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ORIGINAL ARTICLE

The REAL (REctal Anastomotic Leak) score for prediction of anastomotic leak after rectal cancer surgery

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Abstract

Background Anastomotic leak after rectal cancer surgery is a severe complication associated with poorer oncologic outcome and quality of life. Preoperative assessment of the risk for anastomotic leak is a key component of surgical planning, including the opportunity to create a defunctioning stoma.

Objective The purpose of this study was to identify and quantify the risk factors for anastomotic leak to minimize risk by either not restoring bowel continuity or protecting the anastomosis with a temporary diverting stoma.

Methods Potentially relevant studies were identified from the following databases: PubMed, Embase and Cochrane Library. This meta-analysis included studies on transabdominal resection for rectal cancer that reported data about anastomotic leak. The risk for anastomotic leak after rectal cancer surgery was investigated. Preoperative, intraoperative, and postoperative factors were extracted and used to compare anastomotic leak rates. All variables demonstrating a p value < 0.1 in the univariate analysis were entered into a multivariate logistic regression model to determine the risk factors for anastomotic leak.

Results Twenty-six centers provided individual data on 9735 patients. Selected preoperative covariates (time before surgery, age, gender, smoking, previous abdominal surgery, BMI, diabetes, ASA, hemoglobin level, TNM classification stage, anastomotic distance) were used as independent factors in a logistic regression model with anastomotic leak as dependent variable. With a threshold value of the receiver operating characteristics (ROC) curve corresponding to 0.0791 in the training set, the area under the ROC curve (AUC) was 0.585 ($p < 0.0001$). Sensitivity and specificity of the model's probability > 0.0791 to identify anastomotic leak were 79.1% and 32.9%, respectively. Accuracy of the threshold value was confirmed in the validation set with 77.8% sensitivity and 35.2% specificity.

Conclusions We trust that, with further refinement using prospective data, this nomogram based on preoperative risk factors may assist surgeons in decision making. The score is now available online (http://www.real-score.org).

Keywords Rectal cancer · Anastomotic leak · Score

Introduction

Anterior resection is the most common surgical procedure for rectal cancer and forms the cornerstone of curative therapy. The number of sphincter-saving procedures has increased thanks to advances in surgical technique, better stapling devices and bowel reconstruction techniques, and wider acceptance of the concept of total mesorectal excision with less extensive distal margins, as well as improved oncologic outcomes after neoadjuvant therapy.

Restoration of intestinal continuity is a critical step after anterior rectal resection. Colorectal and coloanal anastomoses carry a high risk for leak during the early postoperative period. Additional surgery with creation of a stoma is

REAL Score Collaborators members are listed in "Acknowledgements" section.

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performed to minimize leak complications and avoid potentially life-threatening complications. There is conflicting evidence, however, about the impact of anastomotic leak (AL) after colorectal cancer surgery not only on long-term overall and cancer-specific survival, but also on rates of local recurrence [1–3]. A recent meta-analysis of 21 studies, involving a total of 21,902 patients, demonstrated that AL had a negative impact on local recurrence and long-term survival after restorative resection for rectal cancer [4].

Identifying and quantifying the risk factors for AL are important for minimizing risk by either not restoring bowel continuity or protecting the anastomosis with a temporary diverting stoma.

The need for accurate assessment of risk factors for AL and the relative rarity of this event after anterior rectal resection prompted us to undertake this individual participant data meta-analysis.

Materials and methods

An individual participant data meta-analysis (IPD-MA) of studies on rectal cancer surgery published between 2000 and 2015 was performed. The SYREAL (SYstematic review of risk factors for REctal Anastomotic Leak) study was registered with PROSPERO (CRD42016043053). The literature was systematically reviewed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Individual Participant Data checklist (PRISMA-IPD) guidelines [5].

Search strategy

We systematically searched the electronic databases of Embase, PubMed, and Cochrane Library up to 1 March 2015 using the following syntax ('rectum tumor'/exp/mj or 'colon tumor'/exp/mj or 'colorectal carcinoma'/exp/mj or 'colon carcinoma'/exp/mj or 'rectum carcinoma'/exp/mj) and ('rectum anterior resection'/exp/mj or 'mesorectal excision') and [english]/lim and [2000–2015]/py and [humans]/lim and ([article]/lim or [article in press]/lim). All titles were screened and appropriate abstracts reviewed.

Inclusion criteria

Studies on transabdominal resection for rectal cancer that reported data about AL were selected for inclusion.

Exclusion criteria

Articles not mentioning AL after rectal cancer surgery, overlapping studies, case reports, case series with less than 20 patients treated for rectal cancer, reviews, consensus statements, and opinion articles.

Extraction process

Two reviewers (PC, MMi) performed the search independently; a third author (AA) arbitrated any disagreements on inclusion or exclusion of studies. Studies and results were entered into a standardized database and duplicates removed. The reference lists of the included studies were searched manually. Only the data of patients who had rectal cancer surgery followed by an anastomosis were included. A flowchart of the extraction process is shown in Fig. 1.

Outcomes of interest

Preoperative [age, sex, body-mass index (BMI), tobacco use, diabetes, American Society of Anesthesiologists (ASA) grade, preoperative radiotherapy (RT) and/or chemotherapy (CT), time between the completion of neoadjuvant radiotherapy and surgery], intraoperative (operative time, anastomotic type, tumor distance from anal verge, protective stoma, pelvic drain, TNM classification stage), and postoperative (AL, blood transfusion) factors were extracted and used to compare AL rates.

The authors of the studies deemed suitable were contacted up to four times via e-mail (or phone if no e-mail was available); they were sent an electronic spreadsheet and asked to complete it with their data anonymously. The returned spreadsheets were collected and the data merged into one database for analysis.

Statistical analyses

Values are presented as means and standard deviation, or median and inter-quartile range. Categorical variables are shown with frequency and proportion. Comparison between patients with and without AL was made using the t test for continuous variables and the Chi square for categorical variables.

Missing values were imputed for a set of a priori selected variables: use of tobacco, need of blood transfusions, anastomotic distance and tumor distance from the anal verge, TNM classification stage for colorectal cancer, diabetes, BMI, interval from end of radio(chemo)therapy to surgery and operative time. Multiple Imputation (MI) [6] using fully conditional specification methods was performed [7, 8]. Linear and logistic regression models were used for continuous and categorical variables, respectively. The imputation model includes auxiliary variables (i.e. age, gender, BMI) that are strongly correlated with the dependent variable to obtain an efficient inference [9].

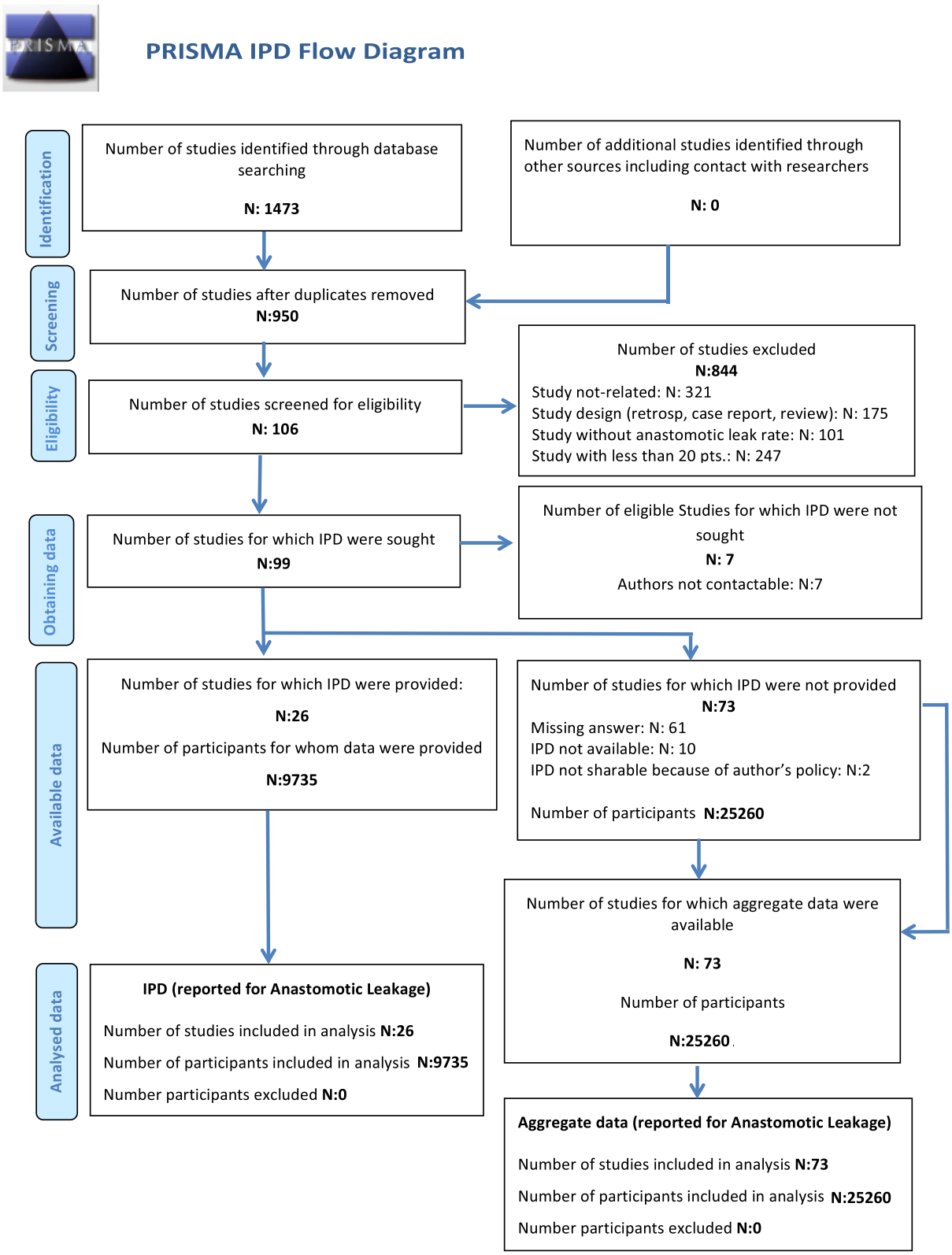

Fig. 1 Flowchart diagram illustrating the systematic search and study selection strategy

Imputed values were used to predict other variables with missing data (MI by chained equations). Eighty data sets were imputed, according to the recommendations for creating data sets in the presence of missing data to obtain more stable parameters estimates and better standard error estimates [10]. A univariate analysis was performed to investigate which variables were candidates to be risk factors for AL. For each variable without MI we performed, a logistic regression model; odds ratio (OR) and 95% relative confidence interval (95% CI) level were calculated. For variables with MI each of the eighty imputed datasets was analyzed separately using logistic regression and parameter estimates were combined into a single set of statistics that appropriately reflect the uncertainty associated with the imputed values.

Finally, all variables demonstrating a p value < 0.1 in the univariate analysis were entered into a multivariate logistic regression model to determine the risk factors for AL.

To avoid working with several multiple datasets we calculated the mean predicted values across all iterations (binary variables will be informed by looking at the most frequent output imputed). A total of 9735 patients were divided into datasets with simple random sampling, without replacement, where each unit has an equal probability of selection. We obtained a training set with 6814 patients (70%); the remaining 30% where allocated in the validation set corresponding to 2931 patients.

All available preoperative covariates (time before surgery, age, gender, smoking, previous abdominal surgery, BMI, diabetes, ASA, hemoglobin level, TNM classification stage, anastomotic distance) were used as independent factors in a logistic regression model with AL as dependent variable. A receiver operating characteristic curve (ROC) analysis was generated to evaluate the model's ability to detect the risk of AL. Results were presented as area undercurve (AUC) with a 95% level of confidence interval (95% CI).

We selected as threshold (cut-off) the value that allowed a missing rate of AL < 2%. The predictive power of the previously selected cut-off was validated in an independent set of patients (validation set); sensitivity and specificity with the relative 95% CI, positive and negative likelihood ratios are reported.

All computations and analyses, including univariate and multivariate approach, were performed using SAS version 9.4 for Windows.

Results

In all, 99 articles were selected and the corresponding authors contacted (Fig. 1). Twenty-six individual participant data (IPD) series were made available [11–36], for a total of 9735 patients who underwent rectal cancer surgery with anastomosis. Patient characteristics are presented in Tables 1, 2, 3 and 4. Tables 1 shows patient characteristics collected before surgery per each center. Table 2 shows the (y)pT and (y)pN of patients included per each center. Table 3 shows intraoperative patient characteristics, stratified per center. Number of AL, number of days between intervention and AL, number of reinterventions for AL and median overall survival per each center are reported in Table 4.

AL was reported in 941 patients (9.7%); the rate ranged from 0.0 to 36.3% and was generally notably higher in the larger trials. A consistent proportion of missing values was observed for some of the variables used in risk analysis for AL. The evaluation of risks associated with AL was based on an outcome variable without missing data per each center, as shown in Table 5. This table presents demographics and most relevant clinical characteristics of patients with and without AL.

Table 6 shows the results of the multivariate binary logistic regression models of risk factors for AL. Significant risk factors were gender (male) [OR = 1.1985, 95% CI 1.1118–1.2920], short-course preoperative RT [OR = 1.2229, 95% CI 1.0781–1.3873], $T(4)$ [OR = 1.2458, 95% CI 1.0674–1.4541], N (≥ 1) [OR = 1.0611, 95% CI 0.9887–1.1389], need for peroperative blood transfusions [OR = 1.4361, 95% CI 1.2962–1.5911] and anastomotic distance from the anal verge [OR = 0.9388, 95% CI 0.9065–0.9723].

Factors not associated with increased risk of AL were advanced age, obesity, tobacco use, diabetes, ASA grade, node and metastasis staging, preoperative long-course CT and RT alone, time between neoadjuvant therapy and surgery > 5 weeks, operative time, manual or stapled anastomosis and the presence of a pelvic drain.

With the aim of generating and validating a specific scoring and grading system for the risk of AL after rectal cancer surgery, we performed a multivariable logistic regression in the training set (6814 patients) using all available preoperative covariates to predict AL (Table 7). The AUC was calculated and reported in Fig. 2; the AUC was found to be statistically significant with $p < 0.0001$. Criterion values and coordinates of the ROC curve are shown with corresponding values of sensitivity and specificity, stratified by percentile (Table 8). Sensitivity and specificity of the model's probability > 0.0791 to identify AL were 79.1% and 32.9%, respectively (Table 9). Accuracy of the threshold value was confirmed in the validation set with 77.8% of sensitivity and 35.2% specificity. Positive and negative likelihood ratios were reported for assessing the value of performing test (Table 9).

In a cross table (Table 10) we summarize and display the results of the predictive score and what was really done according to clinical practice. The table shows that within the validation set 1373 patients (47%) received a stoma, but

Table 1 Preoperative characteristics of patients undergoing surgery for rectal cancer

Authors	*N*	Age, years mean (SD)	Sex, male, *n* (%)	BMI mean (SD)	Smoker no. (%)	Diabetes no. (%)	ASA score 1/2/3/4	Abdominal surgery no. (%)	Hb level (g/dL) (SD)	Neoadjuvant therapy no. (%)	Chemotherapy no. (%)	Long (L) or short (S)-term RT no. (%)	Weeks btw. RT and-surgery (SD)	Pelvic RT no. (%)
Peeters 2004	923	64 (11)	569 (62)	25.4 (3.8)	//	//	//	//	//	440 (48)	0 (0)	S 440(48) L 0 (0)	3.8 (1.6)	//
Law 2004	622	66 (12)	395 (64)	//	//	77 (12)	353/90/2/0	//	12.4 (1.8)	22 (4)	22 (4)	S 0(0) L 21(3)	6.0 (0)	//
Eriksen 2004	1958	68 (11)	1129 (58)	//	//	//	//	//	//	59 (3)	0 (0)	S 0(0) L 59(3)	//	//
Morino 2005	98	64 (13)	55 (56)	//	//	//	35/13/0/0	/	//	1 (1)	0 (0)	S 1(1) L 0(0)	6 (0)	//
Bujko 2005	171	60 (9)	104 (61)	//	//	//	//	//	//	170 (99)	82 (48)	S 87(51) L 81(47)	3.7 (3.0)	//
Palanivelu 2006	170	58 (13)	88 (52)	29.8 (6.1)	39 (23)	34 (20)	23/11/0/0	//	11.6 (1.8)	31 (18)	31 (18)	S 0(0) L 27(16)	6.7 (0.9)	0 (0)
Veenhof 2007	46	65 (13)	29 (63)	25.2 (2.8)	///	1 (2)	//	16 (9)	//	46 (100)	0 (0)	S 46(100) L 0(0)	4.2 (2.8)	//
Navarro 2007	85	63 (12)	55 (65)	28.2 (3.2)	23 (27)	11 (13)	29/7/0/0	13 (28)	12.5 (1.4)	47 (55)	47 (55)	S 0(0) L 47(55)	5.8 (0.5)	0 (0)
Biffi 2007	33	55 (5)	17 (52)	23.2 (2.2)	5 (15)	4 (12)	28/5/0/0	18 (21)	11.4 (1.4)	33 (100)	10 (30)	S 0(0) L 33 (100)	2.3 (0.5)	0 (0)
Bertelsen 2008	1495	66 (10)	863 (58)	25.3 (4.1)	304 (27)	75 (13)	732/164/14/0	16 (49)	//	253 (17)	0 (0)	S 0(0) L 253(17)	//	//
Velenik 2009	28	56 (10)	24 (86)	26.1 (4.0)	2 (7)	2 (7)	//	//	14.0 (1.8)	28 (100)	28 (100)	S 0(0) L 28(100)	6.2 (1.0)	0 (0)
Swellengrebel 2010	47	61 (11)	26 (55)	25.5 (5.2)	14 (37)	2 (9)	//	6 (21)	//	47 (100)	47 (100)	S 0(0) L 47(100)	5.7 (1.3)	2 (4)
Sartori 2010	174	64 (11)	140 (81)	24.2 (4.4)	9 (26)	5 (14)	12/23/0/0	20 (43)	//	68 (39)	68 (39)	S 4(2) L 64(37)	7.0 (0)	6 (3)
Skrovina 2011	114	63 (9)	73 (64)	26.8 (3.0)	//	//	45/65/4/0	7 (20)	//	48 (42)	48 (42)	S 0(0) L 48 (42)	6.3 (0.9)	//
Motson 2011	16	59 (8)	8 (50)	//	//	//	//	//	//	16 (100)	16 (100)	S 0(0) L 16(100)	12.5 (2.7)	//
Jarry 2011	100	63 (12)	70 (70)	//	//	//	34/18/0/0	//	//	70 (70)	18 (18)	S 0(0) L 52 (52)	6 (0)	//
Araujo 2011	26	62 (7)	12 (46)	//	4 (15)	5 (19)	11/0/0/0	15 (58)	12.0 (0.9)	26 (100)	26 (100)	S 0(0) L 26(100)	10.0 (2.6)	0 (0)
Akiyoshi 2011	363	61 (11)	222 (61)	22.8 (3.3)	173 (48)	39 (11)	199/9/0/0	107 (30)	13.3 (1.5)	29 (8)	1 (0.3)	S 1(0.3) L 27(7)	6.8 (1.6)	1 (0.3)

Table 1 (continued)

Authors	*N*	Age, years mean (SD)	Sex, male, *n* (%)	BMI mean (SD)	Smoker no. (%)	Diabetes no. (%)	ASA score 1/2/3/4	Abdominal surgery no. (%)	Hb level (g/dL) (SD)	Neoadjuvant therapy no. (%)	Chemotherapy no. (%)	Long (L) or short (S)-term RT no. (%)	Weeks btw. RT and-surgery (SD)	Pelvic RT no. (%)
Lim 2012	429	55 (10)	287 (67)	23.6 (3.5)	//	41 (10)	//	//	//	429 (100)	424 (99)	S 0(0) L 429(100)	5.2 (1.9)	//
Beirens 2012	1906	66 (11)	1190 (62)	25.7 (4.6)	//	//	507/930/319/7	//	//	1390 (73)	1109 (59)	S 0(0) L 1350(72)	6.6 (1.9)	//
Lange 2013	368	61 (13)	226 (61)	//	//	//	//	//	//	141 (38)	133 (36)	S 0(0) L 136(37)	//	//
Parisi 2014	35	66 (13)	16 (46)	25.6 (3.3)	//	4 (11)	13/6/0/0	9 (26)	//	15 (43)	15 (43)	S 0(0) L 15(43)	//	15 (43)
Maggiori 2014	146	61 (11)	94 (64)	25.3 (4.7)	2 (5)	14 (14)	98/7/0/0	8 (7)	//	146 (100)	146 (100)	S 0(0) L 116(79)	7.5 (3.0)	0 (0)
Hidaka 2014	205	64 (11)	129 (63)	21.5 (3.3)	30 (15)	8 (4)	29/1/0/0	57 (28)	13.7 (1.7)	//	0 (0)	//	//	0 (0)
Brachet-Contul 2014	132	65 (10)	78 (59)	24.8 (4.5)	//	//	80/39/3/0	//	//	68 (52)	36 (27)	S 0(0) L 64(49)	7.0 (0)	1 (0.8)
Barnajian 2014	45	61 (11)	30 (67)	28.2 (5.3)	7 (16)	8 (18)	0/11/32/2	16 (36)	13.3 (1.4)	21 (47)	0 (0)	S 0(0) L 22(49)	12.2 (3.8)	0 (0)

% Are referred to available data without considering missing values

Table 2 Oncologic characteristics of patients having surgery for rectal cancer

Authors	T *n* (%)						N *n* (%)			M1 *n* (%)	Tumor distance from ano-rectal junction, cm mean (SD)
	0	In situ	1	2	3	4	0	1	2		
Peeters 2004	16 (1.7)	7 (0.8)	58 (6.3)	287 (31.1)	527 (57.1)	28 (3.0)	543 (58.8)	217 (23.5)	163 (17.7)	44 (4.8)	8.5 (2.9)
Law 2004	12 (2.0)	7 (1.2)	32 (5.4)	102 (17.2)	416 (70.3)	23 (3.9)	340 (55.1)	177 (28.7)	100 (16.2)	61 (9.8)	9.8 (4.5)
Eriksen 2004	0 (0.0)	11 (0.6)	188 (9.6)	495 (25.3)	1139 (58.2)	125 (6.4)	1305 (66.7)	46 (23.5)	193 (9.9)	0 (0)	10.5 (3.1)
Morino 2005	5 (5.1)	34 (34.7)	13 (13.3)	15 (15.3)	28 (28.6)	3 (3.1)	64 (65.3)	20 (20.4)	14 (14.3)	5 (5.1)	//
Bujko 2005	16 (9.4)	0 (0)	8 (4.7)	64 (37.7)	82 (48.2)	0 (0)	105 (62.1)	37 (21.9)	27 (16.0)	46 (26.9)	6.5 (1.5)
Palanivelu 2006	13 (7.7)	4 (2.35)	19 (11.2)	79 (46.5)	52 (30.6)	3 (1.8)	48 (28.2)	85 (50.0)	37 (21.8)	0 (0)	//
Veenhof 2007	//	//	//	//	//	//	30 (65.2)	16 (34.8)	0 (0)	0 (0)	4.1 (1.1)
Navarro 2007	2 (2.4)	2 (2.4)	0 (0)	3 (3.5)	76 (89.4)	2 (2.4)	56 (65.9)	20 (23.5)	9 (10.6)	0 (0)	//
Biffi 2007	0 (0)	0 (0)	0 (0)	2 (6.1)	27 (81.8)	4 (12.1)	28 (84.9)	4 (12.1)	1 (3.0)	0 (0)	//
Bertelsen 2008	25 (7.9)	9 (2.8)	30 (9.5)	69 (21.8)	167 (52.7)	17 (5.4)	913 (61.8)	564 (38.2)	0 (0)	0 (0)	10.5 (3.1)
Velenik 2009	3 (10.8)	0 (0)	3 (10.7)	10 (35.7)	11 (39.3)	1 (3.6)	22 (78.6)	4 (14.3)	2 (7.1)	0 (0)	6.9 (2.2)
Swellengrebel 2010	9 (19.2)	0 (0)	0 (0)	7 (14.9)	29 (61.7)	2 (4.3)	32 (68.1)	9 (19.2)	6 (12.8)	4 (8.5)	//
Sartori 2010	0 (0)	2 (1.2)	32 (18.4)	70 (40.2)	47 (27.0)	23 (13.2)	71 (40.8)	94 (54.0)	9 (5.2)	0 (0)	5.2 (2.4)
Skrovina 2011	4 (3.6)	3 (2.7)	9 (8.2)	27 (24.6)	64 (58.2)	3 (2.7)	67 (58.8)	30 (26.3)	17 (14.9)	0 (0)	//
Motson 2011	1 (6.3)	0 (0)	0 (0)	5 (31.3)	9 (56.25)	1 (6.3)	8 (50.0)	6 (37.5)	2 (12.5)	0 (0)	//
Jarry 2011	6 (17.1)	1 (2.9)	2 (5.7)	8 (22.9)	16 (45.7)	2 (5.7)	59 (69.4)	26 (30.6)	0 (0)	10 (10.5)	8.3 (2.8)
Araujo 2011	2 (40.0)	0 (0)	0 (0)	0 (0)	3 (60.0)	0 (0)	21 (80.8)	5 (19.2)	0 (0)	0 (0)	6.8 (1.1)
Akiyoshi 2011	6 (1.7)	20 (5.5)	103 (28.4)	101 (27.8)	123 (33.9)	10 (2.8)	248 (68.3)	91 (25.1)	24 (6.6)	16 (4.4)	//
Lim 2012	7 (16.8)	7 (1.6)	19 (4.4)	104 (24.2)	219 (51.1)	8 (1.9)	314 (73.2)	82 (19.1)	33 (7.7)	0 (0)	5.8 (2.1)
Beirens 2012	202 (10.6)	139 (7.3)	170 (8.9)	462 (24.3)	858 (45.0)	74 (3.9)	1174 (65.2)	399 (22.2)	227 (12.6)	189 (10.3)	7.1 (3.3)
Lange 2013	0 (0)	0 (0)	49 (13.3)	123 (33.4)	188 (51.1)	8 (2.2)	239 (65.0)	83 (22.6)	46 (12.5)	0 (0)	//
Parisi 2014	0 (0)	2 (5.7)	6 (17.1)	11 (31.4)	13 (37.1)	3 (8.6)	20 (57.1)	9 (25.7)	6 (17.1)	0 (0)	//
Maggiori 2014	12 (8.3)	5 (3.5)	14 (9.7)	40 (27.6)	66 (45.5)	8 (5.5)	103 (71.0)	32 (22.1)	10 (6.9)	12 (8.2)	5.1 (2.9)
Hidaka 2014	2 (1.0)	5 (2.4)	57 (27.8)	48 (23.4)	84 (41.0)	9 (4.4)	136 (66.3)	56 (27.3)	13 (6.3)	6 (2.9)	//
Brachet-Contul 2014	0 (0)	3 (2.3)	16 (12.2)	26 (19.9)	81 (61.8)	5 (3.8)	84 (64.1)	31 (23.7)	16 (12.2)	17 (13.0)	2.9 (1.7)
Barnajian 2014	3 (6.7)	0 (0)	4 (8.9)	17 (37.8)	20 (44.4)	1 (2.2)	29 (64.4)	13 (28.9)	3 (6.7)	2 (4.4)	9.4 (4.4)

% Are referred to available data without considering missing values

Table 3 Intraoperative characteristics of patients having surgery for rectal cancer

Authors	Operative time, min mean (SD)	Blood transfusion *n* (%)	Stapled anastomosis *n* (%)	Protective stoma *n* (%)	Pelvic drain *n* (%)	Anastomotic distance, cm mean (SD)
Peeters 2004	179 (52)	//	876 (95.0)	522 (56.6)	791 (85.7)	4.4 (2.0)
Law 2004	162 (54)	54 (8.7)	517 (83.1)	310 (49.8)	//	4.1 (1.5)
Eriksen 2004	//	//	1762 (97.7)	622 (31.8)	//	6.0 (2.3)
Morino 2005	160 (41)	3 (3.1)	92 (95.8)	26 (26.5)	//	//
Bujko 2005	//	//	171 (100)	20 (11.7)	//	//
Palanivelu 2006	130 (19)	11 (6.5)	170 (100)	0 (0)	170 (100)	4.9 (1.7)
Veenhof 2007	//	//	//	24 (52.2)	//	//
Navarro 2007	//	//	82 (96.5)	20 (23.5)	85 (100)	//
Biffi 2007	187 (27)	7 (21.2)	33 (100)	33 (100)	33 (100)	6.1 (2.2)
Bertelsen 2008	//	374 (25.3)	//	840 (56.2)	//	//
Velenik 2009	172 (37)	1 (3.6)	27 (96.4)	22 (78.6)	28 (100)	3.5 (1.9)
Swellengrebel 2010	//	5 (10.6)	//	36 (76.6)	//	//
Sartori 2010	231 (36)	//	139 (79.9)	112 (64.4)	174 (100)	4.2 (2.4)
Skrovina 2011	235 (55)	0 (0)	114 (100)	50 (43.9)	114 (100)	//
Motson 2011	270 (0)	0 (0)	16 (100)	15 (93.8)	//	//
Jarry 2011	//	//	0 (0)	0 (0)	//	3.9 (0.3)
Araujo 2011	248 (54)	3 (11.4)	20 (76.9)	26 (100)	26 (100)	3.4 (0.9)
Akiyoshi 2011	250 (84)	0 (0)	363 (100)	62 (17.1)	268 (73.8)	6.0 (2.3)
Lim 2012	//	//	//	148 (34.5)	//	3.3 (1.5)
Beirens 2012	//	241 (12.6)	1579 (84.0)	1180 (61.9)	//	4.1 (1.6)
Lange 2013	//	//	//	155 (42.1)	//	4.3 (2.9)
Parisi 2014	336 (49)	//	35 (100)	22 (62.9)	35 (100)	5.0 (2.0)
Maggiori 2014	256 (56)	//	76 (53.2)	146 (100)	145 (99.3)	1.8 (1.8)
Hidaka 2014	236 (54)	1 (0.5)	205 (100)	0 (0)	205 (100)	4.9 (1.8)
Brachet-Contul 2014	296 (90)	//	88 (74.6)	81 (61.4)	//	//
Barnajian 2014	254 (109)	1 (2.9)	34 (75.6)	29 (64.4)	1 (2.2)	3.2 (1.0)

% Are referred to available data without considering missing values

165 patients (5.6% of patients) experienced a leak without stoma protection. If the predictive score would have been used in the same set of patients, 1931 patients (66%) would have received a stoma, but only 64 patients (2.2%) would have experienced a leak without stoma protection.

Discussion

Risk assessment of AL is crucial for shared decision-making with patients. To this end, several preoperative, intraoperative, and postoperative factors need to be considered. A review of the evidence supported by a large number of data, if possible collected from multiple centers, minimizes the role of local factors such as surgeon's skills and local care protocols. Following this rationale, we systematically reviewed the literature and performed a pooled-analysis. As the standard strategy of meta-analyses does not allow for detailed analysis of risk factors, we applied an individual participant data strategy to identify on a patient-by-patient base the risk factors influencing the outcome. In compliance with the PRISMA-IPD Statement, we used statistical techniques to replace the missing data of the selected variables. Thus, we were able to perform multivariable logistic regression with a consistent number of patients. Although this may generate doubts about the reliability of our results, we used every technique available to limit errors and quantify them. Moreover, our observation of a progressive reduction in factors associated with AL reassured us that the generation of missing data reduces the influence of risk factors, rather than increasing their weight. In addition, because of the broad time span of the studies selected for inclusion (2000–2015), differences in techniques and technologies, as well as surgeons' skills, might be another limitation of this review. Further possible limitations consist of the heterogeneous way AL was assessed in the included studies. Similar studies focusing on colonic resections reported the exclusion from the analysis of patients who had a definitive stoma

Table 4 Anastomotic leak, time intervals, reintervention for leak, and overall survival in patients having surgery for rectal cancer

Authors	Anastomotic leak no (%)	Time interval. days mean (SD)	Reintervention for leak no (%)	Survival, months median (IQR)
Peeters 2004	128 (13.9)	11 (8)	107 (100)	104 (37; 141)
Law 2004	35 (5.6)	1 (2)	//	29 (14; 51)
Eriksen 2004	228 (11.6)	10 (7)	155 (7.9)	58 (41; 76)
Morino 2005	9 (9.2)	//	4 (44.4)	//
Bujko 2005	17 (9.9)	//	17 (9.9)	43 (35; 51)
Palanivelu 2006	11 (76.5)	5 (1)	2 (18.2)	44 (26; 68)
Veenhof 2007	9 (19.6)	//	7 (77.8)	32 (15; 64)
Navarro 2007	5 (5.9)	6 (2)	4 (80.0)	34 (16; 51)
Biffi 2007	2 (6.1)	5 (1)	2 (100)	49 (19;122)
Bertelsen 2008	163 (10.9)	10 (7)	113 (69.3)	17 (7;27)
Velenik 2009	0 (0)	//	0 (0)	72 (62; 81)
Swellengrebel 2010	10 (21.3)	//	10 (100)	1 (0; 1)
Sartori 2010	25 (14.4)	7 (2)	13 (7.5)	//
Skrovina 2011	13 (11.4)	7 (7)	7 (6.1)	//
Motson 2011	3 (18.8)	//	1 (6.3)	//
Jarry 2011	3 (3.0)	//	2 (66.7)	24 (12; 29)
Araujo 2011	0 (0)	//	0 (0)	41 (31; 49)
Akiyoshi 2011	13 (3.6)	6 (5)	5 (38.5)	63 (58; 74)
Lim 2012	25 (5.8)	13 (9)	18 (75.0)	58 (46; 71)
Beirens 2012	139 (7.3)	//	//	//
Lange 2013	8 (2.2)	14 (10)	5 (62.5)	72 (32; 107)
Parisi 2014	3 (8.6)	//	0 (0)	29 (19; 39)
Maggiori 2014	53 (36.3)	//	18 (12.3)	31 (19; 43)
Hidaka 2014	19 (9.3)	6 (3)	11 (5.4)	//
Brachet-Contul 2014	18 (13.6)	//	11 (8.4)	69 (34; 115)
Barnajian 2014	2 (4.4)	12 (7)	2 (100)	35 (0; 51)

% Are referred to available data without considering missing values

IQR interquartile range

[37–39]. While reducing to a minimum the number of subclinical ALs missed, this way a number of patients judged unsuitable for a direct unprotected anastomosis, based on no evidence, were arbitrarily excluded rather than contributing to the determination of risk factors for AL. We, therefore, preferred the less relevant bias of possibly missing a number of subclinical ALs for the presence of a derivative stoma, as in the majority of the included studies the anastomosis was checked anyway by radiology or endoscopy, even in the case of an uneventful progress. Of course, this represents a limitation in the use of the algorithm to make decision about whether to form a loop ileostomy as this has been predetermined in the dataset. Finally, the most severely ill patients, i.e. those with the highest risk for AL, may have had an end colostomy, such as a abdminoerineal resection or a Hartmann procedure and, therefore, are not captured here.

These limitations notwithstanding, the present study still provides a unique source of data from which to quantify a number of risk factors for AL after rectal cancer surgery with anastomosis. Male gender, T4 staging and preoperative short-term radiotherapy were identified as preoperative risk factors, while further risk factors were anastomotic distance from the anal verge and need for blood transfusion.

Male gender being an increased risk factor for AL has been previously reported [20, 40–44] and it may be explained in part by the narrower male pelvis [36] and the influence of hormone-related differences in intestinal microcirculation [45]. The increased risk associated with advanced stage cancer (T4) can be explained with the increased complexity of such cases. Multivariate analysis showed both pT4 cancer and a lymph node ratio > 0.20 to be the only independent predictors of both overall survival and disease-free survival. This suggests that a cautious approach should be taken with routinely protective stomas in more advanced cases to minimize the effects of AL, which might delay or preclude delivery of adjuvant therapy, with negative effects on survival.

It is a common opinion that the frequency of sphincter-saving procedures in patients with mid and low rectal tumors

Table 5 Univariate analysis of risk factors for anastomotic leak

	% Missing data	AL (SD)	No AL (SD)	OR (95%CI)	*P* value
Age, years mean (SD)	–	64.7 (12.0)	64.8 (11.0)	1.001 (0.995, 1.007)	0.7880
Gender, male, *n* (%)	–	646 (68.7)	5283 (60.1)	1.455 (1.260,1.681)	< 0.0001
BMI, mean (SD)	50.8	25.4 (4.4)	25.5(4.7)	1.006 (0.987, 1.025)	0.5473
Smoke, *n* (%)	77.37	313 (33.3)	2524 (28.7)	1.114 (1.012, 1.226)	0.0277
Diabetes, *n* (%)	71.19	122 (13.0)	1059 (12.0)	1.048 (0.915, 1.201)	0.4961
ASA score, (3–4), *n* (%)	58.81	38 (10.6)	345 (9.5)	1.131 (0.793, 1.611)	0.4969
Preoperative CT, *n* (%)	0.35	206 (22.0)	2101 (24.0)	0.891 (0.758, 1.048)	0.1630
Preoperative RT, *n* (%)	0.35	344 (36.6)	3197 (36.5)	1.006 (0.875, 1.157)	0.9288
Short RT, *n* (%)	0.35	80 (8.5)	499 (5.7)	1.542 (1.206 1.973)	0.0005
Long RT, *n* (%)	0.35	264 (28.1)	2697 (30.8)	0.880 (0.758, 1.021)	0.0918
T (4), *n* (%)	13.88	59 (6.3)	365 (4.5)	1.242 (1.067, 1.446)	0.0053
N (≥ 1), *n* (%)	1.52	373 (39.6)	3211 (36.5)	1.068 (0.997, 1.145)	0.0620
M (1), *n* (%)	0.77	53 (5.7)	362 (4.1)	1.181 (1.018, 1.369)	0.0279
Previous abdominal surgery, *n* (%)	87.26	16 (15.0)	292 (25.8)	0.506 (0.293, 0.876)	0.0133
Time before surgery, week, mean (SD)	71.38	5.75 (2.40)	5.76 (2.44)	1.002 (0.963, 1.041)	0.9372
Operative Time, minute, mean (SD)	68.61	210.81 (73.1)	201.1 (73.4)	1.002 (1.000, 1.003)	0.0244
Blood transfusions, *n* (%)	47.2	210 (22.4)	1110 (12.6)	1.983 (1.630, 2.413)	< 0.0001
Stapled anastomosis, *n* (%)	26.6	637 (89.8)	5763 (89.5)	1.039 (0.804, 1.342)	0.7708
Anastomotic distance, cm, mean (SD)	35.96	4.60 (2.11)	4.90 (2.25)	0.941 (0.911, 0.973)	0.0003
Pelvic drain, *n* (%)	75.88	233 (85.04)	1886 (90.94)	0.566 (0.394, 0.815)	0.0022
Protective stoma, *n* (%)	–	365 (42.02)	4107 (46.69)	0.827 (0.722, 0.948)	0.0064
Tumor distance, cm, mean (SD)	16.81	8.33 (3.44)	8.81 (3.73)	0.965 (0.947, 0.983)	0.0002
Hb level, g/dl, mean (SD)	87.87	13.03 (1.91)	12.77 (1.78)	1.087 (0.936, 1.262)	0.2739

OR odds ratio

increased after the introduction of circular stapling devices. Nevertheless, a Cochrane review [46] published in 2012 compared the use of sutures and stapling devices for anterior resection and found that neither technique was superior to the other in terms of AL rate. This observation is shared by the results of our database analysis, which indicated equal leak rates with stapled and hand-sewn anastomoses. Furthermore, the Cochrane review highlighted that the resection of more distal tumors was associated with a greater risk of AL. In the present study, both anastomotic distance > 6 cm from the anal verge and presence of a defunctioning stoma were independently significant protective factors for AL, but not tumor distance which was probably confounded by anastomotic distance as predictor.

Table 6 Multivariate binary logistic regression models of risk factors for anastomotic leak

	OR (95% CI)	*P* value
Gender (male)	1.1989 (1.1118, 1.2928)	< 0.0001
Smoke	1.0760 (0.9792, 1.1824)	0.1284
Short RT*	1.2204 (1.0758, 1.3845)	0.0020
T (4)	1.2429 (1.0622, 1.4545)	0.0067
N (≥ 1)	1.0617 (0.9889, 1.1397)	0.0984
M1	1.1315 (0.9726, 1.3163)	0.1095
Operative Time	1.0005 (0.9993, 1.0017)	0.4255
Blood transfusions	1.4353 (1.3018, 1.5824)	< 0.0001
Anastomotic distance from the anal verge	0.9410 (0.9065, 0.9723)	< 0.0001

OR odds ratio

*Versus any other adjuvant therapy or no adjuvant therapy

Overall neoadjuvant therapy was not found to be associated with AL. Chemoradiotherapy was considered a risk factor for AL in some retrospective studies [47, 48] but was not confirmed in several others, including the Medical Research Council (MRC) CR07 RCT [49], the Dutch total mesorectal excision trial [50], and the study by Chang et al. [51]. A clear distinction should be made between short-course and long-course RT: subgroup analyses of our study revealed an association between short-course RT and AL, but not long-course RT, and AL. This should be kept in mind when deciding whether to protect a colorectal anastomosis or not. Furthermore, delay between RT and surgery, still a subject of debate, was not found to affect the risk of AL when patients receiving long-course (chemo)radiotherapy were divided into two groups by a median interval of 5 weeks between RT and surgery. Importantly, all the studies in the present

Table 7 Patients' characteristics, divided by training and validation sets

	% Missing data	ALL $n=9735$	Training set $n=6814$	Validation set $n=2921$
Age, mean (SD)	–	64.7 (11.5)	64.5 (11.4)	65.0 (11.6)
Gender (male), *n* (%)	–	*5929 (60.9)*	*4132 (64.6)*	*1797 (61.5)*
BMI, mean (SD)	50.8	25.3 (4.5)	25.3 (3.1)	25.3 (3.2)
Tobacco use, *n* (%)	*77.36*	*612 (6.3)*	*624 (9.2)*	*280 (9.6)*
Diabetes, *n* (%)	71.18	330 (3.4)	257 (3.7)	82 (2.8)
ASA score (3–4), *n* (%)	58.81	383 (3.9)	263 (3.9)	120 (4.1)
Preoperative CT, *n* (%)	0.35	2307 (23.7)	1603 (23.5)	704 (24.1)
Preoperative RT, *n* (%)	0.35	3541 (36.4)	2478 (36.4)	1063 (36.4)
*Short RT, n (%)**	*0.35*	*579 (6.0)*	*409 (6.0)*	*170 (5.8)*
*Long RT, n (%)**	*0.35*	*2961(30.5)*	*2068 (30.3)*	*893 (30.6)*
T (4), *n* (%)	*13.88*	*363 (4.3)*	*246 (4.2)*	*117 (4.6)*
N (≥ 1), *n* (%)	1.52	3528 (36.8)	2490 (37.14)	1.038 (36.0)
M (1), *n* (%)	*0.77*	*412 (4.3)*	*292 (4.3)*	*1.120 (4.1)*
Previous abdominal surgery, *n* (%)	*87.26*	*308 (24.8)*	*223 (24.7)*	*85 (25.2)*
Time before surgery (week), mean (SD)	71.38	5.8 (2.4)	5.8 (1.3)	1.5.7 (1.3)
Operative time, mean (SD)	*68.62*	*202.13 (73.1)*	*202.6 (73.1)*	*201.0 (74.5)*
Blood transfusions, *n* (%)	*47.2*	*701 (7.2)*	*494 (7.3)*	*207 (7.1)*
Stapled anastomosis, *n* (%)	26.6	6399 (89.5)	4474 (89.5)	1925 (89.7)
Anastomotic distance, mean (SD)	*35.96*	*4.572 (2.19)*	*4.88 (2.06)*	*4.88 (2.03)*
Pelvic drain, *n* (%)	*75.89*	*2075 (88.41)*	*1473 (88.26)*	*602 (88.79)*
Protective stoma, *n* (%)	–	*4501 (46.24)*	*3128 (45.91)*	*1373 (47.00)*
Tumor distance, mean (SD)	*16.81*	*8.68 (3.68)*	*8.66 (3.71)*	*8.72 (3.69)*
Hemoglobin, mean (SD)	87.88	12.81 (1.78)	12.76 (0.84)	12.78 (0.81)

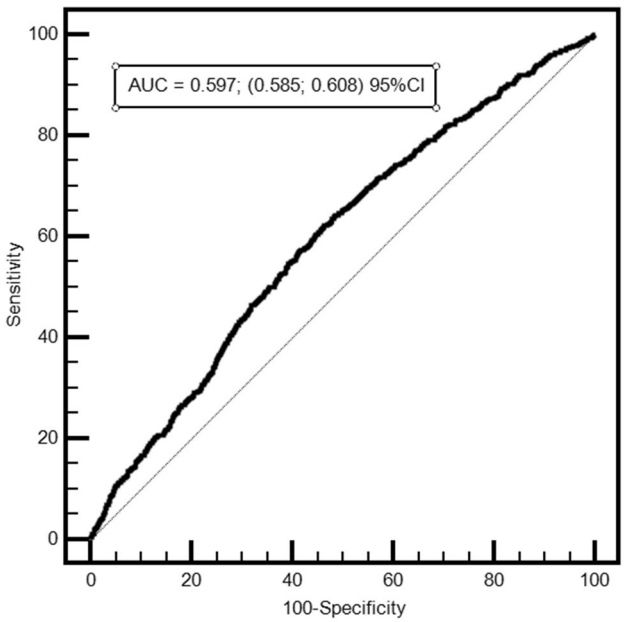

Fig. 2 Receiver operating characteristic (ROC) curve

Table 8 Quantile distribution of criterion values and coordinates of the ROC curve

Cut-off	Sensitivity (95% CI)	Specificity (95% CI)
≥ 0.0309 (max)	100 (99.4–100.0)	0 (0.0–0.06)
> 0.0479 (99%)	99.39 (98.4–99.8)	1.35 (1.1–1.7)
> 0.0564 (95%)	97.39 (95.9–98.5)	5.18 (4.6–5.8)
> 0.0621 (90%)	94.48 (92.4–96.1)	10.66 (9.9–11.5)
> 0.0736 (75% Q3)	83.9 (80.8–86.6)	25.62 (24.5–26.7)
> 0.0925 (50% median)	64.11 (60.3–67.8)	51.38 (50.1–52.6)
> 0.112 (25% Q1)	33.28 (29.7–37.0)	75.93 (74.8–77.0)
> 0.1326 (10%)	15.64 (12.9–18.7)	90.6 (89.8–91.3)
> 0.1498 (5%)	9.36 (7.2–11.9)	95.44 (94.9–95.9)
> 0.1875 (1%)	2.15 (1.2–3.6)	99.14 (98.9–99.4)
> 0.3034 (min)	0 (0.0–0.6)	100 (99.9–100.0)

Table 9 Accuracy of the threshold value

	Sensitivity 95% CI	Specificity 95% CI	+LR	−LR
Training set	79.14 (75.8, 82.2)	32.94 (31.8, 34.1)	1.18	0.63
Validation set	77.85 (72.6, 82.5)	35.22 (33.4, 37.1)	1.20	0.63

analysis reported outcomes after short-term RT immediately followed by surgery. It is unknown whether short-course RT per se is responsible for the increased risk of AL or it is

Table 10 Results of the predictive score and what was really done in clinical practice

Using score	With protective stoma			Without protective stoma			Total	
	N	%C	*%R*	*N*	*%C*	*%R*	*N*	*%C*
Overall								
Positive	1006	73.27	52.10	925	59.76	47.90	1931	66.11
Negative	367	26.73	37.07	623	41.24	62.93	990	33.89
Total	1373	100.00	47.00	1548	100.00	53.00	2921	100.00
With anastomotic leak								
Positive	102	82.26	45.33	123	74.55	54.67	225	77.85
Negative	22	17.74	34.38	42	25.45	65.63	64	22.15
Total	124	100.00	42.91	165	100.00	57.09	289	100.00
Without anastomotic leak								
Positive	904	72.38	52.99	802	57.99	47.01	1706	64.82
Negative	345	27.62	37.26	581	42.01	62.74	926	35.18
Total	1249	100.00	47.45	1383	100.00	52.55	2632	100.00

N sample size, *%C* column percentage, *%R* row percentage

related to the very short (usually less than 5 days) rest period between completion of RT and surgery. The latter possibility is suggested by the Stockholm III randomized trial that compared 5×5 Gy with immediate surgery vs. 5×5 Gy with delayed surgery for 4–8 weeks. The rate of postoperative complications was significantly lower in the delayed surgery group, and the AL rate was 11.8% vs. 7.2% ($p=0.01$) [52].

The last relevant factor associated with the risk of AL we found, was the need for blood transfusion, which is notoriously difficult to predict. It is unclear whether this is a consequence of the hypoperfusion of the anastomosis due to blood loss or a consequence of tissue repair impairment due to transfusion related immunological suppression, or simply a surrogate for poor operative technique or challenging surgery. Despite the difficulty of predicting the need for blood transfusion, it was found to be probably the most relevant risk factor for AL. Further study of this specific risk factor is warranted. In light of this finding, adequate measures should be implemented to obviate the need for transfusion.

Previous studies demonstrated that the risk of AL is higher among active smokers [20, 53–55]. We noted that smoking (both previous and persisting) was associated with AL before the missing data imputation, while in the multivariate analysis it was probably confounded by other predictors. Part of the problem in interpreting this finding stems from the relevant number of missing data regarding tobacco use and the techniques of missing value replacement we adopted. Future studies may answer this question. The same occurred, in our opinion, for BMI, also found not predictive for AL.

Based on the present results we developed and validated a specific scoring and grading system for the risk of AL after rectal cancer surgery, similar to the colon leak score (CLS) for left-sided colonic resection [56]. The choice of the threshold value of the ROC curve corresponded to a 2% incidence of AL in the training set. We believe 2% is a reasonable rate of risk for AL, to justify not to perform a protective stoma routinely. In fact, the validation set showed that by increasing the rate of stoma creation from about 1/2 to 2/3 of the patients, the incidence of clinical AL decreases by about 60% becoming as low as about 2%. Although the statistically significant value of the AUC has shown weak accuracy of the predictive model, we trust that the real-score, now available online (http://www.real-score.org), is a useful tool for assessing the risk of symptomatic AL and, therefore, will help surgeons decide whether or not to propose a protective stoma creation when performing transabdominal rectal cancer surgery.

Conclusions

AL after rectal cancer surgery is a serious complication that continues to occur despite consistent surgical and technological advances. Individualized preoperative assessment of the risk of AL would be a useful component of surgical planning. Based on the results of a multivariable logistic regression of a vast multi-centric IPD database, we were able to develop and validate a specific scoring and grading system to assess the risk of AL after rectal cancer surgery.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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