 4.8% in 2017–2019 and increased from 8.6% to 11.9% after RC surgery. In 2011–2013, male sex, ASA ≥ 3 , (y)pT3–4, neoadjuvant therapy, emergency surgery and multivisceral resection were identified as risk factors for AL after CC surgery. In 2017–2019, only male sex and ASA ≥ 3 were risk factors for AL. For RC patients, male sex and neoadjuvant therapy were a risk factor for AL in 2011–2013. In 2017–2019, transanal approach was also a risk factor for AL. Postoperative mortality rate after AL was 12% (CC) and 2% (RC) in 2017–2019, without significant changes over time.

Conclusion: Contradictory trends in incidence and mortality for AL were observed among CC and RC surgery with changing risk factors over the past 9 years. High mortality after AL is only observed after CC surgery and remains unchanged. Continued efforts should be made to improve early detection and treatment of AL for these patients.

KEYWORDS

anastomotic leakage, colorectal cancer, risk factor

INTRODUCTION

Colorectal cancer (CRC) is the fourth most common cancer worldwide [1]. The cornerstone of CRC treatment is surgical resection

with tumour removal and restoring continuity by constructing an anastomosis. Anastomotic leakage (AL) is a feared postoperative complication and the incidence varies between 1% and 20% [2–4]. AL often requires reintervention and is associated with prolonged

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hospitalization, severe morbidity and increased mortality rates [5–8].

Over the years, multiple (surgical) treatment strategies have evolved that might have influenced the incidence, risk factors and clinical impact of AL. Traditionally, CRC was resected using midline laparotomy, but more recently a shift was made towards minimally invasive surgery, which led to shorter hospitalisation, faster postoperative recovery and decreased mortality rates [9, 10]. In addition, the construction of a defunctioning ileostomy to prevent complications from AL after TME surgery has been under debate. Although it decreases the severity of AL, there are evident disadvantages and the preventive effect of defunctioning stomas is ambiguous [9–13]. As a consequence, in the Netherlands, defunctioning stoma construction after RC resection decreased from 51.3% in 2011 to 40% in 2016 [14]. Concomitantly, the number of patients with a primary anastomosis increased as a result of the decline in Hartmann's procedures [14]. Another modification in the treatment strategy of RC patients was the use of neoadjuvant radiotherapy. Previously, 80% of the Dutch patients were irradiated preoperatively. Despite these high radiation rates, local recurrence rates were comparable to European countries using less preoperative radiation [15, 16]. Therefore, the national guidelines were revised and recommended more restrictive use of neoadjuvant radiotherapy. A recent study showed that as a result a decrease in radiotherapy was observed in the Netherlands while maintaining similar local recurrence rates [17]. With the introduction of the CRC screening program in 2014, patient characteristics have also changed. Screen-detected patients were younger, had fewer comorbidities, and were associated with lower risk of postoperative complications [18].

The majority of the previously published risk factor studies included patients that had been operated upon more than a decade ago. Given the numerous changes in CRC care that might have affected the occurrence and consequences of AL, this study aimed to update the incidence, risk profile, and mortality from AL requiring reintervention during the period 2011–2019 based on data from the Dutch Colorectal Audit (DCRA).

METHODS

Data was retrieved from the DCRA, a nationwide audit that annually collects data on patient, tumour, and treatment characteristics, in-hospital and postoperative outcomes of patients undergoing resection of primary CRC in the Netherlands. This is a mandatory registry in which all hospitals participate.

Patients

No ethical approval or informed consent was required under Dutch law. All patients undergoing CRC resection with primary anastomosis between January 2011 and January 2020 were evaluated. Minimal data requirement for inclusion was information on the type

What does this paper add to the literature?

This study updates the current risk profile for colorectal anastomotic leakage and demonstrates that, throughout the past nine years, changes in patient characteristics led to a different incidence and risk profile for AL.

of surgical resection and the presence of an anastomosis. Patients were excluded if they underwent abdominoperineal resection, Hartmann's procedure, total proctocolectomy or had a tumour located in the appendix. In total, 70,229 patients were included (Figure 1).

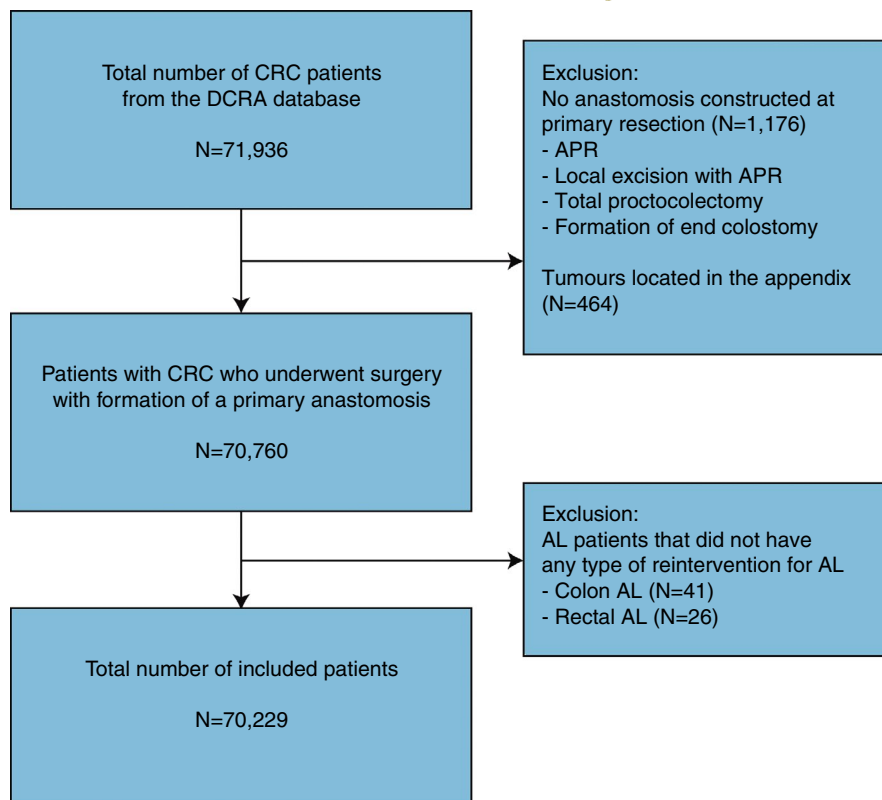
Outcomes

The primary outcome in this study was AL, defined as requiring reintervention. Reintervention could consist of surgical, radiological or endoscopic reintervention within 30 days (2011–2017) or 90 days after resection (2018–2019). Since 2018, the DCRA also registers AL that did not require any type of reintervention, but these data are not available for the preceding years. Therefore, AL patients in 2018–2019 that did not require any type of reintervention ($N = 67$) were excluded. The following variables were extracted from the DCRA registry: patient characteristics (gender, age, ASA, BMI, history of abdominal surgery), tumour characteristics (preoperative tumour complications, location, cancer stage), treatment characteristics (neoadjuvant therapy, urgency of surgery, surgical approach, type of resection, defunctioning stoma construction, multivisceral resection), and postoperative outcomes (AL, length of hospital stay (LOS), postoperative mortality).

Statistics

All patients were divided into three cohorts based on year of resection: 2011–2013, 2014–2016 and 2017–2019. Analyses were stratified for colon cancer (CC) and rectal cancer (RC), and outcomes were compared between AL and non-AL patients. Categorical variables were described by frequencies and percentages. Continuous, non-normally distributed variables are described as median with interquartile range (IQR). Univariable analysis was performed to assess the association of potential risk factors with AL using a X^2 test. To detect changes of patient, tumour, and treatment characteristics over time, a comparison was made between the eldest and most recent time cohort (2011–2013 vs. 2017–2019) using chi-square test for categorical variables and Mann-Whitney U test for (non-normally distributed) continuous variables. Trends in incidence of AL and postoperative mortality over time were assessed using logistic regression with operation year as continuous variable. To identify risk factors for AL, variables that reached statistical significance in the univariable analysis or with clinical relevance were included in the multivariable regression. Results are displayed by

FIGURE 1 Flowchart



odds ratios (OR) and 95% confidence intervals (CI), with AL as dependent variable. A p -value <0.05 was considered statistically significant. All analyses were performed in SPSS v25.

RESULTS

Baseline characteristics

Between 1 January 2011 and 1 January 2020, 56,503 CC patients and 13,726 RC patients underwent surgical resection with primary anastomosis (Table 1). When comparing cohort 2011–2013 to 2017–2019, CC and RC patients treated in 2017–2019 were significantly more likely to have an ASA score of ≥ 3 and a BMI ≥ 30 . There has been a shift towards more restrictive use of neoadjuvant radiotherapy for RC patients, with 66% receiving neoadjuvant radiotherapy in 2011–2013 and 26% in 2017–2019. Emergency resection of CC decreased from 14% (2011–2013) to 7% (2017–2019). For both CC and RC patients, there has been a shift towards minimally invasive surgery, accounting for 86% and 94% of the patients in 2017–2019, respectively. Application of TaTME increased to 13% in 2017–2019. Defunctioning stoma creation decreased, from 68% to 34% after RC resection and from 4% to 1% after CC resection in 2011–2013 and 2017–2019, respectively. However, defunctioning stoma creation increased for TaTME patients from 49% (2014–2016) to 57% (2017–2019). Median LOS of CC patients decreased significantly, from seven (IQR 5–11) to five days (IQR 3–7). For RC patients, LOS significantly decreased from eight (IQR 5–13) to five days (IQR 4–8).

Anastomotic leakage

Over the years, the incidence of AL decreased for CC patients from 6.6% to 4.5% in 2017–2019 (OR 0.68, 95% CI: 0.62–0.74; $p < 0.01$). For RC patients, the incidence increased from 8.6% to 11.4% in 2017–2019 (OR 1.38, 95% CI: 1.19–1.59; $p < 0.01$, Figure 2). In 2017–2019, median time until reintervention for AL was 6 days (IQR 3–10) in CC patients and 8 days (IQR 4–15) in RC patients, without significant changes over the years. Stoma creation rate at reoperation for AL did not change for CC patients, and was 73% in 2017–2019. Of these patients, 35% received a defunctioning stoma, and 65% an end stoma. In contrast, stoma creation rate at reoperation for AL increased significantly for RC patients from 50% (2011–2013) to 70% (2017–2019), which is related to the decrease in defunctioning stomas during primary surgery. Fifty-eight percent of these patients received a defunctioning stoma and 42% an end stoma. Median LOS in CC patients with AL decreased from 22 (IQR 14–34, 2011–2013) to 18 days (IQR 11–28, 2017–2019, $p = 0.00$). For RC patients, a similar reduction in LOS was found: 20 (IQR 9–31) to 15 days (IQR 7–24) ($p < 0.01$).

Risk factors associated with AL

For CC patients in 2011–2013, multivariable analysis revealed male sex, ASA ≥ 3 , neoadjuvant therapy, emergency surgery, multi-visceral resection, and (y)pT3–4 to be independently associated with an increased AL risk (Figure 3). Age of 70 years and older was demonstrated to be associated with a lower AL risk (OR 0.85, 95% CI:

TABLE 1 Baseline patient-, tumour-, and treatment characteristics per cohort

		Colon					
		2011–2013		2014–2016		2017–2019	
		Total (N)	AL (N)	Total (N)	AL (N)	Total (N)	AL (N)
		17,074	1,122	21,354	1,108	18,075	822
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Gender	Male	8,812	682 (7.7)	11,300	667 (5.9)	9,189	507 (5.5)
	Female	8,175	433 (5.3)	9,857	432 (4.4)	8,783	308 (3.5)
Age	<70	7,334	520 (7.1)	10,006	509 (5.1)	7,659	358 (4.7)
	≥70	9,697	598 (6.2)	11,259	597 (5.3)	10,372	460 (4.4)
ASA	I	3,243	188 (5.8)	3,710	156 (4.2)	2,279	81 (3.6)
	II	9,705	622 (6.4)	12,672	598 (4.7)	10,312	426 (4.3)
	III+	4,084	310 (7.6)	4,965	354 (7.1)	5,484	315 (5.7)
BMI (kg/m ²)	<18.5	293	30 (10.2)	310	16 (5.2)	288	16 (5.6)
	18.5–24.9	6,682	426 (6.4)	7,895	409 (5.2)	6,941	296(4.3)
	25.0–29.9	6,554	431 (6.6)	8,431	426 (5.0)	7,001	315 (4.5)
	≥30.0	2,655	174 (6.6)	4,166	234 (5.6)	3,540	185 (5.2)
History of abdominal surgery	No	13,447	868 (6.5)	14,295	737 (5.2)	15,593	686 (4.4)
	Yes	3,627	254 (7.0)	7,059	371 (5.3)	2,477	136 (5.5)
Preoperative tumour complications	No	10,179	604 (5.9)	14,724	724 (4.9)	12,176	506 (4.2)
	Yes	6,895	518 (7.5)	6,582	383 (5.8)	5,881	316 (5.4)
Pathological T Classification	(y)pT0-2	3,939	201 (5.1)	6,657	288 (4.3)	697	211 (3.7)
	(y)pT3-4	12,884	908 (7.0)	14,606	819 (5.6)	12,096	603 (5.0)
Pathological N Classification	pN0	9,873	636 (6.4)	13,106	662 (5.1)	10,992	491 (4.5)
	pN1-2	7,063	478 (6.8)	8,179	444 (5.4)	6,788	319 (4.7)
Metastatic disease	No	13,822	890 (6.4)	18,871	934 (5.0)	9,582	445 (4.6)
	Yes	1,936	141 (7.3)	1,783	139 (7.8)	1,223	74(6.1)
Neoadjuvant therapy	No neoadjuvant therapy	16,728	1083 (6.5)	20,960	1070 (5.1)	17,530	786 (4.5)
	Neoadjuvant chemotherapy	265	30 (11.3)	323	30 (9.3)	359	24 (6.7)
	Neoadjuvant (short-course) radiotherapy	51	6 (11.8)	40	4 (10.0)	26	2 (7.7)
	Neoadjuvant chemoradiation	30	3 (10.0)	31	4 (12.9)	27	2 (7.4)
Timing of surgery	Elective	14,658	909 (6.2)	19,503	973 (5.0)	16,789	741 (4.4)
	Emergency	2,405	213 (8.9)	1,844	135 (7.3)	1,277	81(6.3)
Surgical approach	Open surgery	8,292	595 (7.2)	5,202	372 (7.2)	2,317	159 (6.9)
	Laparoscopic surgery with conversion	1,168	98 (8.4)	1,765	129 (7.3)	1,437	105 (7.3)
	Laparoscopic surgery without conversion	7,174	409 (5.7)	14,028	587 (4.2)	12,735	495 (3.9)
	TaTME						
	Robot-assisted surgery	-	-	-	-	596	20(3.4)



Rectum							
	2011-2013		2014-2016		2017-2019		Total N 2011-2013 vs 2017-2019
	Total (N)	AL (N)	Total (N)	AL (N)	Total (N)	AL (N)	
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	
0.16	2,354	217 (9.2)	3,207	345 (10.8)	2,954	399 (13.5)	0.97
	1,477	111 (7.5)	1,830	117 (6.4)	1,858	150 (8.1)	
0.27	2,455	240 (9.8)	3,297	319 (9.7)	3,019	368 (12.2)	0.23
	1,383	89 (6.5)	1,754	145 (8.3)	1,795	181 (10.1)	
<0.01	1,152	96 (8.4)	1,289	116 (9.0)	898	94 (10.5)	<0.01
	2,230	181 (8.1)	3,157	293 (9.3)	3,116	349 (11.2)	
	456	52 (11.4)	621	57 (9.2)	805	107 (13.3)	
<0.01	53	1 (1.9)	57	4 (7.0)	61	10 (16.4)	<0.01
	1,599	137 (8.6)	1,946	173 (8.9)	1,926	209 (10.9)	
	1,569	146 (9.3)	2,136	210 (9.9)	1,935	217 (11.2)	
	525	41 (7.8)	818	71 (8.7)	820	105 (12.8)	
<0.01	3,127	269 (8.6)	3,711	367 (9.9)	4,306	497 (11.5)	<0.01
	713	60 (8.4)	1,356	99 (7.3)	513	53 (10.3)	
<0.01	2,893	254 (8.8)	4,219	377 (8.9)	4,318	487 (11.3)	<0.01
	947	75 (7.9)	843	89 (10.6)	496	63 (12.7)	
<0.01	1,773	144 (8.1)	2,574	225 (8.7)	2,389	282 (11.8)	<0.01
	2,001	180 (9.0)	2,445	238 (9.7)	2,306	253 (11.0)	
<0.01	2,444	204 (8.3)	3,371	289 (8.6)	2,972	341 (11.5)	0.22
	1,369	124 (9.1)	1,681	175 (10.4)	1,760	202 (11.5)	
0.04	3,430	300 (8.8)	4,696	427 (9.1)	2,669	285 (10.7)	<0.01
	207	18 (8.7)	246	26 (10.6)	275	26 (9.5)	
0.08	702	44 (6.3)	2,310	214 (9.3)	2,659	266 (10.0)	<0.01
	27	4 (14.8)	24	2 (8.3)	53	3 (5.7)	
	2,520	223 (8.8)	2,094	186 (8.9)	1,269	172 (13.6)	
	591	58 (9.8)	639	64 (10.0)	817	108 (13.2)	
<0.01	3,806	328 (8.6)	5,039	461 (9.1)	4,778	545 (11.4)	0.72
	29	1 (3.4)	28	5 (17.9)	40	5 (12.5)	
<0.01	1,433	146 (10.2)	639	48 (7.5)	258	27 (10.5)	<0.01
	297	20 (6.7)	339	28 (8.3)	186	24 (12.9)	
	1,967	156 (7.9)	3,772	365 (9.7)	2,976	306 (10.3)	
	23	3 (13.0)	238	22 (9.2)	633	111 (17.5)	
	-	-	-	-	590	65 (11.0)	

(Continuous)

TABLE 1 Continued

		Colon					
		2011–2013		2014–2016		2017–2019	
		Total (N)	AL (N)	Total (N)	AL (N)	Total (N)	AL (N)
		17,074	1,122	21,354	1,108	18,075	822
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Surgical resection	Ileocecal resection/ Right hemicolectomy	8,684	470 (5.4)	10,477	472 (4.5)	9,826	395 (4.0)
	Transverse resection	462	32 (6.9)	471	34 (7.2)	396	30 (7.6)
	Left hemicolectomy	1,856	170 (9.2)	2,318	175 (7.5)	2,162	120 (5.6)
	Sigmoid resection	5,707	396 (6.9)	7,767	381 (4.9)	5,346	245 (4.6)
	Subtotal colectomy	357	54 (15.1)	306	45 (14.7)	253	26 (10.3)
	Low anterior resection						
	Missing/not specified	10	0 (0.0)	15	1 (6.7)	92	6 (6.5)
Stoma construction at primary surgery	No stoma	16,211	1050 (6.5)	20,751	1074 (5.2)	17,869	813 (4.5)
	Stoma	729	67 (9.2)	558	34 (6.1)	203	8 (3.9)
Multivisceral resection	No	14,476	879 (6.1)	19,739	985 (5.0)	16,735	726 (4.3)
	Yes	1,653	156 (9.4)	1,609	123 (7.6)	1,337	96 (7.2)

Bold values indicate a significance level of $p < 0.05$.

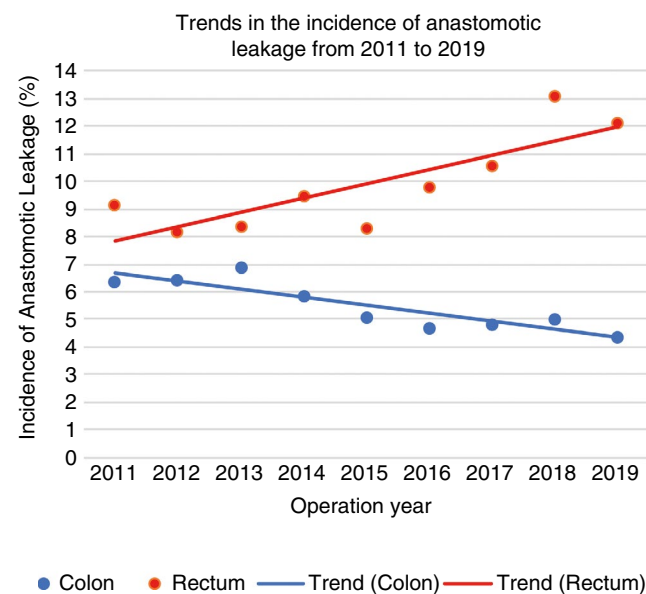


FIGURE 2 Trends in the incidence of anastomotic leakage between 2011–2019

0.73–0.98). In 2017–2019, only male sex and ASA ≥ 3 were identified as independent risk factors for AL. Conventional laparoscopic surgery (excluding TaTME) was associated with a significantly lower AL risk compared to open surgery (OR 0.60, 95% CI: 0.46–0.79). Treatment period also remained associated with AL in multivariable analysis, with a lower risk in 2017–2019 (AOR 0.68, 95% CI: 0.62–0.74).

Multivariable regression analysis of RC patients in 2011–2013 revealed male sex and neoadjuvant therapy to be risk factors for AL (Figure 3), while conventional laparoscopic surgery, defunctioning stomas and age of 70 years or older were protective for AL. The risk profile changed slightly in 2017–2019. TaTME was also identified as risk factor for AL; 17.5% of the TaTME patients developed AL. Defunctioning stoma construction was the only risk factor that significantly decreased the AL risk during all cohorts. Treatment period remained significantly associated with AL after RC surgery after correction for confounders, with a higher risk for patients treated between 2017–2019 (AOR 1.38, 95% CI: 1.19–1.59).

Mortality

Compared to 2011–2013, overall postoperative mortality was significantly lower for CC patients in 2017–2019 (3.3%–2.0%, AOR 0.58, 95% CI: 0.52–0.67, Figure 4). A similar reduction was found for RC patients (1.5%–0.8%, AOR 0.52, 95% CI: 0.35–0.79). During the whole study period (2011–2019), AL was associated with a significantly higher overall postoperative mortality compared to non-AL patients for both CC and RC. Postoperative mortality rate in CC patients with AL remained high over the years, and was 11% in 2017–2019. In RC patients, the postoperative mortality rate after AL did not significantly change over the years and was 3% in 2017–2019. Multivariable analysis identified ASA ≥ 3 and age ≥ 70 years as risk factors for postoperative mortality in 2017–2019 for CC patients with AL, without changes over the years. For RC patients, only age ≥ 70 years was a risk factor for postoperative mortality



	Rectum						Total N 2011-2013 vs. 2017-2019
	2011-2013		2014-2016		2017-2019		
	Total (N)	AL (N)	Total (N)	AL (N)	Total (N)	AL (N)	
Total N 2011-2013 vs. 2017-2019	3,840	329	5,067	466	4,819	550	
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	
<0.01							
	3,840	329 (8.6)	5,067	466 (9.2)	4,819	550 (11.4)	-
<0.01	1,188	130 (11.0)	2,399	268 (11.2)	3,171	390 (12.3)	<0.01
	2,629	198 (7.5)	2,661	198 (7.4)	1,648	160 (9.7)	
<0.01	3,508	297 (8.5)	4,851	453 (9.3)	4,677	538 (11.5)	0.06
	131	16 (12.2)	212	13 (6.1)	138	12 (8.7)	

in 2011-2013 (OR 5.9, 95% CI: 1.57-22.09). In 2017-2019, age ≥ 70 years, ASA ≥ 3 and preoperative tumour complications were risk factors for postoperative mortality after AL.

DISCUSSION

This population-based study provides trends in incidence, risk factors, and postoperative mortality for AL after CRC resection throughout 9 years of auditing in the Netherlands. We demonstrated a significant decrease in incidence of AL after CC resection, while the incidence of AL after RC resection significantly increased over the years. Risk profiles for AL changed over the years. Whereas many risk factors were identified for AL after CC resection in 2011-2013, only male sex and ASA ≥ 3 were identified in 2017-2019. In RC patients, male sex and neoadjuvant radiotherapy were risk factors throughout the years and TaTME was identified as new risk factor for AL in 2017-2019. Interestingly, a defunctioning stoma was identified as protective for AL after RC resection in all consecutive cohorts. In addition, postoperative mortality after colonic AL was persistently high while substantially lower rates were found for RC patients, and these rates did not change over time.

The incidence of AL after RC surgery increased significantly over the past nine years, with the largest increase between 2017-2018 (10.6%-13.1%). Although the overall AL rate is in line with literature, the increase is noteworthy [2, 19]. There are several explanations. First, there has been a reduction in defunctioning stoma construction at primary surgery. Defunctioning stomas were

identified as a protective factor, however, fewer patients received a stoma and as a consequence the AL rate increased. Second, another contributing factor may be the implementation and increased application of TaTME since 2012. TaTME is mainly performed for distal RC and was introduced to overcome the difficulties of conventional laparoscopic TME. However, TaTME is difficult to learn and in order to pass the learning curve and reduce postoperative complications, high case-volumes are necessary [20, 21]. Detering et al. concluded that three centres in the Netherlands surpassed the threshold for the learning curve of 40 cases/year. Moreover, while there are 44 Dutch hospitals performing TaTME, only fifteen finalized the training programme. Although a comparison between trained and untrained centers was not possible [22], it is reasonable to assume that low case-volume centres contributed to higher AL rates. Therefore, we expect that TaTME operations will be centralized in expert centers in the future. This might cause a reduction of overall TaTME cases, but could also contribute to a reduction of postoperative complications. In a recent nationwide study of Rutgers et al., TaTME was associated with higher AL rates than conventional laparoscopic TME of a tumour < 5 cm from the anorectal junction (15.9% vs. 12.8%, $p < 0.01$) [23]. This study also identified TaTME as risk factor for AL with an absolute 18% leak rate in 2017-2019. While defunctioning stoma construction after RC resection decreased over the years, the number of defunctioning stomas in TaTME patients increased from 49% (2014-2016) to 57% (2017-2019). Although defunctioning stomas were a protective factor for AL throughout the years in the total RC population, this phenomenon is not seen in TaTME patients.

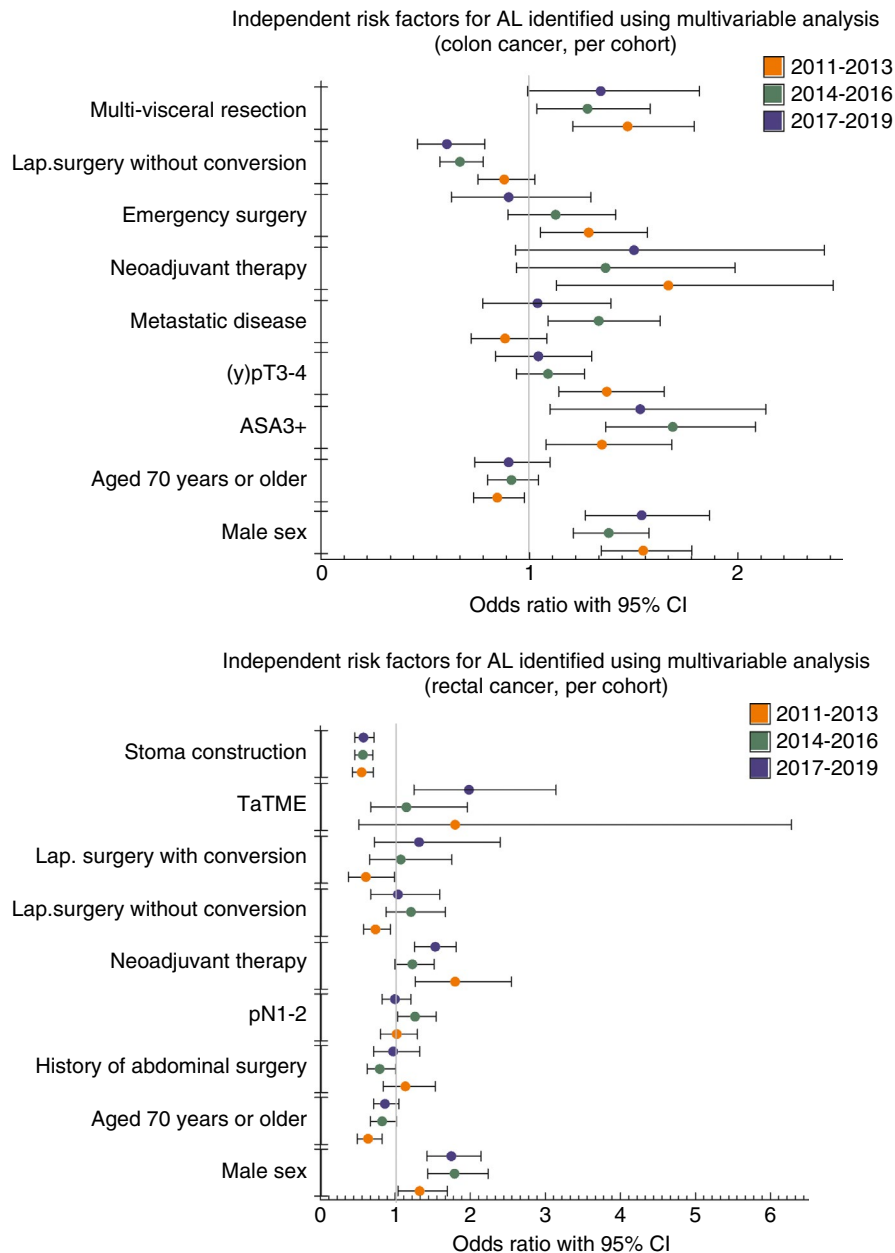
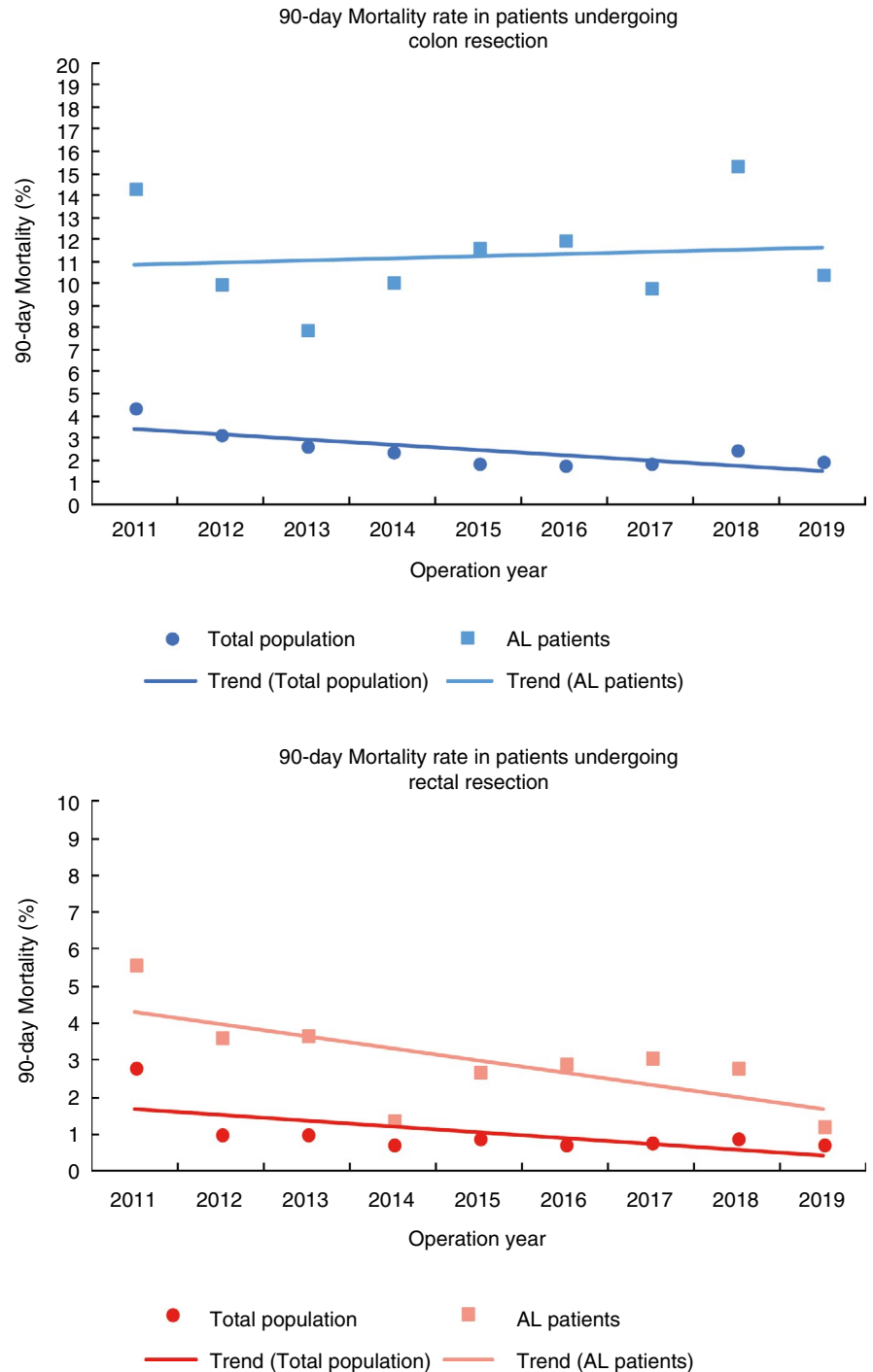


FIGURE 3 Independent risk factors for AL identified using multivariable analysis

Adjusted multivariable analysis revealed several risk factors for AL for both CC and RC patients. Consistent with literature, male sex was an independent risk factor for AL in both CC and RC patients [24–26]. Although the increased risk for men undergoing RC resection might be related to the narrow pelvis, which can complicate restoration of bowel continuity, this is not applicable to CC resections [27]. Another explanation might be the fact that androgens inhibit the endothelial function, which can negatively affect anastomotic healing [28]. Besides, for CC patients, higher ASA classification (≥ 3) was identified as a risk factor for AL. ASA classification is a reflection of the patients' comorbidities and was identified as a risk factor for colonic AL in a previous nationwide study [29]. Furthermore, this study suggests that surgical approach is related with the risk of AL. Conventional laparoscopy protects for AL, which is in line with previous studies. In contrast, both open and converted surgery were

associated with an increased AL risk after CC surgery. Case selection can be an explanation for these findings. Compared to laparoscopic surgery, patients undergoing open surgery have more comorbidities and are obese [30, 31]. These are also risk factors for AL [29, 32, 33]. In addition, patients that are preoperatively assigned to open surgery are usually expected to have intraabdominal adhesions, which may complicate surgery with an increased AL risk as a consequence. In case of conversion, there is inability to correctly visualize the anatomy, intraoperative complications have developed or intraabdominal adhesions are detected. Therefore, technical difficulties during the surgical procedure may have increased the risk of AL. With the introduction of minimally invasive techniques the surgical practice has been optimized. Robot-assisted laparoscopic surgery might be beneficial for more challenging surgical pathologies. Whether robotic surgery will become the preferred modality in the upcoming

FIGURE 4 90-day mortality rate in patients undergoing colon or rectal resection



years is debated due to lacking evidence regarding cost effectiveness and long-term oncological outcomes [34].

During the past nine years, there has been a decline in the use of neoadjuvant therapy. Nevertheless, neoadjuvant therapy is still a risk factor for AL after RC resection [3]. Finally, this study confirms the generally found association between defunctioning stoma and lower risk of AL [9–12]. However, this does not necessarily mean that a stoma is protective for the occurrence of AL, as illustrated by studies with long term follow-up that include the late leakages that might even become apparent after closure of the defunctioning stoma [2].

In line with previous studies, a difference between mortality rates after CC and RC surgery was found [29, 33]. This can be explained by the location of the anastomosis. CC patients are at higher risk of generalized peritonitis with a relatively high risk of mortality, because of the intraperitoneally located anastomosis. In contrast, RC patients with AL often have sealed-off leakage at the level of the pelvic inlet. These leaks often result in extraperitoneal abscess formation and rarely result in 'failure to rescue'. In this study, postoperative mortality rate among colonic AL patients remained high over the years. This is in line with previous published European cohorts that presented postoperative mortality rates varying between

16%–29% [6, 35–37]. Although these mortality rates are higher compared to our 2017–2019 cohort, there is room for improvement. Early detection and more aggressive treatment modalities for AL in CC patients to prevent postoperative mortality should be a priority. Den Dulk et al. developed the DULK-score in 2014, a clinical diagnostic tool for early detection of AL based on clinical parameters, physical examination, laboratory investigation and nutritional status [38]. Although the DULK score can detect AL almost four days ahead of clinical judgement, it is not widely implemented and apparently did not affect mortality rates [39]. The persistently high mortality rates after colonic AL warrants further studies to explore potential diagnostic tools or interventions that can reduce the failure to rescue rate.

This study was strengthened by the inclusion of all patients that underwent CRC surgery in Dutch hospitals during 2011–2019. By analysing data of nine years, trends in risk factors, incidence and mortality from AL after CC and RC surgery were identified. Although almost all data was complete, it is inevitable that there is still a minor degree of incomplete data. However, this is not expected to bias the results. AL was defined as requiring any type of reintervention, therefore, conclusions for grade A leakages cannot be drawn. However, the most important limitation lies in the fact that the DCRA has a limited follow-up. Before 2018, the DCRA registered 30-day outcomes and it started registering 90-day outcomes in 2018. Since the majority of the patients underwent surgery before 2018, this study excludes information about late ALs and the related mortality. Borstlap et al. concluded that approximately one third of the patients with a defunctioning stoma develop AL after 30 days [2]. In this study, the majority of the RC patients operated before 2018 received a defunctioning stoma (68% in 2011–2013 and 53% in 2014–2016) and we observed a decline in construction of defunctioning stomas in 2017–2019 (34%). Therefore, the incidence of AL may have been underestimated in this study between 2011 and 2017. Reporting 90-day outcomes in 2017–2019 may have led to a better reflection of the true incidence of AL.

In conclusion, this study demonstrates that, throughout the past 9 years, changes in population characteristics led to a different incidence, risk profile and mortality from AL. Clinicians should be aware of these changes and adjust patient counselling accordingly. Further research should focus on the early detection of AL after CC resection with optimized management to reduce postoperative mortality.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Melissa Arron, Nynke Greijdanus, Pieter Tanis and Hans de Wilt contributed to the conception of the study. Melissa Arron and Nynke Greijdanus performed the data analysis and manuscript preparation. All authors reviewed the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

No ethical approval or informed consent was required under Dutch law.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of the article at the publisher's website.

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