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Stoma-free survival after rectal cancer resection with anastomotic leakage: development and validation of a prediction model in a large international cohort

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Abstract

Objective: This study aimed to develop and validate a prediction model (STOMA-score) for one-year stoma-free survival in rectal cancer (RC) patients with anastomotic leakage (AL).

Background: AL after RC resection often results in a permanent stoma.

Methods: This international retrospective cohort study (TENTACLE–Rectum) encompassed 216 participating centres, and included patients who developed AL after RC surgery between 2014-2018. Clinically relevant predictors for one-year stoma-free survival were included in uni- and multivariable logistic regression models. The STOMA-score was developed and internally validated in a cohort of patients operated between 2014-2017, with subsequent temporal validation in a 2018 cohort. The discriminative power and calibration of the models' performance were evaluated.

Results: This study included 2499 AL patients; 1954 in the development cohort and 545 in the validation cohort. Baseline characteristics were comparable. One-year stoma-free survival was 45.0% in the development cohort and 43.7% in the validation cohort. The following predictors were included in the STOMA-score: sex, age, ASA-classification, body mass index, clinical M-disease, neoadjuvant therapy, abdominal- and transanal approach, primary defunctioning stoma, multivisceral resection, clinical setting in which AL was diagnosed, postoperative day of AL diagnosis, abdominal contamination, anastomotic defect circumference, bowel wall ischemia, anastomotic fistula, retraction and reactivation leakage. The STOMA-score showed good discrimination and calibration (c-index 0.71, 95%CI 0.66-0.76).

Conclusion: The STOMA-score consists of eighteen clinically relevant factors and estimates the individual risk for one-year stoma-free survival in patients with AL after RC surgery,

which may improve patient counselling and give guidance when analyzing efficacy of different treatment strategies in future studies.

Introduction

Despite developments in surgical techniques and perioperative care, anastomotic leakage (AL) occurs up to 20% after restorative rectal cancer (RC) resection (1), and remains a severe complication (2-5). AL is associated with increased mortality (6-8), a negative impact on survival and leads to more reinterventions with subsequently higher healthcare costs (9, 10). In addition, half of the patients with symptomatic AL will end up with a permanent stoma (11). This might be either an initial- or secondary defunctioning stoma or end-colostomy following salvage surgery. A permanent stoma is an unintended outcome for a patient who expected restoration of bowel continuity, which likely contributes to inferior quality of life (12, 13).

Considerable heterogeneity exists in clinical presentation of AL, which ranges from occult leakages to severe sepsis, and it is debated to which extent this correlates with a permanent stoma (14, 15). Furthermore, several patient- and leakage-related factors as well as surgical characteristics for treatment of the primary RC might influence the chance of healing of an AL and risk of permanent stoma. Although AL has been studied extensively, long-term outcomes in terms of restoration of bowel continuity is an understudied topic as previous studies mainly focussed on identification of risk factors, prevention and early diagnosis of AL (7, 16, 17). This emphasizes the need to explore predictive factors related to restoration of bowel continuity.

This study aimed to develop and validate a prediction score for one-year stoma-free survival (STOMA-score) using data from a large international retrospective cohort study that included patients with AL after RC surgery. The STOMA-score can be used in clinical practice for the purpose of patient counselling or in research setting for future intervention studies.

Methods

The 'TreatmENT of AnastomotiC Leakage after rEctal cancer resection (TENTACLE – Rectum, Supplemental Digital Content 1, http://links.lww.com/SLA/E780) study is an international multicentre retrospective cohort study encompassing patients who developed AL after RC resection, who were operated between the 1st of January 2014 and the 31st of December 2018. The study was reported according to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD-guidelines, Supplemental Digital Content 1, http://links.lww.com/SLA/E780) (18). All centres performing RC surgery were eligible to participate without limitations based on case-volume or geographic location. In total, the collaborative group consists of 216 centres from 45 countries. The study was reviewed and approved on the 17th of October 2019 by the Research Ethics Committee of the Radboud University Medical Centre Nijmegen. According to Dutch law, informed consent was not required for observational studies. All participating centres adhered to their own legislation regarding approval and informed consent procedures. The full study protocol has been published previously (14), and the study is registered in the Clinical Trials registry: NCT04127734.

Patient selection

Patients were included if they were aged 18 years or older and diagnosed with AL within one-year after RC resection with formation of a primary anastomosis with- or without defunctioning stoma for either primary RC, regrowth (i.e. after watch-and-wait strategy), or as completion surgery after local excision between 2014-2018. Exclusion criteria were emergency RC resection, resection for benign disease or recurrent RC.

Definitions

The international consensus about the definition of the rectum was used to include homogeneous RC patients. This definition encompasses tumors with their lower border at or below the level of the sigmoid take-off (19). AL was defined according to the definition of the International Study Group of Rectal Cancer (ISREC): “a defect of the integrity of the intestinal wall at the anastomotic site (including leakage originating from suture and staple lines of neorectal reservoirs)”(20). This definition includes a pelvic abscess near the anastomosis, without a clear bowel wall defect.

Data collection, verification, and validation

Local investigators collected data pseudonymized in an online database (www.castoredc.com) and individual data was only traceable and accessible for the participating centres. Data verification and quality validation were performed to substantiate that all consecutive cases were included and to minimize inconsistencies and missing data (Supplementary Materials 1, Supplemental Digital Content 1, http://links.lww.com/SLA/E780). To reduce bias due to missing data, multiple imputation with chained equations was performed (21). Information about handling of missing data (Supplementary Table 3, Supplemental Digital Content 1, http://links.lww.com/SLA/E780) can be found in the Supplementary Materials 2, Supplemental Digital Content 1, http://links.lww.com/SLA/E780.

Outcome

The outcome of this study was one-year stoma-free survival, which was defined as being alive without a defunctioning stoma or end-colostomy one-year after RC surgery.

Predictors for stoma-free survival

Selection of potential clinically relevant predictors for stoma-free survival was done based on literature review and expert opinion among the lead investigators. Predictors selected through literature review consisted of patient demographics (e.g. age, comorbidity), disease-related and perioperative factors (e.g. metastasis, abdominal approach) and leakage-related factors at diagnosis (e.g. ischemia). Literature review and subsequent confirmation by the lead investigators yielded inclusion of the following predictors: age, American Society of Anaesthesiologists (ASA)-classification, clinical M-disease, neoadjuvant therapy, abdominal approach, defunctioning stoma created at index surgery, multivisceral resection, postoperative day of AL diagnosis, fistulas, retraction afferent colon, abdominal contamination, ischemia bowel wall, anastomotic defect circumference and reactivation leakage (5, 22-28). Additionally, four predictors with substantial clinical relevance were identified merely on expert opinion, comprising: sex, body mass index (BMI), transanal total mesorectal excision (TaTME) and clinical setting of AL diagnosis. Based on this selection process, eighteen predictors were included into the analysis. The predictors are depicted in Table 3 and additional information concerning sample size calculations and predictor selection can be found in the Supplementary Materials 3-4, Supplemental Digital Content 1, http://links.lww.com/SLA/E780.

Definitions predictors

Clinical setting of AL diagnosis was included to make a proxy of the patients clinical condition at time of diagnosis and was categorized into: intensive care unit or high-dependency care unit (ICU/HC), surgical ward, emergency department (ED) and outpatient clinic. Defect circumference was classified based on the degree of anastomotic dehiscence measured endoscopically: 0-25% (mild), 25-50% (moderate) and 50-100% (severe). Abdominal contamination was defined as spill- or leakage of bowel content into the abdominal cavity confirmed at reoperation. Anastomotic fistulas could either be present as a

postoperative iatrogenic complication or as a secondary infection due to chronic pelvic sepsis, with tracks to organs or structures (e.g. vagina, small bowel, skin). Reactivation leakage was defined as AL that was diagnosed after closure of a defunctioning stoma, even though diagnostic workup before stoma closure showed an intact anastomosis.

Statistical analysis

The study deviated from the original analysis plan as described in the study protocol (14), for development of a prediction model according to the TRIPOD-guidelines, Supplemental Digital Content 1, http://links.lww.com/SLA/E780. The total cohort was dived into a development cohort (2014-2017) and temporal validation cohort (2018). The model was developed based on a multivariable logistic regression model that predicts one-year stoma-free survival following AL after RC resection. All eighteen *a priori* predictors were included in the final multivariable model. Restricted cubic spline functions were used to test for non-linearity of the continuous variable (i.e. age).

Internal validation with bootstrap resampling (500 replicates) was applied to reduce optimism of the prognostic model. The obtained shrinkage factor was used to correct the regression coefficients, which contributes to generalizability and reduction of overfitting of the model. Based on the final bootstrapped multivariable regression analysis, a nomogram was created. In the development cohort, the models performance was assessed with discrimination (concordance (c)-index) and calibration. The flexible calibration curve allows examination of calibration across a range of predicted values. A curve close to the diagonal line (i.e. perfect calibration) indicates that predicted (x-axis) and observed probabilities (y-axis) correspond well.

To assess the models predictive performance in another cohort with similar patients, external validation was performed using a temporal approach (29-31). Temporal validation was done

with a cohort of patients who underwent RC resection in 2018. The pooled performance strategy (Rubin's rule) was used to pool performance measures (32). The internally validated model was implemented in a web application that provides patients' one-year stoma-free survival predictions. All analyses were carried out in R version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients

In total, 2710 patients were included in the database. A total of 211 patients were excluded based on: incorrect year of RC resection (n= 189), AL diagnosis beyond one-year from index surgery (n= 21) and absence of AL (n= 1). This resulted in 2499 AL patients, of whom 1954 were included in the development cohort and 545 in the validation cohort. Figure 1 presents the flowchart of patient inclusion.

Data quality validation

After correlating the expected with the uploaded cases, all 216 centres included their consecutive cases within the range of expected number of AL patients between 2014-2018. Of the 2499 patients, 164 cases (7%) from 33 different centres (15%) were validated and the overall accuracy was 96.6%. Hospital characteristics (e.g. annual case volume) can be found in the Supplementary Tables 1-2, Supplemental Digital Content 1, http://links.lww.com/SLA/E780.

Baseline characteristics

Table 1 presents the baseline characteristics in the development- and validation cohorts, which were predominantly comparable. Small proportional differences were found in abdominal approach and configuration of the anastomosis. In the validation cohort, less

defunctioning stoma's were created during primary RC resection (66.4% vs. 61.1%) and abdominal contamination was reported more frequently at AL diagnosis (31.9% vs. 36.7%). Median postoperative day of AL diagnosis did not differ between cohorts, which was after 8 days (IQR 4-18) in the development cohort, and after 7 days (IQR 4-15) in the validation cohort.

Predictors for one-year stoma-free survival

In the development- and validation cohorts, one-year stoma-free survival was 45.0% and 43.7%, respectively. Table 2 shows the univariable- and multivariable ORs of the eighteen tested predictors for stoma-free survival in the development cohort. Presented multivariable ORs are after internal validation. The most important predictors for a stoma at one-year in the univariable analysis were: age (IQR OR 1.21, 95%CI: 1.07-1.36), ASA-classification III/IV (OR 1.48, 95%CI: 1.11-1.98), clinical M1-disease (OR 2.08, 95%CI: 1.44-3.01), setting of diagnosis AL at the ICU/HC (OR 1.64, 95%CI: 1.02-2.63), open resection (OR 1.58, 95%CI: 1.29-1.94), degree of anastomotic dehiscence (moderate: OR 2.15, 95%CI: 1.55-2.97 and severe: OR 4.05, 95%CI: 2.65-6.20), ischemia (OR 2.53 95%CI 1.83-3.50), retraction of the afferent colon (OR 2.85, 95%CI: 1.71-4.72), abdominal contamination (OR 2.33, 95%CI: 1.90-2.85) and reactivation leakage (OR 1.71, 95%CI: 1.20-2.43). Predictors for not having a stoma-at one-year were: setting of diagnosis AL at the outpatient clinic (OR 0.66, 95%CI: 0.52-0.85) and TaTME (OR 0.71, 95%CI: 0.56-0.90). The following predictors did not reach statistical significance but contributed to the prediction of one-year stoma-free survival: BMI, multivisceral resection, neoadjuvant therapy and postoperative day of AL diagnosis. In the multivariable analysis, predictors that remained significant for a stoma at one-year were: age (OR 1.22, 95%CI 1.06-1.41), open resection (OR 1.31, 95%CI 1.04-1.65), degree of anastomotic dehiscence (moderate: OR 1.72 95%CI 1.21-2.45, severe: OR 2.53, 95%CI 1.53-4.19), ischemia (OR 1.51 95%CI 1.03-2.21), abdominal contamination (OR 1.81, 95%CI

1.41-2.32) and reactivation leakage (OR 1.50 95%CI 1.02-2.20), and creation of a defunctioning stoma at index surgery became significant (OR 1.31, 95%CI 1.04-1.66).

STOMA-score after internal- and temporal validation

The STOMA-score was developed using a multivariable logistic regression modelling consisting of eighteen clinically relevant predictors for one-year stoma-free survival. After internal validation, the c-index was 0.70 (95%CI: 0.66-0.76). The nomogram is presented in the Supplementary Figure 1, Supplemental Digital Content 1, http://links.lww.com/SLA/E780. Following temporal validation, the c-index was 0.71 (95%CI: 0.66-0.76). The scores' flexible calibration (figure 2) curve shows that predicted probabilities correlated with the observed probabilities across the entire risk range, indicating near perfect calibration.

Web application

To aid clinical utility, the internally validated STOMA-score was implemented in a web application. This application shows the predicted probabilities for one-year stoma-free survival in individual AL patients after RC resection. The STOMA-score and example cases will be accessible at: https://www.tentaclestudy.com/stoma-score.

Discussion

This large international, collaborative, retrospective study was the first to develop and validate a prediction model (STOMA-score) for one-year stoma-free survival in AL patients after RC resection. The STOMA-score consists of eighteen clinically relevant factors, including patient demographics (e.g. age, ASA-classification), disease-related and perioperative factors (e.g. metastasis, abdominal approach) and, uniquely, leakage-related

factors at diagnosis (e.g. ischemia, degree of anastomotic dehiscence). After temporal validation, the STOMA-score showed good predictive performance.

The main contributor for the risk of a permanent stoma after RC resection is AL, and among patients who developed AL, this is often the underlying reason (33). In line with previous studies (33-35), almost half of the leakage patients in this study had an unplanned stoma one-year after surgery. Also, temporary stomas that are not closed within one-year are highly likely to become permanent, as stoma closure is uncommonly performed after this time (33, 36). The role of defunctioning stoma creation at index surgery to decrease severity of AL has been debated previously (37, 38), but this current study demonstrated the long-term negative consequences. Holmgren et al. previously confirmed the phenomena that defunctioning stoma's created at index surgery are significantly associated with permanent stoma's, and in this study the effect of AL was considered as small (39).

Although AL has been studied extensively as outcome parameter to identify patients at risk for development of AL or to facilitate early diagnosis (16, 17), there is a lack of studies investigating the individual risk for a permanent stoma after AL. Available studies included all RC resection patients and not only AL patients, but similar patient- and tumor-related predictors have been reported, such as age, ASA-classification and metastatic disease (35, 36, 40). Elderly patients are more likely to refuse additional surgical procedures, and fear of frailty or increased morbidity might dissuade surgeons from stoma closure (36, 41). This phenomenon is also seen in patients with metastatic disease who tend to have a deteriorated condition, making them unsuitable candidates for stoma closure (35). Another predictor for a permanent stoma was primary open surgical resection. This might be explained by selection of more difficult cases, related to a narrow and irradiated pelvis (42, 43), or low- or advanced tumors (stage III-IV) with a threatened mesorectal fascia (44, 45).

Leakage-related factors such larger degree of anastomotic dehiscence, abdominal contamination and ischemia were strong predictors for a permanent stoma. Although the derangement in the anastomotic healing process by ischemia has been attributed to development of AL (25), the current study underlines their negative long-term effects. This is an important finding, indicating the necessity for further research investigating if presence of these factors should prompt different treatment strategies.

An interesting but underreported phenomenon is reactivation leakage, which occurs after closure of a defunctioning stoma following confirmation of anastomotic healing by endoscopy or contrast imaging (28, 46, 47). This condition was associated with a stoma one-year after RC resection, which might partly be explained by the fact that these leakages are difficult to treat since they have not fully healed despite prolonged deviation. Another aspect of these reactivation leakages is the relatively late diagnosis. Surprisingly, postoperative day of AL diagnosis was comparable between patients with- and without stoma-free survival (Supplementary Figure 2, Supplemental Digital Content 1, http://links.lww.com/SLA/E780), and no significant association was found with a permanent stoma. Regardless of this observation, lately diagnosed leakages did contribute to a higher predicted risk for a permanent stoma, which is visualized in the nomogram. Nonetheless, this effect may be diminished by the relatively small number of patients with lately diagnosed ALs.

Several strengths and limitations of the current study can be named. First, the retrospective nature of this study contributed to missing data. To prevent bias, multiple imputation with chained equations was used (21). Second, collaborating centers had to identify and include their cases retrospectively, potentially leading to selection bias. To ensure high-quality data, local independent validators performed data validation, and proved high overall accuracy. Third, four leakage-related predictors can only be confirmed after diagnostic work-up (e.g. endoscopy or computed tomography (CT)-scan) or during reoperation and might not be

available at time of AL diagnosis. In these cases, caution is advised when counseling the patients about the risk for a permanent stoma. Fourth, the STOMA-score showed good discrimination after temporal validation with a c-index of 0.71, but these results emphasize that it remains difficult to predict stoma-free survival. Compared to e.g. postoperative mortality, stoma-free survival is a complex endpoint, affected by more factors than this study could capture. For example, defunctioning stoma's will not be closed in RC patients with progressive disease after surgery (48, 49), which could have modestly affected stoma-free survival in the current study. Moreover, socioeconomic status and cultural and geographical differences such as acceptance of stomas and availability of stoma-care could have influenced decision-making (36, 50). Related to this, a permanent stoma due to impaired bowel function after AL might be necessary or favored by the patient (51), but patients preference cannot be incorporated in the model. Nonetheless, the vast amount of data from AL patients originating from 216 centres in 45 countries contributes to the generalizability of the STOMA-score.

It is intended that the STOMA-score can be used in clinical practice for patient counseling. Future studies might investigate whether individual/combined factors from the score could facilitate treatment decision making, which will shed more light on an individualized patient approach. Periodically updating of the STOMA-score based on new experience and data will be necessary, as use of deteriorated models may lead to under- or overestimation of the patients' risk (30).

In conclusion, this large, international collaborative study was the first to develop and validate a prediction model (STOMA-score) for one-year stoma-free survival in RC patients with AL. The STOMA-score can be used in clinical practice to estimate the risk of a permanent stoma after AL diagnosis, which will aid in counseling patients and management of expectations. Future studies that evaluate different treatment strategies for AL after RC resection can use the predictors from the STOMA-score to stratify or correct for potential confounding factors.

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Table 1. Baseline characteristics development- and validation cohort

	Development cohort (2014-2017) ***N= 1954***	**Validation cohort (2018)** ***N= 545***
Patient demographics		
Age in years, median (IQR)	65 (57-72)	64 (57-72)
Sex (%)		
Female	540 (27.6)	154 (28.3)
Male	1414 (72.4)	391 (71.7)
BMI (kg/m^2) (%)		
Underweight (<18.5)	91 (4.7)	30 (5.5)
Normal (18.5-24.9)	579 (29.6)	169 (31)
Overweight (25.0-29.9)	738 (37.8)	193 (35.4)
Obese (>30)	380 (19.4)	119 (21.8)
Missing	166 (8.5)	34 (6.2)
ASA-classification (%)		
ASA-I	302 (15.5)	80 (14.7)
ASA-II	1098 (56.2)	290 (53.2)
ASA-III/IV	508 (25.9)	162 (29.7)
Missing	46 (2.4)	13 (2.4)
Tumor characteristics		
Clinical T-classification (%)	6 (0.3)	4 (0.6)
T0	73 (3.7)	10 (1.8)
T1	390 (20)	117 (21.6)
T2	1206 (61.7)	340 (62.4)
T3	190 (9.7)	57 (10.5)
T4	89 (4.6)	17 (3.1)
Missing		
Clinical N-classification (%)	716 (36.6)	218 (40)
N0	590 (30.2)	182 (33.4)
N1	393 (20.1)	110 (20.2)
N2	125 (6.4)	23 (5.1)
N+	130 (6.7)	12 (2.2)
Missing		
Clinical M-disease (%)		
M0	1536 (78.6)	428 (78.5)
M1	150 (7.7)	43 (7.9)
Missing	268 (13.7)	74 (13.6)
Neoadjuvant therapy (%)	839 (42.9)	241 (44.2)
None	238 (12.2)	57 (10.5)
Radiotherapy only	41 (2.1)	7 (1.3)
Chemotherapy	836 (42.8)	240 (44)
Chemoradiation		

Tumor distance from anorectal junction in mm's, median (IQR)	60 (32-90)	60 (30-82)
Surgical characteristics		
Abdominal approach (%)	1181 (60.4)	357 (65.5)
Laparoscopic	179 (9.2)	58 (10.6)
Robot-assisted	593 (30.3)	130 (23.9)
Laparotomy	1 (0.05)	-
Missing		
Transanal TME (%)		
No	1599 (81.8)	433 (79.4)
Yes	355 (18.2)	111 (20.4)
Missing	-	1 (0.2)
Specification approach (%)	82 (23.1)	13 (11.7)
Open (TATA)	243 (68.5)	90 (81.1)
Transanal platform	30 (8.4)	8 (7.2)
Missing		
Configuration anastomosis (%)	1184 (60.6)	382 (70.1)
End-to-end	604 (30.9)	138 (25.3)
Side-to-end	81 (4.1)	10 (1.8)
Other*	85 (4.4)	15 (2.8)
Missing		
Multivisceral resection (%)	1781 (91.1)	494 (90.6)
No	127 (6.5)	41 (7.5)
Yes	46 (2.4)	10 (1.9)
Missing		
Splenic flexure mobilization (%)	630 (32.2)	183 (33.6)
No	1014 (51.9)	294 (53.9)
Yes	310 (15.9)	68 (12.5)
Missing		
Defunctioning stoma created at index surgery		
No	656 (33.6)	212 (38.9)
Yes	1298 (66.4)	333 (61.1)
Diagnostic characteristics		
Clinical setting diagnosis AL (%)	1324 (67.8)	387 (71.0)
Surgical ward	84 (4.3)	24 (4.4)
ICU/HC	198 (10.1)	51 (9.4)
Emergency department	346 (17.7)	81 (14.9)
Out-patient clinic	2 (0.1)	1 (0.2)
Missing		

Postoperatieve day of AL diagnosis, median (IQR)	8 (5-18)	7 (4-15)
Leakage characteristics		
Leakage location (%)		
Circular	1090 (55.8)	337 (61.8)
Side-to-end	183 (9.3)	47 (8.6)
Missing	681 (34.9)	161 (29.6)
Anastomotic defect circumference (%)		
0-25%	433 (39.7)	139 (41.3)
25-50%	230 (21.1)	79 (23.4)
50-100%	142 (13.0)	55 (16.3)
Missing	285 (26.2)	64 (19)
Ischemia bowel wall (%)		
No	1406 (72.0)	376 (69.0)
Yes	197 (10.1)	64 (11.7)
Missing	351 (17.9)	105 (19.3)
Retraction afferent colon (%)		
No	1426 (73.0)	402 (73.8)
Yes	76 (3.9)	23 (4.2)
Missing	452 (23.1)	123 (22.6)
Fistula(s) (%)		
No	1721 (88.1)	473 (86.8)
Yes	130 (6.7)	47 (8.6)
Missing	103 (5.2)	25 (4.6)
Abdominal contamination (%)		
No	1160 (59.4)	294 (53.9)
Yes	623 (31.9)	200 (36.7)
Missing	171 (8.7)	51 (9.4)
Reactivation leakage (%)		
No	1253 (64.1)	354 (64.9)
Yes	130 (6.7)	31 (5.7)
Missing	571 (29.2)	160 (29.4)
Mortality		
Mortality within one-year after index surgery (%)		
No	1738 (88.9)	485 (89.0)
Yes	103 (5.3)	27 (4.9)
Missing	113 (5.8)	33 (6.1)
Outcome		
Stoma-free survival (%)		
No	891 (45.6)	252 (46.2)
Yes	880 (45.0)	238 (43.7)
Missing	183 (9.4)	55 (10.1)

*BMI= body mass index, ASA= American Society of Anesthesiologists, *other= colonpouch, coloplasty, ileal pouch-anal anastomosis (IPAA)*

Table 2. STOMA-scores predictive accuracy in the development cohort

Predictor	***Univariable model OR (95% CI)***	***Multivariable model OR (95% CI)****
Sex		
Male	1.00 *(reference)*	1.00 (*reference*)
Female	1.19 (0.97-1.46)	1.14 (0.90-1.43)
Age in years, median (57-72 IQR)**	1.21 (1.07-1.36)	1.22 (1.06-1.41)
ASA-classification		
ASA-I	1.00 *(reference)*	1.00 *(reference)*
ASA-II	1.15 (0.90-1.50)	1.08 (0.81-1.44)
ASA-III/IV	1.48 (1.11-1.98)	1.12 (0.80-1.59)
Body mass index		
Normal	1.00 *(reference)*	1.00 *(reference)*
Underweight	1.41 (0.90-2.22)	1.30 (0.79-2.14)
Overweight	1.08 (0.86-1.34)	1.13 (0.89-1.43)
Obese	0.95 (0.73-1.24)	0.90 (0.68-1.21)
Clinical M-disease		
M0	1.00 *(reference)*	1.00 *(reference)*
M1	2.08 (1.44-3.01)	1.80 (1.19-2.72)
Neoadjuvant therapy		
None	1.00 *(reference)*	1.00 *(reference)*
Radiotherapy	1.05 (0.79-1.41)	1.17 (0.84-1.62)
Chemotherapy	1.61 (0.83-3.13)	1.10 (0.52-2.36)
Chemoradiation	1.03 (0.85-1.25)	1.13 (0.89-1.42)
Abdominal approach		
Laparoscopic	1.00 *(reference)*	1.00 *(reference)*
Robot-assisted	0.83 (0.60-1.14)	0.86 (0.60-1.23)
Laparotomy	1.58 (1.29-1.94)	1.31 (1.04-1.65)
Defunctioning stoma created at index surgery	1.04 (0.86-1.26)	1.31 (1.04-1.66)
Transanal TME	0.71 (0.56-0.90)	0.79 (0.61-1.04)
Multivisceral resection	1.36 (0.94-1.98)	1.18 (0.78-1.78)
Clinical setting diagnosis AL		
Surgical ward	1.00 *(reference)*	1.00 *(reference)*
Intensive care/high care unit	1.64 (1.02-2.63)	1.22 (0.72-2.06)
Emergency department	0.89 (0.66-1.20)	1.01 (0.73-1.42)
Outpatient clinic	0.66 (0.52-0.85)	0.75 (0.56-1.01)
Postoperative day of AL diagnosis, median (5-18 IQR)**	1.00 (0.97-1.03)	1.02 (0.99-1.06)
Anastomotic defect circumference	1.00 *(reference)*	1.00 *(reference)*
0-25%	2.15 (1.55-2.97)	1.72 (1.21-2.45)
25-50%	4.05 (2.65-6.20)	2.53 (1.53-4.19)
50-100%		
Ischemia bowel wall	2.53 (1.83-3.50)	1.51 (1.03-2.21)

Retraction afferent colon	2.85 (1.71-4.72)	1.30 (0.70-2.42)
Fistula(s)	1.33 (0.92-1.92)	1.10 (0.73-1.68)
Abdominal contamination	2.33 (1.90-2.85)	1.81 (1.41-2.32)
Reactivation leakage	1.71 (1.20-2.43)	1.50 (1.02-2.20)

Presented odds ratios after internal validation. For continuous variables, odds ratios represent interquartile range odds ratios. The odds ratio presented gives insight into the importance of predictors, which are expressed on a relative scale. These can be considered as a representation of the contribution to the predicted risk. A causal relation between predictor and outcome or the magnitude of the effect is not necessarily presented by the odds ratios.*

Table 3. Clinically relevant predictors for stoma-free survival in patients with AL following rectal cancer surgery*

Demographic factors	**Surgical- and diagnostic factors**	**Leakage-related factors**
Sex	Abdominal approach	Fistula(s)
Age	Defunctioning stoma created at index surgery	Retraction afferent colon
Body mass index	TaTME	Abdominal contamination
ASA-classification	Multivisceral resection	Ischemia bowel wall
Clinical M-disease	Clinical setting diagnosis AL	Anastomotic defect circumference
Neoadjuvant therapy	Postoperative day of AL diagnosis	Reactivation leakage

**A more detailed description regarding selection of predictors can be found in the Supplementary Materials. AL: anastomotic leakage, ASA: American Society of Anesthesiologists, TaTME: transanal total mesorectal excision*

Figure 1. Flowchart patient inclusion

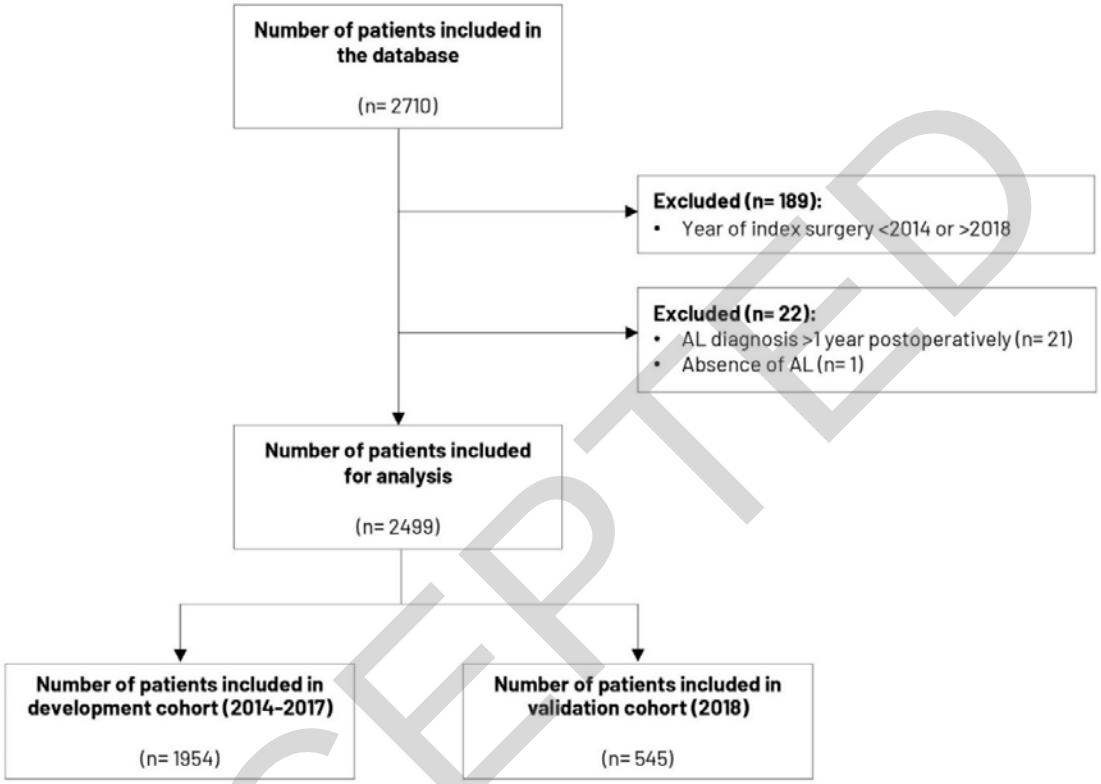
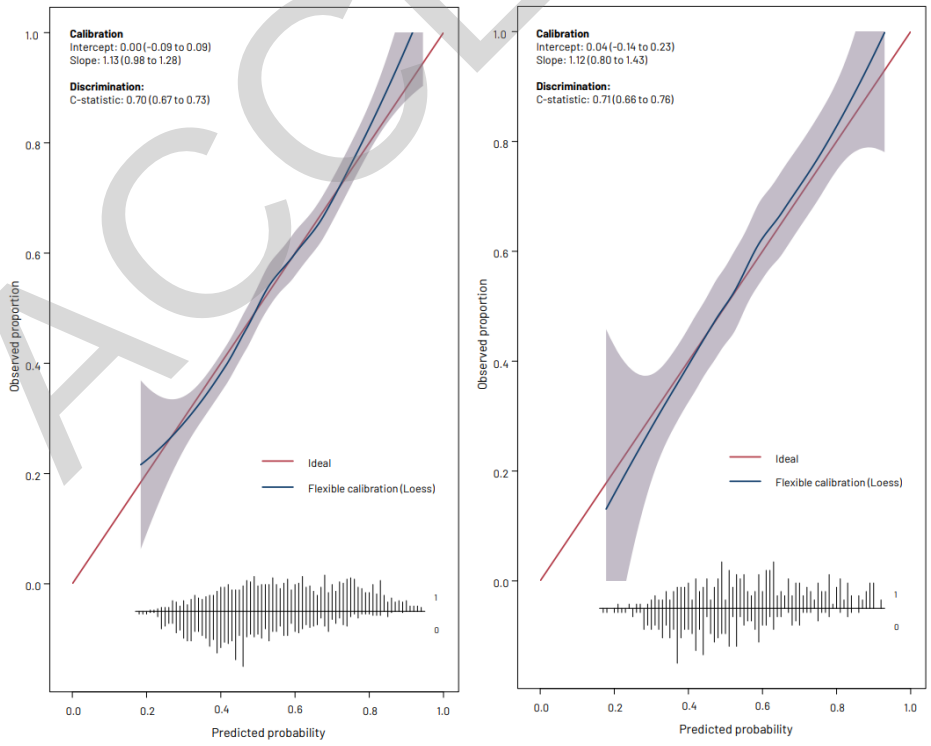


Figure 2. Flexible calibration curves of the internally- and temporal validated model

Figure (left): flexible calibration curve after internal validation, and figure (right): flexible calibration curve after temporal validation. Discrimination represents the ability to distinguish high-risk patients from low-risk patients and is quantified by concordance statistic (c-index), in which a 0.5 represents a non-informative model and a 1 a perfectly discriminating model. Calibration represents the agreement between the predicted risks and the observed outcome. Calibration is presented with a flexible calibration curve for prediction of stoma-free survival and by calculating the slope and intercept. The flexible calibration curve allows examination of calibration across a range of predicted values. A curve close to the diagonal line (i.e. perfect calibration) indicates that predicted (x-axis) and observed probabilities (y-axis) correspond well. The flexible calibration curve shows that predicted probabilities are in line with the observed probabilities across the entire risk range, indicating near perfect calibration.The slope is ideally equal to 1 and describes the effect of the predictors in the validation sample versus in the development sample. The intercept is ideally to 0 and measures if the model tends to under- or overestimate probability. At the bottom, the broom plot shows the distribution of the predicted probabilities for 1-year stoma free survival in patients who did (0) and patients who did not (1) have stoma-free survival.



#22

ANNSURG-D-23-00323	**Johannes De Wilt**	**Stoma-free survival after rectal cancer resection with anastomotic leakage: development and validation of a prediction model in a large international cohort**	**ESA Paper**

First Discussant: Dieter Hahnloser (Lausanne, Switzerland)

I would like to thank the ESA for the privilege of being the first discussant of this paper, and the authors for this interesting study. Scores in surgery should be clinically relevant and easy to use. The herein described score is clinically relevant, but not very practical. I have two questions.

First, some items are not available before re-operation, which makes counselling the patient based on the score difficult. Please comment.

Second, the finding that the day the leak is diagnosed neither influences the rate of salvage of the anastomosis nor impacts on stoma-free survival is very surprising. Please clarify and comment.

Response From Nynke Greijdanus (Nijmegen, The Netherlands)

Thank you for your questions and remarks. To answer the first question, we know that not all items might be available before re-operation, and this can affect patient counselling. However, most items will be available, and you can discuss two possible clinical scenarios with a patient: (1) there is no fecal contamination or presence of ischemia, which will lead to acceptable stoma-free survival rates; (2) if ischemia or fecal contamination is present, this will undoubtedly lead to lower stoma-free survival rates and a change in the treatment strategy. So, although not all items may be present, we believe that you can still advise the patient based on the two different scenarios, thereby improving expectation management, and guiding better treatment decision-making.

Regarding your second remark, we observed that most patients in this study were post-operatively diagnosed as having an anastomotic leakage within the first 20 days. This is in line with previous studies because most patients are diagnosed within the first 30 days. Although this was not a significant factor, we have incorporated the day of diagnosis into the model, and as you could see in our presentation, the later the diagnosis, the higher the chance of having a permanent stoma. For patients in clinical scenario 2, if they were post-operatively diagnosed on day 100, rather than day 5, this would reduce stoma-free survival from 72% to 62%; if they were diagnosed on day 200, then the stoma-free survival rate would drop down even further to 52%. So, contrarily to the situation you describe, we observed that the earlier the diagnosis was made, the better the outcomes for the patients were, and vice versa.

Discussant: Tomas Poškus (Vilnius, Finland)

Thank you for your excellent data. Did preventive ileostomy play a role in preventing long-term stoma-free survival?

Response From Nynke Greijdanus (Nijmegen, The Netherlands)

Yes, indeed. Placing a stoma was associated with the risk of a permanent stoma. So, patients who had a primary stoma were also likely to have a stoma after one year. There was a significant association.

Discussant: Felix Aigner (Graz, Austria)

Thank you for this wonderful study. I have one question regarding patient perspective. Have you also planned to look at this based on a lower stoma-free survival score, for example, and then, comparing it with the physician's perspective? I would expect to see some differences in perspective, especially when it comes to the removal of the stoma.

Response From Nynke Greijdanus (Nijmegen, The Netherlands)

This is a very good suggestion, but it was not included in our study. However, we believe that by advising patients on the risk related to a permanent stoma, it could also lead to shared decision-making. We believe that taking the patients into account and advising them properly is very important.

Discussant: Bas Wijnhoven (Rotterdam, The Netherlands)

Congratulations on this wonderful study. You spoke about the validation of the data, which I think is very important. However, I don't know how you did it. Many of the studies we've already been presented with, haven't talked about data validation. So, how did you check for completeness and validity? Did you find discrepancies between the data entered and the data found on validation?

Response From Nynke Greijdanus (Nijmegen, The Netherlands)

Thank you for your questions. Yes, we completed data validation in the participating centers. We randomly selected 30% of the centers to validate the data. We asked them to provide an independent validator, meaning a person outside of their group. This validator had the job of checking 15 key parameters for us, which would be checked against the data we had received. We saw that the majority of cases had a high validity of around 96%.

Discussant: André D'Hoore (Leuven, Belgium)

When you look at your score, it's going to be clinically relevant in the end. However, most of the patients are going to end up in a grey zone, between 40% and 70%. At that moment, it won't be very helpful. We know that most of the scores are at their most accurate in that grey zone, and problems always arise near the end, when you see an increasing number of mistakes.

Response From Nynke Greijdanus (Nijmegen, The Netherlands)

This is true. However, we believe that you can still advise the patient within this grey zone. With shared decision-making, you can, for example, tell them that their stoma-free survival risk is around 50%, making it hard for us to confirm whether they will end up with a stoma or not. Together, with the patient, you can discuss whether to try to aim for stoma-free survival. In the case of these patients, it's also useful to use a stoma score because they need some form of advice and shared decision-making to decide whether they want to aim for stoma-free survival.