



Universiteit
Leiden
The Netherlands

A preoperative prediction model for anastomotic leakage after rectal cancer resection based on 13.175 patients

Hoek, V.T.; Buettner, S.; Sparreboom, C.L.; Detering, R.; Menon, A.G.; Kleinrensink, G.J.; ...
; Dutch ColoRectal Audit Grp

Citation

Hoek, V. T., Buettner, S., Sparreboom, C. L., Detering, R., Menon, A. G., Kleinrensink, G. J., ... Wiggers, J. K. (2022). A preoperative prediction model for anastomotic leakage after rectal cancer resection based on 13.175 patients. *European Journal Of Surgical Oncology*, 48(12), 2495-2501. doi:10.1016/j.ejso.2022.06.016

Version: Not Applicable (or Unknown)

License: [Licensed under Article 25fa Copyright Act/Law \(Amendment Taverne\)](#)

Downloaded from: <https://hdl.handle.net/1887/3564037>

Note: To cite this publication please use the final published version (if applicable).



Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

A preoperative prediction model for anastomotic leakage after rectal cancer resection based on 13.175 patients



V.T. Hoek^{a,*}, S. Buettner^a, C.L. Sparreboom^a, R. Detering^b, A.G. Menon^{a,c},
G.J. Kleinrensink^d, M.W.J.M. Wouters^{e,f,g}, J.F. Lange^{a,1},
J.K. Wiggers^{h,1}, On behalf of the Dutch ColoRectal Audit group

^a Department of Surgery, Erasmus University Medical Centre, Rotterdam, the Netherlands

^b Department of Surgery, OLVG, Amsterdam, the Netherlands

^c Department of Surgery, IJsselland Hospital, Capelle aan den IJssel, the Netherlands

^d Department of Neuroscience-Anatomy, Erasmus University Medical Centre, Rotterdam, the Netherlands

^e Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, the Netherlands

^f Department of Surgical Oncology, Netherlands Cancer Institute-Antoni van Leeuwenhoek, Amsterdam, the Netherlands

^g Scientific Bureau, Dutch Institute for Clinical Auditing, Leiden, the Netherlands

^h Department of Colorectal Surgery, Amsterdam University Medical Centers, University of Amsterdam, Cancer Centre Amsterdam, the Netherlands

ARTICLE INFO

Article history:

Received 14 February 2022

Received in revised form

10 May 2022

Accepted 13 June 2022

Available online 22 June 2022

Keywords:

Rectal cancer surgery

Anastomotic leakage

Prediction model

ABSTRACT

Introduction: This study aims to develop a robust preoperative prediction model for anastomotic leakage (AL) after surgical resection for rectal cancer, based on established risk factors and with the power of a large prospective nation-wide population-based study cohort.

Materials and methods: A development cohort was formed by using the DCRA (Dutch ColoRectal Audit), a mandatory population-based repository of all patients who undergo colorectal cancer resection in the Netherlands. Patients aged 18 years or older were included who underwent surgical resection for rectal cancer with primary anastomosis (with or without deviating ileostomy) between 2011 and 2019. Anastomotic leakage was defined as clinically relevant leakage requiring reintervention. Multivariable logistic regression was used to build a prediction model and cross-validation was used to validate the model.

Results: A total of 13.175 patients were included for analysis. AL was diagnosed in 1319 patients (10%). A deviating stoma was constructed in 6853 patients (52%). The following variables were identified as significant risk factors and included in the prediction model: gender, age, BMI, ASA classification, neo-adjuvant (chemo)radiotherapy, CT stage, distance of the tumor from anal verge, and deviating ileostomy. The model had a concordance-index of 0.664, which remained 0.658 after cross-validation. In addition, a nomogram was developed.

Conclusion: The present study generated a discriminative prediction model based on preoperatively available variables. The proposed score can be used for patient counselling and risk-stratification before undergoing rectal resection for cancer.

© 2022 Published by Elsevier Ltd.

1. Introduction

Anastomotic leakage (AL) is one of the most complex problems after restorative rectal cancer surgery leading to reoperations,

readmission, increased length of hospital stay, a higher risk for postoperative mortality and worse oncologic outcomes [1–6]. Despite many preventive efforts, it remains a major problem with a reported prevalence between 1 and 19% [4,7–9]. Risk factors have extensively been analyzed and include male gender, height of the anastomosis, ASA score, diabetes, obesity, smoking, malnutrition, corticosteroid use, and neo-adjuvant (chemo)radiotherapy [4,8,10–13].

* Corresponding author. Department of Surgery, Erasmus University Medical Centre, Wytemaweg 80 3015 CN Rotterdam, Room Ee-173, the Netherlands.

E-mail address: v.hoek@erasmusmc.nl (V.T. Hoek).

¹ Both authors contributed equally and should both be considered as last authors.

Patients discussing an operation for rectal cancer with their physician face the difficult surgical decision whether to have a colorectal/coloanal anastomosis or a permanent colostomy. Most patients consider the idea of a colostomy unfavorable and desire an anastomosis. On the other hand, some patients find that restorative rectal surgery is associated with significantly impaired bowel function, and, moreover, wish to avoid the risk of AL. Such patient preferences should play a major role to improve the quality of shared decision-making. Nevertheless, tools that allow patients to adequately understand the benefits, risks, and potential harms of both treatment methods are scarce and mostly insufficient [14]. A recent study developed and validated a nomogram to predict bowel dysfunction following restorative rectal cancer resection [15]. Available prediction models for AL however are based on small number of patients or lack sufficient discriminative power to be used in clinical practice [16–18].

This study aims to develop a preoperative prediction model, designed to be used during shared-decision making, for anastomotic leakage after rectal cancer resection. To ensure validity, the design uses variables that are established risk factors in literature and the power of a large nation-wide cohort.

2. Methods

A development cohort was formed by using the DCRA (Dutch ColoRectal Audit), a mandatory population-based repository of all patients who undergo colorectal cancer resection in the Netherlands. The database includes patient-level data regarding preoperative clinical staging, co-morbidities, operative details, as well as postoperative course and definitive pathological result. For the present study, no ethical approval or informed consent was required under Dutch law. Details regarding collection and methodology of the DCRA dataset have been published previously [19]. The TRIPOD (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis) statement is followed to report multivariable prediction model development and validation [20].

2.1. Study population

Data was assembled of patients operated between January 1, 2011 and December 31, 2019. Patients aged 18 years or older were included who underwent an elective rectal resection for cancer with primary anastomosis (with or without deviating stoma) and curative intention. The more recent 'sigmoid take-off' definition for rectal carcinoma was not available in this historical dataset. Therefore, the carcinoma had to be located within 150 mm of the anal verge to be defined as rectal carcinoma, similar to clinical trials [21]. Patients who underwent a successful procedure to treat obstruction (by stoma or stent) prior to an elective rectal resection were included. Excluded were patients who underwent acute resection for obstructive cancer because this group entails a different treatment setting (i.e. inevitable higher risk of AL) [22]. Patients who underwent intra-operative radiotherapy or rectal resection as part of cytoreductive surgery and hyperthermic intraoperative chemotherapy for peritoneal metastases (HIPEC) were also excluded.

2.2. Study outcomes

The outcome of the study is anastomotic leakage within 30 days, defined as the need for endoscopic, percutaneous or operative re-intervention due to the leakage [23]. Within the DCRA database, anastomotic leakage was recorded up to 30 days until the year 2018, afterwards 90 days follow-up was applied [24].

2.3. Predictor variables

Candidate predictor variables were identified by reviewing literature and these variables required to be applicable to the pre-operative setting. Variables entered in the model were: age [4], sex [4,8,12,25], BMI [25,26], American Society of Anaesthesiologists (ASA) physical status classification [4,8,25], diabetes [4], lung disease [11], ileo- or colostomy [27], tumor invasion on imaging (clinical T-stage according to TNM) [8,25], tumor height from anal verge as assessed by treating radiologist on pre-treatment sagittal MRI and verified during local multidisciplinary team meeting [8,12,25], neo-adjuvant therapy [8,12,25], and approach (trans-abdominal (open), transabdominal (scopic), transanal local open, TAMIS, transanal and transabdominal, robot) [4,28].

2.4. Statistical analyses

Summary statistics were provided as whole numbers and percentages for categorical variables, and medians with interquartile range (IQR) for continuous variables. The distribution of categorical variables was tested using the χ^2 test. The distribution of continuous variables was tested using the Mann-Whitney *U* test. Logistic regression analyses were utilized to determine correlation between the primary outcome and predictor variables. Results from the models were reported as odds ratios (OR) and their corresponding 95% confidence intervals (CI). Continuous predictors were transformed using restricted cubic splines if this improved the model fit. Multiple imputation was used to correct for missing data in the multivariable analysis. Backwards selection based on a $p < 0.05$ was used to select predictors in the final model from the previously described predictor variables. Linear predictors from the final model were used to construct a point-based score and nomogram for clinical application. Cross-validation using 10 random samples was used to validate the model. Model performance was evaluated using Harrel's C-index, the Brier score, and a calibration plot of the apparent and cross-validated model. The concordance index (C-index) was used to quantify discriminative value, which is comparable to the area under the receiver operating characteristic (ROC) curve [29]. The Brier score is used to measure the difference between observed and predicted survival per stage, 0 signifies total accuracy, whereas a score of 0.250 indicates no prognostic value. The model was validated on patients operated before- and after 2018 to identify whether difference in follow-up time (30 days vs 90 days) affected discriminative value. All analyses were performed using the *rms*, *TableOne*, and *mice* packages for R 4.0.5 (<https://cran.r-project.org/>). All tests were 2-sided and $p < 0.05$ defined statistical significance.

3. Results

3.1. Study population

A total of 92,392 patients who underwent colorectal surgery for cancer in the Netherlands were included in the database between 2011 and 2019. After exclusion of patients undergoing colonic surgery ($n = 66,055$) a total of 26,337 patients remained eligible. Patients were excluded because either emergency surgery was performed ($n = 114$), intraoperative chemo/radiotherapy was applied ($n = 120$) or no primary colorectal or coloanal anastomosis was constructed (12,928). Eventually, a total of 13,175 were included for analyses.

3.2. Baseline and perioperative characteristics

Among the patients who were included for analyses, the median age was 66 (IQR 59–72) with a majority of patients being male

(n = 8225, (62%)). 7551 (58%) patients received neoadjuvant radio(-chemo)therapy, a laparoscopic approach was performed in 9528 (73%), and a deviating stoma was constructed in 6853 patients (52%). Baseline and perioperative characteristics are provided in [Supplementary Table 1](#).

3.3. Prediction model

3.3.1. Risk factors associated with anastomotic leakage

A total of 1319 (10%) patients were diagnosed with AL. The following parameters were associated with AL in univariable analysis: gender, age, BMI, ASA classification, neoadjuvant radiotherapy, clinical T-stage, approach, procedure, tumor height from anal verge, and deviating ileostomy. Univariable analyses are shown in [Table 1](#).

The definitive multivariable model identified the following variables to independently increase risk for AL: male gender (OR 1.62), ASA III/IV (OR 1.33), BMI (OR 1.11, for each 5 kg/m² increase), short-course radiotherapy 5 × 5 Gy (OR 1.35), chemoradiotherapy (OR 1.11), and clinical T-stage (T1; reference, T2 (OR 1.12), T3 (OR 1.35), T4 (OR 1.15)). In addition, the following variables reduced the risk for AL: increase in age (non-linear, overall p = 0.0005),

construction of a deviating stoma (OR 0.45), and greater distance between location of the tumor and the anal verge (OR 0.89 for each increase in millimetres). Outcomes of multivariable analyses are shown in [Table 2](#). The model had a C-index of 0.664 for prediction of AL and the Brier score was 0.087. After cross-validation the C-index remained 0.658 and the Brier score remained 0.087. Calibration is plotted in [Fig. 1](#). In patients operated before 2018 (AL recorded up to 30 days) the model had a c-index of 0.653. A c-index of 0.683 was found in those operated after 2018 (AL recorded up to 90 days).

3.4. Development of risk-stratification score

A point weighted risk-stratification score for AL after reconstructive rectal cancer surgery was generated by point estimates obtained from the final multivariable model ([Table 2](#)). In addition, a nomogram was composed ([Fig. 2](#)). Risk to develop AL was calculated for the three tertiles of patients in the dataset. Prevalence of AL was noted to be 5.0% among patients with a score of 0–138 (low risk), 8.5% among patients scoring 138–165 (intermediate risk), and 16.4% among patients scoring 165 and higher (high risk, p < 0.001, [Supplementary Fig. 1](#)).

Table 1
Baseline & (post)operative characteristics.

		No anastomotic leakage	Anastomotic leakage	P-value
Gender	Male	11856 (90)	1319 [10]	<0.001
	Female	7280 (88)	945 [12]	
Age (years)		4572 (92)	374 [8]	<0.001
BMI (kg/m ^{Dev})		66.0 [59.0, 73.0]	65.0 [58.0, 71.0]	0.012
ASA score ^c		25.7 [23.5, 28.4]	25.9 [23.8, 28.7]	0.005
Comorbidities	I/II	10,291 (90)	1108 [10]	0.144
	III/IV	1563 (88)	211 [12]	
	Myocardinfarction in history	532(88)	71(12)	
	Heart disease	168(90)	18(10)	
	Peripheral vascular disease	459(90)	48(10)	
	Lung disease	1022(89)	124(11)	
	Cerebrovasulair accident (CVA)	668(90)	71(10)	
	Diabetes	1390(90)	146(10)	
(Chemo)Radiotherapy	Kidney disease	186(88)	25(12)	0.498
	No	4936 (90)	524 [10]	0.036
	5x5 Gray	3691 (89)	459 [11]	
cT Stage	50 Gray and chemotherapy	3074 (91)	327 [10]	0.005
	T1	567 (92)	50 [8]	
	T2	3246 (91)	328 [9]	
	T3	6824 (89)	831 [11]	
Tumor height from anal verge, mm	T4	640 (92)	59 [8]	<0.001
	100.0 [70.0, 120.0]	80.0 [50.0, 100.0]		
Approach	Open	1928 (91)	196 [9]	<0.001
	Laparoscopic	8614 (90)	914 [10]	
	Transanal and open	4 (67)	2 [33]	
	Transanal Minimally Invasive Surgery ^b	96 (96)	4 [4]	
	Transanal and laparoscopic	628 (83)	128 [17]	
	Robot-assisted	502 (88)	66 [12]	
	Additional resection	No	11,495 (90)	
Type of resection	Advanced	190 (92)	17 [8]	0.483
	Limited	161 (90)	17 [10]	
	Elective	11,765 (90)	1312(10)	
Tumor related complications prior to surgery ^a	Elective after treatment with decompromosing stent or deviating stomy	85(92)	7(8)	0.844
	No	9931(90)	1109(10)	
Surgical procedure	Yes	1916(90)	210(10)	<0.001
	Low anterior resection	10,420(91)	1178(10)	
	Partial Mesorectal Excision	1177(91)	119(9)	
Deviating Stoma	Subtotal colectomy	28(88)	4(12)	<0.001
	No	5550 (88)	769 [12]	
	Yes	6303 (92)	550 [8]	

^a (i.e. anemia, obstruction, abscess.

^b Transanal Minimally Invasive Surgery was followed by Total Mesorectal Excision.

^c American Society of Anesthesiology score.

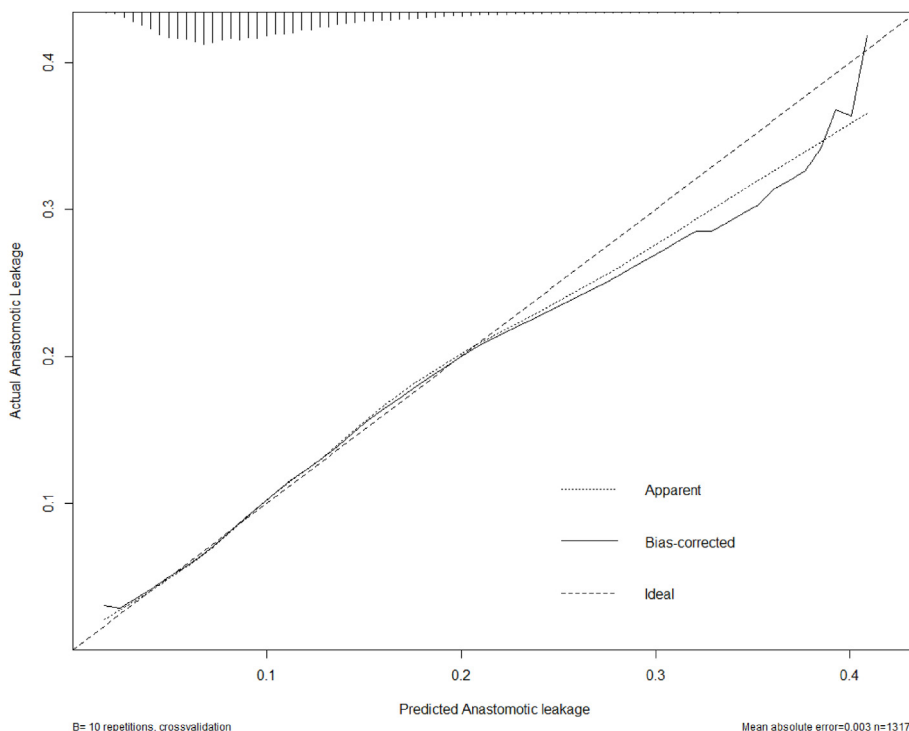


Fig. 1. Calibration model performance
 Apparent: AL predicted versus actually observed. The model overvalues slightly when AL is predicted to be >20%, which means that the model predicts slightly higher AL rates than actually observed. Bias-corrected: AL predicted versus actually observed after cross-validation.

Table 2
 Multivariable Cox proportional regression analysis.

	Points	Odds ratio	95% CI	p-value
Male gender	26	1.62	(1.79–9.17)	<0.0001
Age	^a	^a	^a	0.005
BMI, 5 kg/m ²	6	1.11	(1.03–1.19)	0.0046
Stoma				
None	43	Ref	–	–
Deviating Stoma	0	0.45	(0.39–0.51)	<0.0001
ASA III/IV	15	1.33	(1.13–1.57)	0.0007
Radiotherapy				
None	0	Ref	–	–
5x5 Gy	16	1.35	(1.17–1.56)	<0.0001
50 Gray and chemotherapy	5	1.11	(0.93–1.32)	0.2504
cT Stage				
T1	0	Ref	–	–
T2	6	1.12	(0.81–1.53)	0.5013
T3	16	1.35	(0.99–1.84)	0.0669
T4	7	1.15	(0.75–1.70)	0.5687
Tumor height from anal verge, mm	–6	0.89	(0.87–0.90)	<0.0001

^a Variable due to restricted cubic splines; $0.08 \times \text{Age} - 0.001 \times \text{Age}^3 + 0.003 \times \text{Age}^3 - 0.001 \times \text{Age}^3$; C-index of 0.66365 and Brier score of 0.0872.

4. Discussion

Anastomotic leakage remains one of the most dreadful complications within colorectal surgery. Over the last decades AL rates have been reduced, although the average AL rate of rectum surgery is still two times higher than colon surgery [4,7–9]. Given the potential morbidity and even mortality after a leakage, appropriate risk-stratification before surgery is critical to help better predict AL. Using a cohort of 13.175 patients who underwent an elective rectum resection for cancer, the present study developed an accurate pre-operative risk-stratification tool to identify patients at high risk for AL. With the inclusion of a deviating ileostomy in the model, the risk-stratification tool transparently shows the risk reduction

which could be gained by construction of such a stoma. Moreover, the model can be used for patient counselling prior to their operation. Identification of high-risk patients may assist during shared decision making, when patients and their physician plan to create an anastomosis (with or without deviating ileostomy) or maybe choose for a permanent colostomy instead.

Previous studies have identified multiple risk factors for AL after rectum surgery but failed to produce an established prediction model. Attempts have been made but most prediction models lacked accuracy or applicability to a preoperative clinical setting. For example, Watanabe et al. introduced a prediction model for AL after rectum surgery and mainly focused on preoperative baseline characteristics without considering imaging related data such as

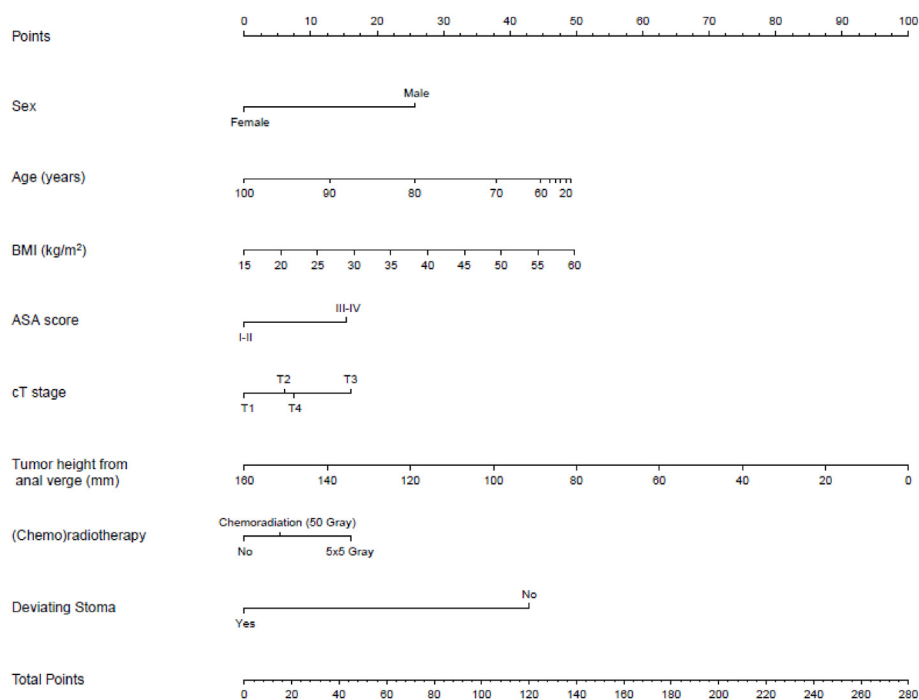


Fig. 2. Nomogram.

tumor size and distance to the anal verge [16]. Eventually a c-index of 0.625 for AL was found, which is lower than the c-index in the present study. Zheng et al. included preoperative and perioperative variables, including duration of operation, anastomotic bleeding and surgical approach [28]. Obviously, the addition of these extra variables increased discriminative power of the model, and the authors reported a c-index of 0.722. However, perioperative variables preclude use of the model during shared decision making before surgery. The Rectal Anastomotic Leak score used variables that were comparable to those used in the present study [18]. Nevertheless, the reported c-index was 0.585, which can be considered a relatively poor model. The candidate risk factors in the present study were selected by reviewing literature. Noteworthy, a higher age was associated with a risk reduction in the model. Although counter intuitive, this finding is supported by previous studies [30–35]. An experimental study found that aging tissues develop more chronic inflammation without overt infection, which may contribute to more subclinical—instead of severe morbidity in elderly patients [30,36]. Subclinical AL was not reported in the current database. Other explanations include selection of the fittest and survivor bias [30]. Despite the ‘protective’ effect of age, mortality rates of elderly patients following AL increases drastically [30,37,38]. Clinical T stage three was associated with a higher risk for AL compared to patients with a clinical T stage four carcinoma. Bias might have been introduced by preoperative selection of patients with favourable expected outcome, while high-risk patients with a T4 staged carcinoma were excluded from surgical curative treatment. The finding that short-course radiotherapy ($5 \times 5\text{Gy}$) is associated with a larger increase in risk for AL compared to chemoradiation has been described previously [39,40].

Within the current prediction model, deviating ileostomy was included. Although this is an operative variable, the decision to construct a stoma is often based on preoperatively available characteristics. Absence of a deviating ileostomy was pointed out as a strong predictor for AL requiring reintervention. A deviating stoma could effectively prevent patients from developing severe

symptomatic AL which has been demonstrated previously [41–43]. Importantly, it should be considered that AL on itself is not reduced but severe morbidity requiring reinterventions is minimized [44]. Despite the potential benefits, it should be taken into account that a stoma introduces the risk for additional complications during reversal and could have significant impact on quality of life [1,45]. Therefore, the current risk-stratification tool might help to identify those who will potentially benefit from a deviating stoma and preserve patients who do not need a stoma due to low risk.

The present study had several limitations that need to be addressed. Only leakages that required reintervention were considered in the definition of AL, and subclinical leakages, which may be prevalent especially among patients with a deviating ileostomy, were not registered. Furthermore, the definition slightly changed during the study period. AL was recorded up to 30 days postoperatively in patients operated until 2017 and up to 90 days since 2018, after it was shown leakages are also diagnosed beyond 30 days [24]. Nonetheless, validation showed comparable model performance in both study periods, with even slightly better discriminative power for patients with a 90-day follow-up. Although this study used a comprehensive list of patient characteristics and imaging variables, a few potential risk factors, such as corticosteroid use and smoking, were not available in the DCRA database and therefore not considered in the model. It is recommended to subject the model to external validation on another population-based repository.

Despite these limitations, the strength of the present study was that results were based on a nationwide cohort representing a population which could not be affected by selection bias based on required informed consent. In addition, the large sample size induces statistical power to detect differences between risk factors and generate an accurate prediction model. Furthermore, heterogeneity was minimized by considering rectum surgery for cancer only. Finally, all parameters included in the risk-stratification tool are commonly known, clearly defined, and therefore easily accessible in a clinical setting. With a c-index <0.7 the prediction model

lacks discriminative value. Based on the strengths described, it should be considered that the current model has approached the maximum discriminative value which could be obtained from the currently known, preoperatively available, parameters associated with AL. However, there is much to gain in terms of discriminative value which means that there is still a lot to discover with regards to the pathophysiology of AL. Therefore, the colorectal community should strive for identification of additional (out of the box) factors that could compromise anastomotic healing such as expertise, microbiomes, macro/micro vascular calcification, or modifiable risk factors (i.e. preoperative haemoglobin, hyperglycemia, antibiotic prophylaxis and analgesia) [46–48].

The present study generated a discriminative prediction model based on preoperatively available variables. The proposed score can be used for patient counselling and risk-stratification before undergoing rectal resection for cancer.

CRedit authorship contribution statement

V.T. Hoek: Conceptualization, Methodology, Investigation, Data Validation, Writing – original draft. **S. Buettner:** Data curation, Methodology, Investigation, Writing – original draft. **C.L. Sparreboom:** Conceptualization, Data curation, Methodology, Investigation, Writing – original draft. **R. Detering:** Data curation, Methodology, Investigation, Writing – review & editing. **A.G. Menon:** Conceptualization, Methodology, Writing – review & editing, Supervision. **G.J. Kleinrensink:** Conceptualization, Methodology, Writing – review & editing, Supervision. **M.W.J.M. Wouters:** Conceptualization, Methodology, Writing – review & editing, Supervision. **J.F. Lange:** Conceptualization, Methodology, Writing – review & editing, Supervision. **J.K. Wiggers:** Conceptualization, Methodology, Data curation, Investigation, Writing – original draft, Supervision.

Declaration of competing interest

On behalf of the REPAIR research group of the Erasmus University Medical Center (Rotterdam, the Netherlands), I am very pleased to send you this manuscript entitled “A preoperative prediction model for anastomotic leakage after rectal cancer resection based on 13,175 patients” for peer review to *European Journal of Surgical Oncology* on behalf of the following authors V.T. Hoek, M.D., S. Buettner, M.D. Ph.D., C.L. Sparreboom M.D. Ph.D., R. Detering, M.D. Ph.D., A.G. Menon, M.D. Ph.D., G.J. Kleinrensink Ph.D., M.W.J.M. Wouters, M.D. Ph.D., J.F. Lange, M.D. Ph.D., J.K. Wiggers M.D. Ph.D. All authors have read and complied with the author guidelines and did declare there is no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejso.2022.06.016>.

References

- [1] den Dulk M, Smit M, Peeters KC, Kranenburg EM, Rutten HJ, Wiggers T, et al. A multivariate analysis of limiting factors for stoma reversal in patients with rectal cancer entered into the total mesorectal excision (TME) trial: a retrospective study. *Lancet Oncol* 2007;8(4):297–303.
- [2] Kawada K, Sakai Y. Preoperative, intraoperative and postoperative risk factors for anastomotic leakage after laparoscopic low anterior resection with double stapling technique anastomosis. *World J Gastroenterol* 2016;22(25):5718–27.
- [3] Teloken PE, Spilbury K, Platell C, Committee BO. Analysis of mortality in colorectal surgery in the Bi-national colorectal cancer audit. *ANZ J Surg* 2016;86(6):454–8.
- [4] Parthasarathy M, Greensmith M, Bowers D, Groot-Wassink T. Risk factors for anastomotic leakage after colorectal resection: a retrospective analysis of 17 518 patients. *Colorectal Dis* 2017;19(3):288–98.
- [5] Snijders HS, Wouters MW, van Leersum NJ, Kolfshoten NE, Henneman D, de Vries AC, et al. Meta-analysis of the risk for anastomotic leakage, the postoperative mortality caused by leakage in relation to the overall postoperative mortality. *Eur J Surg Oncol* 2012;38(11):1013–9.
- [6] Kang J, Choi G-S, Oh JH, Kim NK, Park JS, Kim MJ, et al. Multicenter analysis of long-term oncologic impact of anastomotic leakage after laparoscopic total mesorectal excision: the Korean laparoscopic colorectal surgery study group. *Medicine* 2015;94(29):e1202.
- [7] Paun BC, Cassie S, MacLean AR, Dixon E, Buie WD. Postoperative complications following surgery for rectal cancer. *Ann Surg* 2010;251(5):807–18.
- [8] McDermott FD, Heeney A, Kelly ME, Steele RJ, Carlson GL, Winter DC. Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks. *Br J Surg* 2015;102(5):462–79.
- [9] Frouws MA, Snijders HS, Malm SH, Liefers GJ, Van de Velde CJH, Neijenhuis PA, et al. Clinical relevance of a grading system for anastomotic leakage after low anterior resection: analysis from a national cohort database. *Dis Colon Rectum* 2017;60(7):706–13.
- [10] Sliker JC, Komen N, Mannaerts GH, et al. Long-term and perioperative corticosteroids in anastomotic leakage: a prospective study of 259 left-sided colorectal anastomoses. *Archives of*; 2012.
- [11] Kang CY, Halabi WJ, Chaudhry OO, Nguyen V, Pigazzi A, Carmichael JC, et al. Risk factors for anastomotic leakage after anterior resection for rectal cancer. *JAMA Surg* 2013;148(1):65–71.
- [12] Pommergaard HC, Gessler B, Burcharth J, et al. Preoperative risk factors for anastomotic leakage after resection for colorectal cancer: a systematic review and meta-analysis. *Colorectal* 2014.
- [13] Park JS, Huh JW, Park YA, Cho YB, Yun SH, Kim HC, et al. Risk factors of anastomotic leakage and long-term survival after colorectal surgery. *Medicine (Baltim)* 2016;95(8):e2890.
- [14] Ivatury SJ, Durand MA, Elwyn G. Shared decision-making for rectal cancer treatment: a path forward. *Dis Colon Rectum* 2019;62(12):1412–3.
- [15] Guo G, Chen X, He W, Wang H, Wang Y, Hu P, et al. Establishment of inflammation biomarkers-based nomograms to predict prognosis of advanced colorectal cancer patients based on real world data. *PLoS One* 2018;13(12):e0208547.
- [16] Watanabe T, Miyata H, Konno H, Kawai K, Ishihara S, Sunami E, et al. Prediction model for complications after low anterior resection based on data from 33,411 Japanese patients included in the National Clinical Database. *Surgery* 2017;161(6):1597–608.
- [17] Klose J, Tarantino I, von Fournier A, Stowitzki MJ, Kulu Y, Bruckner T, et al. A nomogram to predict anastomotic leakage in open rectal surgery—hope or hype? *J Gastrointest Surg* 2018;22(9):1619–30.
- [18] Arezzo A, Migliore M, Chiaro P, Arolfo S, Filippini C, Di Cuonzo D, et al. The REAL (REctal Anastomotic Leak) score for prediction of anastomotic leak after rectal cancer surgery. *Tech Coloproctol* 2019;23(7):649–63.
- [19] Van Leersum NJ, Snijders HS, Henneman D, Kolfshoten NE, Gooiker GA, ten Berge MG, et al. The Dutch surgical colorectal audit. *Eur J Surg Oncol* 2013;39(10):1063–70.
- [20] Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or Diagnosis (TRIPOD): the TRIPOD statement. *Ann Intern Med* 2015;162(1):55–63.
- [21] Breugom AJ, van Gijn W, Muller EW, Berglund A, van den Broek CBM, Fokstuen T, et al. Adjuvant chemotherapy for rectal cancer patients treated with preoperative (chemo)radiotherapy and total mesorectal excision: a Dutch Colorectal Cancer Group (DCCG) randomized phase III trial¹. *Ann Oncol* 2015;26(4):696–701.
- [22] The European Society of Coloproctology collaborating g. Safety of primary anastomosis following emergency left sided colorectal resection: an international, multi-centre prospective audit. *Colorectal Dis* 2018;20(S6):47–57.
- [23] Rahbari NN, Weitz J, Hohenberger W, Heald RJ, Moran B, Ulrich A, et al. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. *Surgery* 2010;147(3):339–51.
- [24] Borstlap WAA, Westerduin E, Aukema TS, Bemelman WA, Tanis PJ. Dutch snapshot research G. Anastomotic leakage and chronic presacral sinus formation after low anterior resection: results from a large cross-sectional study. *Ann Surg* 2017;266(5):870–7.
- [25] Qu H, Liu Y, Bi DS. Clinical risk factors for anastomotic leakage after laparoscopic anterior resection for rectal cancer: a systematic review and meta-analysis. *Surg Endosc* 2015;29(12):3608–17.
- [26] Nugent TS, Kelly ME, Donlon NE, Fahy MR, Larkin JO, McCormick PH, et al. Obesity and anastomotic leak rates in colorectal cancer: a meta-analysis. *Int J Colorectal Dis* 2021;36(9):1819–29.
- [27] Peeters K, Tollenaar R, Marijnen CAM, et al. Risk factors for anastomotic failure after total mesorectal excision of rectal cancer. *British Journal of* 2005.
- [28] Zheng H, Wu Z, Wu Y, Mo S, Dai W, Liu F, et al. Laparoscopic surgery may decrease the risk of clinical anastomotic leakage and a nomogram to predict anastomotic leakage after anterior resection for rectal cancer. *Int J Colorectal Dis* 2019;34(2):319–28.
- [29] Harrell Jr FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;15(4):361–87.
- [30] Zaimi I, Sparreboom CL, Lingsma HF, Doornebosch PG, Menon AG, Kleinrensink G-J, et al. The effect of age on anastomotic leakage in colorectal cancer surgery: a population-based study. *J Surg Oncol* 2018;118(1):113–20.

- [31] Krarup PM, Jorgensen LN, Andreassen AH, Harling H, Danish Colorectal Cancer G. A nationwide study on anastomotic leakage after colonic cancer surgery. *Colorectal Dis* 2012;14(10):e661–7.
- [32] Jannasch O, Klinge T, Otto R, Chiapponi C, Udelnow A, Lippert H, et al. Risk factors, short and long term outcome of anastomotic leaks in rectal cancer. *Oncotarget* 2015;6(34):36884–93.
- [33] Midura EF, Hanseman D, Davis BR, Atkinson SJ, Abbott DE, Shah SA, et al. Risk factors and consequences of anastomotic leak after colectomy: a national analysis. *Dis Colon Rectum* 2015;58(3):333–8.
- [34] Nikolian VC, Kamdar NS, Regenbogen SE, Morris AM, Byrn JC, Suwanabol PA, et al. Anastomotic leak after colorectal resection: a population-based study of risk factors and hospital variation. *Surgery* 2017;161(6):1619–27.
- [35] Parthasarathy M, Greensmith M, Bowers D, Groot-Wassink T. Risk factors for anastomotic leakage after colorectal resection: a retrospective analysis of 17 518 patients. *Colorectal Dis* 2017;19(3):288–98.
- [36] Franceschi C, Capri M, Monti D, Giunta S, Olivieri F, Sevini F, et al. Inflammation and anti-inflammation: a systemic perspective on aging and longevity emerged from studies in humans. *Mech Ageing Dev* 2007;128(1):92–105.
- [37] Bakker IS, Grossmann I, Henneman D, Havgana K, Wiggers T. Risk factors for anastomotic leakage and leak-related mortality after colonic cancer surgery in a nationwide audit. *Br J Surg* 2014;101(4):424–32. ; discussion 32.
- [38] Tevis SE, Carchman EH, Foley EF, Heise CP, Harms BA, Kennedy GD. Does anastomotic leak contribute to high failure-to-rescue rates? *Ann Surg* 2016;263(6):1148–51.
- [39] Matthiessen P, Hallböök O, Rutegård J, Sjødahl R. Population-based study of risk factors for postoperative death after anterior resection of the rectum. *Br J Surg* 2006;93(4):498–503.
- [40] Duldulao MP, Lee W, Le M, Wiatrek R, Nelson RA, Chen Z, et al. Surgical complications and pathologic complete response after neoadjuvant chemoradiation in locally advanced rectal cancer. *Am Surg* 2011;77(10):1281–5.
- [41] Matthiessen P, Hallböök O, Rutegård J, Simert G, Sjødahl R. Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum for cancer: a randomized multicenter trial. *Ann Surg* 2007;246(2):207–14.
- [42] Gu WL, Wu SW. Meta-analysis of defunctioning stoma in low anterior resection with total mesorectal excision for rectal cancer: evidence based on thirteen studies. *World J Surg Oncol* 2015;13:9.
- [43] Mrak K, Uranitsch S, Pedross F, Heuberger A, Klingler A, Jagoditsch M, et al. Diverting ileostomy versus no diversion after low anterior resection for rectal cancer: a prospective, randomized, multicenter trial. *Surgery* 2016;159(4):1129–39.
- [44] Shiomi A, Ito M, Maeda K, Kinugasa Y, Ota M, Yamaue H, et al. Effects of a diverting stoma on symptomatic anastomotic leakage after low anterior resection for rectal cancer: a propensity score matching analysis of 1,014 consecutive patients. *J Am Coll Surg* 2015;220(2):186–94.
- [45] Tsunoda A, Tsunoda Y, Narita K, Watanabe M, Nakao K, Kusano M. Quality of life after low anterior resection and temporary loop ileostomy. *Dis Colon Rectum* 2008;51(2).
- [46] van Praagh JB, de Goffau MC, Bakker IS, van Goor H, Harmsen HJM, Olinga P, et al. Mucus microbiome of anastomotic tissue during surgery has predictive value for colorectal anastomotic leakage. *Ann Surg* 2019;269(5).
- [47] Huisman DE, Reudink M, van Rooijen SJ, Bootsma BT, van de Brug T, Stens J, et al. LekCheck: a prospective study to identify perioperative modifiable risk factors for anastomotic leakage in colorectal surgery. *Ann Surg* 2020.
- [48] Hoek VT, Edomskis PP, Menon AG, Dwarkasing RS, Kleinrensink GJ, Jeekel J, et al. Calcification of the aorta-iliac trajectory as a risk factor for anastomotic leakage in colorectal surgery: individual patient data meta-analysis and systematic review. *Surg Technol Int* 2021;39.