

# Stoma-free Survival After Rectal Cancer Resection With Anastomotic Leakage

## Development and Validation of a Prediction Model in a Large International Cohort

Nynke G. Greijdanus, MD,\*✉ Kiedo Wienholts, MD,†‡§ Sander Ubels, MD,\*  
 Kevin Talboom, MD,†‡§ Gerjon Hannink, PhD,|| Albert Wolthuis, MD, PhD,¶  
 Francisco B. de Lacy, MD, PhD,# Jérémie H. Lefevre, MD, PhD,\*\*  
 Michael Solomon, MSc, DMed,†† Matteo Frasson, MD, PhD,‡‡  
 Nicolas Rotholtz, MD, PhD,§§ Quentin Denost, MD, PhD,|||  
 Rodrigo O. Perez, MD, PhD,¶¶ Tsuyoshi Konishi, MD, PhD,##  
 Yves Panis, MD, PhD,\*\*\* Martin Rutegård, MD, PhD,†††††  
 Roel Hompes, MD, PhD,†‡§ Camiel Rosman, MD, PhD,\*  
 Frans van Workum, MD, PhD,§§§ Pieter J. Tanis, MD, PhD,†‡§|||  
 Johannes H. W. de Wilt, MD, PhD,\* and TENTACLE-Rectum Collaborative Group

**Objective:** To develop and validate a prediction model (STOMA score) for 1-year stoma-free survival in patients with rectal cancer (RC) 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 and 2018. Clinically relevant predictors for 1-year stoma-free survival were included in uni and multi-variable logistic regression models. The STOMA score was developed and internally validated in a cohort of patients operated between 2014 and 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 patients with AL, 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, American Society of Anesthesiologist 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).

**Conclusions:** The STOMA score consists of 18 clinically relevant factors and estimates the individual risk for 1-year stoma-free survival in patients with AL after RC surgery, which may improve patient counseling and give guidance when analyzing the efficacy of different treatment strategies in future studies.

**Keywords:** anastomotic leakage, logistic regression model, permanent stoma, prediction model, rectal cancer, rectal cancer resection, stoma-free survival, STOMA score

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Despite developments in surgical techniques and perioperative care, anastomotic leakage (AL) occurs up to 20% after restorative rectal cancer (RC) resection,<sup>1</sup> and remains a severe complication.<sup>2–5</sup> AL is associated with increased mortality,<sup>6–8</sup> a negative impact on survival, and leads to more reinterventions with subsequently higher health care costs.<sup>9,10</sup> In addition, half of the patients with symptomatic AL will end up with a

From the \*Department of Surgery, Radboud university medical centre, Radboud Institute for Health Sciences, Nijmegen, the Netherlands; †Department of Surgery, Amsterdam University Medical Centers, University of Amsterdam, The Netherlands; ‡Treatment and Quality of Life, Cancer Center Amsterdam, Amsterdam, The Netherlands; §Imaging and Biomarkers, Cancer Center Amsterdam, Amsterdam, The Netherlands; ||Department of Medical Imaging, Radboud University Medical Centre, Radboud Institute for Health Sciences, Nijmegen, the Netherlands; ¶Department of Surgery, UZ Leuven, Leuven, Belgium; #Department of Gastrointestinal Surgery, Hospital Clinic of Barcelona, University of Barcelona, Barcelona, Spain; \*\*Department of Digestive Surgery, Sorbonne Université, AP-HP, Hôpital Saint Antoine, Paris, France; ††Department of Surgery, University of Sydney Central Clinical School, Camperdown, New South Wales, Australia; ‡‡Department of Surgery, Valencia University Hospital La Fe, Valencia, Spain; §§Department of Surgery, Hospital Alemán, Buenos Aires, Argentina; |||Bordeaux Colorectal Institute, Clinique Tivoli, Bordeaux, France; ¶¶Department of Colorectal Surgery, Hospital Alemão Oswaldo Cruz, São Paulo, Brazil; ##Department of Colon and Rectal Surgery, Division of Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX; \*\*\*Department of Colorectal Surgery, Colorectal

Surgery Center, Groupe Hospitalier Privé Ambroise Paré-Hartmann, Neuilly Seine, France; †††Department of Surgery, Surgical and Perioperative Sciences, Surgery, Umeå University, Umeå, Sweden; ‡‡‡Wallenberg Centre for Molecular Medicine, Umeå University, Umeå, Sweden; §§§Department of Surgery, Canisius Wilhelmina Hospital, Nijmegen, The Netherlands; and |||||Department of Surgical Oncology and Gastrointestinal Surgery, Erasmus Medical Centre, Rotterdam, The Netherlands.

✉nynke.greijdanus@radboudumc.nl

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permanent stoma.<sup>11</sup> This might be either an initial or secondary defunctioning stoma or end-colostomy after 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.<sup>12,13</sup>

Considerable heterogeneity exists in the 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.<sup>14,15</sup> 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 the 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 the identification of risk factors, prevention, and early diagnosis of AL.<sup>7,16,17</sup> This emphasizes the need to explore predictive factors related to the restoration of bowel continuity.

This study aimed to develop and validate a prediction score for 1-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 counseling or in the 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 January 1, 2014 and December 31, 2018. The study was reported according to the “Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis” guidelines (Supplemental Digital Content 1, <http://links.lww.com/SLA/E780>).<sup>18</sup> 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 October 17, 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,<sup>14</sup> 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 1 year after RC resection with the formation of a primary anastomosis with or without defunctioning stoma for either primary RC, regrowth (ie, after watch-and-wait strategy), or as completion surgery after local excision between 2014 and 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 patients with RC. This definition encompasses tumors with their lower border at or below the level of the sigmoid take-off.<sup>19</sup> AL was defined according to the definition of the International Study Group of Rectal Cancer: “a defect of the integrity of the intestinal wall at the anastomotic site (including leakage originating from the suture and staple lines of

neorectal reservoirs).”<sup>20</sup> 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](http://www.castoredc.com)) and individual data were 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 (Supplemental Digital Content Material 1, <http://links.lww.com/SLA/E780>). To reduce bias due to missing data, multiple imputation with chained equations was performed.<sup>21</sup> Information about handling of missing data (Supplemental Digital Content Table 3, <http://links.lww.com/SLA/E780>) can be found in Supplemental Material (Supplemental Digital Content Material 2, <http://links.lww.com/SLA/E780>).

### Outcome

The outcome of this study was 1-year stoma-free survival, which was defined as being alive without a defunctioning stoma or end-colostomy 1-year after RC surgery.

### Predictors for Stoma-free Survival

The selection of potential clinically relevant predictors for stoma-free survival was done based on a literature review and expert opinion among the lead investigators. Predictors selected through the literature review consisted of patient demographics (eg, age and comorbidity), disease-related and perioperative factors (eg, metastasis and abdominal approach), and leakage-related factors at diagnosis (eg, ischemia). Literature review and subsequent confirmation by the lead investigators yielded the inclusion of the following predictors: age, American Society of Anesthesiologists (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.<sup>5,22–28</sup> In addition, 4 predictors with substantial clinical relevance were identified merely on expert opinion, comprising: sex, body mass index, transanal total mesorectal excision, and clinical setting of AL diagnosis. Based on this selection process, 18 predictors were included in the analysis. The predictors are depicted in Table 1, and additional information concerning sample size calculations and predictor selection can be found in Supplemental Materials (Supplemental Digital Content Materials 3 and 4, <http://links.lww.com/SLA/E780>).

### Definitions Predictors

The clinical setting of AL diagnosis was included to make a proxy of the patient’s clinical condition at the time of diagnosis and was categorized into: intensive care unit or high-dependency care unit, surgical ward, emergency department, and out-patient clinic. Defect circumference was classified based on the degree of anastomotic dehiscence measured endoscopically: 0% to 25% (mild), 25% to 50% (moderate), and 50% to 100% (severe). Abdominal contamination was defined as a 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 (eg, vagina, small bowel, and skin). Reactivation leakage was defined as AL that was diagnosed after the closure of a defunctioning stoma, even though diagnostic workup before stoma closure showed intact anastomosis.

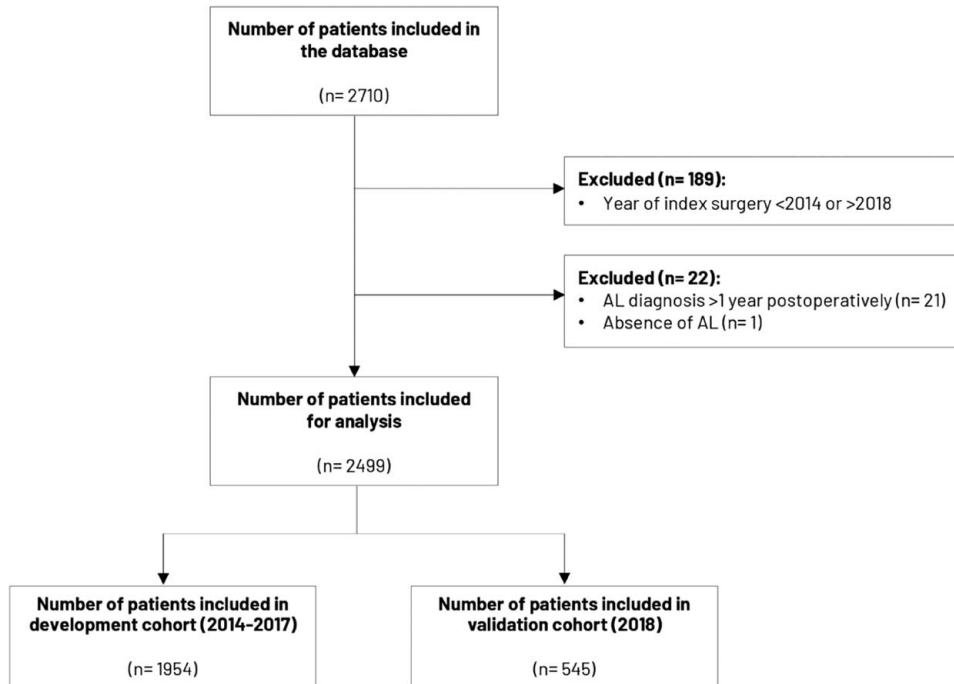


FIGURE 1. Flowchart of patient inclusion.

**Statistical Analyses**

The study deviated from the original analysis plan as described in the study protocol,<sup>14</sup> for the development of a prediction model according to the “Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis” guidelines (Supplemental Digital Content 1, <http://links.lww.com/SLA/E780>). The total cohort was divided into a development cohort (2014–2017) and a temporal validation cohort (2018). The model was developed based on a multivariable logistic regression model that predicts 1-year stoma-free survival following AL after RC resection. All 18 a priori predictors were included in the final multivariable model. Restricted cubic spline functions were used to test for the nonlinearity of the continuous variable (ie, age).

Internal validation with bootstrap resampling (500 replicates) was applied to reduce the 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 model’s performance was assessed with discrimination [concordance (c)-index] and calibration. The flexible calibration curve allows the examination of calibration across a range of predicted values. A curve close to the diagonal line (ie,

perfect calibration) indicates that the predicted (x-axis) and observed probabilities (y-axis) correspond well.

To assess the model’s predictive performance in another cohort with similar patients, external validation was performed using a temporal approach.<sup>29–31</sup> 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.<sup>32</sup> The internally validated model was implemented in a web application that provides patients’ 1-year stoma-free survival predictions. All analyses were carried out in R version 4.1.3 (R Foundation for Statistical Computing).

**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 1 year from index surgery (n = 21), and absence of AL (n = 1). This resulted in 2499 patients with AL, of whom 1954 were included in the development cohort and 545 in the validation cohort. Figure 1 presents the flowchart of patient inclusion.

**TABLE 1. Clinically Relevant Predictors for Stoma-free Survival in Patients With AL After RC 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
BMI	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 the selection of predictors can be found in the Supplemental Materials, Supplemental Digital Content, <http://links.lww.com/SLA/E780>. BMI indicates body mass index; TaTME, transanal total mesorectal excision.

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**TABLE 2.** Baseline Characteristics Development and Validation Cohort

	Development cohort (2014–2017); N = 1954; n (%)	Validation cohort (2018); N = 545; n (%)
<b>Patient demographics</b>		
Age (yr); median (IQR)	65 (57–72)	64 (57–72)
<b>Sex</b>		
Female	540 (27.6)	154 (28.3)
Male	1414 (72.4)	391 (71.7)
<b>BMI (kg/m<sup>2</sup>)</b>		
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)
<b>ASA classification</b>		
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)
<b>Tumor characteristics</b>		
<b>Clinical T-classification</b>		
T0	6 (0.3)	4 (0.6)
T1	73 (3.7)	10 (1.8)
T2	390 (20)	117 (21.6)
T3	1206 (61.7)	340 (62.4)
T4	190 (9.7)	57 (10.5)
Missing	89 (4.6)	17 (3.1)
<b>Clinical N-classification</b>		
N0	716 (36.6)	218 (40)
N1	590 (30.2)	182 (33.4)
N2	393 (20.1)	110 (20.2)
N+	125 (6.4)	23 (5.1)
Missing	130 (6.7)	12 (2.2)
<b>Clinical M-disease</b>		
M0	1536 (78.6)	428 (78.5)
M1	150 (7.7)	43 (7.9)
Missing	268 (13.7)	74 (13.6)
<b>Neoadjuvant therapy</b>		
None	839 (42.9)	241 (44.2)
Radiotherapy only	238 (12.2)	57 (10.5)
Chemotherapy	41 (2.1)	7 (1.3)
Chemoradiation	836 (42.8)	240 (44)
Tumor distance from the anorectal junction (mm); median (IQR)	60 (32–90)	60 (30–82)
<b>Surgical characteristics</b>		
<b>Abdominal approach</b>		
Laparoscopic	1181 (60.4)	357 (65.5)
Robot-assisted	179 (9.2)	58 (10.6)
Laparotomy	593 (30.3)	130 (23.9)
Missing	1 (0.05)	—
<b>TaTME</b>		
No	1599 (81.8)	433 (79.4)
Yes	355 (18.2)	111 (20.4)
Missing	—	1 (0.2)
<b>Specification approach</b>		
Open (TATA)	82 (23.1)	13 (11.7)
Transanal platform	243 (68.5)	90 (81.1)
Missing	30 (8.4)	8 (7.2)
<b>Configuration anastomosis</b>		
End-to-end	1184 (60.6)	382 (70.1)
Side-to-end	604 (30.9)	138 (25.3)
Other*	81 (4.1)	10 (1.8)
Missing	85 (4.4)	15 (2.8)
<b>Multivisceral resection</b>		
No	1781 (91.1)	494 (90.6)
Yes	127 (6.5)	41 (7.5)
Missing	46 (2.4)	10 (1.9)

**TABLE 2.** (Continued)

	Development cohort (2014–2017); N = 1954; n (%)	Validation cohort (2018); N = 545; n (%)
<b>Splenic flexure mobilization</b>		
No	630 (32.2)	183 (33.6)
Yes	1014 (51.9)	294 (53.9)
Missing	310 (15.9)	68 (12.5)
<b>Defunctioning stoma created at index surgery</b>		
No	656 (33.6)	212 (38.9)
Yes	1298 (66.4)	333 (61.1)
<b>Diagnostic characteristics</b>		
<b>Clinical setting diagnosis AL</b>		
Surgical ward	1324 (67.8)	387 (71.0)
ICU/HC	84 (4.3)	24 (4.4)
ED	198 (10.1)	51 (9.4)
Out-patient clinic	346 (17.7)	81 (14.9)
Missing	2 (0.1)	1 (0.2)
Postoperative day of AL diagnosis; median (IQR)	8 (5–18)	7 (4–15)
<b>Leakage characteristics</b>		
<b>Leakage location</b>		
Circular	1090 (55.8)	337 (61.8)
Side-to-end	183 (9.3)	47 (8.6)
Missing	681 (34.9)	161 (29.6)
<b>Anastomotic defect circumference</b>		
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)
<b>Ischemia bowel wall</b>		
No	1406 (72.0)	376 (69.0)
Yes	197 (10.1)	64 (11.7)
Missing	351 (17.9)	105 (19.3)
<b>Retraction afferent colon</b>		
No	1426 (73.0)	402 (73.8)
Yes	76 (3.9)	23 (4.2)
Missing	452 (23.1)	123 (22.6)
<b>Fistula(s)</b>		
No	1721 (88.1)	473 (86.8)
Yes	130 (6.7)	47 (8.6)
Missing	103 (5.2)	25 (4.6)
<b>Abdominal contamination</b>		
No	1160 (59.4)	294 (53.9)
Yes	623 (31.9)	200 (36.7)
Missing	171 (8.7)	51 (9.4)
<b>Reactivation leakage</b>		
No	1253 (64.1)	354 (64.9)
Yes	130 (6.7)	31 (5.7)
Missing	571 (29.2)	160 (29.4)
<b>Mortality</b>		
<b>Mortality within 1 yr after index surgery</b>		
No	1738 (88.9)	485 (89.0)
Yes	103 (5.3)	27 (4.9)
Missing	113 (5.8)	33 (6.1)
<b>Outcome</b>		
<b>Stoma-free survival</b>		
No	891 (45.6)	252 (46.2)
Yes	880 (45.0)	238 (43.7)
Missing	183 (9.4)	55 (10.1)

\*Other = colon pouch, coloplasty, ileal pouch-anal anastomosis.  
 BMI indicates body mass index; ED, emergency department; HC, high-dependency care; ICU, intensive care unit; TaTME, transanal total mesorectal excision; TATA, Transanal Abdominal Transanal Resection.

**TABLE 3.** 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 (yr); 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)
BMI		
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)
TaTME	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)
ED	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		
0%–25%	1.00 (reference)	1.00 (reference)
25%–50%	2.15 (1.55–2.97)	1.72 (1.21–2.45)
50%–100%	4.05 (2.65–6.20)	2.53 (1.53–4.19)
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.

BMI indicates body mass index; ED, emergency department; TaTME, transanal total mesorectal excision.

## Data Quality Validation

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

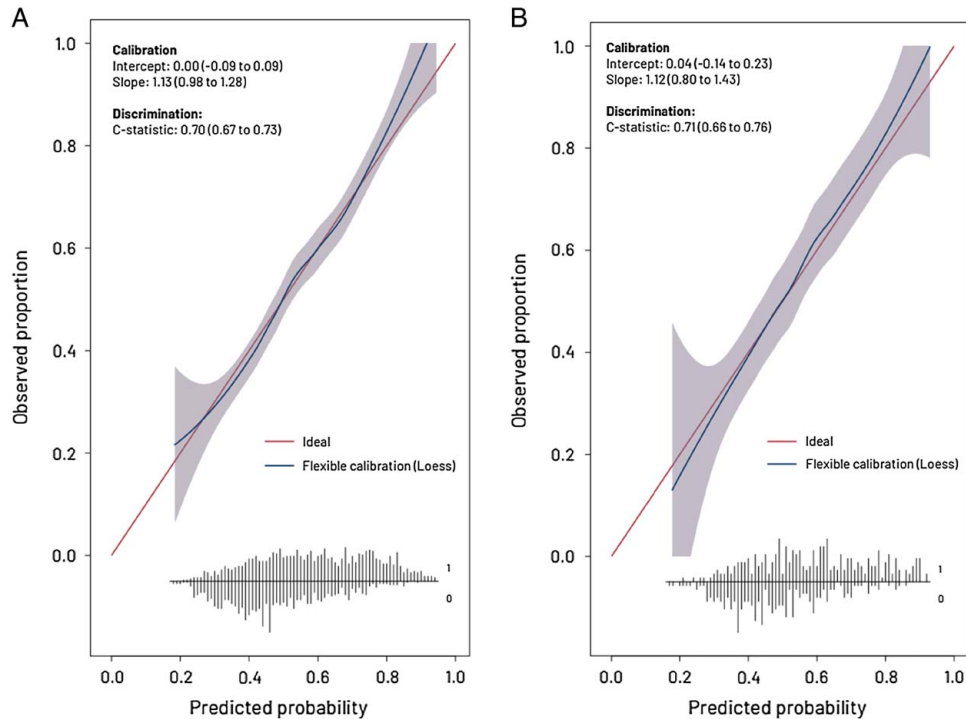
## Baseline Characteristics

Table 2 presents the baseline characteristics in the development and validation cohorts, which were predominantly comparable. Small proportional differences were found in the abdominal approach and configuration of the anastomosis. In the validation cohort, less defunctioning stomas 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 [interquartile range (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, 1-year stoma-free survival was 45.0% and 43.7%, respectively. Table 3 shows the univariable and multivariable odds ratios (ORs) of the 18 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 1 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:



**FIGURE 2.** Flexible calibration curves of the internally and temporal-validated model. A, Flexible calibration curve after internal validation. B, 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 noninformative model and a 1 is 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 the prediction of stoma-free survival and by calculating the slope and intercept. The flexible calibration curve allows the examination of calibration across a range of predicted values. A curve close to the diagonal line (ie, perfect calibration) indicates that the 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 the development sample. The intercept is ideally 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.

1.11–1.98), clinical M1-disease (OR: 2.08, 95% CI: 1.44–3.01), setting of diagnosis AL at the intensive care unit/high-dependency care (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 1 year were: setting of diagnosis AL at the out-patient clinic (OR: 0.66, 95% CI: 0.52–0.85) and transanal total mesorectal excision (OR: 0.71, 95% CI: 0.56–0.90). The following predictors did not reach statistical significance but contributed to the prediction of 1-year stoma-free survival: body mass index, multivisceral resection, neoadjuvant therapy, and postoperative day of AL diagnosis. In the multivariable analysis, predictors that remained significant for a stoma at 1 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), 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 modeling consisting of 18 clinically relevant predictors for 1-year stoma-free survival. After internal validation, the c-index was 0.70 (95% CI: 0.67–0.73). The nomogram is presented in Supplemental Figure (Supplemental Digital Content Fig. 1, <http://links.lww.com/SLA/E780>). After temporal validation, the c-index was 0.71 (95% CI: 0.66–0.76). The scores' flexible calibration (Fig. 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 1-year stoma-free survival in individual patients with AL after RC resection. The STOMA score and example cases will be accessible (at: [https://www.tentaclestudy.com/stoma score](https://www.tentaclestudy.com/stoma%20score)).

## DISCUSSION

This large international, collaborative, and retrospective study was the first to develop and validate a prediction model (STOMA score) for 1-year stoma-free survival in patients with AL after RC resection. The STOMA score consists of 18 clinically relevant factors, including patient demographics (eg, age and ASA classification), disease-related and perioperative factors (eg, metastasis and abdominal approach), and uniquely, leakage-related factors at diagnosis (eg, ischemia and degree of anastomotic dehiscence). After temporal validation, the STOMA score showed good predictive performance.

The main contributor to the risk of a permanent stoma after RC resection is AL, and among patients who developed AL, this is often the underlying reason.<sup>33</sup> In line with previous studies,<sup>33–35</sup> almost half of the leakage patients in this study had an unplanned stoma 1 year after surgery. Also, temporary stomas that are not closed within 1 year are highly likely to become permanent, as stoma closure is uncommonly performed after this time.<sup>33,36</sup> The role of defunctioning stoma creation at index surgery to decrease the severity of AL has been debated,<sup>37,38</sup> but this current study demonstrated the long-term negative consequences. Holmgren et al<sup>39</sup> confirmed the phenomena that defunctioning stomas created at index surgery are significantly associated with permanent stomas, and in this study, the effect of AL was considered small.

Although AL has been studied extensively as an outcome parameter to identify patients at risk for the development of AL or to facilitate early diagnosis,<sup>16,17</sup> 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 patients with AL but similar patient and tumor-related predictors have been reported, such as age, ASA classification, and metastatic disease.<sup>35,36,40</sup> Elderly patients are more likely to refuse additional surgical procedures, and fear of frailty or increased morbidity might dissuade surgeons from stoma closure.<sup>36,41</sup> This phenomenon is also seen in patients with metastatic disease who tend to have a deteriorated condition, making them unsuitable candidates for stoma closure.<sup>35</sup> Another predictor for a permanent stoma was primary open surgical resection. This might be explained by the selection of more difficult cases, related to a narrow and irradiated pelvis,<sup>42,43</sup> or low or advanced tumors (stage, III–IV) with a threatened mesorectal fascia.<sup>44,45</sup>

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

An interesting but underreported phenomenon is reactivation leakage, which occurs after the closure of a defunctioning stoma after the confirmation of anastomotic healing by endoscopy or contrast imaging.<sup>28,46,47</sup> This condition was associated with a stoma 1 year after RC resection, which might partly be explained by the fact that these leakages are difficult to treat as 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 (Supplemental Digital Content Fig. 2, <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.<sup>21</sup> 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, 4 leakage-related predictors can only be confirmed after diagnostic workup (eg, endoscopy or computed tomography scan) or during reoperation and might not be available at the time of AL diagnosis. In these cases, caution is advised when counseling the patients about the risk of 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 with the example of postoperative mortality, stoma-free survival is a complex endpoint affected by more factors than this study could capture. For example, defunctioning stomas will not be closed in patients with RC with progressive disease after surgery,<sup>48,49</sup> 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.<sup>36,50</sup> Related to this, a permanent stoma due to impaired bowel function after AL might be necessary or favored by the patients,<sup>51</sup> but the patients' preference cannot be incorporated in the model. Nonetheless, the vast amount of data from patients with AL originating from 216 centres in 45 countries contribute 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 the STOMA score, based on new experience and data, will be necessary, as the use of deteriorated models may lead to under or overestimation of the patients' risk.<sup>30</sup>

## CONCLUSIONS

This large, international collaborative study was the first to develop and validate a prediction model (STOMA score) for 1-year stoma-free survival in patients with RC with AL. The STOMA score can be used in clinical practice to estimate the risk of a permanent stoma after an 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 the potential confounding factors.

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## DISCUSSANT

### Dieter Hahnloser (Lausanne, Switzerland)

I would like to thank the European Surgical Association 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 2 questions.

First, some items are not available before reoperation, which makes counseling 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 stoma-free survival is very surprising. Please clarify and comment.

### Response from Nynke G. 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 reoperation, and this can affect patient counseling. However, most items will be available, and you can discuss 2 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 and (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 2 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 postoperatively diagnosed as having an AL 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 postoperatively 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, contrary 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.

### 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 G. 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.

### Felix Aigner (Graz, Austria)

Thank you for this wonderful study. I have one question regarding the patients' perspective. Have you also planned to look at this based on a lower stoma-free survival score, for example, and then, compare 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 G. Greijdanus (Nijmegen, The Netherlands)

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

### 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 do not know how you did it. Many of the studies we have already been presented with have not 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 G. 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%.

### André D'Hoore (Leuven, Belgium)

When you look at your score, it is 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 would not 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 G. 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 is 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.

## **Appendix Supplementary 1: Data verification and data quality validation**

Data verification and quality validation were performed in order to minimize the risk of selection bias and to ensure robustness of data.

### ***Data verification***

To screen the data for missing values, typos and inconsistent entries an algorithm was developed. After identification of incorrect values by the algorithm, revision was asked by the local investigator. If necessary, corrections were made in the database.

### ***Data quality validation***

Data quality validation was performed to assess case ascertainment (i.e. whether all eligible patients were included) and data accuracy (i.e. accuracy of the recorded data).

#### *Case ascertainment*

Case ascertainment was evaluated qualitatively by making an estimation of the eligible cases. This was calculated based on the annual case-volume of a participating centre and a conservative leakage rate of 3%. Centres that uploaded less patients than the estimated number of eligible patients were asked to substantiate their screening and inclusion procedure.

#### *Data accuracy*

In a representative sample of centres, the participating investigators recruited a local independent validator. To assess data accuracy, the independent validator was asked to retrieve a key set of 15 parameters from the medical records in a random sample of the included patients. The following parameters were retrieved:

#### *Preoperative parameters:*

1. Year of birth (yyyy)
2. Baseline ASA-classification
3. Baseline tumor-, node-, metastasis (TNM)-classification
4. Neoadjuvant therapy (yes/no)

#### *Perioperative parameters:*

5. Date of surgery (dd-mm-yyyy)
6. Abdominal approach (laparoscopy/robot assisted/laparotomy)
7. Configuration anastomosis (end-to-end/side-to-end/other)
8. Defunctioning stoma created at index surgery (yes/no)

#### *Diagnosis of leakage and treatment parameters:*

9. Location of the leakage (circular/blind loop)
10. Setting of diagnosis anastomotic leakage (surgical ward/intensive care unit or high care unit/emergency department/out-patient clinic)
11. Treatment within one-year after index surgery – radiological intervention (yes/no)
12. Treatment within one-year after index surgery – endoscopic intervention (yes/no)
13. Treatment within one-year after index surgery – surgical intervention (yes/no)

#### *Mortality:*

14. Mortality within one-year after index surgery (yes/no)

#### *Outcome:*

15. Stoma one-year after index surgery (yes/no)

The local independent validators did not receive access to the online Castor database, which was done to ensure independency of data quality validation. Validation of the data retrieved by the local independent validator was reviewed by the coordinating investigator from the TENTACLE-Rectum study. The coordinator compared the data recorded in the Castor database with the data retrieved

from the medical records by the independent local validator. Missing data in the dataset and in the medical records confirmed by the local independent validator was not considered as an error. Any discrepancies between the two data sources were confirmed by the local independent validator. To define and quantify data accuracy, a percentage was calculated by dividing the correct data fields by the total number of data fields. The analysis was performed in Microsoft Excel (version 2016), Microsoft Corporation.

### **Results data accuracy**

The screening and inclusion process was reviewed of all participating centres. Baseline characteristics, annual case-volume, diagnostic- and treatment modalities can be found in the Supplementary Table 1 and 2. The minimum of expected leakage cases were calculated based on their annual case-volume and a conservative leakage rate of 3%. These numbers were compared with the actual provided cases and none of the participating centres included less cases than expected in the database.

Independent local validators were asked to participate in data quality validation and this was performed in 33 of 216 participating centres (15.2%). A total of 164 patients (7%) were selected at random, and local validators had to retrieve 15-key parameters from the patients' (electronic) medical files. These 15-key parameters were compared to the data from the Castor database and for each centre, a percentage of data accuracy was calculated. The mean overall data accuracy was 96.6% (standard deviation (SD) 4.7).

### **Appendix Supplementary 2: Handling of missing data**

In clinical and epidemiological research, missing data is inevitable but the consequences are often overlooked (1). The default way of handling incomplete data is performing a complete-case analysis (listwise deletion). In the complete-case analysis, all cases with one or more missing values are eliminated from the analysis (1, 2). However, this is potentially wasteful because it is not uncommon that more than half of the sample will be lost, especially when using large datasets with different variables (3). Consequently, there will be loss of statistical power. Besides, missing data can introduce bias and this can contribute to undermining the validity of data (1).

In order to use the complete sample in the analysis and to reduce bias, multiple imputation was used, which is an efficient way of dealing with missing data. We performed multivariate imputation by chained equations (MICE) using predictive mean matching (PMM) in patients who had missing values in the predictors or outcome (4). This method is based on the assumption that the data is missing at random (MAR), which attributes systematic differences between the observed and missing values to differences in the observed data. If an observation is missing, it is not related to the missing values but it is conditional on another variable (e.g. age, sex) (1). To substantiate the MAR assumption, it is advised to perform an inclusive analysis strategy. This strategy includes a number of auxiliary variables into the imputation process. Auxiliary variables are variables that are present in the original data but will not be used in the analysis. Nonetheless, these variables are correlated to the variables of interest and they keep the missing process random (5). The following auxiliary variables were included into the inclusive analysis strategy: baseline characteristics, tumor-, resection-, leakage and outcome parameters.

In multiple imputation,  $m$  copies of the dataset are created. The number of  $m$  copies of the data should at least be equal to the percentage of missing cases (see Supplementary table 3), but larger number of imputations may be required (6). It is often beneficial to set  $m$  higher, between 20-100 imputations (3). Therefore, we used one-hundred imputed datasets with five iterations. During the imputation procedure, the missing value is imputed in a dataset through an iterative series of the predictive models. In each iteration, the specified variable in the dataset is imputed using the other variables in the dataset, which was done with PMM. To assess the convergence of the chained imputation procedure, visual trace plots were made of the mean and standard deviation of the

imputed data against iteration number. Finally, the imputed data was evaluated for plausibility and consistency amongst the different dataset. In each imputed dataset, the statistical analyses were performed. The results were pooled subsequently, which was done according to Rubin's rule. All analyses were performed with R version 4.1.3 with packages rms and mice (R Foundation for Statistical Computing, Vienna, Austria).

### **Appendix Supplementary 3: Sample size, development and validation STOMA-score**

#### **Sample size**

In order to create a prediction model with an estimated one-year stoma-free survival rate of 70% and a Nagelkerke  $R^2$  of 0.15, a minimum of 1097 patients with anastomotic leakage were required. This study included 2499 patients of whom 1954 were included in the prediction models' development cohort and 545 in the validation cohort.

#### **Model development, performance and validation**

##### **1. Development and internal validation**

The model was developed to predict the probability of stoma-free survival one-year after index surgery. In the uni- and multivariable logistic regression analysis patients were analyzed who did (0) and patients who did not have (1) stoma-free survival.

The model was developed based on a development cohort of patients operated between 2014-2017 ( $n= 1954$ ). Data were derived from 216 collaborating centres from 45 countries worldwide, without restrictions based on geographical location or case-volume. Baseline hospital characteristics from collaborating centres can be found in the Supplementary Tables 1 and 2. The following predictors were incorporated in the model: sex, age, ASA-classification (ASA-I, ASA-II, ASA-III/IV), body mass index (underweight, normal, overweight, obese), clinical M-disease (M0, M1), neoadjuvant therapy (none, radiotherapy, chemotherapy, chemoradiation), abdominal approach (laparoscopic, robot-assisted, laparotomy), defunctioning stoma created at index surgery, transanal total mesorectal excision, multivisceral resection, clinical setting of anastomotic leakage diagnosis (surgical ward, intensive care unit/high care unit, emergency department, out-patient clinic), postoperative day of anastomotic leakage diagnosis, anastomotic defect circumference (0-25%, 25-50%, 50-100%), ischemia bowel wall, retraction afferent colon, fistulas, abdominal contamination and reactivation leakage. After development of the model it was internally validated with bootstrapping using 500 replicates to estimate the degree of optimism in the STOMA-score. In order to correct for this optimism, the shrinkage factor obtained in bootstrapping was used to reduce the regression coefficients.

After internal validation the model is presented as:

$$\begin{aligned} \text{LP} = & -1.3538 \\ & + 0.076741 [\text{ASA-II}] + 0.098319^* [\text{ASA-III/IV}] \\ & + 0.199250^* [\text{Age}] \\ & + 0.127570 [\text{Sex: female}] \\ & + 0.265480^* [\text{underweight BMI}] + 0.121240^* [\text{overweight BMI}] - 0.100580^* [\text{obese BMI}] \\ & + 0.585300^* [\text{Clinical M1-disease}] \\ & + 0.155010^* [\text{Neoadjuvant therapy: RT}] + 0.098901^* [\text{Neoadjuvant therapy: CT}] + 0.118070^* [\text{Neoadjuvant therapy: CRT}] \\ & - 0.150790^* [\text{Abdominal approach: robot-assisted}] + 0.268250^* [\text{Abdominal approach: laparotomy}] \\ & + 0.273320^* [\text{Defunctioning stoma created at index surgery: yes}] \\ & - 0.232970^* [\text{Transanal TME: yes}] \end{aligned}$$

+ 0.165480\* [Multivisceral resection: yes]  
+ 0.199660\* [Clinical setting diagnosis AL: ICU/HC] + 0.014535\* [Clinical setting diagnosis AL: emergency department]  
-0.289930\* [Clinical setting diagnosis AL: out-patient clinic]  
+ 0.027823\* [Postoperative day of AL diagnosis]  
+ 0.098435\* [Fistulas: yes]  
+ 0.261440\* [Retraction afferent colon: yes]  
+ 0.410840\* [Ischemia bowel wall: yes]  
+ 0.592250\* [Abdominal contamination: yes]  
+ 0.542150\* [Anastomotic defect circumference: 25-50%] + 0.929040\* [anastomotic defect circumference: 50-100%]  
+ 0.404420\* [Reactivation leakage: yes]

LP = linear predictor; the linear predictor is the weighted sum of the values of the predictors in the model, where the weights are the regression coefficients.

In line with outcomes such as 'overall survival' and 'disease-free survival' the model estimates the probability of having a negative outcome; which was equivalent to no stoma-free survival one-year rectal cancer resection. In order to calculate one-year stoma-free survival, the following calculation can be used:

$$P_{1\text{-year stoma-free survival}} = 1 - \frac{1}{1+e^{(-LP)}}$$

## 2. Temporal external validation

For external validation of the model, temporal validation was performed with a cohort of patients operated in 2018 ( $n= 545$ ). The estimated area under the ROC curve (AUC) was 0.71 (0.66-0.76 95%CI), which suggest an acceptable discrimination between patients who did have stoma-free survival and patients who did not have stoma-free survival one-year after index surgery in our data.

### 2.2 Calibration intercept and calibration slope

To estimate the calibration intercept, the logistic model  $Y = \alpha + LP$  was fitted. In logistic regression,  $Y$  is the logarithm of the estimated risk ( $P_{\text{no stoma-free survival at 1-year}}$ ) divided by 1 minus the estimated risk, i.e.,  $\log(P_{\text{no stoma-free survival at 1-year}} / (1 - P_{\text{no stoma-free survival at 1-year}}))$ . Notice that there is no regression coefficient for the effect of LP, which is equivalent to setting the coefficient of LP to 1. In a practical sense, this means that a regression model is fitted with LP as an 'offset term'. The estimated value of the intercept  $\alpha$  is the calibration intercept.

To obtain the calibration slope, the logistic model  $Y = \alpha' + \beta * LP$  was fitted. The estimated value of the slope  $\beta$  is the calibration slope.

The target value of the calibration intercept is zero, and in the current study the calibration intercept was -0.04 (95%CI: -0.14-0.23). This was close to the target value of 0, suggesting that the model did not systematically under- or overestimate the risk. The calibration slope was 1.12 (95%CI: 0.80-1.43), which was close to the target value of one. This calibration slope suggests that risk estimates were not systematically too extreme or systematically too moderate.

### 2.3 Flexible calibration curves

Based on the logistic model  $Y = \alpha'' + f(LP)$ , the flexible calibration curve was plotted. The flexible calibration curve of both the original model (internally validated) and temporal (externally) validated model are shown in Figure 2. The Calibration Curve package was used in R (<https://cran.r->

project.org/web/packages/CalibrationCurves/index.html) and plots were generated using the function 'val.prob.ci2'. For analysis, R version 4.1.3 was used ([www.R-project.org](http://www.R-project.org)).

Figure 2 presents the flexible calibration curve of the original (internally validated) model and information regarding the calibration intercept, slope and discrimination. 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. 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. Calibration is presented with a flexible calibration plot for prediction of stoma-free survival and by calculating the slope and intercept. 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 close to 0 and measures if the model tends to under- or overestimate predictions.

#### **Appendix Supplementary 4: Selection of predictors**

In order to identify predictors for an outcome, two main strategies can be used: data-driven and clinically-driven. The latter strategy was used in the current study and encompasses selection of candidate predictors by literature review or expert opinion (7). As literature studies about predictors for stoma-free survival in anastomotic leakage patients after rectal cancer resection are lacking, predictors for a permanent stoma after rectal cancer resection were reviewed (8-23). After literature review and subsequent confirmation among the lead investigators, fourteen clinically relevant predictors for one-year stoma-free survival were identified. According to expert opinion among the TENTACLE-Rectum study team, four additional predictors were identified as clinically relevant and were therefore added to the analysis. Predictors for one-year stoma-free survival were categorized into: demographic factors (i.e. patient and tumor characteristics), surgical- and diagnostic factors and leakage-related factors at diagnosis. An overview of the eighteen included predictors can be found in Table 3.

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**Supplementary Figure 1. Nomogram**

**Points**

ASA-classification

Age in years

Sex

Body mass index

Clinical M-disease

Neoadjuvant therapy

Abdominal approach

Defunctioning stoma created at index surgery

Transanal TME

Multivisceral resection

Clinical setting AL diagnosis

Postoperative day of AL diagnosis

Fistulas

Retraction afferent colon

Ischemia bowel wall

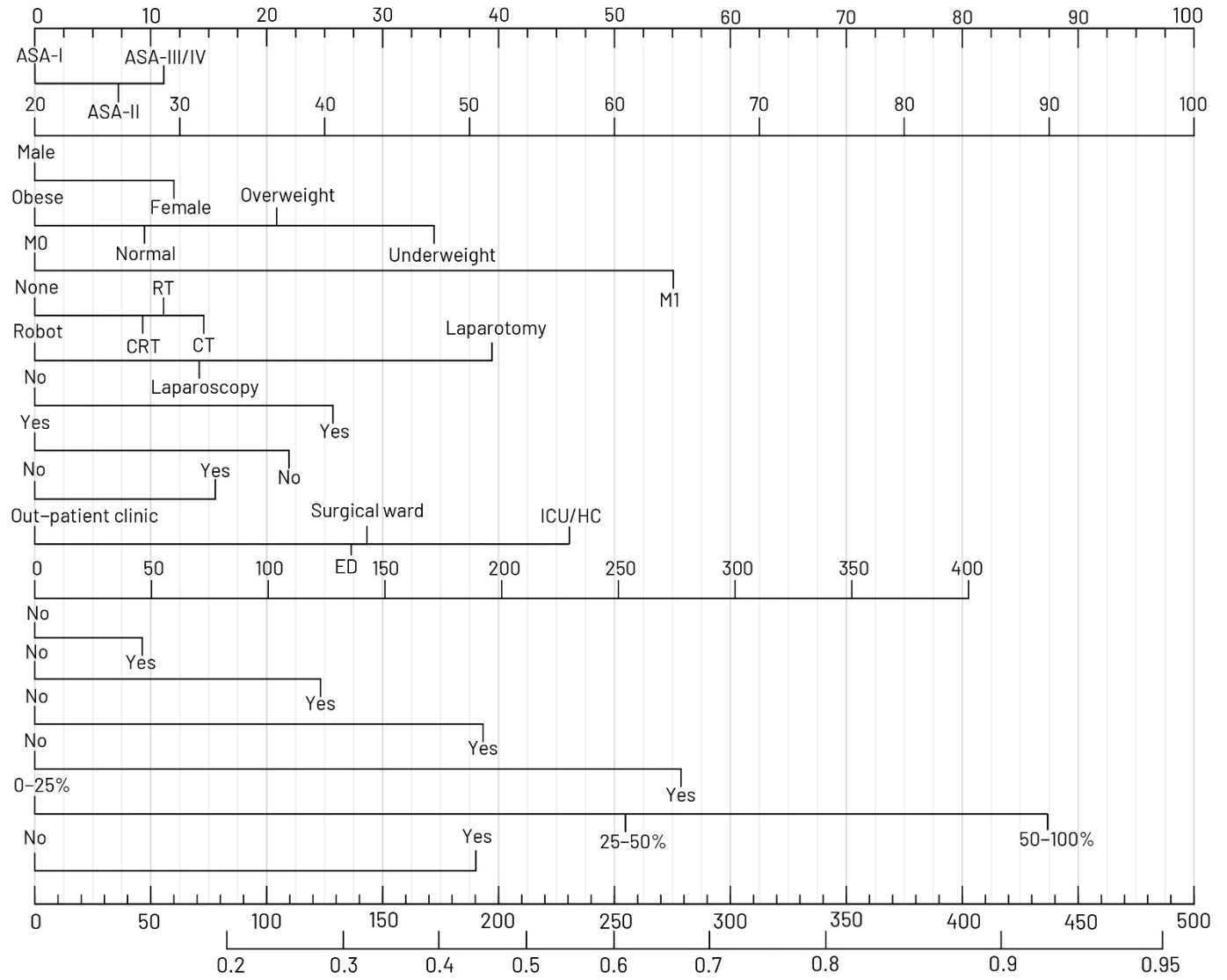
Abdominal contamination

Anastomotic defect circumference

Reactivation leakage

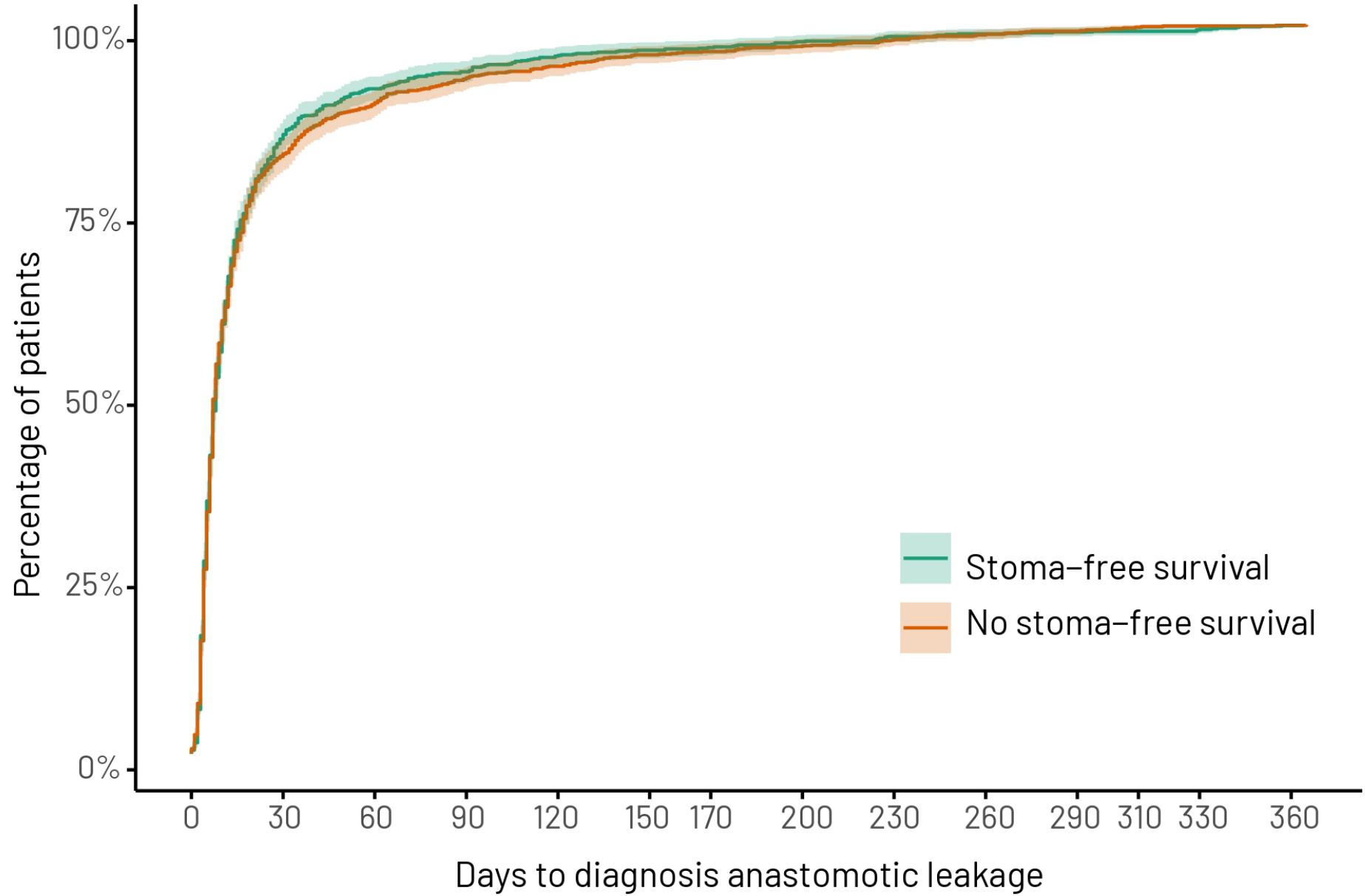
**Total points**

**Predicted probability**





**Supplementary Figure 2. Postoperative day of AL diagnosis differentiated between patients with- and without stoma-free survival**



**Supplementary Table 1. Baseline characteristics participating centres**

<b>Characteristics</b>	<b>N= 216 (%)</b>
<b>Hospital type</b>	
Academic, teaching	104 (48.2)
Cancer center	15 (6.9)
General, teaching	84 (38.9)
General, non-teaching	13 (6.0)
<b>Complication management</b>	
Dedicated colorectal surgeon	108 (50.0)
Dedicated gastrointestinal surgeon	42 (19.4)
Surgeon on call	43 (19.9)
Combination	23 (10.7)
<b>MRI/CT access (24/7)</b>	
No	4 (1.8)
Yes	212 (98.2)
<b>Availability gastroenterologist (24/7)</b>	
No	43 (19.9)
Yes	173 (80.1)
<b>Availability interventional radiologist (24/7)</b>	
No	66 (30.6)
Yes	150 (69.4)
<b>Annual case-volume, median (IQR)</b>	38 (23-60)
<b>Annual case-volume classification</b>	
Low (0-19)	40 (18.5)
Middle (20-49)	100 (46.3)
High (>50)	76 (35.2)
<b>Therapeutic modalities (n= 216)</b>	
Ultrasound drainage	209 (96.8)
CT-guided drainage	203 (93.9)
Endoscopic drainage	180 (83.3)
EVAC/Endo-SPONGE®	149 (68.9)
Endoscopic clipping	195 (90.3)
EUA/Transanal drainage	207 (95.8)
Laparoscopy	215 (99.5)
<b>Transanal modalities (n= 216)</b>	
TAMIS	148 (68.5)
Transanal platform	102 (47.2)
TEM	116 (53.7)
TEO	52 (24.1)

*MRI= magnetic resonance imaging, CT= computed tomography, EVAC= endoscopic vacuum assisted closure, EAU= examination under anesthesia, TAMIS= transanal minimally invasive surgery, TEM= transanal endoscopic microsurgery, TEO= transanal endoscopic operation*

**Supplementary Table 2. Table of individual hospital characteristics**

	<b>Hospital type</b>	<b>Annual case volume</b>	<b>Postoperative complication management</b>	<b>Availability of diagnostic modalities and medical specialist (24/7)</b>	<b>Therapeutic modalities</b>	<b>Transanal modalities</b>
1.	General, teaching	12	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS
2.	General, teaching	41	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, transanal platform
3.	General, teaching	29	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, transanal platform
4.	Academic, training	5	Dedicated colorectal surgeon	CT/MRI, interventional radiologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, EUA/transanal drainage, laparoscopy	TAMIS, transanal platform
5.	Academic, training	62	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM, transanal platform, TEO
6.	Academic, training	50	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM, transanal platform
7.	Academic, training	38	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM, transanal platform
8.	Academic, training	27	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM
9.	General, teaching	20	General surgeon on call	CT/MRI	Ultrasound drainage, CT-guided drainage, endoscopic drainage, endoscopic clipping, EUA/transanal drainage, laparoscopy	-
10.	Academic, training	26	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TEM, transanal platform
11.	General, teaching	39	Dedicated GI-surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM, transanal platform
12.	General, teaching	20	General surgeon on call	CT/MRI, gastroenterologist	CT-guided drainage, EVAC, endoscopic clipping, EAU/transanal drainage, laparoscopy	TAMIS, transanal platform
13.	General, teaching	30	Dedicated GI-surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TEM, transanal platform
14.	Academic, training	65	Combination	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, transanal platform
15.	Academic, training	82	General surgeon on call	CT/MRI, gastroenterologist	Ultrasound drainage, endoscopic clipping, EUA/transanal drainage, laparoscopy	TEM
16.	Academic, training	110	Dedicated colorectal surgeon	CT/MRI, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM
17.	Academic, training	46	Dedicated colorectal surgeon	CT/MRI, gastroenterologist	Ultrasound drainage, endoscopic drainage, EUA/transanal drainage, laparoscopy	TAMIS, TEM, transanal platform
18.	General, non-teaching	36	Dedicated colorectal surgeon	CT/MRI interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, transanal platform, TEO
19.	General, teaching	70	Dedicated colorectal surgeon	CT/MRI	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM, transanal platform, TEO
20.	Academic, training	24	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM
21.	Academic, training	40	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM
22.	General, teaching	12	Dedicated colorectal surgeon	CT/MRI, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM, transanal platform



48.	General, teaching	17	Dedicated colorectal surgeon	CT/MRI	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, EUA/transanal drainage, laparoscopy	TEM
49.	General, teaching	60	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, transanal platform
50.	General, teaching	15	Dedicated GI-surgeon	CT/MRI	Ultrasound drainage, CT-guided drainage, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS
51.	General, teaching	27	General surgeon on call	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, transanal platform
52.	Academic, training	56	General surgeon on call	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM, transanal platform
53.	General, teaching	76	General surgeon on call	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, transanal platform, TEO
54.	General, teaching	50	Dedicated GI-surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM, transanal platform
55.	Academic, training	80	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM
56.	Academic, training	160	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM, transanal platform
57.	Academic, training	136	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM, transanal platform, TEO
58.	General, teaching	70	Dedicated colorectal surgeon	CT/MRI, interventional radiologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM
59.	Academic, training	23	Dedicated GI-surgeon	CT/MRI	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM, transanal platform
60.	Academic, training	220	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM, transanal platform, TEO
61.	Cancer centre	12	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM, transanal platform
62.	General, teaching	19	Dedicated GI-surgeon	CT/MRI	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS
63.	General, teaching	59	Dedicated GI-surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, endoscopic clipping, EUA/transanal drainage, laparoscopy	TEM
64.	General, teaching	29	Dedicated colorectal surgeon	CT/MRI	Ultrasound drainage, CT-guided drainage, EUA/transanal drainage, laparoscopy	TAMIS
65.	General, teaching	26	General surgeon on call	CT/MRI, interventional radiologist	Ultrasound drainage, CT-guided drainage, EUA/transanal drainage, laparoscopy	TAMIS
66.	General, teaching	22	Combination	CT/MRI, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, EUA/transanal drainage, laparoscopy	TAMIS, TEM
67.	Academic, training	50	Combination	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEO
68.	General, non-teaching	75	General surgeon on call	CT/MRI, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS
69.	General, teaching	72	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TEM, transanal platform, TEO
70.	General, teaching	47	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM
71.	General, teaching	33	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	-
72.	Academic, training	10	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, transanal platform, TEO

73.	General, teaching	56	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic clipping, EUA/transanal drainage, laparoscopy	TEM
74.	General, non-teaching	70	Dedicated colorectal surgeon	CT/MRI	Ultrasound drainage, CT-guided drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM
75.	General, teaching	14	Dedicated GI-surgeon	CT/MRI, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS
76.	Academic, training	16	Dedicated GI-surgeon	CT/MRI, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, endoscopic clipping, EUA/transanal drainage, laparoscopy	-
77.	Cancer centre	64	Dedicated GI-surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM
78.	Academic, training	36	Dedicated GI-surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, endoscopic clipping, EUA/transanal drainage, laparoscopy	Transanal platform
79.	Academic, training	39	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM
80.	Academic, training	70	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, transanal platform, TEO
81.	General, teaching	7	Dedicated GI-surgeon	CT/MRI, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM
82.	Academic, training	49	Dedicated colorectal surgeon	CT/MRI	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM, transanal platform
83.	Academic, training	40	Dedicated colorectal surgeon	CT/MRI, interventional radiologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM, transanal platform
84.	Academic, training	99	General surgeon on call	CT/MRI	Ultrasound drainage, CT-guided drainage, endoscopic drainage, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM, transanal platform
85.	General, teaching	20	Dedicated GI-surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, EVAC, endoscopic clipping, laparoscopy	TAMIS
86.	General, teaching	36	General surgeon on call	CT/MRI, gastroenterologist	Ultrasound drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS
87.	General, teaching	6	Dedicated GI-surgeon	CT/MRI, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, endoscopic clipping, EUA/transanal drainage, laparoscopy	TEM
88.	General, non-teaching	16	General surgeon on call	CT/MRI, gastroenterologist	Ultrasound drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS
89.	General, non-teaching	20	General surgeon on call	CT/MRI	CT-guided drainage, EUA/transanal drainage, laparoscopy	TAMIS, TEM
90.	General, teaching	12	Combination	CT/MRI, gastroenterologist	Ultrasound drainage, endoscopic clipping, laparoscopy	TAMIS, TEM, transanal platform
91.	General, non-teaching	16	General surgeon on call	CT/MRI	Ultrasound drainage, CT-guided drainage, laparoscopy	-
92.	Academic, training	50	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM, transanal platform
93.	Academic, training	50	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM, transanal platform
94.	Academic, training	92	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM, transanal platform, TEO
95.	General, non-teaching	22	Dedicated GI-surgeon	CT/MRI, interventional radiologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM, transanal platform
96.	Cancer centre	75	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM
97.	General, teaching	29	Dedicated GI-surgeon	CT/MRI, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM



123.	Academic, training	2	General surgeon on call	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, endoscopic clipping, laparoscopy	TAMIS, transanal platform
124.	Academic, training	26	General surgeon on call	CT/MRI, gastroenterologist	CT-guided drainage, EVAC, EUA/transanal drainage, laparoscopy	-
125.	Academic, training	40	Combination	CT/MRI, gastroenterologist	Ultrasound drainage, endoscopic drainage, endoscopic clipping, EUA/transanal drainage, laparoscopy	TEM, TEO
126.	Cancer centre	17	Combination	CT/MRI	Ultrasound drainage, CT-guided drainage, endoscopic drainage, endoscopic clipping, EUA/transanal drainage, laparoscopy	TEO
127.	General, teaching	28	Combination	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM
128.	Academic, training	40	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, transanal platform
129.	General, teaching	25	Dedicated colorectal surgeon	CT/MRI	Ultrasound drainage, CT-guided drainage, EUA/transanal drainage, laparoscopy	TAMIS
130.	General, teaching	36	Combination	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, transanal platform
131.	Academic, training	30	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS
132.	General, teaching	57	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM
133.	Cancer centre	65	Dedicated GI-surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM, transanal platform, TEO
134.	General, teaching	58	Dedicated GI-surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TEM, transanal platform
135.	Cancer centre	98	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, EUA/transanal drainage, laparoscopy	TEM, transanal platform
136.	Cancer centre	4	Dedicated colorectal surgeon	CT/MRI, interventional radiologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, endoscopic clipping, EUA/transanal drainage, laparoscopy	-
137.	General, teaching	40	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, EUA/transanal drainage, laparoscopy	TAMIS
138.	Cancer centre	21	Dedicated GI-surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TEM
139.	Academic, training	33	Combination	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, transanal platform
140.	General, teaching	43	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, EUA/transanal drainage, laparoscopy	TEM
141.	General, teaching	64	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, transanal platform, TEO
142.	General, teaching	50	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS
143.	General, teaching	82	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS
144.	General, teaching	30	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM
145.	General, teaching	59	Dedicated GI-surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM
146.	Academic, training	33	Combination	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TEO
147.	General, non-teaching	35	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM





173.	Academic, training	35	Combination	-	EVAC, endoscopic clipping, laparoscopy	TAMIS
174.	General, teaching	21	Combination	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS
175.	General, teaching	27	Dedicated colorectal surgeon	CT/MRI, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS
176.	General, non-teaching	23	General surgeon on call	CT/MRI	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, laparoscopy	TAMIS
177.	Academic, training	36	Dedicated colorectal surgeon	CT/MRI, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	-
178.	Academic, training	32	Dedicated GI-surgeon	CT/MRI, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic clipping, EUA/transanal drainage, laparoscopy	-
179.	General, teaching	192	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, transanal platform
180.	Academic, training	136	Combination	CT/MRI, gastroenterologist	Ultrasound drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, transanal platform
181.	Academic, training	120	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, endoscopic clipping, EUA/transanal drainage, laparoscopy	Transanal platform
182.	Academic, training	81	Dedicated colorectal surgeon	CT/MRI	Ultrasound drainage, endoscopic clipping, laparoscopy	TAMIS
183.	General, teaching	30	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TEM, transanal platform, TEO
184.	Cancer centre	70	General surgeon on call	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TEO
185.	General, teaching	18	General surgeon on call	CT/MRI	Ultrasound drainage, CT-guided drainage, endoscopic drainage, endoscopic clipping, EUA/transanal drainage, laparoscopy	Transanal platform
186.	Academic, training	43	Dedicated colorectal surgeon	CT/MRI, interventional radiologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TEM, transanal platform
187.	General, Teaching	26	General surgeon on call	CT/MRI	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TEM
188.	Academic, training	108	General surgeon on call	CT/MRI, interventional radiologist	Ultrasound drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TEM
189.	Academic, training	95	Dedicated colorectal surgeon	CT/MRI	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	-
190.	General, non-teaching	40	Dedicated GI-surgeon	CT/MRI, interventional radiologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, endoscopic clipping, EUA/transanal drainage, laparoscopy	-
191.	Academic, training	36	Dedicated colorectal surgeon	CT/MRI, interventional radiologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TEM
192.	General, teaching	27	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TEM
193.	Academic, training	84	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, EUA/transanal drainage, laparoscopy	TAMIS, transanal platform
194.	Academic, training	4	Dedicated GI-surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, EUA/transanal drainage, laparoscopy	-
195.	General, non-teaching	8	Dedicated GI-surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, EUA/transanal drainage, laparoscopy	-
196.	General, teaching	2	General surgeon on call	CT/MRI, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM, transanal platform, TEO
197.	Academic, training	30	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, endoscopic clipping, EUA/transanal drainage, laparoscopy	TEM

198.	Cancer centre	34	Combination	CT/MRI	Ultrasound drainage, CT-guided drainage, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, transanal platform
199.	General, teaching	39	Dedicated GI-surgeon	CT/MRI, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM, transanal platform
200.	Academic, training	42	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEO
201.	Cancer centre	16	Dedicated GI-surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	Transanal platform
202.	Academic, training	91	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EUA/transanal drainage, laparoscopy	TEM, TEO
203.	Academic, training	60	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM, TEO
204.	Academic, training	98	Combination	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TEM
205.	Academic, training	41	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM, TEO
206.	Academic, training	73	Dedicated colorectal surgeon	CT/MRI, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM, transanal platform
207.	Academic, training	40	Combination	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM, TEO
208.	Academic, training	40	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM, transanal platform
209.	Academic, training	27	General surgeon on call	CT/MRI, gastroenterologist	Ultrasound drainage, CT-guided drainage, EUA/transanal drainage, laparoscopy	-
210.	Academic, training	46	Dedicated GI-surgeon	CT/MRI, gastroenterologist	Ultrasound drainage, endoscopic drainage, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS
211.	Academic, training	67	Dedicated colorectal surgeon	CT/MRI, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	-
212.	Academic, training	60	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM, transanal platform
213.	General, teaching	9	General surgeon on call	CT/MRI	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, TEM, transanal platform, TEO
214.	General, non-teaching	75	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS, transanal platform, TEO
215.	Academic, training	36	Dedicated colorectal surgeon	CT/MRI, interventional radiologist, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TEO
216.	Academic, training	30	Dedicated colorectal surgeon	CT/MRI, gastroenterologist	Ultrasound drainage, CT-guided drainage, endoscopic drainage, EVAC, endoscopic clipping, EUA/transanal drainage, laparoscopy	TAMIS

*GI-surgeon= gastrointestinal surgeon, CT= computerized tomography, MRI= Magnetic resonance imaging, EVAC= endoscopic vacuum-assisted closure (Endo-SPONGE®), EUA= examination under anesthesia, TAMIS= transanal minimally invasive surgery, TEM= transanal endoscopic microsurgery, TEO= transanal endoscopic operation*

**Supplementary Table 3. Missing data in predictors of the STOMA-score**

<b>Predictor</b>	<b>Definition</b>	<b>Missing data (%)</b>
<i>Age</i>	Age in years at time of restorative rectal cancer resection	0.1
<i>ASA-classification</i>	ASA-classification: ASA-I (normal health), ASA-II (mild systemic disease), ASA-III/IV (severe systemic disease and severe systemic disease with a constant threat to life)	2.4
<i>BMI (kg/m<sup>2</sup>)</i>	BMI-classification: underweight (<18.5), normal weight (18.5-24.9), overweight (25-29.9) and obese (>30)	8.0
<i>Sex</i>	Male, female	0.0
<i>Clinical M-disease</i>	Clinical diagnosis of distant metastases: M0 (no distant metastases), M1 (distant metastases present)	13.7
<i>Neoadjuvant therapy</i>	None, radiotherapy only, chemotherapy or chemoradiation	0.0
<i>Clinical setting diagnosis AL</i>	Clinical setting in which anastomotic leakage was diagnosed: intensive care unit (ICU)/high-dependency care (HC), surgical ward, emergency department (ED), outpatient clinic	0.1
<i>Postoperative day of AL diagnosis</i>	Number of days between primary rectal cancer resection and diagnosis of anastomotic leakage	0.28
<i>TaTME</i>	Transanal total mesorectal excision (TaTME): a 'bottom-up' approach performed with transanal endoscopic platforms and laparoscopic or robotic abdominal assistance	0.1
<i>Multivisceral resection</i>	En bloc resection of a structure or organ adherent to the primary tumor	2.2
<i>Abdominal approach</i>	Laparoscopic, robot-assisted or laparotomy	0.1
<i>Defunctioning stoma created at index surgery</i>	Defunctioning stoma created at rectal cancer resection, could be either a (double loop) ileostomy or a (double loop) colostomy	0.0
<i>Anastomotic defect circumference</i>	Leakage characteristics at diagnosis: estimated defect circumference measured endoscopically: 0-25% (mild), 25-50% (moderate), >50-100% (severe)	14.0
<i>Ischemia bowel wall</i>	Leakage characteristics at diagnosis: ischemia of the bowel wall	18.2
<i>Retraction afferent colon</i>	Leakage characteristics at diagnosis: retraction afferent colon	22.9
<i>Fistula(s)</i>	Leakage characteristic at diagnosis: anastomotic fistulas (i.e. postoperative iatrogenic, secondary infection due to chronic pelvic sepsis). Fistulas could have tracks to the following organs or structures: vagina, bladder, small bowel, skin, urethra or seminal vesicles.	5.1
<i>Abdominal contamination</i>	Leakage characteristics at diagnosis: spill- or leakage of colonic content into abdominal cavity	8.9
<i>Reactivation leakage</i>	AL that was diagnosed after closure of primary- or secondary defunctioning stoma, despite diagnostic before stoma closure revealed an intact anastomosis	29.3

Section/Topic	Item		Checklist Item	Page
<b>Title and abstract</b>				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	Frontpage
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	1
<b>Introduction</b>				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	1
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	1
<b>Methods</b>				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	2,4
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	2
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	2
	5b	D;V	Describe eligibility criteria for participants.	3
	5c	D;V	Give details of treatments received, if relevant.	n.a.
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	3
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	n.a.
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	4, Supplementary 4
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	n.a.
Sample size	8	D;V	Explain how the study size was arrived at.	Supplementary 3
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	Supplementary 2
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	4, 5
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	4, 5
	10c	V	For validation, describe how the predictions were calculated.	4, 5
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	4, 5
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	n.a.
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	n.a.
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	5
<b>Results</b>				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	5, Figure 1
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	5, Table 1
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	5, Table 1
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	5, 6, Table 1
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	n.a.
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Supplementary 3
	15b	D	Explain how to use the prediction model.	Supplementary 3
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	6, Table 2
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	6
<b>Discussion</b>				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	8,9
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	8,9
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	8,9
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	
<b>Other information</b>				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	See supplementary
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	Frontpage

\*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

## Appendix 1: TENTACLE – Rectum Collaborative Group

Collaborators – all to be PUBMED citable

Andreas J.A. Bremers, Floris T. Ferenschild (Radboud University Medical Centre, Radboud Institute for Health Sciences, Nijmegen, The Netherlands) Stefanie de Vriendt, André D’Hoore, Gabriele Bislenghi (University Hospitals Leuven, Leuven, Belgium); Jordi Farguell, Antonio M. Lacy, Paula González Atienza (Hospital Clínic de Barcelona, Barcelona, Spain); Charlotte S. van Kessel (Royal Prince Albert Hospital, Sydney, Australia); Yann Parc, Thibault Voron, Maxime K. Collard (Sorbonne Université, AP-HP, Hôpital Saint Antoine, Paris, France); Jorge Sancho Muriel, Hannia Cholewa (Valencia University Hospital La Fe, Valencia, Spain); Laura A. Mattioni (Hospital Alemán, Buenos Aires, Argentina); Alice Frontali (Beaujon Hospital, Clichy, and University of Paris, Clichy, France); Sebastiaan W. Polle, Fatih Polat, Ndidi J. Obihara (Canisius Wilhelmina Hospital, Nijmegen, the Netherlands); Bruna B. Vailati (Hospital Alemão Oswaldo Cruz, São Paulo, Brazil); Miranda Kusters, Jurriaan B. Tuynmann, Sanne J.A. Hazen, Alexander A.J. Grüter (Amsterdam University Medical Centers, location VUmc, Amsterdam, The Netherlands; Cancer Center Amsterdam, Treatment and Quality of Life, Amsterdam, The Netherlands; Cancer Center Amsterdam, Imaging and Biomarkers, Amsterdam, The Netherlands); Takahiro Amano, Hajime Fujiwara (Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan); Mario Salomon, Hernán Ruiz, Ricardo Gonzalez, Diego Estefanía (Buenos Aires British Hospital, Buenos Aires, Argentina); Nicolas Avellaneda, Augusto Carrie, Mateo Santillan (CEMIC University Hospital, Buenos Aires, Argentina); Diana A. Pantoja Pachajoa, Matias Parodi, Manuel Gielis (Clínica Universitaria Reina Fabiola, Córdoba, Argentina); Alf-Dorian Binder, Thomas Gürtler, Peter Riedl (Universitätsklinikum Tulln, Tulln an der Donau, Austria); Sarit Badiani, Christophe Berney, Matthew Morgan (Bankstown-Lidcombe Hospital, Sydney, New South Wales, Australia); Paul Hollington, Nigel da Silva, Gavin Nair (Flinders Medical Centre, Adelaide, South Australia, Australia); Yiu M. Ho, Michael Lamparelli, Raj Kapadia (Rockhampton Hospital, Queensland, Australia); 19 Hidde M. Kroon, Nagendra N. Dudi-Venkata, Jianliang Liu, Tarik Sammour (Royal Adelaide Hospital, Adelaide, South Australia, Australia); Nicolas Flamey, Paul Pattyn, Ahmed Chaoui, Louis Vansteenbrugge (AZ Delta, Roeselare, Belgium); Nathalie E.J. van den Broek, Patrick Vanclooster, Charles de Gheldere (Heilig-Hartziekenhuis, Lier, Belgium); Pieter Pletinckx, Barbara Defoort, Maxime Dewulf (Maria Middelaes Ghent, Belgium); Mihail Slavchev, Nikolay Belev, Boyko Atanasov, Panche Krastev (University Hospital Eurohospital - Medical University Plovdiv, Plovdiv, Bulgaria); Manol Sokolov, Svilen Maslyankov, Petar Gribnev, Vasil Pavlov (Aleksandrovska University Hospital, Sofia, Bulgaria); Tsvetomir Ivanov, Martin Karamanliev, Emil Filipov, Pencho Tonchev (Medical University Pleven, Pleven, Bulgaria); Felix Aigner, Martin Mitteregger, Caterina Allmer, Gerald Seitinger (St. John of God Hospital Graz, Graz, Austria); Nicola Colucci, Nicolas Buchs, Frédéric Ris, Christian Toso (Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland); Eleftherios Gialamas, Aurélie Vuagniaux, Roland Chautems, Marc-Olivier Sauvain (Neuchâtel Hospital, Neuchâtel, Switzerland); Silvio Daester, Markus von Flüe, Marc-Olivier Guenin, Stephanie Taha-Mehlitz, Gabriel F. Hess (St. Clara Hospital and University Hospital Basel, Basel, Switzerland); Lubomír Martínek, Matej Skrovina, Maria Machackova, Vladimír Benčurik (Hospital Nový Jičín, Nový Jičín, Czech Republic); Deniz Uluk, Johann Pratschke, Luca S. Dittrich, Safak Guel-Klein (Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin and Berlin Institut of Health, Berlin, Germany); Daniel Perez (Asclepios Clinic Altona, Hamburg, Germany); Julia-Kristin Grass, Nathaniel Melling, Simone Mueller (University Medical Centre of Hamburg-Eppendorf, Hamburg, Germany); Lene H. Iversen, Jacob D. Eriksen (Aarhus University Hospital, Aarhus, Denmark); Gunnar Baatrup, Issam Al-Najami, Thomas Bjørsum-Meyer (Odense University Hospital, Svendborg Sygehus, Denmark); Jüri Teras, Roland M. Teras (North Estonia Medical Centre Foundation, Tallinn, Estonia); Fatma A. Monib, Nagm Eldin Abu Elnga Ahmed, Eithar Alkady, Ahmed K. Ali (Assiut University Hospital, Assiut, Egypt); Gehan Abd Elatti

Khedr, Ahmed Samir Abdelaal, Fouad M. Bassyouni Ashoush, Moataz Ewedah (Alexandria Main University Hospital, Alexandria Governorate, Egypt); Eslam M. Elshennawy, Mohamed Hussein (Kafr Elshikh University Hospital, Kafr el-Sheikh, Egypt); Daniel Fernández-Martínez, Luis J. García-Flórez, María Fernández-Hevia, Aida Suárez-Sánchez (Central University Hospital of Asturias, Asturias, Spain); Izaskun del Hoyo Aretxabala, Iria Losada Docampo, Jesús Gómez Zabala (Basurto University Hospital, Bilbao, Spain); Patricia Tejedor, Javier T. Morales Bernaldo de Quirós, Ignacio Bodega Quiroga (Hospital Universitario Gómez Ulla, Spain); Antonio Navarro-Sánchez, Iván Soto Darias, Cristina López Fernández, Cristina de La Cruz Cuadrado (Hospital Materno Infantil de Gran Canaria, Las Palmas, Spain); Luis Sánchez-Guillén, Francisco López-Rodríguez-Arias, Álvaro Soler-Silva, Antonio Arroyo (University Hospital of Elche, Elche, Spain); Juan C. Bernal-Sprekelsen, Segundo Á. Gómez-Abril, Paula González, María T. Torres (Hospital Universitario Dr. Peset, Valencia, Spain); Teresa Rubio Sánchez, Francisco Blanco Antona, Juan E. Sánchez Lara, José A. Alcázar Montero (University Hospital of Salamanca, Salamanca, Spain); Daniel Fernández-Martínez, Luis J. García-Flórez, María Fernández-Hevia, Aida Suárez-Sánchez (Central University Hospital of Asturias, Asturias, Spain); Enrique Colás-Ruiz, Marta M. Tasende-Presedo, Ignacio Fernández-Hurtado, José A. Cifuentes-Ródenas, Marta Castro Suárez (Son Llätzer Hospital, Illes Balears, Spain); Manuel Losada, Miguel Hernández, Alfredo Alonso, Beatriz Diéguez (Hospital Universitario del Sureste, Madrid, Spain); Daniel Serralta, Rita E. Medina Quintana, Jose M. Gil Lopez, Francisca Lima Pinto, Elena Nieto-Moreno (Hospital Infanta Leonor, San Sebastián de los Reyes, Madrid, Spain); Alba Correa Bonito, Carlos Cerdán Santacruz, Elena Bermejo Marcos, Javier García Septiem (University Hospital de La Princesa, Madrid, Spain); Aránzazu Calero-Lillo, Javier Alanez-Saavedra, Salvador Muñoz-Collado,, Manuel López-Lara (Fundación Hospital del Espíritu Santo, Santa Coloma de Gramenet, Barcelona, Spain); María Labalde Martínez, Eduardo Ferrero Herrero, Francisco Javier García Borda, Óscar García Villar (12 de Octubre University Hospital, Madrid, Spain); Jorge Escartín, Juan L. Blas, Rocío Ferrer, Jorge García Egea (Hospital Royo Villanova, Zaragoza, Spain); Antonio Rodríguez-Infante, Germán Mínguez-Ruiz, Guillermo Carreño-Villarreal, Gerardo Pire-Abaitua (Hospital Universitario San Agustín, Avilés, Spain); Jana Dziakova, Carlos Sáez-Cazallas Rodríguez, María J. Pizarro Aranda, José M. Muguerza Huguet (Hospital Universitario Clínico San Carlos, Madrid, Spain); Nerea Borda-Arrizabalaga, José M. Enriquez-Navascués, Garazi Elorza Echaniz, Yolanda Saralegui Ansorena (Donostia University Hospital, Donostia, Spain); Mercedes Estaire-Gómez, Carlos Martínez-Pinedo, Alejandro Barbero-Valenzuela, Pablo Ruíz-García (Hospital General Universitario de Ciudad Real, Ciudad Real, Spain); Miquel Kraft, María J. Gómez-Jurado, Gianluca Pellino, Eloy Espín-Basany (Vall d'Hebron University Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain); Eddy Cotte, Nathalie Panel, Claire-Angéline Goutard (Hospices Civils de Lyon, Lyon Sud University Hospital, Pierre Bénite, France); Nicola deÁngelis, Lelde Lauka (Henri Mondor Hospital, AP-HP, Créteil, France); Shafaque Shaikh, Laura Osborne, George Ramsay (Aberdeen Royal Infirmary, NHS Grampian, Aberdeen, United Kingdom); Vladimir-Ion Nichita, Santosh Bhandari, Panchali Sarmah (Cambridgeshire in Peterborough City Hospital, Peterborough, United Kingdom); Rob M. Bethune, Heather C.M. Pringle, Lisa Massey, George E. Fowler (Royal Devon and Exeter Hospital, Exeter, United Kingdom); Hytham K.S. Hamid, Belinda D. de Simone (East Kent Hospitals University NHS Foundation Trust, Ashford, United Kingdom); James Kynaston, Nicholas Bradley, Roxane M. Stienstra (Forth Valley Royal Hospital, Larbert, Scotland); Shashank Gurjar, Tanmoy Mukherjee, Ashfaq Chandio, Safia Ahmed (Bedfordshire Hospitals NHS Foundation Trust, Luton, United Kingdom); Baljit Singh, Francois Runau, Sanjay Chaudhri, Oliver Siaw (Leicester General Hospital, Leicester, United Kingdom); Janahan Sarveswaran, Victor Miu, Daniel Ashmore, Haitham Darwich (Pinderfields Hospital, Wakefield, United Kingdom); Deepak Singh-Ranger, Nirbhaibir Singh (The Royal Wolverhampton NHS Trust, Wolverhampton, West Midlands, United Kingdom); Mohamed Shaban (Newcastle upon Tyne NHS Foundation Trust, Newcastle upon Tyne, United Kingdom); Fahed Gareb (Queen Elizabeth The Queen Mother Hospital, Margate, United Kingdom); Thalia Petropolou, Adreas Polydorou (Euroclinic Athens, Athens, Greece); Mit Dattani, Asma Afzal

(University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom); Akshay Bavikatte, Bobby Sebastian, Nicholas Ward, Amitabh Mishra (West Suffolk Hospital, Suffolk, United Kingdom); Dimitrios Manatakis, Christos Agalinos, Nikolaos Tasis, Maria-Ioanna Antonopoulou (Athens Naval and Veterans Hospital, Athens, Greece); Ioannis Karavokyros, Alexandros Charalabopoulos, Dimitrios Schizas, Efstratia Bailli, Athanasios Syllaios, Lysandros Karydakakis, Michail Vailas (Laikon General Hospital- National and Kapodistrian University of Athens, Greece); Dimitrios Balalis, Dimitrios Korkolis, Aris Plastiras, Alike Rompou (Saint Savvas Anti-Cancer Hospital, Athens Greece); Sofia Xenaki, Evangelos Xynos, Emmanuel Chrysos, Maria Venianaki (University Hospital of Heraklion Crete, Greece); Grigorios Christodoulidis, Konstantinos Perivoliotis, George Tzovaras, Ioannis Baloyiannis (University Hospital of Larissa, Larissa Greece); Man-Fung Ho, Simon Siu-man Ng, Tony Wing-chung Mak, Kaori Futaba (Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong); Goran Šantak, Damir Šimleša, Jurica Ćosić, Goran Zukanović (General County Hospital Požega, Požega, Croatia); Michael E. Kelly, John O. Larkin, Paul H. McCormick, Brian J. Mehigan (The Trinity St. James's Cancer Institute, Dublin + School of Medicine, Trinity College Dublin, Ireland); Tara M. Connelly, Peter Neary, Jessica Ryan, Peter McCullough (University Hospital Waterford, Waterford, Ireland); Maytham A. Al-Juaifari, Hayder Hammoodi, Ali Hashim Abbood (Al-Sadder Teaching Hospital, Najaf, Iraq); Marcello Calabrò, Andrea Muratore, Antonio La Terra, Francesca Farnesi (Edoardo Agnelli Hospital, Pinerolo, Italy); Carlo V. Feo, Nicolò Fabbri, Antonio Pesce, Marta Fazzin (Azienda Unità Sanitaria Locale di Ferrara, Università di Ferrara, Ferrara, Italy); Francesco Roscio, Federico Clerici (ASST Valle Olona Busto Arsizio Italy, Busto Arsizio VA, Italy); Andrea Lucchi, Laura Vittori, Laura Agostinelli, Maria Cristina Ripoli (AUSL Romagna Ceccarini Hospital, Riccione, Italy); Daniele Sambucci, Andrea Porta (Fatebenefratelli Hospital "Holy Family", Erba, Italy); Giovanni Sinibaldi, Giacomo Crescentini, Antonella Iarcinese, Emanuele Picone (Fatebenefratelli Hospital, Isola Tiberina, Rome, Italy); Roberto Persiani, Alberto Biondi, Roberto Pezzuto, Laura Lorenzon, Gianluca Rizzo, Claudio Coco, Luca D'Agostino ("A. Gemelli" University Hospital, Catholic University of Rome, Rome, Italy); Antonino Spinelli, Matteo M. Sacchi, Michele Carvello, Caterina Foppa (Humanitas University, Milan, Italy); Antonino Spinelli, Matteo M. Sacchi, Michele Carvello, Caterina Foppa, Annalisa Maroli (IRCCS Humanitas Research Hospital, Milan, Italy); Gian M. Palini, Gianluca Garulli, Nicola Zanini (Infermi Hospital of Rimini, AUSL Della Romagna, Rimini, Italy); Paolo Delrio, Daniela Rega, Fabio Carbone, Alessia Aversano (Fondazione Giovanni Pascale - IRCCS, Naples, Italy); Giovanni Pirozzolo, Alfonso Recordare, Lucrezia D'Alimonte, Chiara Vignotto (Dell'Angelo Hospital, Venice, Italy); Carlo Corbellini, Gianluca M. Sampietro, Leonardo Lorusso, Carlo A. Manzo (ASST Rhodense, Rho Memorial Hospital, Milano, Italy); Federico Ghignone, Giampaolo Ugolini, Isacco Montroni, Francesco Pasini (Ospedale Santa Maria delle Croci, Ravenna, Italy); Francesco Pasini (Ospedale per gli Infermi, Faenza, Italy); Michele Ballabio, Pietro Bisagni, Francesca T. Armao, Marco Longhi (Maggiore Hospital in Lodi, Lodi, Italy); Omar Ghazouani, Raffaele Galleano (Santa Corona Hospital, Pietra Ligure, Italy); Nicolò Tamini, Massimo Oldani, Luca Nespoli (San Gerardo Hospital, Monza, Italy); Arcangelo Picciariello, Donato F. Altomare, Giovanni Tomasicchio, Giuliano Lantone (University of Bari Aldo Moro, Bari, Italy); Fausto Catena, Mario Giuffrida, Alfredo Annicchiarico, Gennaro Perrone (Parma University Hospital, Parma, Italy); Ugo Grossi, Giulio A. Santoro, Giacomo Zanus, Alessandro Iacomino, Simone Novello, Nicola Passuello, Martino Zucchella (Regional Hospital Treviso, Treviso, Italy); Lucia Puca, Maurizio deGiuli, Rossella Reddavid (San Luigi University Hospital, Orbassano, Torino, Italy); Stefano Scabini, Alessandra Aprile, Domenico Soriero, Emanuela Fioravanti (AOU San Martino Hospital, Genoa, Italy); Matteo Rottoli, Angela Romano, Marta Tanzanu, Angela Belvedere (IRCCS Azienda Ospedaliero Universitaria di Bologna, Bologna, Italy); Nicolò M. Mariani, Andrea P. Ceretti, Enrico Opocher (ASST Santi Paolo e Carlo, Milan, Italy); Gaetano Gallo, Giuseppe Sammarco (University of Catanzaro, Catanzaro, Italy); Gilda de Paola (University of Milano, Milano, Italy); Salvatore Pucciarelli, Francesco Marchegiani, Gaya Spolverato, Gianluca Buzzi (Azienda Ospedale-Università



di Padova, Padova, Italy); Salomone Di Saverio, Paola Meroni, Cristiano Parise, Elisa I. Bottazzoli (University of Insubria, University Hospital of Varese, ASST Sette Laghi, Regione Lombardia, Varese, Italy); Pierfrancesco Lapolla, Gioia Brachini, Bruno Cirillo, Andrea Mingoli ("P. Valdoni", Policlinico Umberto I University Hospital, Sapienza University of Rome, Rome, Italy); Giuseppe Sica, Leandro Siragusa, Vittoria Bellato, Daniele Cerbo (University of Rome "Tor Vergata", Rome, Italy); Carlo A. de Pasqual, Giovanni de Manzoni, Maria A. di Cosmo (University of Verona, Verona, Italy); Bourhan M.H. Alrayes, Mahmoud W. M. Qandeel (Islamic Hospital Amman, Amman, Jordan); Mohammad Bani Hani (King Abdullah University Hospital, Ar-Ramtha, Jordan); Alexander Rabadi, Mohammad S. el Muhtaseb, Basel Abdeen, Fahed Karmi (The University of Jordan, Amman, Jordan); Justas Žilinskas, Tadas Latkauskas, Algimantas Tamelis, Ingrida Pikūnienė, Vygintas Šlenfuktas (Hospital of Lithuanian University of Health Sciences Kaunas Clinics, Kaunas, Lithuania); Tomas Poskus, Marius Kryzauskas, Matas Jakubauskas, Saulius Mikalauskas, Lina Jakubauskiene (Vilnius University, Vilnius, Lithuania); Soha Y. Hassan, Amani Altrabulsi (Benghazi Medical Center, Benghazi, Libya); Eman Abdulwahed, Reem Ghmagh, Abdulqudus Deeknah, Entisar Alshareea (Tripoli Central Hospital, Tripoli, Libya); Muhammed Elhadi, Saleh Abujamra, Ahmed A. Msherghi, Osama W.E. Tababa (Tripoli University Hospital, Tripoli, Libya); Mohammed A. Majbar, Amine Souadka, Amine Benkabbou, Raouf Mohsine, Sabrillah Echiguer (National Institute of Oncology, University Mohammed V in Rabat, Rabat, Morocco); Paulina Moctezuma-Velázquez, Noel Salgado-Nesme, Omar Vergara-Fernández, Juan C. Sainz-Hernández, Francisco E. Alvarez-Bautista (Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico); Andee D. Zakaria, Zaidi Zakaria, Michael P.K. Wong, Razif Ismail (Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia); Aini F. Ibrahim, Nik A.N. Abdullah, Rokayah Julaihi (Universiti Malaysia Sarawak, Kota Samarahan, Sarawak); Sameer Bhat, Greg O'Grady, Ian Bissett (University of Auckland, Auckland, New Zealand); Bas Lamme, Gijsbert D. Musters, Anne M. Dinaux (Albert Schweitzer Hospital, Dordrecht, The Netherlands); Brechtje A. Grotenhuis, Ernst J. Steller Arend G.J. Aalbers, Marjolein M. Leeuwenburgh (Netherlands Cancer Institute-Antoni van Leeuwenhoek, Amsterdam, The Netherlands); Harm J.T. Rutten, Jacobus W.A. Burger, Johanne G. Bloemen, Stijn H.J. Ketelaers (Catharina Hospital, Eindhoven, The Netherlands); Usama Waqar, Tabish Chawla, Hareem Rauf, Pallavi Rani (Aga Khan University, Karachi City, Pakistan); Aaldert K. Talsma, Lieke Scheurink, Jasper B. van Praagh (Deventer Hospital, Deventer, The Netherlands); Josefina Segelman, Jonas Nygren, Kajsa Anderin, Marit Tiefenthal (Ersta Hospital, Stockholm, Sweden); Beatriz de Andrés, Juan P. Beltrán de Heredia, Andrea Vázquez, Tania Gómez (University Clinical Hospital of Valladolid, Valladolid, Spain); Parisa Golshani, Rawaz Kader, Abudi Mohamed (Gävle Hospital, Gävle, Sweden); Marinke Westerterp, Andreas Marinelli, Quirine Niemer (Medical Center Haaglanden, Westeinde, Den Haag, Netherlands); Pascal G. Doornebosch, Joël Shapiro, Maarten Vermaas, Eelco J.R. de Graaf (Jsselland Hospital, Capelle Aan Den IJssel, The Netherlands); Hendrik L. van Westreenen, Marije Zwakman, Annette D. van Dalsen (Isala Hospital, Zwolle, The Netherlands); Wouter J. Vles, Joost Nonner, Boudewijn R. Toorenvliet, Paul T.J. Janssen (Ikazia Hospital, Rotterdam, the Netherlands); Emiel G.G. Verdaasdonk, Femke J. Amelung (Jeroen Bosch Hospital, 's-Hertogenbosch, The Netherlands); Koen C.M.J. Peeters Renu R. Bahadoer, Fabian A. Holman (Leiden University Medical Center, Leiden, Netherlands); Jeroen Heemskerk, Noortje Vosbeek, Jeroen W.A. Leijtens, Sophie B.M. Taverne (Laurentius Hospital, Roermond, the Netherlands); Bob H.M. Heijnen, Youssef El-Massoudi, Irene de Groot-van Veen (LangeLand Hospital, Zoetermeer, The Netherlands); Christiaan Hoff, Daniela Jou-Valencia (Medical Centre Leeuwarden, Leeuwarden, the Netherlands); Esther C.J. Consten Thijs A. Burghgraef, Ritch Geitenbeek, Lorenzo G.W.L. Hulshof (Meander Medical Centre, Amersfoort, Netherlands); Gerrit D. Slooter, Muriël Reudink (Máxima Medical Centre, Veldhoven, Netherlands); Nicole D. Bouvy, Aurelia C. L. Wildeboer, Sonja Verstappen, Alexander J. Pennings (Maastricht University Medical Centre, Maastricht, The Netherlands); Berber van den Hengel, Allard G. Wijma, Jael de Haan (Martini Hospital, Groningen, The Netherlands); Lindsey C.F. de Nes, Vera Heesink

(Maasziekenhuis Pantein, Boxmeer, The Netherlands); Tom Karsten, Charlotte M. Heidsma, Willem J. Koemans (Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands); Jan-Willem T. Dekker, Charlène J. van der Zijden, Daphne Roos (Reinier de Graaf Gasthuis, Delft, The Netherlands); Ahmet Demirkiran, Sjirk van der Burg (Red Cross Hospital, Beverwijk, The Netherlands); Steven J. Oosterling, Tijs J. Hoogteijling (Spaarne Gasthuis, Haarlem, The Netherlands); Bastiaan Wiering, Diederik P.J. Smeeing (Slingeland Ziekenhuis, Doetinchem, Netherlands); Klaas Havenga, Hamid Lutfi, Esther C.J. Consten (University Medical Centre Groningen, Groningen, The Netherlands); Konstantinos Tsimogiannis, Filip Sköldberg, Joakim Folkesson (Uppsala University, Uppsala, Sweden); Frank den Boer, Ted G. van Schaik, Pieter van Gerven (Zaans Medical Center, Zaandam, the Netherlands); Colin Sietses, Jeroen C. Hol (Gelderse Vallei Hospital Ede, Ede, The Netherlands); Evert-Jan G. Boerma, Davy M.J. Creemers (Zuyderland Medical Center, Sittard/Heerlen, The Netherlands); Johannes K. Schultz, Tone Frivold, Rolf Riis (Akershus University Hospital, Lørenskog, Norway); Hilde Gregussen, Sondre Busund (Hospital inland Hamar, Hamar, Norway); Ole H. Sjø, Maria Gaard, Nina Krohn, Amanda L. Ersryd (Ullevål Oslo University Hospital, Oslo, Norway); Edmund Leung (Hereford County Hospital, Hereford, United Kingdom); Usama Waqar, Tabish Chawla, Hareem Rauf, Pallavi Rani (Aga Khan University, Karachi City, Pakistan); Hytham Sultan, Baraa Nabil Hajjaj, Ahmed Jehad Alhisi, Ahmed A.E. Khader (Al-Shifa Hospital, Gaza City, Palestine); Ana Filipa Dias Mendes, Miguel Semião, Luis Queiroz Faria, Constança Azevedo (Centro Hospitalar Universitário Cova da Beira, Covilha, Portugal); Helena M. da Costa Devesa, Sónia Fortuna Martins, Aldo M. Rodrigues Jarimba, Sónia M. Ribeiro Marques (Hospital Distrital de Santarém, Santarém, Portugal); Rita Marques Ferreira, António Oliveira, Cátia Ferreira, Ricardo Pereira (Centro Hospitalar de Trás-os-Montes e Alto Douro EPE, Vila Real, Portugal); Valeriu M. Surlin, Giorgiana M. Graure, Stefan Patrascu Sandu D. Ramboiu (Clinical County Emergency Hospital of Craiova, University of Medicine and Pharmacy of Craiova, Romania); Ionut Negoii, Cezar Ciubotaru, Bogdan Stoica, Ioan Tanase (Carol Davila University of Medicine and Pharmacy Bucharest, Bucharest, Romania); Bogdan Stoica, Cezar Ciubotaru, Valentina M. Negoita (Clinical Emergency Hospital Bucharest, Bucharest, Romania); Sabrina Florea, Florin Macau, Mihai Vasile, Victor Stefanescu (Central Military Emergency Hospital Dr. Carol Davila, Bucharest, Romania); Gabriel-Mihail Dimofte, Sorinel Luncă, Cristian-Ene Roată, Ana-Maria Muşină (Regional Oncology Institute, Iasi, Romania); Tatiana Garmanova, Mikhail N. Agapov, Daniil G. Markaryan, Galliamov Eduard (Lomonosov Moscow State University, Moscow, Russia); Alexey Yanishev, Alexander Abelevich, Andrey Bazaev (Privolzhsky Research Medical University, Nizhny Novgorod, Russia); Sergey V. Rodimov, Victor B. Filimonov, Andrey A. Melnikov, Igor A. Suchkov (Ryazan State Medical University, Ryazan, Russia); Evgeniy S. Drozdov, Dmitriy N. Kostromitskiy (Siberian State Medical University, Tomsk, Russia); Olle Sjöström (Östersund Hospital, Östersund, Sweden); Peter Matthiessen, Bayar Baban, Soran Gadan, Kaveh Dehlaghi Jadid (School of Medical Sciences, Örebro University, Örebro, Sweden); Maria Staffan (Region Dalarna Hospital, Dalarna University, Falun, Sweden); Jennifer M. Park, Daniel Rydbeck (Scandinavian Surgical Outcomes Research Group, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, Region Västra Götaland, Sahlgrenska University Hospital/Östra, Gothenburg, Sweden); Marie-Louise Lydrup, Pamela Buchwald, Henrik Jutesten, Lotten Darlin, Ebba Lindqvist (Skåne University Hospital, Malmö, Sweden); Karl Nilsson, Per-Anders Larsson (Skaraborgs Hospital, Skövde, Sweden); 186 Staffan Jangmalm (Växjö Hospital, Växjö, Sweden); Jurij A. Košir, Aleš Tomažič, Jan Grosek, Tajda Košir Božič (Ljubljana University Medical Center, Ljubljana, Slovenia); Aya Zazo, Rama Zazo, Hala Fares, Kusay Ayoub (University of Aleppo, Aleppo, Syria); Ammar Niazi, Ali Mansour, Ayman Abbas, Mohammad Tantoura (The Arabic Medicine Hospital, Aleppo, Syria); Alaa Hamdan, Naya Hassan, Bassam Hasan, Ahmad Saad (Tishreen University, Latakia, Syria); Amine Sebai, Anis Haddad, Houcine Maghrebi, Montasser Kacem (La Rabta Hospital, Tunis, Tunisia); Ömer Yalkın, Mehmet Veysi Samsa, İbrahim Atak (Ali Osman Sönmez Oncology Hospital, Bursa, Türkiye); Bengi Balci, Elifcan Haberal, Lütfi Dogan (Ankara Oncology Training and Research Hospital, Ankara, Türkiye); Ibrahim

E. Gecim, Cihangir Akyol, Mehmet A. Koc (Ankara University Medical School, Ankara, Türkiye); Emre Sivrikoz, Deniz Piyadeođlu (Bahçeşehir University, İstanbul, Türkiye); John O. Larkin, Dara O. avanagh (St. James's, Hospital, Dublin, Ireland); Selman Sökmen, Tayfun Bişgin, Erşan Güneç, Melek Güzel (Dokuz Eylül University, Balçova, İzmir, Türkiye); Sezai Leventođlu, Osman Yüksel, Ramazan Kozan, Hüseyin Göbüt (Gazi University Medical School, Ankara, Türkiye); Fevzi Cengiz, Kemal Erdinc, Nihan Coşgun Acar, Erdinc Kamer (İzmir Katip Celebi University, İzmir, Türkiye); İlker Özgür, Oguzhan Aydın, Metin Keskin, Mehmet Türker Bulut, Cemil B. Kulle (İstanbul University, İstanbul Faculty of Medicine, İstanbul, Türkiye); Yasin Kara, Osman Sıbiç (University of Health Sciences, Kanuni Sultan Suleyman Training and Research Hospital, İstanbul, Türkiye); İbrahim H. Özata, Dursun Buğra, Emre Balık, Cemil B. Kulle (Koç University Hospital, İstanbul, Türkiye); Murat Çakır, Anas Alhardan (Meram Tıp Faculty Hospital, Meram/Konya, Türkiye); Elif Colak, Ahmet B. CiftciEngin Aybar, Ahmet Can Sari (University of Samsun, Samsun Training and Research Hospital, Samsun, Türkiye); Semra Demirli Atici, Tayfun Kaya, Ayberk Dursun, Bulent Calik (University of Health Sciences, Tepecik Training and Research Hospital, İzmir, Türkiye); Ömer Faruk Özkan, Hanife Şeyda Ülgür, Özgül Düzgün (University of Health Sciences Türkiye, Ümraniye Training and Research Hospital, İstanbul, Türkiye); John Monson, Sarah George, Kayla Woods (AdventHealth Orlando, Orlando, Florida, United States of America); Fatima Al-Eryani, Rudaina Albakry (Al-Kuwait Hospital, Sana'a, Yemen); Emile Coetzee (Life St. George's Hospital, Port Elizabeth, Eastern Cape, South Africa); Adam Boutall, Ayesiga Herman, Claire Warden, Naser Mugla (Groote Schuur Hospital and University of Cape Town, Cape Town, South Africa); Tim Forgan, Imraan Mia, Anton Lambrechts (Tygerberg Academic Hospital, Parow, Cape Town, South Africa)