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Impact of Anastomotic Leakage After Colorectal Cancer Surgery on Quality of Life: A Systematic Review

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BACKGROUND: Colorectal anastomotic leakage remains one of the most frequent and dreaded postoperative complications after colorectal resection. However, limited research has been conducted on the impact of this complication on the quality of life of patients who have undergone colorectal cancer surgery.

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OBJECTIVE: The aim of this systematic review was to identify, appraise, and synthesize the available evidence regarding the quality of life in patients with anastomotic leakage after oncological colorectal resections to inform clinical decision-making.

DATA SOURCES AND STUDY SELECTION: PubMed, Embase, and the Cochrane Library were searched for studies reporting quality of life using validated questionnaires in patients with anastomotic leakage after oncological colorectal resections. The literature search was performed systematically and according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

OUTCOMES: Outcomes from quality-of-life questionnaires of patients with and without anastomotic leakage were analyzed.

RESULTS: Thirteen articles reporting on 4618 individual patients were included, among which 527 patients developed anastomotic leakage. Quality of life was evaluated using 10 distinct questionnaires administered at various postoperative time points, ranging from 1 month to 14 years. Quality-of-life outcomes differed across studies and time points, but overall scores were most negatively affected by anastomotic leakage up to 12 months postoperatively.

LIMITATIONS: There was a high heterogeneity between the included studies based on the questionnaires used and the time of assessment.

CONCLUSIONS: The published evidence suggests that anastomotic leakage after oncologic colorectal resection is associated with impaired quality of life, especially within the first postoperative year. The impact of anastomotic

leakage on quality of life warrants further evaluation and discussion with patients.

KEY WORDS: Anastomotic leakage; Colorectal cancer surgery; Quality of life.

Oncological colorectal resection with or without primary anastomosis remains the cornerstone in the treatment of colorectal cancer (CRC). In patients undergoing restorative procedures, anastomotic leakage (AL) remains one of the most frequent and dreaded postoperative complications, with a reported incidence varying from 1.5% to 20%.¹⁻⁴ This wide-ranging incidence in the literature may be due to differences in surgical risk among different study populations and variability in surgical techniques, but it also reflects significant differences in reporting standards for AL. Although several classifications and definitions of AL have been described in the literature, there is no consensus on definitive diagnostic or clinical criteria for AL.⁵⁻⁸

Several important risk factors for AL have been identified during the past few decades, such as active smoking, malnutrition, male sex, obesity, emergency surgery, operative time, postoperative use of nonsteroidal anti-inflammatory drugs, and neoadjuvant chemotherapy.⁹⁻¹¹ Despite innovations in surgical techniques, preoperative optimization, and intraoperative interventions to further minimize the risk of AL, rates of anastomotic complications have not decreased. AL ranges in clinical severity from minor, subclinical, and contained leaks to fulminant sepsis and organ failure with increased short-term mortality rates.¹²

A standardized consensus framework for defining, reporting, and grading colorectal AL is currently being developed by the Consensus on Reporting and Defining Colorectal Anastomotic Leaks. This expert group noticed gaps in knowledge about the short- and long-term impact AL on functional outcomes and overall quality of life (QoL). As patients should be fully informed not only regarding the immediate surgical risks but also on the impact surgical complications may have on long-term function and QoL, this systematic review was undertaken to address this important question about the short- and long-term impacts of AL in patients with CRC. The aim of this systematic review was to identify, appraise, and synthesize the available evidence regarding short- and long-term QoL in patients who have undergone oncological colorectal resections complicated by AL.

MATERIALS AND METHODS

Study Protocol and Registration

This systematic review was conducted according to the latest edition of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.¹³ The

study protocol was developed a priori and registered at PROSPERO (ID 411065).

Outcomes and Definitions

The primary outcomes were QoL and health-related QoL (HRQoL). QoL was defined using the World Health Organization definition of “an individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns.”¹⁴ HRQoL in cancer is often used interchangeably with QoL because there is no consensus on a standardized definition. We have applied the definition of Testa and Simonson¹⁵ on HRQoL as the “physical, psychological and social domains of health, seen as distinct areas that are influenced by a person’s experiences, beliefs, expectations and perceptions.”

AL was defined as a combination of clinical signs and symptoms (eg, abdominal pain or tenderness, peritonitis, fever, tachycardia, purulent or fecal discharge from an abdominal drain or the vagina, purulent discharge per anus), biochemical elements (elevated white blood cell count and/or C-reactive protein), and radiological confirmation of an interruption of the anastomosis and/or a perianastomotic collection on CT.^{6,16}

Search and Information Sources

The literature search was performed on March 13, 2023, and repeated on August 14, 2023. PubMed, Cochrane Library, and Embase were searched with the use of MeSH-, Emtree-, and free terms, including “colorectal neoplasms,” “(adeno)carcinoma,” “colorectal surgery,” “anastomotic leak,” “complications,” “quality of life (QoL),” and “health-related quality of life (HRQoL)” (see Supplemental S1 at <http://links.lww.com/DCR/C410>). Reference lists of relevant publications were cross-checked to identify additional studies. This hand-search method was continued until no further relevant studies were identified.

Selection Process

Eligibility criteria and selection process. All English or Dutch articles published in peer-reviewed index journals reporting on QoL in patients older than 18 years with AL after oncological colorectal resections were considered eligible for inclusion. Analysis of QoL after AL had to be identified as a predetermined aim in the Methods section of the study to be eligible for inclusion. Trials were included irrespective of blinding.

Systematic reviews and secondary sources such as letters to the editor, technical descriptions, conference proceedings, and commentaries were excluded. Articles reporting on fewer than 10 patients or solely reporting on outcomes after colorectal resections for benign indications were excluded. Since the first systematic review on the definition of AL was published in the year 2001, all

articles published before January 1, 2000, were excluded.⁸ Furthermore, articles were excluded when no validated HRQoL instrument had been applied.

All search results were imported into an online tool designed for systematic reviews (Rayyan).¹⁷ After the removal of duplicates, articles were screened for eligibility by 2 independent researchers (A.H.C.G. and D.J.I.H.) according to the predefined criteria. First, articles were screened on the basis of titles and abstracts. Definitive article inclusion followed if the eligibility criteria were met after full-text screening by both reviewers. Disagreements were resolved through discussion. All references were stored in the Endnote Reference Management Tool (version 20.4, Clarivate, Chandler, United States).

Data Extraction and Synthesis of Results

Two independent researchers (A.H.C.G. and D.J.I.H.) performed a qualitative analysis and extracted data from the main text, tables, and figures using a predefined and standardized data extraction table. Extracted data included first author, year of publication, country, study design, study period, inclusion and exclusion criteria, aim of the study, number of patients, general patient characteristics, indication for surgery, surgical procedures performed, the applied (validated) QoL questionnaires, time of assessment, and secondary outcomes. Furthermore, definitions, time frame, and criteria for diagnosis of AL were collected. Data acquired via the outlined search strategy were summarized in tables. Findings were described using a narrative approach (ie, primarily words and text were used to summarize and explain the findings). Because of the heterogeneity among included studies in terms of the definition of AL and questionnaires used to assess QoL, pooling in a meta-analysis was impossible.

Assessment of Risk of Bias in Individual Studies

To ascertain the validity of the included studies, the risk of bias in each study was assessed by 2 reviewers (A.H.C.G. and D.J.I.H.) with a revised Risk of Bias in Non-randomized Studies of Interventions tool to assess the risk of bias in nonrandomized studies.¹⁸ All types of bias were evaluated for every study and judged to be “low risk,” “moderate risk,” or “high risk.” Possible confounding domains were a priori defined as active smoking, malnutrition, male sex, BMI, comorbidities or higher ASA classification, emergency surgery, and longer operative time.

RESULTS

Study Selection

The electronic literature search generated 1323 articles and 980 unique articles after removing duplicates. Of these, 866 were excluded after title and abstract screening. A full-text screening of the resulting 114 articles was performed

and another 101 were excluded. Cross-reference checking generated 1 additional article, and 1 more additional publication was identified after repeating the search before submission. Ultimately, 13 articles were included in the analysis (Fig. 1A).

Study and Patient Characteristics

All 13 articles included were cohort or case-matched studies and comprised 4618 individual patients, with study sample sizes ranging from 32 to 1207 patients (Table 1).^{19–26,28–31} Four studies reported on colorectal resections,^{19,21,24,29} and all other studies focused on rectal resections. All studies included patients diagnosed with CRC, with only 2 studies also including patients with benign indications for colorectal resections (eg, diverticulitis, IBD). Because benign indications were presented separately, the outcomes of these patients were excluded from this review.^{24,29} The final population consisted of 4618 patients, of whom 2946 (64%) were men and 1672 (36%) women, with a mean age of 61.9 years. Among these patients, 527 (11%) developed AL and 4091 (89%) recovered without clinical, radiological, or biochemical signs of AL (Table 2).^{19–26,28–31} The median time of follow-up was 4.3 years (4.8 months–14.4 years). Additional study information on the perioperative care of patients in each study is provided in Supplemental S2 at <http://links.lww.com/DCR/C410>.

Risk of Bias in Studies

The relevant categories from the Risk of Bias in Non-randomized Studies of Interventions tool were used to assess the risk of bias (Fig. 1B). We reported a serious risk of bias in 9 studies, primarily attributed to the nonrandomized design of these studies^{21,22,24–26,28–31} and a moderate risk of bias in the other 4 studies.^{19,20,23,27}

AL Characteristics

All details on AL and specific characteristics reported by each study are summarized in Supplemental S3 at <http://links.lww.com/DCR/C410>. The reported definitions and diagnostic modalities for AL varied widely among the studies reviewed. Four studies (33%) did not report any specific definition for AL.^{21,28,30,32} Furthermore, none of the studies applied the same definition for AL. The severity of AL was assessed using various classifications across the included studies. Four studies applied the International Study Group of Rectal Cancer classification,^{19,26,27,30} whereas 2 studies used the Clavien-Dindo classification.^{21,25} Four studies divided AL cases into symptomatic and asymptomatic or clinical and subclinical manifestations.^{22,24,28,29} The other studies did not provide a specific classification or grading of severity of AL. The time frame in which AL was suspected or diagnosed was reported in 4 articles, with the latest reporting time being 6 months after surgery.^{19,22,24,27} One study reported biochemical characteristics that might

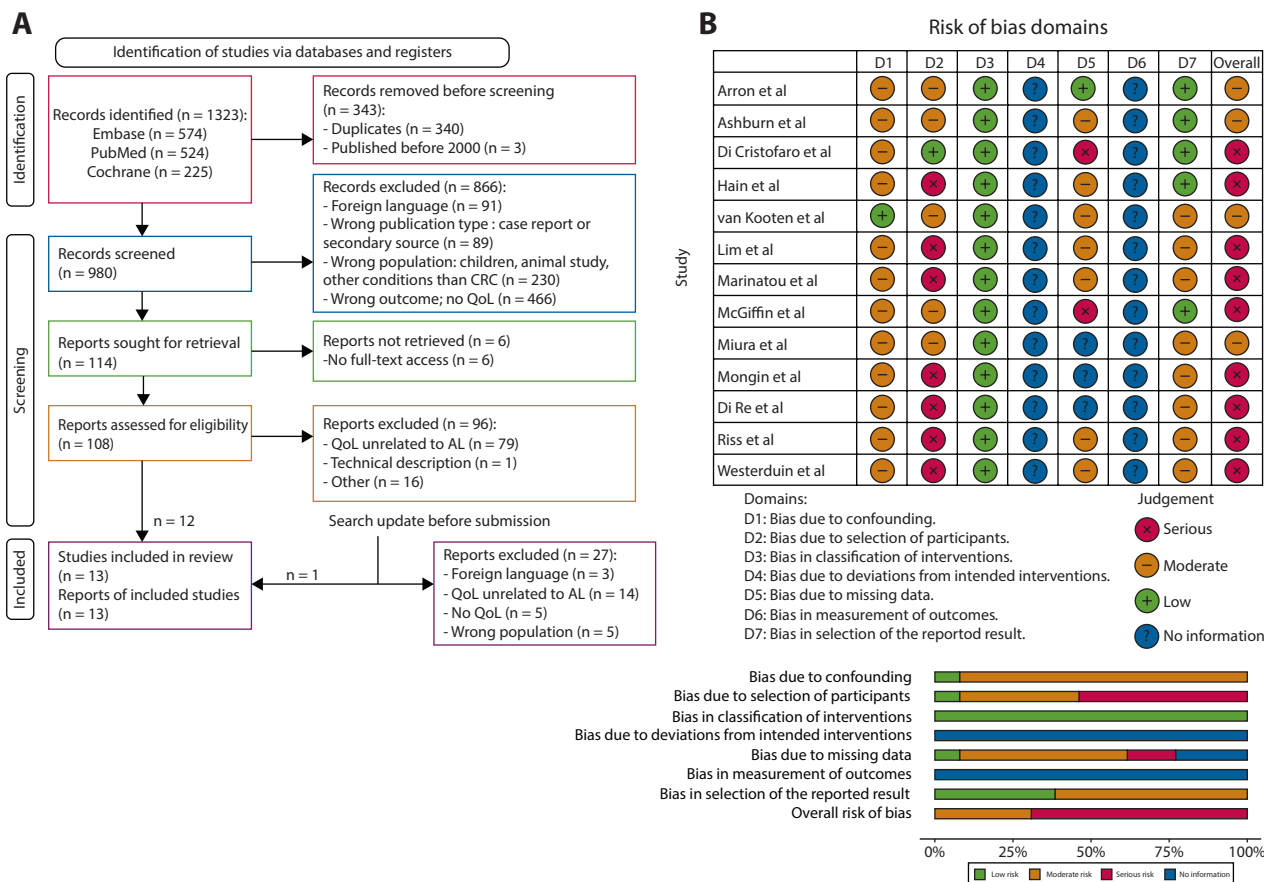


FIGURE 1. Study selection. A, PRISMA flow chart outlining study selection strategy. B, Adapted ROBINS-I tool Risk of Bias from included studies. CRC = colorectal cancer; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QoL = quality of life; ROBINS-I = Risk of Bias in Non-randomized Studies of Interventions.

indicate surgical complications.²⁴ Eight studies (67%) used CT with or without contrast to confirm the diagnosis of AL.^{20,22–25,27–29} Four studies reported performing radiological assessment and subsequent AL assessment only when clinical symptoms occurred.^{19,20,25,27} Three other studies additionally performed routine scanning for AL before ileostomy closure (range, 6 weeks–3 months after surgery).^{22,24,28} The type of reinterventions was specified in 10 studies^{19,21,22,24–30} and ranged from antibiotic treatment to reoperation (laparotomy) with take down of anastomosis and end-colostomy construction.

Questionnaires

A total of 10 validated QoL questionnaires were administered at different time points within the studies. Four validated instruments were administered across the majority of studies (see Supplemental S4 at <http://links.lww.com/DCR/C410>: The European Organization for Research and Treatment of Cancer QoL Questionnaire [EORTC QLQ]-C30 [Core] and -CR29 [CRC-specific], the 36-item Short-Form survey [SF-36] encompassing both a physical component summary [PCS] and a mental component summary [MCS], and the Fecal Incontinence QoL

[FIQL] questionnaire). Six additional questionnaires were used in only 1 study (Supplemental S5 at <http://links.lww.com/DCR/C410>). These included the Cleveland Global QoL (CGQL), the EORTC IN-PATSAT32 questionnaire for assessing cancer care satisfaction, the GI QoL Index (GIQLI) addressing digestive disorders with both physical and emotional components, the EuroQoL Visual Analog Scale for patient self-rated health, the 12-item Short-Form survey evaluating health impact on daily life, and the Rotterdam Symptoms Check List (RSCL) questionnaire, which generally evaluates HRQoL.

QoL Scores

QoL was evaluated at different time points. Almost all studies compared QoL scores between patients with AL and patients without AL at specific time points but not always relative to baseline assessment (Fig. 2; Table 3).

QoL up to 6 months after surgery. Based on EORTC QLQ-CR29 and -CR30 scores at 1 and 6 months post-operatively, Di Cristofaro et al identified AL as an independent predictor of lower QoL in multivariate analysis ($p < 0.001$ and $p = 0.004$, respectively).²¹

TABLE 1. Characteristics of included studies

Reference	Year	Country	Study design	Study period	No. of patients	Inclusion criteria	Exclusion criteria	Aim of the study
Arron et al ¹⁹	2023	The Netherlands	Observational cohort study	2010–2019	1197	Patients aged 18 y or older, diagnosed with stage I–III CRC	History of CRC, IBD, hereditary CRC syndromes, non-Dutch speaking or diagnosed with a mental condition that limited the ability to fill out questionnaires, nonelective surgery, resection without primary anastomosis, or with end stoma reconstruction	To assess whether AL is associated with HRQoL at 6 mo and 2 y postdiagnosis and whether AL is associated with a clinically relevant decrease in HRQoL at 6 mo and 2 y postdiagnosis compared to at the time of diagnosis
Ashburn et al ²⁰	2013	United States of America	Retrospective cohort study	1980–2010	864	Restorative resection for rectal cancers for tumors <15 cm from the anal verge	Patients with IBD, familial adenomatous polyposis, and hereditary and nonpolyposis colon cancer; patients undergoing nonrestorative resections	To evaluate the impact of AL, when intestinal continuity can still be maintained, on bowel function and QoL in patients undergoing rectal cancer resection with low colorectal or coloanal anastomoses
Di Cristoforo et al ²¹	2014	Italy	Prospective cohort study	2020–2011	116	Patients admitted for elective CRC surgery	Emergency surgery, explorative laparotomy, inoperable CRC, or recurrence at follow-up	To investigate how postoperative complications affect patients' QoL and satisfaction with care
Hain et al ²²	2017	France	Case-matched study	2005–2014	135	All patients undergoing laparoscopic sphincter-saving partial or total mesorectal excision	Patients with temporary or permanent stoma, no minimum follow-up of 1 y, and no current chemotherapy, and patients who were included in a previous study from the group that evaluated a postoperative program	To assess long-term functional outcomes after laparoscopic, sphincter-preserving operative intervention for rectal cancer according to the type of AL
van Kooten et al ²³	2022	The Netherlands	Observational cohort study	1996–1999	1207	Clinically resectable adenocarcinoma with an inferior tumor margin below the level of S1/S2 and within 15 cm from the anal verge without evidence of distant metastasis	Not having filled out the baseline HRQoL questionnaire, deceased within 30 d after surgery	To objectify the difference in short- and long-term HRQoL between uncomplicated and complicated postoperative recovery after TME for rectal cancer
Lim et al ²⁴	2006	United Kingdom	Observational cohort study	2000–2014	138	All patients undergoing surgical procedures with low rectal anastomosis (<10 cm from the anal verge).	NA	To evaluate the effect of (sub) clinical AL on QoL and the significance of features seen on water-soluble contrast enemas in the prediction of subsequent anastomotic healing

(Continued)

TABLE 1. Continued

Reference	Year	Country	Study design	Study period	No. of patients	Inclusion criteria	Exclusion criteria	Aim of the study
Marinatos et al ²⁵	2014	Greece	Retrospective case-matched study	2007–2012	75	Biopsy-proven CRC	Age <18 y or >80 y, distant metastatic disease at presentation, initially managed on an emergency basis, history of IBD or hereditary cancer	To explore the effect of clinically evident AL on HRQoL
McGiffin et al ²⁶	2022	Australia	Retrospective cross-sectional study	2004–2018	224	Patients undergoing minimally invasive proctectomy with a low extraperitoneal anastomosis and without a temporary diverting ileostomy	Age <18 y and inability to give consent for survey participation, patients with temporary diverting ileostomy	To analyze the timing and management of AL and to evaluate the effect on long-term QoL and functional outcomes using validated instruments
Miura et al ²⁷	2018	Japan	Retrospective cohort study	2000–2012	275	Low rectal adenocarcinoma	Diverting stoma	To evaluate permanent stoma formation and defecation in long-term follow-up after surgery for low rectal cancer without a diverting stoma
Mongin et al ²⁸	2014	France	Retrospective case-matched study	2004–2010	63	Laparoscopic TME for rectal cancer with a follow-up of ≥6 mo and consent to fill in the questionnaires	Permanent or temporary stoma	To assess the influence of AL on long-term functional results and QoL after laparoscopic TME for cancer
Di Re et al ²⁹	2023	Australia	Retrospective case-matched study	2010–2020	122	AL, adult population, benign or malignant colorectal disease	IBD, pouch formation, and redo resections	To assess bowel function and QoL after AL from rectal resections
Riss et al ³⁰	2011	Austria	Retrospective case-matched study	1995–2006	32	TME for rectal cancer; Control group: uneventful postoperative course	Died during follow-up and had no response to questionnaire	To investigate the impact of AL after rectal resection for malignancies on overall pelvic organ function and QoL
Westerduin et al ³¹	2021	The Netherlands, Belgium, and France	Retrospective comparative cohort study	2007–2017	170	TME for rectal cancer, all indications for redo anastomosis; Control group: successful primary anastomosis	Partial mesorectal excision, stoma at the time of questionnaire, inability to read or understand the questionnaires	To compare functional outcomes and the QoL between redo anastomosis and primary successful anastomosis after TME for rectal cancer

AL = anastomotic leakage; CRC = colorectal cancer; HRQoL = health-related quality of life; NA = not applicable; TME = total mesorectal excision.

TABLE 2. Patient characteristics

Reference	Indication for surgery	Type of surgery	AL rate, yes: no (%)		Sex (M:F)		Age, y, mean ± SD or median (IQR)		Comorbidities/ASA				
			AL	No AL	AL	No AL	AL	No AL	ASA	AL	No AL	Clavien-Dindo	
Arron et al ¹⁹	Colon cancer (n = 895)	Open and laparoscopic ileocecal resection, right and left hemicolectomy, transverse resection, sigmoid resection, subtotal colectomy, and LAR	63: 1134 (5.26%)	45: 18	706: 428	64.8	66.6	I	20	343	NA		
	Rectal cancer (n = 302)					(59.7 to 69.7)	(61.7 to 71.6)	II III+	32	635			
Ashburn et al ²⁰	Rectal cancer	Any open or laparoscopic restorative rectal resection	52: 812 (6.02%)	43: 9	519: 293	56.9 ± NA	61.3 ± NA	I	232	8	NA		
								II	1910	395			
								III	26	369			
								IV	1	18			
								V	0	0			
Di Cristofaro et al ²¹	Colon cancer (n = 82)	Any open and laparoscopic colorectal resection	5: 111 (4.31%)		71: 45	69.5 (61–75)		NA			Grade I: 3		
	Rectal cancer (n = 34)										Grade II: 17		
Hain et al ²²	Rectal cancer	Laparoscopic sphincter-saving PME or TME according to the principles of extrafascial dissection	46: 89 (34%) ^a	35: 11	65: 24	60.9 ± 8.3	63.5 ± 9.4	I	13	22	NA		
								II	29	62			
								III	3	3			
van Kooten et al ²³	Rectal cancer	LAR, APR, and Hartmann resection	79: 1128 (6.55%)		767: 440				NA		NA		
						A: 64 (23–88)							
						B: 65 (41–86)							
						C: 66 (26–92)							
Lim et al ²⁴	Rectal cancer (n = 126), adenoma (n = 4), endometriosis (n = 2), Crohn's disease (n = 1), diverticulitis (n = 3) or post-tendomucosal resection (n = 2)	TME with anastomotic distance of ≤ 10 cm from the anal verge	23: 115 (16.67%)	11: 12	72: 43	Clinical 66 (54–81)	Subclinical 62 (51–75)	II	6	4	NA		
								III	5	5			
								IV	2	1			
Marinatos et al ²⁵	Rectal cancer	TME for lower and mid rectum tumors, and PME with transection of the mesorectum at least 5 cm distal to the tumor for upper rectum tumors	25: 50 (33.33%) ^a	15: 10	30: 20	62 ± 15.2	61 ± 16.3	I	1	5	NA		
								II	9	20			
								III	13	23			
								IV	2	2			

(Continued)

TABLE 2. Continued

Reference	Indication for surgery	Type of surgery	AL rate, yes: no (%)	Sex (M:F)		Age, y, mean ± SD or median (IQR)		Comorbidities/ASA				Clavien-Dindo
				AL	No AL	AL	No AL	ASA	AL	No AL		
McGiffin et al ²⁶	Rectal cancer	Laparoscopic and robotic LAR with an extraperitoneal anastomosis	24:200 (10.71%)	15:9	119:81	62 (52–69.8)	65 (56.3–73)	I II III–V	9 14 1	56 106 32	Used but not specified	
Miura et al ²⁷	Rectal cancer	LAR (n = 157) and ISR (n = 118)	60:215 (21.81%)	199:76			64		ASA III–IV 30		Grade I/II: 62 Grade III: 66 Grade IV: 6 Grade V: 1 NA	
Mongin et al ²⁸	Rectal cancer	Laparoscopic sphincter-saving TME	21:42 (33.33%) ^a	4:17	11:31	61 ± 9	60 ± 11		NA			
Di Re et al ²⁹	Colon cancer (n = 16), rectal cancer (n = 55), benign (n = 28) ^c	Laparoscopically, open, robotically, or with conversion LAR (n = 25), ultralow LAR (n = 50), and high anterior resection (n = 25)	61:61 (50%) ^a	43:18	41:20	62.4 ± 12.3	64.1 ± 8.6		Cardiovascular disease n = 14 Diabetes mellitus n = 24 Renal failure n = 4 Lung disease n = 10 Liver disease n = 7		Grade I: 0 Grade II: 39 Grade IIIa: 49 Grade IIIb: 32 Grade IV: NA Grade V: 0	
Riss et al ³⁰	Rectal cancer	ISR, LAR, and APR	16:16 (50%) ^a	11:5	11:5	67 ± 11.2	70 ± 8.4		NA		NA	
Westerduin et al ³¹	Rectal cancer	Open and laparoscopic TME with anastomosis within 3 cm from the dentate line	52:118 (30.59%) ^a	34:18	79:39	63 ± 8.9	68 ± 9.9		NA		NA	

AL = anastomotic leakage; APR = abdominoperineal resection; IQR = interquartile range; ISR = intersphincteric rectal resection; LAR = low anterior resection; NA = not applicable; PME = partial mesorectal excision; TME = total mesorectal excision.

^aAL rates do not reflect the incidence of AL due to the study design.

^bGroup A: no complications, group B: surgical complications, group C: nonsurgical complications, and group D: surgical and nonsurgical complications.

^cBenign indications for resection were irresectable polyps or diverticulitis.

	EORTC QLQ-CR29	EORTC QLQ-C30	SF-36 PCS	SF-36 MCS	Global GIQLI	EORTC IN-PATSAT32	RSCL	FIQL	EQ-VAS	SF-12	CGQL
1 mo											
Di Cristofaro et al. (CR)	⊗	⊗				⊗					
3 mo											
van Kooten et al. (R)							⊖				
Marinatu et al. (R)	⊖	⊖	⊗	⊗	⊖						
6 mo											
Ashburn et al. (R)			⊖	⊖							⊗
Arron et al. (CR)		⊖*									
Di Cristofaro et al. (CR)	⊗	⊗				⊗					
van Kooten et al. (R)							⊖				
Marinatu et al. (R)	⊖	⊖	⊖	⊖	⊖						
>6 mo											
Monging et al.** (R)	⊖		⊗	⊗				⊖			
12 mo											
Ashburn et al. (R)			⊖	⊖							⊗
van Kooten et al. (R)							⊗				
Marinatu et al. (R)	⊖	⊖	⊖	⊖	⊖						
>1 Y											
Ashburn et al. (R)			⊗	⊖							⊗
Westerduin et al. (R)	⊖	⊖									
Hain et al. (R)	⊖										
Di Re et al. (CR)								⊗			
18 mo											
van Kooten et al. (R)							⊗				
2 Y											
Arron et al. (CR)		⊗									
van Kooten et al. (R)							⊗				
>2 Y											
McGiffin et al. (R)			⊗	⊗							
Riss et al. (R)										⊗	
14 Y											
van Kooten et al. (R)	⊗	⊗									
Variable time points (assessed at time of the study)											
Lim et al. (R) Median 26 mo (IQR 19-37 mo)		⊗ ⊖ ***									
Miura et al. (R) Median 63.5 and 63 mo								⊗ ****			
<p>⊖ Significant worse outcomes for AL patients ⊖ Some subscores were significant difference, but not all domains or global QoL</p> <p>⊗ No significant differences between AL and non-AL patients ⊗ Overall score unclear or not specified for AL</p>											

FIGURE 2. Schematic overview of results of QoL questionnaires based on different time points. *Not statistically significant but on an individual level AL was a determinant of a clinically relevant decrease; **at least 6 mo after the restoration of bowel continuity; ***subgroup: in patients with no stoma closure, there was a difference; ****modified version of the questionnaire. AL = anastomotic leakage; CGQL = Cleveland Global QoL questionnaire; EORTC = European Organization for Research and Treatment of Cancer; EQ-VAS = the EuroQoL Visual Analog Scale; FIQL = Fecal Incontinence; GIQLI = GI QoL Index; IQR = interquartile range; IN-PATSAT32 = inpatient satisfaction; MCS = mental component summary; PCS = physical component summary; QLQ-CR29 = QoL Questionnaire colorectal cancer-specific; QLQ-CR30 = QoL Questionnaire cancer-specific; QoL = quality of life; SF-12 = 12-item Short-Form survey; SF-36 = 36-item Short-Form survey; RSCL = Rotterdam Symptoms Check List.

TABLE 3. Detailed overview of questionnaires and impaired domains if applicable

Reference	Time of assessment after surgery	Questionnaire	Significant impaired domains (in favor of patients without AL patient)	p	Groups compared
Arron et al ^{19a}	6 mo	EORTC QLQ-C30	Summary score ^b Role function Social function Global QoL ^b Physical function ^b Emotional function ^b Multivariable linear regression analysis	0.00 0.00 0.00 0.01 0.01 Not significant	AL vs non-AL after colorectal surgery at time of assessment and compared to baseline
	2 y	EORTC QLQ-C30	No significant outcomes Multivariable linear regression analysis	- Not significant	
Ashburn et al ^{20c}	6 mo and 1 y > 1 y (range, 1–6 y)	SF-36 PCS SF-36 MCS CGQL SF-36 PCS SF-36 MCS CGQL	NA NA Unclear NA NA Unclear	0.01 0.007 Unclear Not significant 0.02 Unclear	AL vs non-AL after restorative proctectomy at time of assessment (not compared to baseline)
Di Cristofaro et al ^{21d,ef}	1 mo	EORTC QLQ-CR29 EORTC QLQ-C30 EORTC IN-PATSAT32	Outcomes of questionnaires not specified for patients with AL Multivariate analysis for AL: $\beta = 0.42$	0.01	Patients without complications vs with complications at time of assessment (not compared to baseline)
	6 mo	EORTC QLQ-CR29 EORTC QLQ-C30 EORTC IN-PATSAT32	Outcomes of questionnaires not specified for patients with AL Multivariate analysis for AL: $\beta = 0.52$	0.004	
Hain et al ^{22g}	Variable, at time of the study (ranging from 1 to 10 y; mean 46 mo \pm 26 after restoration of bowel continuity)	EORTC QLQ-CR29	Blood and mucus in stool Frequent bowel movements per day	0.045 0.04 0.03	Patients with symptomatic AL vs nonsymptomatic AL and patients without AL after rectal surgery at time of assessment (no baseline assessment performed)
van Kooten et al ^{23g}	3, 6, 12, 18, and 24 mo 14 y	RSCL EORTC QLQ-C30 EORTC QLQ-CR29 EORTC QLQ-C30	Frequent urination per day Global health Activity level NA NA NA (only global score given)	.01 0.01 Not significant Not significant 0.03	AL vs non-AL after rectal surgery compared to baseline
Lim et al ^{24d,e}	Variable, at time of the study (median 26 mo; IQR, 19–37 mo)	EORTC QLQ-C30	Clinical leaks without stoma closure compared to subclinical leaks, clinical leaks with stoma closure and patients without AL after rectal surgery at time of assessment (no baseline assessment performed)	0.03	

(Continued)

TABLE 3. Continued

Reference	Time of assessment after surgery	Questionnaire	Significant impaired domains (in favor of patients without AL patient)	p	Groups compared			
Marinatou et al ^{25d}	3 mo	EORTC QLQ-C30	Physical function	0.008	AL vs non-AL after rectal surgery at time of assessment (not compared to baseline)			
		GIQLI	Physical function	0.03				
		EORTC QLQ-CR29	Abdominal and pelvic pain	0.03				
			Stoma-related problems	0.03				
	6 mo	SF-36	Sore skin	0.04				
			NA	Not significant				
		EORTC QLQ-C30	Physical function	0.03				
			Global health status/QoL	0.002				
		GIQLI	Emotional function	0.008				
			Physical function	0.004				
McGiffin et al ^{26d}	12 mo	EORTC QLQ-CR29	Global score	0.01	AL vs non-AL after colorectal surgery at time of assessment (no baseline assessment)			
			Stoma-related problems	0.002				
		SF-36	Sore skin	0.03				
			Role limitations due to physical health	0.01				
	EORTC QLQ-C30	Role limitations due to emotional problems	0.02					
		Social functioning	0.008					
		General health	0.03					
		Global health status/QoL	0.004					
		Emotional function	0.007					
		GIQLI	Physical function	0.03				
Miura et al ^{27d}	12 mo	EORTC QLQ-CR29	Global score	0.005	AL vs non-AL after rectal surgery at time of assessment (no baseline assessment)			
			Sore skin	0.005				
		SF-36	Physical functioning	0.04				
			Role limitations due to physical health	0.001				
	EORTC QLQ-C30	Role limitations due to emotional problems	0.003					
		Social functioning	0.009					
		General health	0.002					
		NA	Not significant					
		SF-36 PCS	NA	Not significant				
			SF-36 MCS	NA				
Mongin et al ^{28d}	Variable, at time of the study (median 6.4 y [IQR, 3.1–8.6]) and 4 y [IQR, 2.7–8.5] for no AL and AL group, respectively)	modified FIQL	NA	Not significant	AL vs non-AL after rectal surgery at time of assessment (no baseline assessment)			
			NA	Not significant				
		SF-36 PCS	NA	Not significant				
			SF-36 MCS	NA				
	Variable, at time of the study (median 63.5 and 63 mo for no AL and AL group, respectively)	SF-36 PCS	NA	Not significant				
			SF-36 MCS	NA				
		EQ-VAS	NA	Not significant				
			SF-12	NA				
		Di Re et al ^{29h}	Variable, at time of the study (range, 1–>5 y)	EQ-VAS		NA	Not significant	AL vs non-AL after colorectal surgery at time of assessment (no baseline assessment)
						NA	Not significant	
SF-12	NA			Not significant				
	NA			Not significant				
Variable, at time of the study (median 106.8 mo [range, 32.4–170.4])	EQ-VAS		NA	Not significant				
			SF-12	NA				
	EQ-VAS		NA	Not significant				
			SF-12	NA				
	EQ-VAS		NA	Not significant				
			SF-12	NA				

(Continued)

TABLE 3. Continued

Reference	Time of assessment after surgery	Questionnaire	Significant impaired domains (in favor of patients without AL patient)	p	Groups compared
Westerduin et al ^{31d}	> 1 y (median of 41 mo [IQR, 23–71] and 27 mo [IQR, 16–43] for no AL and AL group, respectively)	EORTC QLQ-C30	Role function Social function Overall global health Fatigue Pain Body image Anxiety	0.049 0.006 0.002 0.04 0.002 0.03 0.02	AL vs non-AL after rectal surgery at time of assessment (no baseline assessment)
		EORTC QLQ-CR29	Abdominal pain Buttock pain Flatulence Fecal incontinence Sore skin	0.03 0.005 0.008 0.03 0.0007	

AL = anastomotic leakage; CGQL = Cleveland Global QoL; EORTC = European Organization for Research and Treatment of Cancer; EQ-VAS = the EuroQoL Visual Analog Scale; FIQL = Fecal Incontinence QoL; FIJI = Fecal Incontinence Severity Index; GIQJ = Gastrointestinal QoL Index; IN-PATSAT32 = inpatient satisfaction; IQR = interquartile range; MCS = mental component score; NA = not applicable; PCS = physical component score; QLQ-CR29 = QLQ colorectal cancer-specific; QLQ-CR30 = QoL Questionnaire cancer-specific; QoL = quality of life; RSCL = Rotterdam Symptom Check List; SF-12 = 12-item Short-Form survey; SF-36 = 36-item Short-Form survey.

^dNot clinically relevant.

^eWilcoxon rank sum tests.

^fMann-Whitney U test.

^gKruskal-Wallis ANOVA.

^hMultivariate analysis.

ⁱUnivariate and multivariate logistic regression.

^jWald's tests using linear mixed-effects model and univariable Poisson regression analysis; Paired samples t test.

^kStatistical analysis unclear.

van Kooten et al²³ found that patients who developed AL reported a decrease in RSCL global health status and activity level within the first 3 months compared to preoperative scores, with some improvement at 6 months. In contrast, Marinatou et al²⁵ did not document any improvement based on GIQLI and EORTC QLQ-C30 questionnaires administered at 3 and 6 months. Instead, a significant decline in physical functioning and global and overall QoL scores was documented among patients with AL relative to patients without AL at 6 months.²⁵ Additional results from EORTC QLQ-C29 demonstrated significantly worse scores with respect to pain, stoma, and perianal skin-related complaints at 3 and 6 months in patients with AL. Also, SF-36 scores demonstrated significantly worse function among patients with AL versus patients without AL at 6 months, especially along emotional and social domains, which was not seen at 3 months. Impairments in functional outcomes based on SF-36 scores were also reported by Ashburn et al²⁰ among patients with AL compared to patients without AL after proctectomy. Arron et al¹⁹ demonstrated that the decrease in EORTC QLQ-C30 scores observed among patients with AL at 6 months relative to patients without AL did not meet the threshold for clinical relevance, and AL status was not associated with the observed decrease. Among patients with a clinically relevant decrease in their 6-month scores relative to baseline, AL was an independent predictor of this decrease based on multivariate regression analysis.¹⁹

QoL at 12 months after surgery. Three studies reported QoL at 1 year after CRC resection.^{20,23,25} van Kooten et al²³ demonstrated that HRQoL scores returned to baseline preoperative levels among rectal cancer patients with and without complications, whereas Marinatou et al²⁵ demonstrated persistently significant differences between AL and non-AL groups for perianal skin soreness and worse overall EORTC QLQ-C30, global GIQLI, and SF-36 scores. Ashburn et al²⁰ also documented significantly worse SF-36 scores in both the PCS and MCS domains at 1 year postoperatively in patients with AL compared to those without AL after restorative proctectomy.

Beyond 1 year after surgery. Mongin et al²⁸ evaluated QoL in patients undergoing restoration of bowel continuity at least 6 months before the assessment. Given that the median time of QoL assessment was 33 versus 30 months in patients with versus without AL, results were interpreted as representing longer-term QoL. No difference in SF-36 scores were found between the 2 groups. However, “blood and mucus in stool” scores of the EORTC QLQ-CR29 indicated significantly worse function in patients with AL, as did depression/self-perception FIQL scores. Ashburn et al noted that although the SF-36 PCS scores did not show significant differences beyond 12 months postoperatively (median, 3.2 years), MCS scores were still significantly

worse in patients with AL after proctectomy.²⁰ Westerduin et al³¹ identified 5 domains of the EORTC QLQ-30 and 2 functional and 5 emotional domains of the -CR29, which were significantly better beyond 1 year postoperatively in patients with AL compared to patients without AL. Hain et al²² reported additional impaired -CR29 outcomes (more blood and mucus in stool, frequent bowel movements, and frequent urination per day) in patients with symptomatic AL compared to the combined groups of patients with no or asymptomatic AL. Di Re et al²⁹ also demonstrated lower mean EuroQoL visual analog scale scores among patients with AL versus patients without AL in a matched cohort at 1 year after surgery (range up to 5 years), although the difference did not reach statistical significance.

At 18 and 24 months postoperatively, van Kooten et al found no differences in RSCL scores between patients with AL and patients without AL.²³ Arron et al¹⁹ found no difference in overall HRQoL scores between patients with AL and patients without AL at 2 years relative to baseline EORTC QLQ-C30 scores.¹⁹ Similar results were described when SF-36 scores were compared >2 years after surgery between patients with AL (median of 4 years postoperatively) and without AL (median of 6.4 years postoperatively).²⁶ Riss et al³⁰ described no significant difference in mental and physical QoL scores measured by the 12-item Short-Form survey at a median follow-up time of 106.8 months after rectal surgery (range of 32.5–170.4 months) comparing AL to no AL patients from a matched cohort.

Two additional studies evaluated the longer-term impact of AL on QoL.^{24,27} Lim et al²⁴ assessed the EORTC QLQ-C30 in patients without AL, with subclinical leaks, and with clinical leaks with and without ileostomy closure (overall median follow-up time of 26 months; interquartile range, 19–37 months). They found worse scores in patients with clinical leaks in whom ileostomy reversal was not possible. Miura et al²⁷ did not find significant differences in overall modified FIQL scores when comparing patients with AL and patients without AL at a median time of 63 months after low rectal cancer surgery.

van Kooten et al²³ conducted a supplementary analysis on EORTC QLQ-C30 and -CR29 outcomes 14 years postsurgery but found statistically significant differences between patients with AL and patients without AL.²³

Other Outcomes Related to QoL

Some additional outcomes that might influence QoL are summarized in Supplemental S6 at <http://links.lww.com/DCR/C410>. Neoadjuvant treatments were described by 9 studies,^{19,20,22,24,25,28–31} 1 of which found chemoradiation to be significantly different between patients with AL and patients without AL and 1 of which found radiotherapy to be significantly different.^{25,31} Diverting stoma rates between patients with AL and patients without AL were compared in 6 studies,^{19,20,25,29–31} of which 2 found significant differences (more diverting in the AL group).^{20,30}

Stoma status during follow-up was clearly described by 2 studies,^{19,25} which showed significant differences between patients with AL and patients without AL within the first year after surgery. Two additional studies described permanent stoma rates related to AL.^{24,27} Di Re et al²⁹ additionally analyzed oncological outcomes as disease-free survival at 1, 3, and 5 years after surgery, and they found that rates were not significantly different between patients with AL and patients without AL. Overall, there was a lack of comparing types of (re-)interventions.

DISCUSSION

This systematic review appraised and synthesized the evidence on the impact of AL on QoL after oncological colorectal resections. In total, the studies comprised 4618 individual patients, with an overall incidence of AL of 12.4% (N = 572). QoL was assessed using 10 validated questionnaires administered at postoperative time points ranging from 1 month to 14 years. Overall, AL was found to negatively impact QoL at 6 and even 12 months postoperatively, with variable degrees of subsequent improvement. The heterogeneity in questionnaires administered and variable times of assessment hindered our data analysis and may account for some conflicting results across studies. In a comprehensive systematic review of research studies on QoL and HRQoL, Haraldstad et al³³ concluded that the majority experienced conceptual and methodological challenges with no clear consensus on how QoL should be measured. The use of various assessment tools and questionnaires in different studies hinders meaningful comparisons between similar study populations.³⁴ Adoption of the standard set of outcomes for CRC proposed by the International Consortium for Health Outcomes Measurements (ICHOM) may avoid some of these issues.³⁵ In this consortium, it was recommended to use the EORTC QLQ-C30 tool to capture overall QoL and the -CR29 to capture CRC-specific outcomes. The optimal time for QoL assessment was also addressed, with recommendations to administer questionnaires at baseline (before surgery), 6 months after surgery, and then annually for up to 10 years. Our research team suggests following the ICHOM recommendations.

Other patient and treatment variables such as the ASA score, BMI, anastomotic height, and adjuvant radiotherapy may impact QoL after CRC resections.³⁶⁻³⁹ Only 2 of the 13 included studies performed multivariate logistic regression analyses to investigate whether differences in QoL scores observed between AL and non-AL groups were due to the leak or driven by other factors such as neoadjuvant treatment, surgical procedure, or reintervention.^{19,22} Ideally, all studies should have performed such an analysis to verify whether AL is an independent factor that influences QoL. Besides, not all studies compare outcomes relative to baseline function, which weakens the

interpretation of the functional scores at subsequent postoperative time points. As a result, it was difficult to draw valid conclusions comparing the included studies.

The observed decline in QoL scores reported among patients with AL in the first 6 and even 12 months may be due to several reasons. AL delays recovery and results in additional postoperative complications, higher rates of reintervention, and increased mortality within the first 30 days after surgery.^{4,40} This often prolongs the length of hospital stay and adversely impacts mobility and the ability of patients to care for themselves.⁴¹⁻⁴³ Furthermore, some patients require stoma construction, which impairs role and social functioning scores.⁴⁴ In the current study, there was a lack of correlation between stoma status and QoL outcomes. One study excluded patients with a stoma,²⁸ whereas other studies did include them but did not draw strong conclusions on any association between stoma formation and QoL scores. AL has also been associated with higher rates of local recurrence and distant metastases in patients with CRC.^{45,46} Although smaller cohort studies have not found the same association between AL and colon cancer outcomes, the fear of (local) recurrence, as well as additional treatments required to mitigate the higher risk of recurrence, may further negatively impact QoL.^{47,48} Moreover, AL has been shown to be an independent risk factor for worse defecatory function (low anterior resection syndrome) and sexual function after CRC resections.⁴⁹⁻⁵² Although these functional outcomes were not specifically assessed in the current study, it is crucial to consider their impact on overall QoL.⁵³

To our knowledge, this is the first systematic review of the effects of AL on QoL in patients undergoing oncological colon and rectal resections. This study has limitations. First, a high heterogeneity in AL reporting was found in the included articles. It was often unclear what type of intervention and reoperation was performed to manage leaks. Because these elements are important when comparing outcomes, standardizing the reporting and management of leaks would be helpful. Subsequently, some studies only included patients with rectal cancer, whereas others included all types of colorectal surgeries. Second, a wide range of QoL questionnaires and time frames for assessment was used across the different studies. Although only studies using validated instruments were included, the heterogeneity of questionnaires created challenges when comparing outcomes across studies and interpreting results. The use of patient-centered methods, such as patient-reported outcome measures, may be even more informative to gain more insight into overall changes.⁵⁴ Due to the heterogeneity of the included studies, comparisons across studies are limited and a meta-analysis was not possible to perform. Finally, all included studies demonstrated a moderate to serious risk of bias, which results in a low level of evidence, and caution is warranted by the presented findings.

CONCLUSIONS

This systematic review demonstrated that QoL of patients with CRC may be compromised after AL up to 1 year, but assessment and reporting of QoL needs to be standardized to draw clear conclusions. In addition to exploring strategies for preventing and effectively managing AL, it is crucial to investigate long-term sequelae on patients' QoL in future research. We recommend incorporating a standardized QoL assessment for patients with CRC who have experienced AL and integrating this outcome measure into a core outcome set for research focused on AL in the colorectal field. Continuous assessment and monitoring of QoL in patients undergoing CRC resection is essential to better support patients throughout their recovery. We emphasize the relevance of uniform reporting of AL outcomes to facilitate comparisons of results in future research. To reach this goal, we advise following the proposed questionnaires and time point as described by the CRC ICHOM working group,³⁵ and work on a standardized reporting framework for AL-related research within the Consensus on Reporting and Defining Colorectal Anastomotic Leaks project.

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