Universiteit Leiden
The Netherlands

Risk nomogram does not predict anastomotic leakage after colon surgery accurately: results of the multi-center LekCheck study

Ozmen, I.; Grupa, V.E.M.; Bedrikovetski, S.; Dudi-Venkata, N.N.; Huisman, D.E.; Reudink, M.; ... ; LekCheck Study Grp

Citation
Ozmen, I., Grupa, V. E. M., Bedrikovetski, S., Dudi-Venkata, N. N., Huisman, D. E., Reudink, M., … Daams, F. (2022). Risk nomogram does not predict anastomotic leakage after colon surgery accurately: results of the multi-center LekCheck study. *Journal Of Gastrointestinal Surgery*, *26*(4), 900-910. doi:10.1007/s11605-021-05119-6

Version:	Publisher's Version
License:	Licensed under Article 25fa Copyright Act/Law (Amendment Taverne)
Downloaded from:	https://hdl.handle.net/1887/3567533

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

Journal of Gastrointestinal Surgery (2022) 26:900–910
https://doi.org/10.1007/s11605-021-05119-6

ORIGINAL ARTICLE

Risk Nomogram Does Not Predict Anastomotic Leakage After Colon Surgery Accurately: Results of the Multi-center LekCheck Study

Izel Ozmen[1,2] · Vera E. M. Grupa[1,2] · Sergei Bedrikovetski[1,3] · Nagendra N. Dudi-Venkata[1,3] · Daitlin E. Huisman[4] · Muriël Reudink[5] · Gerrit D. Slooter[5] · Tarik Sammour[1,3] · Hidde M. Kroon[1,3] · Freek Daams[4] · on behalf of the LekCheck Study Group

Received: 21 March 2021 / Accepted: 10 July 2021 / Published online: 8 January 2022
© The Society for Surgery of the Alimentary Tract 2021

Abstract

Purpose Anastomotic leakage (AL) is a dreaded complication after colorectal surgery. Preoperatively identifying high-risk patients can help to reduce the incidence of this complication. For this reason, AL risk nomograms have been developed. The objective of this study was to test the AL risk nomogram developed by Frasson, et al. for validity and to identify risk-factors for AL.

Methods From the international multi-center LekCheck study database, patients who underwent colonic surgery with the formation of an anastomosis were included. Data were prospectively collected between 2016 and 2019 at 14 hospitals. Univariate and multivariable regression analyses, and area under receiver operating characteristic curve analysis (AUROC) were performed.

Results A total of 643 patients were included. The median age was 70 years and 51% were male. The majority underwent surgery for malignancies (80.7%). The overall AL rate was 9.2%. The risk nomogram was not predictive for AL in the population tested (AUROC 0.572). Low preoperative haemoglobin ($p=0.006$), intraoperative hypothermia ($p=0.02$), contamination of the operative field ($p=0.004$), and use of epidural analgesia ($p=0.02$) were independent risk-factors for AL.

Conclusion The AL risk nomogram could not be validated using the international LekCheck study database. In the future, intraoperative predictive factors for AL, as identified in this study, should also be included in AL risk predictors.

Keywords Colonic surgery · Colon cancer · Anastomotic leakage · Risk score validation

Introduction

Anastomotic leakage (AL) is a dreaded complication after colorectal surgery, with a reported range of its incidence of 3.8 to 19.2%.[1,2] When AL occurs, a reoperation is often required, during which the anastomosis has to be dismantled in most cases, forming a stoma. Therefore, AL results in increased morbidity and mortality, longer hospital stay, higher costs of healthcare, lower quality of life and worse oncological outcomes.[3–5]

Preoperatively identifying patients with a high AL risk can help to prevent this complication from occurring or mitigate its risk.[6] A high anticipated risk of AL, for instance, creates more awareness of postoperative complications among clinicians, or may convince surgeons to avoid forming an anastomosis altogether. In view of this, instruments have been developed with the aim of predicting AL risk. Frasson, et al. conducted a multi-center study, identifying six independent risk-factors

Hidde M. Kroon and Freek Daams shared senior authorship.

✉ Hidde M. Kroon
Hidde.Kroon@sa.gov.au

1 Colorectal Unit, Department of Surgery, Royal Adelaide Hospital, Adelaide, South Australia, Australia

2 Faculty of Medical Sciences, Leiden University, Leiden, the Netherlands

3 Faculty of Health and Medical Science, Adelaide Medical School, University of Adelaide, Adelaide, South Australia, Australia

4 Department of Surgery, VU Medical Center Amsterdam, Amsterdam, the Netherlands

5 Department of Surgery, Máxima Medical Center Veldhoven, Veldhoven, the Netherlands

and created an AL predicting nomogram.[6]. This has since been attempted to be validated twice, however, both in single-center studies.[7,8] Despite the fact that the AL risk nomogram by Frasson, et al. has not been validated in an independent multicenter prospective dataset, the nomogram is a commonly used tool in clinical practice (www.anastomoticleak.com), used to develop new policies and to conduct further studies on AL.[9]

The international multi-center LekCheck study prospectively collects pre- and intraoperative variables potentially predictive for AL. [10,11] The large patient numbers and collected variables in this study make it suitable to test existing AL risk nomograms. Therefore, the primary aim of the current study was to validate the AL risk nomogram as proposed by Frasson, et al., using the LekCheck study database, and secondly to identify intraoperative variables as predictors for AL after colonic surgery.[6,10]

Patients and Methods

Patients who underwent elective colonic surgery for benign or malignant causes with the formation of a primary anastomosis between October 2016 and October 2019 were included from the prospectively collected international LekCheck study database. Fourteen hospitals across the Netherlands ($n=11$), Belgium ($n=1$), Italy ($n=1$) and Australia ($n=1$) participated in this study. The study was approved by the local Human Research Ethics Committees of all participating hospitals. For the current study, patients undergoing rectum surgery, those undergoing emergency surgery and patients with incomplete datasets for the variables of the AL risk nomogram were not selected from the LekCheck database.[6]

Demographic characteristics and preoperative, intraoperative and postoperative data were prospectively collected and recorded in the online LekCheck study database. Intraoperative variables were collected real-time by a member of the operating team at the time of forming the anastomosis as per the protocol of the LekCheck Study (appendix A).[10] The modified definition for AL by Reisinger was used: clinically relevant AL was defined as extra luminal presence of contrast fluid, and/or leakage with evidence of extravasation of bowel content, intraabdominal collection or gas on (contrast-enhanced) CT scan, radiographic enema, upon (re-)laparotomy or endoscopy, requiring reintervention or treatment.[12] Similar to Frasson, et al., colonic surgery was defined as patients receiving an anastomosis with its distal edge located more than 15 cm from the anal verge.[6] The following definitions of the LekCheck study were used:[10] temperatures below 36° C were considerate low. Hyperglycemia was defined as a glucose level above 6.1 mmol/L. Administration of vasopressors, the requirement of blood transfusion and the application of epidural analgesia were all classified as yes/no. A low preoperative haemoglobin (Hb) was defined as less than 6.5 mmol/L in males and less than 6.0 mmol/L in females. High blood loss was defined as 100 mL or more. This was calculated from the volume extracted with suction and/or additional weight from the operative gauzes minus the total volume used for irrigation. Oxygen saturation below 95% was considerate low. A low mean arterial pressure (MAP) was defined as 60 mmHg or lower. High intraoperative fluid management was defined as administration of 1000 mL or more per hour. Prolonged surgery was considered 3 h or more. Faecal contamination was reported (yes/no) by the operating surgeon when the operative field was contaminated more than the regular loss of bowel content during a colorectal resection without bowel preparation. Intraoperative events that were recorded included (amongst others): hypoxia, hypo- or hypertension, hypercarbia, bradycardia, DVT or embolism, reanimation, bleeding, more extensive resection than planned, serosal tear, bladder and ureter injuries, and splenectomy. For the evaluation of the local perfusion of the anastomosis, the operating surgeon was asked to rate the local blood supply of the two bowel ends prior to the creation of the anastomosis on a scale from 4 to 10 as follows: moderate (4), reasonable (5), sufficient (6), amply sufficient (7), good (8), very good (9), excellent (10).

In the nomogram by Frasson, et al., the AL risk-factors are as follows: male gender, obesity (body mass index [BMI] > 30 kg/m^2), oral anticoagulant use, low preoperative serum total protein level, a lower number of beds per hospital, and intraoperative complication (www.anastomoticleak.com).[6,7] Anticoagulant use and preoperative (< 3 months before surgery) serum total protein were collected retrospectively from the electronic patient records of the participating hospitals. In case serum total protein levels could not be retrieved ($n=462$), serum albumin levels were converted to serum total protein levels by extrapolating the median serum albumin:serum total protein ratio from the patient group that had both variables available. This method was validated in an external cohort of patients ($n=1{,}000$) who had both measures available (unpublished data). Anticoagulant use was defined as preoperative use of medications with the intent to prevent thrombotic events that were still active at the time of surgery (i.e. had not preoperatively been ceased with enough time to be metabolised). These medications include antiplatelets (such as acetylsalicylic acid and clopidogrel), vitamin K antagonists (such as acenocoumarol and phenprocoumon), and direct blood clot factor inhibitors (such as apixaban, rivaroxaban, dabigatran).[7]

Comparisons between patients with and without AL after colon surgery were performed using the *T*-test or Mann–Whitney *U* test for continuous variables and the χ^2 test for categorical variables. Multivariable logistic regression analysis with the stepwise backward method was performed on the statistically significant variables from the univariate analysis to identify independent risk-factors for AL and to correct for possible confounders. A significant difference was assumed for a probability value of < 0.05. To

determine the predictive value of the AL risk nomogram, an area under receiver operating curve analysis (AUROC) was used for the complete cohort, with a subset analysis performed in patients with a malignancy, as the AL risk nomogram was based on a malignant cohort.[6] An AUROC of > 0.9 is considered outstanding, 0.8–0.9 is excellent, 0.7–0.8 is acceptable and 0.5 suggests no discrimination.[13] Statistical analyses were performed using SPSS 24.0 for Mac (SPSS Inc.) and Prism 8.0 for Mac (GraphPad Software Inc.).

Results

Of the 1386 patients in the LekCheck database, 1075 underwent colonic surgery. Of these, 643 patients with complete datasets could be included in the current analysis to test the nomogram by Frasson, et al. (Fig. 1).

Of the included patients, 328 were male (51.0%) and the median age was 70 years (range 19–94 years). There were 518 patients who underwent colonic surgery for a malignancy (80.7%) and 124 for benign diseases (19.3%; missing $n = 1$).

The overall AL rate was 9.2% ($n = 59$), at a median of 4 days (range 1–40 days). The median predicted risk according to the AL risk nomogram was 9% (range 3–50) for the total study population; 11% (range 3–50) for patients with AL, and 9% (range 3–39) for patients without AL ($p = 0.07$; Table 1). The AUROC for the AL risk nomogram was 0.572 (95%CI: 0.50–0.65, $p = 0.07$; Fig. 2) for the complete cohort, and 0.563 (95%CI: 0.47–0.66, $p = 0.17$; Fig. 3) for the subgroup of patients with malignancies.

Baseline and intraoperative characteristics are presented in Tables 2 and 3, and a detailed description of the type of resection, anastomosis type and technique is displayed in Table 4. Preoperative haemoglobin was significantly lower in patients with AL ($p = 0.03$). Patients who developed AL more often had intraoperative hypothermia below 36˚C (32.2 vs. 19.1% for those without AL, $p = 0.02$), and lost more than 100 mL blood intraoperatively more frequently (41.5 vs. 24.6%, $p = 0.008$). Also, intraoperative complications (40.7 vs. 20.9%, $p = 0.001$) and intraoperative faecal contamination (20.3 vs. 3.3%, $p < 0.0001$) occurred significantly more often in patients with AL. The surgeon's evaluation of the anastomotic perfusion was lower in patients who developed AL ($p = 0.002$) and epidural analgesia was administered more often to patients with AL (33.9 vs. 17.4%, $p = 0.002$). Patients with AL had undergone more open procedures than patients without AL (30.5 vs. 17.2%, $p = 0.01$) and a duration of surgery of longer than 3 h was more frequent in patients with AL (42.4 vs. 25.0%, $p = 0.004$).

Table 5 shows postoperative outcomes and complications. Ten AL patients were managed conservatively with antibiotics (16.9%), six patients received a percutaneous

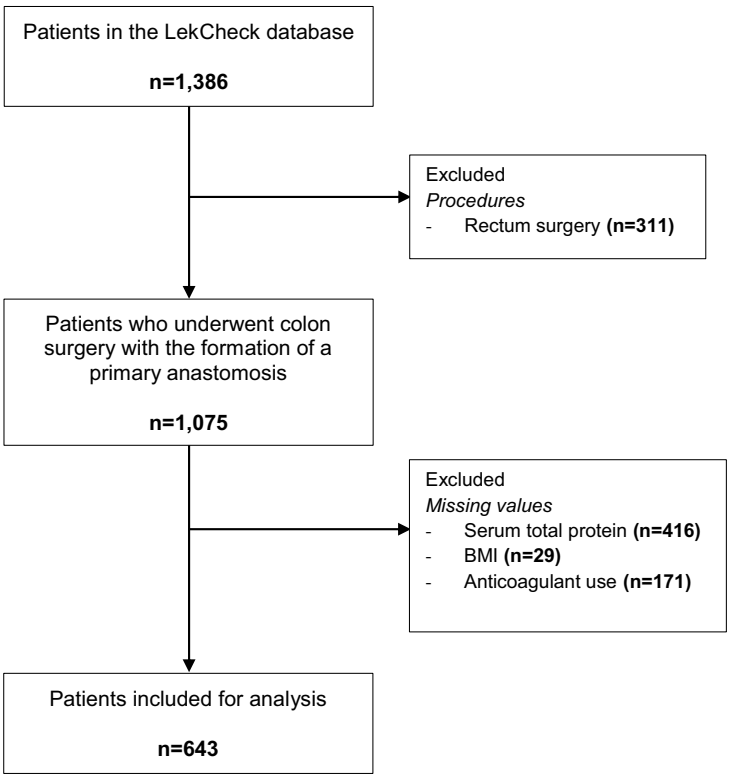


Fig. 1 Flow-chart of in- and excluded patients

BMI Body mass index

Table 1 Predicted risk for anastomotic leakage

	Total ($N=643$)	Anastomotic leak ($N=59$)	No anastomotic leak ($N=584$)	P-value
Median predicted risk according to AL nomogram,[6,7] in % (range)	9 (3–50)	11 (3–39)	9 (3–50)	0.07

AL anastomotic leakage

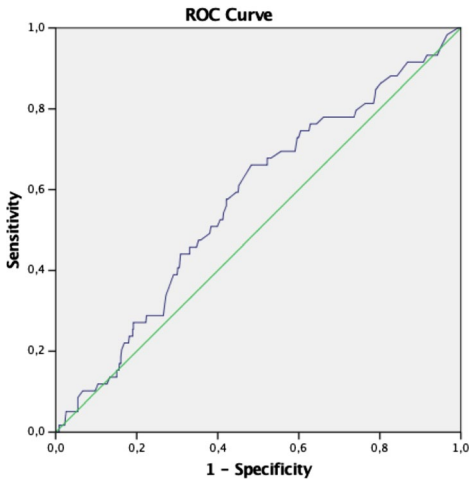
drain (10.2%), and 43 patients required a re-operation (72.9%). The overall 30-day postoperative mortality rate was 1.6% and was similar between both groups (1.7 vs. 1.5%, $p=0.93$). The length of hospitalization was longer for patients with AL (13 vs. 4 days, $p<0.0001$).

In the multivariable analysis, the following variables were independent risk-factors for AL (Table 6): low preoperative haemoglobin (OR 4.21, 95%CI 1.52–11.69, $p=0.006$), intraoperative hypothermia (OR 2.39, 95%CI 1.19–4.80, $p=0.02$), intraoperative faecal contamination (OR 4.22, 95%CI 1.59–11.22, $p=0.004$) and use of epidural analgesia (OR 2.35, 95%CI 1.13–4.88, $p=0.02$).

Discussion

This study used the prospectively collected international multi-center LekCheck study database and found an AL rate of 9.2% after colonic surgery. An AUROC of 0.572 for the complete cohort and an AUROC of 0.563 for the malignant cohort were found when testing the validity of the AL risk nomogram as proposed by Frasson, et al., showing that the nomogram cannot accurately determine the AL risk after colonic surgery in this population.[6,13]

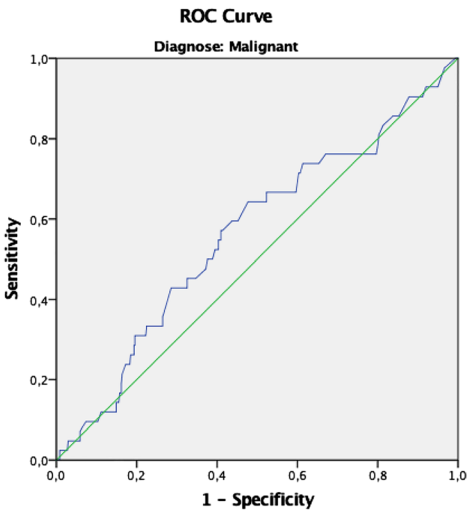
Validation of proposed risk nomograms is important, as its outcomes are increasingly used in clinical practice and research.[9] The tested AL risk nomogram has previously been attempted to be validated, but in smaller single-center studies.[6–8] Sammour, et al., found an AUROC of 0.84 in a study including 83 patients and concluded that the nomogram was highly predictive of AL.[7] However, this study was likely underpowered since only eight patients developed AL. A second study, including 402 patients, was conducted at the same institution and found an AUROC of 0.73.[8] Although larger in patient numbers, this was also a single-center study and was based on retrospective data. Er, et al. also analysed the nomogram and found an AUROC of 0.77, but again this was a small single-center study including only 59 patients of whom only six developed AL.[15] Klose, et al. reported a low predictive value (AUROC 0.69) after testing the nomogram in a cohort of 972 patients.[16] Although their study included a large patient number, they tested the colonic specific nomogram in patients



	AUROC	SE	P-value	95%CI
Nomogram	0.572	0.038	0.07	0.50-0.65

ROC curve analysis. P-value indicates comparison between AUROC and 0.5 value (null hypothesis)
AUROC area under receiver operating characteristic curve, *SE* standard error, *CI* confidence interval

Fig. 2 Receiver operating characteristic (ROC) curve of the anastomotic leak risk nomogram using data of the complete cohort of the LekCheck study ($N=643$) [6,7,10]



	AUROC	SE	P-value	95%CI
Nomogram	0.563	0.047	0.17	0.47-0.66

ROC curve analysis. P-value indicates comparison between AUROC and 0.5 value (null hypothesis)
AUROC area under receiver operating characteristic curve, *SE* standard error, *CI* confidence interval

Fig. 3 Receiver operating characteristic (ROC) curve of the anastomotic leak risk nomogram using data of patients operated for malignancies only of the LekCheck study ($N=518$) [6,7,10]

Table 2 Patient and baseline characteristics

	Total ($N=643$)	Anastomotic leak ($N=59$)	No anastomotic leak ($N=584$)	P-value	Odds ratio	95%CI
Hospital size: number of beds (%)						
< 300	32 (5.0)	3 (5.1)	29 (5.0)	0.16		
301–400	249 (38.7)	20 (33.9)	229 (39.2)			
401–500	54 (8.4)	10 (16.9)	44 (7.5)			
501–600	42 (6.5)	2 (3.4)	40 (6.8)			
601–700	90 (14.0)	6 (10.2)	84 (14.4)			
701–800	176 (27.4)	18 (30.5)	158 (27.1)			
Age (%)						
< 70 years	316 (49.1)	25 (42.4)	291 (49.8)	0.28	1.35	0.79–2.32
≥ 70 years	327 (50.9)	34 (57.6)	293 (50.2)			
Gender (%)						
Female	315 (49.0)	29 (49.2)	286 (49.0)	0.98	0.99	0.58–1.70
Male	328 (51.0)	30 (50.8)	298 (51.0)			
Weight (%)						
BMI ≤ 30 kg/m^2	496 (77.1)	47 (79.7)	449 (76.9)	0.63	0.85	0.44–1.65
BMI > 30 kg/m^2	147 (22.9)	12 (20.3)	135 (23.1)			
Albumin (%)						
≥ 35 g/dL	359 (56.3)	31 (52.5)	328 (56.6)	0.55	1.18	0.69–2.02
< 35 g/dL	279 (43.7)	28 (47.5)	251 (43.4)			
Total protein (%)						
≥ 60 g/dL	527 (82.0)	48 81.4)	479 (82.0)	0.90	1.05	0.53–2.08
< 60 g/dL	116 (18.0)	11 (18.6)	105 (18.0)			
Anticoagulant use at surgery (%)						
No	533 (82.9)	46 (78.0)	487 (83.4)	0.29	1.42	0.74–2.73
Yes	110 (17.1)	13 (22.0)	97 (16.6)			
ASA classification (%)						
< 3	424 (66.1)	39 (66.1)	385 (66.2)	0.99	1.00	0.57–1.77
≥ 3	217 (33.9)	20 (33.9)	197 (33.8)			
Diagnosis (%)						
Malignant	518 (80.7)	42 (71.2)	476 (81.6)	0.05	1.80	0.99–3.29
Benign	124 (19.3)	17 (28.8)	107 (18.4)			
AJCC stage [14] in case of malignancy: n = 518 (%)						
I	190 (36.9)	17 (40.5)	173 (36.6)	0.15		
II	154 (29.9)	12 (28.6)	142 (30.0)			
III	138 (26.8)	8 (19.0)	130 (27.5)			
IV	33 (6.4)	5 (11.9)	28 (5.9)			
Detected by screening (%)						
No	322 (58.3)	21 (45.7)	301 (59.5)	0.07	1.75	0.95–3.21
Yes	230 (41.7)	25 (54.3)	205 (40.5)			
Preoperative haemoglobin (%)						
Male ≥ 6.5, female ≥ 6 mmol/L	591 (94.3)	51 (87.9)	540 (94.9)	**0.03**	2.56	1.07–6.12
Male < 6.5, female < 6 mmol/L	36 (5.7)	7 (12.1)	29 (5.1)			
Current smoker (%)						
No	529 (85.0)	47 (82.5)	482 (85.3)	0.57	1.24	0.60–2.54
Yes	93 (15.0)	10 (17.5)	83 (14.7)			
Pack years (%)						
< 15	392 (70.4)	33 (66.0)	359 (70.8)	0.48	1.25	0.68–2.31
≥ 15	165 (29.6)	17 (34.0)	148 (29.2)			

Table 2 (continued)

	Total ($N=643$)	Anastomotic leak ($N=59$)	No anastomotic leak ($N=584$)	*P*-value	Odds ratio	95%CI
Steroid use (%)						
No	611 (95.3)	55 (93.2)	556 (95.5)	0.42	1.56	0.52–4.62
Yes	30 (4.7)	4 (6.8)	26 (4.5)			
Alcohol intake in units per day (%)						
< 3	590 (94.9)	53 (91.4)	537 (95.2)	0.21	1.88	0.43–1.28
≥ 3	32 (5.1)	5 (8.6)	27 (4.8)			
Diabetes mellitus (%)						
No	542 (84.4)	45 (76.3)	497 (85.2)	0.07	1.80	0.95–3.42
Yes	100 (15.6)	14 (23.7)	86 (14.8)			

BMI body mass index, *ASA* American Society of Anaesthesiologists, *AJCC* American Joint Committee on Cancer

Table 3 Intraoperative and surgery-related characteristics

	Total ($N=643$)	Anastomotic leak ($N=59$)	No anastomotic leak ($N=584$)	*P*-value	Odds ratio	95%CI
Temperature (%)						
≥ 36˚ Celsius	511(79.7)	40 (67.8)	471 (80.9)	**0.02**	2.02	1.12-3.61
< 36˚ Celsius	130 (20.3)	19 (32.2)	111 (19.1)			
Glucose (%)						
≤ 6.1 mmol/L	157 (25.3)	9 (15.5)	148 (26.3)	0.07	1.95	0.93-4.06
> 6.1 mmol/L	463 (74.7)	49 (84.5)	414 (73.7)			
Blood loss (%)						
≤ 100 mL	423 (73.8)	31 (58.5)	392 (75.4)	**0.008**	2.17	1.22-3.89
> 100 mL	150 (26.2)	22 (41.5)	128 (24.6)			
Blood transfusion (%)						
No	622 (96.7)	56 (94.9)	566 (96.9)	0.41	1.69	0.48-5.90
Yes	21 (3.3)	3 (5.1)	18 (3.1)			
Intraoperative complications (%)						
No	497 (77.3)	35 (59.3)	462 (79.1)	**0.001**	2.60	1.49-4.53
Yes	146 (22.7)	24 (40.7)	122 (20.9)			
Intraoperative vasopressors (%)						
No	334 (52.2)	27 (45.8)	307 (52.8)	0.30	1.33	0.78-2.27
Yes	306 (47.8)	32 (54.2)	274 (47.2)			
Oxygen saturation (%)						
≥ 95%	634 (98.9)	59 (100.0)	575 (98.8)	0.40	-	-
< 95%	7 (1.1)	0	7 (1.2)			
MAP (%)						
≥ 60 mmHg	634 (98.9)	58 (98.3)	576 (99.0)	0.64	1.66	0.20-13.99
< 60 mmHg	7 (1.1)	1 (1.7)	6 (1.0)			
Surgeon evaluation of the local perfusion (%)						
6	1 (0.2)	0	1 (0.2)	**0.002**		
7	19 (3.0)	5 (8.8)	14 (2.5)			
8	172 (27.5)	22 (38.6)	150 (26.4)			
9	180 (28.8)	19 (33.3)	161 (28.3)			
10	253 (40.5)	11 (19.3)	242 (42.6)			
Goal directed therapy (%)						
Yes	145 (22.6)	18 (30.5)	127 (21.7)	0.13	0.63	0.35-1.14
No	498 (77.4)	41 (69.5)	457 (78.3)			

Table 3 (continued)

	Total ($N=643$)	Anastomotic leak ($N=59$)	No anastomotic leak ($N=584$)	*P*-value	Odds ratio	95%CI
Urine production per hour (%)						
≥ 25 mL	492 (83.2)	43 (76.8)	449 (83.9)	0.17	1.58	0.81-3.06
< 25 mL	99 (16.8)	13 (23.2)	86 (16.1)			
Fluid suppletion per hour (%)						
≤ 1000 mL	592 (94.6)	55 (93.2)	537 (94.7)	0.63	1.30	0.44-3.83
> 1000 mL	34 (5.4)	4 (6.8)	30 (5.3)			
Intraoperative faecal contamination (%)						
No	610 (95.2)	47 (79.7)	563 (96.7)	**< 0.0001**	7.57	3.46-16.53
Yes	31 (4.8)	12 (20.3)	19 (3.3)			
Epidural (%)						
No	520 (81.1)	39 (66.1)	481 (82.6)	**0.002**	2.44	1.37-4.36
Yes	121 (18.9)	20 (33.9)	101 (17.4)			
Seniority of surgeon (%)						
Consultant surgeon	469 (72.9)	41 (69.5)	428 (73.3)	0.76		
Fellow	109 (17.0)	12 (20.3)	97 (16.6)			
Resident	65 (10.1)	6 (10.2)	59 (10.1)			
Type of anastomosis (%)						
ETE	143 (22.3)	13 (22.4)	130 (22.3)	0.75		
ETS	17 (2.7)	1 (1.7)	16 (2.8)			
STE	113 (17.7)	13 (22.4)	100 (17.2)			
STS	367 (57.3)	31 (53.5)	336 (57.7)			
Anastomosis technique (%)						
Hand-sewn	92 (15.3)	4 (7.1)	88 (16.1)	0.19		
Stapled	495 (82.4)	51 (91.1)	444 (81.5)			
Both	14 (2.3)	1 (1.8)	13 (2.4)			
Suture reinforcement (%)						
Yes	275 (42.8)	19 (32.2)	256 (43.9)	0.08	1.65	0.93-2.92
No	367 (57.2)	40 (67.8)	327 (56.1)			
Surgical approach (%)						
Laparoscopic	524 (81.6)	41 (69.5)	483 (82.8)	**0.01**	2.12	1.17-3.84
Open	118 (18.4)	18 (30.5)	100 (17.2)			
Conversion to open, laparoscopic only, n = 524 (%)						
No	489 (93.3)	33 (80.5)	456 (94.4)	**0.001**	4.10	1.73-9.72
Yes	35 (6.7)	8 (19.5)	27 (5.6)			
Stoma formation (%)						
No	623 (96.9)	55 (93.2)	568 (97.3)	0.09	2.58	0.83-7.99
Yes	20 (3.1)	4 (6.8)	16 (2.7)			
Resection type (%)						
(Sub)total colectomy	46 (7.2)	7 (11.9)	39 (6.7)	0.25		
(Extended) right hemicolectomy	279 (43.4)	29 (49.1)	250 (42.8)			
Left hemicolectomy/High anterior resection	285 (44.3)	20 (33.9)	265 (45.4)			
Stoma reversal	33 (5.1)	3 (5.1)	30 (5.1)			
Duration of surgery (%)						
≤ 3 h	463 (73.4)	34 (57.6)	429 (75.0)	**0.004**	2.21	1.27-3.82
> 3 h	168 (26.2)	25 (42.4)	143 (25.0)			

MAP mean arterial pressure, *ETE* end-to-end, *ETS* end-to-side, *STE* side-to-end, *STS* side-to-side

Table 4 Types of resection and anastomosis

	ETE	ETS	STE	STS	*Missing*	Total
Resection type vs. type of anastomosis (*N* = 643)						
(Sub)total colectomy	14	3	4	24	*1*	46
(Extended) rsight hemicolectomy	26	3	1	254	*1*	285
Left hemicolectomy / high anterior resection	83	11	106	78	*1*	279
Stoma reversal	20	0	2	11	*0*	33
Resection type vs. anastomosis technique (*N* = 643)						
	Handsewn		Stapled	Both	*Missing*	Total
(Sub)total colectomy	14		27	3	*2*	46
(Extended) right hemicolectomy	50		213	8	*14*	285
Left hemicolectomy /high anterior resection	21		230	3	*25*	279
Stoma reversal	7		25	0	*1*	33
Type of anastomosis vs anastomosis technique (*N* = 640)						
	Handsewn		Stapled	Both	*Missing*	Total
ETE	47		93	0	*3*	143
ETS	1		15	1	*0*	17
STE	1		98	1	*13*	113
STS	43		298	12	*23*	367

ETE end to end anastomosis, *ETS* end to side anastomosis, *STE* side to end anastomosis, *STS* side to side anastomosis

undergoing rectal surgery, who represent a different cohort with its own specific AL risk-factors.[17] Therefore, to our opinion, this cannot be considered a true validation attempt. Finally, the AUROC after cross-validation that was reported by Frasson, et al. was also rather low (AUROC 0.62), which was attributed to the difficult anticipation of complications since AL is also affected by the type of surgical procedure.[6,18]

Interestingly, in the current study, none of the variables from the AL risk nomogram that were tested differed significantly between the patients who developed AL and those who did not, indicating that these factors may not be reliable predictors for AL. It is therefore not surprising that the AL risk nomogram could not accurately predict AL in this population.

Several other AL risk nomograms have been developed. One was based on 10,392 patients aged ≥ 65 years undergoing colonic surgery.[19] Despite the large patient number, this nomogram was based on retrospective data, and could not be validated when tested in an external database with an AUROC of 0.65. Most other nomograms that have been developed are for predicting AL after rectal surgery, and none have been validated.[20–22]

The current study found an AL rate of 9.2%. The highest AL rates (as high as 19%) are reported after rectal surgery.[2,23] Since rectal anastomoses were not included in the current study, the AL rate we found is relatively high for colon resections only. However, previously reported AL rates after colon surgery range between 3.8% and 9%, where the higher rates have been reported in prospective studies and trials while the lower percentages mostly came from national audits or retrospective series, potentially recording AL less accurately.[3,10,24–26] Furthermore, the AL rate of 9.2% found in the current study is similar to that reported by Frasson, et al. (AL rate 8.7%), confirming the comparability of included patients and the definitions used in both studies.[6]

Multivariable analysis revealed four independent predictors for AL, of which three were also identified in the LekCheck study.[10] Low preoperative haemoglobin, which is commonly observed in patients undergoing colonic surgery, may affect the perfusion and oxygenation of anastomotic margins and can therefore predispose AL.[27,28] Furthermore, preoperative anaemia is associated with poor physical status, increasing the risk of complications.[29,30] The mechanism between epidural analgesia and AL remains unclear but could be related to a hypotensive state during surgery, resulting in relative ischemia of the colon.[11,31] Intraoperative faecal contamination as a risk-factor for AL has to be interpreted with care, as it mostly occurs during more challenging procedures and cannot be avoided. Theoretically, mechanical bowel preparation could be an effective approach to reduce the AL rate, but evidence for using this, even when combined with antibiotics, is controversial.[32,33] This is the first study to identify intraoperative hypothermia as a risk-factor for AL. Hypothermia results in vasoconstriction, increasing hypoxia and impairing the immune response, leading to worse healing.[34,35] Therefore, active intraoperative warming is recommended to maintain normothermia.[36]

Some limitations of the current study have to be addressed. Not all patients from the LekCheck study database could be

Table 5 Postoperative outcomes and complications

	Total ($N=643$)	Anastomotic leak (N=59)	No anastomotic leak (N=584)	*P*-value	Odds ratio	95%CI
Clinical suspicion of anastomotic leakage (%)						
No	544 (84.7)	0	544 (93.3)	N/A		
Yes	98 (15.3)	59 (100.0)	39 (6.7)			
Diagnosis modality to detect anastomotic leakage (%)						
Clinically and blood results	13 (13.4)	6 (10.2)	7 (18.4)	N/A		
CT-scan and percutaneous drain	73 (75.3)	44 (74.6)	29 (76.3)			
Re-operation	11 (11.3)	9 (15.2)	2 (5.3)			
Median number of days after surgery until anastomotic leakage (range)		4 (1–40)				
Leakage treatment (%)						
Antibiotics		10 (16.9)				
Percutaneous drain		6 (10.2)				
Re-operation		43 (72.9)				
Leakage re-operation type (%)						
Suture reinforcement of anastomosis		6 (14.0)				
Construction of new anastomosis without covering stoma		11 (25.5)				
Construction of new anastomosis with covering stoma		6 (14.0)				
Anastomosis dismantled, end stoma formation		20 (46.5)				
Median hospital stay in days (range)	4 (2–46)	13 (5–46)	4 (2–33)	**<0.0001**		
30-day postoperative mortality (%)						
No	633 (98.4)	58 (98.3)	575 (98.5)	0.93	1.10	0.13–8.85
Yes	10 (1.6)	1 (1.7)	9 (1.5)			

N/A: non-applicable

included in the current analysis, mostly because serum protein level was not a variable collected for that study and could not be retrieved retrospectively. Since preoperative serum total protein is one of the six variables in the nomogram by Frasson, et al., including these patients would have resulted in less accurate validation. However, we did analyse these patients and found a similar AL rate (9.0%) compared to the included patients (9.2%), limiting potential selection bias. Furthermore, serum total protein was derived from the serum albumin in most patients. This could have influenced the validation of the AL risk nomogram. Also, inter-observer variability could have biased data entry of some variables, such as evaluation of the local perfusion and faecal contamination, although these variables did not affect the validation of the nomogram.

Table 6 Multivariable analysis of variables associated with anastomotic leakage

	P-value	Odds ratio	95%CI
Preoperative haemoglobin (male < 6.5, female < 6 mmol/L)	**0.006**	4.21	1.52–11.69
Temperature (< 36 °C)	**0.02**	2.39	1.19–4.80
Blood loss (> 100 mL)	0.69	1.16	0.55–2.45
Intraoperative complications	0.61	1.24	0.54–2.83
Surgeon's estimate of local perfusion			
10	0.23	1	-
9		2.26	0.93–5.50
8		2.16	0.89–5.25
7		3.01	0.70–12.97
Intraoperative faecal contamination	**0.004**	4.22	1.59–11.22
Epidural analgesia	**0.02**	2.35	1.13–4.88
Surgical approach			
Laparoscopic	0.15	1	-
Laparoscopic, converted		2.78	0.91–8.54
Open		1.79	0.78–4.09
Duration of surgery (> 3 h)	0.19	1.59	0.79–3.20

In the future, the results of the current study suggest that studies on AL risk prediction should also incorporate intraoperative variables, as these are currently missing. The LekCheck study collaborative aims to report such a comprehensive nomogram with both pre- and intraoperative factors in the near future.

In conclusion, an AL rate of 9.2% was found in this patient cohort. The AL risk nomogram as proposed by Frasson, et al. could not be validated using the international Lekcheck study database.

In the future, intraoperative predictive factors for AL, as identified in this study, should also be included in AL risk predictors.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11605-021-05119-6.

Acknowledgements Collaborators of the LekCheck Study Group#:

Stefanus J. van Rooijen, MD, PhD[6], Boukje T. Bootsma, MD[4], Tim van de Brug, PhD[7], Jurre Stens, MD[8], Wim Bleeker, MD[9], Laurents P.S. Stassen, MD, PhD[10], Audrey Jongen, MD, PhD[10], Carlo V. Feo, MD, FACS[11], Simone Targa, MD[12], Niels Komen, MD, PhD[12,13], Emmanuel A.G.L. Lagae, MD[14], Aalbert K. Talsma, MD, PhD[15], Johannes A. Wegdam, MD[16], Tammo S. de Vries Reilingh, MD[16], Bob van Wely, MD[17], Marie J. van Hoogstraten, MD[17], Dirk J.A. Sonneveld, MD[18], Sanne C. Veltkamp, MD[19], Emiel G.G. Verdaasdonk, MD, PhD[20], Rudi M.H. Roumen, MD, PhD.[5]

[4] Department of Surgery, VU Medical Center Amsterdam, Amsterdam, the Netherlands

[5] Department of Surgery, Máxima Medical Center Veldhoven, Veldhoven, the Netherlands

[6] Care and Public Health Research Institute, Maastricht University, Maastricht, the Netherlands

[7] Department of Epidemiology and Biostatistics, VU Medical Center Amsterdam, Amsterdam, the Netherlands

[8] Department of Anesthesiology, VU Medical Center Amsterdam, Amsterdam, the Netherlands

[9] Department of Surgery, Wilhelmina Ziekenhuis, Assen, The Netherlands

[10] Department of Surgery, Maastricht University Medical Center, Maastricht, the Netherlands

[11] Department of Surgery, Ospedale del Delta, Lagosanto, Ferrara, Italy

[12] Department of Surgery, Antwerp University Hospital, Antwerp, Belgium

[13] Antwerp Surgical Training, Anatomy and Research Centre (ASTARC), Faculty of Medicine and Health Sciences, Wilrijk, Belgium

[14] Department of Surgery, ZorgSaam, Terneuzen, the Netherlands

[15] Department of Surgery, Deventer Ziekenhuis, Deventer, the Netherlands

[16] Department of Surgery, Elkerliek Ziekenhuis, Helmond, the Netherlands

[17] Department of Surgery, Bernhoven, Uden, the Netherlands

[18] Department of Surgery, Dijklander Ziekenhuis, Hoorn, the Netherlands

[19] Department of Surgery, Amstelland Ziekenhuis, Amstelveen, the Netherlands

[20] Department of Surgery, Jeroen Bosch Ziekenhuis, Den Bosch, the Netherlands

Author Contribution All authors

- made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work.
- drafted the work or revised it critically for important intellectual content.
- provided final approval of the version to be published.
- agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The study has been presented as verbal presentations at the following congresses:

- Ozmen I, Kroon HM, Grupa V, Bedrikovetski S, Dudi-Venkata NN, Huisman DE, Reudink M, Van Rooijen SJ, Bootsma BT, Van de Brug T, Stens J, Bleeker W, Stassen LPS, Jongen A, Feo CV, Targa S, Komen N, Lagae EAGL, Talsma AK, Wegdam JA, De Vries Reilingh TS, Van Wely B, Van Hoogstraten MJ, Sonneveld DJA, Veltkamp SC, Verdaasdonk EGG, Roumen RMH, Slooter GD, Daams F, Sammour T. Anastomotic leakage risk nomogram does not predict leakage accurately in all populations: Results of the international multi-center prospective LekCheck study. The European Society of Surgical Oncology virtual conference, October 2020 (abstract: Eur J Surg Oncol 2021;47:e21-2).
- Ozmen I, Grupa V, Kroon HM, Bedrikovetski S, Dudi- Venkata NN, Huisman DE, Reudink M, Van Rooijen SJ, Bootsma BT, Van de Brug T, Stens J, Bleeker W, Stassen LPS, Jongen A, Feo CV, Targa S, Komen N, Lagae EAGL, Talsma AK, Wegdam JA, De Vries Reilingh TS, Van Wely B, Van Hoogstraten MJ, Sonneveld DJA, Veltkamp SC, Verdaasdonk EGG, Roumen RMH, Slooter GD, Daams F, Sammour T. Peri-operative predictors of anastomotic leak after colonic resections – both pre-operative and intra-operative variables matter. Royal Australasian College of Surgeons 89th annual scientific meeting, May 2020, Melbourne, Australia (abstract: ANZ J Surg 2020;90(S1):32).

Funding IO and VEMG were personally supported by the Stichting Prof. Michaël-van Vloten Fonds, Dr. Edith Frederiksfonds, LUSTRA + Scholarship (Leiden University) and DOO International Office Scholarship (Leiden University Medical Center).

HMK: This project was undertaken whilst holding a Royal Adelaide Hospital Florey Fellowship.

Declarations

Ethics Approval Ethics approved at all participating sites.

Consent to Participate and for Publication All patients provided signed informed consent to participate in the study and for publication.

Conflict of Interest The authors declare no competing interests.

References

1. Buchs NC, Gervaz P, Secic M, Bucher P, Mugnier-Konrad B, Morel P (2008) Incidence, consequences, and risk factors for anastomotic dehiscence after colorectal surgery: a prospective monocentric study. Int J Colorectal Dis 23: 265–270. https://doi.org/10.1007/s00384-007-0399-3
2. Matthiessen P, Hallböök O, Rutegård J, Simert G, Sjödahl R (2007) Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum for cancer: A randomized multicenter trial. Ann Surg 246: 207–214. https://doi.org/10.1097/SLA.0b013e3180603024
3. Midura EF, Hanseman D, Davis BR, et al. (2015) Risk factors and consequences of anastomotic leak after colectomy: A national analysis. Dis Colon Rectum 58: 333–338. https://doi.org/10.1097/DCR.0000000000000249
4. La Regina D, Di Giuseppe M, Lucchelli M, et al. (2019) Financial impact of anastomotic leakage in colorectal surgery. J Gastrointest Surg 23: 580-586. https://doi.org/10.1007/s11605-018-3954-z
5. Ha GW, Kim JH, Lee MR (2017) Oncologic impact of anastomotic leakage following colorectal cancer surgery: A systematic review and meta-analysis. Ann Surg Oncol 24: 3289-3299. https://doi.org/10.1245/s10434-017-5881-8
6. Frasson M, Flor-Lorente B, Rodríguez JL, et al. (2015) Risk factors for anastomotic leak after colon resection for cancer: Multivariate analysis and nomogram from a multicentric, prospective, national study with 3193 patients. Ann Surg 262: 321-330. https://doi.org/10.1097/SLA.0000000000000973
7. Sammour T, Lewis M, Thomas ML, Lawrence MJ, Hunter A, Moore JW (2017) A simple web-based risk calculator (www.anast

omoticleak.com) is superior to the surgeon's estimate of anastomotic leak after colon cancer resection. Tech Coloproctol 21: 35-41. https://doi.org/10.1007/s10151-016-1567-7
8. Sammour T, Cohen L, Karunatillake AI, et al. (2017) Validation of an online risk calculator for the prediction of anastomotic leak after colon cancer surgery and preliminary exploration of artificial intelligence-based analytics. Tech Coloproctol 21: 869–877. https://doi.org/10.1007/s10151-017-1701-1
9. University of Birmingham (2020) ESCP Safe Anastomosis proGramme in coLorectal surgEry (EAGLE). ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04270721. Accessed 24 August 2020.
10. Huisman DE, Reudink M, van Rooijen SJ, et al. (2020) LekCheck: A prospective study to identify perioperative modifiable risk factors for anastomotic leakage in colorectal surgery. Ann Surg: published online. https://doi.org/10.1097/SLA.0000000000003853
11. van Rooijen SJ, Huisman D, Stuijvenberg M, et al. (2016) Intraoperative modifiable risk factors of colorectal anastomotic leakage: why surgeons and anesthesiologists should act together. Int J Surg 36: 183–200. https://doi.org/10.1016/j.ijsu.2016.09.098
12. Reisinger KW, Poeze M, Hulsewe KW, et al. (2014) Accurate prediction of anastomotic leakage after colorectal surgery using plasma markers for intestinal damage and inflammation. J Am Coll Surg 219: 744-751. https://doi.org/10.1016/j.jamcollsurg.2014.06.011
13. Mandrekar JN (2010) Receiver operating characteristic curve in diagnostic test assessment. J Thorac Oncol 5: 1315-1316. https://doi.org/10.1097/JTO.0b013e3181ec173d
14. Amin MB, Greene FL, Edge SB, et al. (2017) The eighth edition AJCC cancer staging manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin 67: 93-99. https://doi.org/10.3322/caac.21388
15. Er S, Ozden S, Koca F, Yildiz BD, Yuksel BC, Tez M (2019) External validation of anastomotic leakage risk analysis system in patients who underwent colorectal resection. Turk J Med Sci 49: 279-282. https://doi.org/10.3906/sag-1807-205
16. Klose J, Tarantino I, Von Fournier A, et al. (2018) A nomogram to predict anastomotic leakage in open rectal surgery-hope or hype? J Gastrointest Surg 22: 1619-1630. https://doi.org/10.1007/s11605-018-3782-1
17. Arezzo A, Migliore M, Chiaro P, et al. (2019) The REAL (REctal Anastomotic Leak) score for prediction of anastomotic leak after rectal cancer surgery. Tech Coloproctol 23: 649-663. https://doi.org/10.1007/s10151-019-02028-4
18. Kawai K, Sunami E, Yamaguchi H, et al. (2015) Nomograms for colorectal cancer: A systematic review. World J Gastroenterol 21: 11877-11886. https://doi.org/10.3748/wjg.v21.i41.11877
19. Rencuzogullari A, Benlice C, Valente M, Abbas MA, Remzi FH, Gorgun E (2017) Predictors of anastomotic leak in elderly patients after colectomy: Nomogram-based assessment from the American College of Surgeons National Surgical Quality Program procedure-targeted cohort. Dis Colon Rectum 60: 527–536. 0.1097/DCR.0000000000000789
20. Yao HH, Shao F, Huang Q, Wu Y, Qiang Zhu Z, Liang W (2014) Nomogram to predict anastomotic leakage after laparoscopic anterior resection with intracorporeal rectal transection and double-stapling technique anastomosis for rectal cancer. Hepatogastroenterology 61: 1257-1261.
21. Kim CH, Lee SY, Kim HR, Kim YJ (2017) Nomogram prediction of anastomotic leakage and determination of an effective surgical strategy for reducing anastomotic leakage after laparoscopic rectal cancer surgery. Gastroenterol Res Pract 2017: 4510561. https://doi.org/10.1155/2017/4510561
22. Zheng H, Wu Z, Wu Y, et al. (2019) Laparoscopic surgery may decrease the risk of clinical anastomotic leakage and a nomogram to predict anastomotic leakage after anterior resection for rectal cancer. Int J Colorectal Dis 34: 319-328. https://doi.org/10.1007/s00384-018-3199-z
23. Heald RJ, Leicester RJ (1981) The low stapled anastomosis. Br J Surg 68: 333–337. https://doi.org/10.1002/bjs.1800680514
24. Bakker IS, Grossmann I, Henneman D, Havenga K, Wiggers T (2014) Risk factors for anastomotic leakage and leak-related mortality after colonic cancer surgery in a nationwide audit. Br J Surg 101: 424-432. https://doi.org/10.1002/bjs.9395
25. Eickhoff R, Eickhoff SB, Katurman S, et al. (2019) Influence of suture technique on anastomotic leakage rate-a retrospective analyses comparing interrupted-versus continuous-sutures. Int J Colorectal Dis 34: 55-61. https://doi.org/10.1007/s00384-018-3168-6
26. 2015 European Society of Coloproctology collaborating group (2017) The relationship between method of anastomosis and anastomotic failure after right hemicolectomy and ileo-caecal resection: an international snapshot audit. Colorectal Dis: published online. https://doi.org/10.1111/codi.13646
27. Munoz M, Gomez-Ramirez S, Martin-Montanez E, et al. (2014) Perioperative anemia management in colorectal cancer patients: a pragmatic approach. World J Gastroenterol 20: 1972–85. https://doi.org/10.3748/wjg.v20.i8.1972
28. Choudhuri AH, Uppal R, Kumar M. (2013) Influence of non-surgical risk factors on anastomotic leakage after major gastrointestinal surgery: Audit from a tertiary care teaching institute. Int J Crit Illn Inj Sci 3: 246-9. https://doi.org/10.4103/2229-5151.124117
29. Wilson MJ, Dekker JWT, Harlaar JJ, Jeekel J, Schipperus M, Zwaginga JJ. (2017) The role of preoperative iron deficiency in colorectal cancer patients: prevalence and treatment. Int J Colorectal Dis 32: 1617-24. https://doi.org/10.1007/s00384-017-2898-1
30. Leichtle SW, Mouawad NJ, Lampman R, Singal B, Cleary RK. (2011) Does preoperative anemia adversely affect colon and rectal surgery outcomes? J Am Coll Surg 212: 187-94. https://doi.org/10.1016/j.jamcollsurg.2010.09.013
31. Carpenter RL, Caplan RA, Brown DL, Stephenson C, Wu R. (1992) Incidence and risk factors for side effects of spinal anesthesia. Anesthesiology 76: 906-16. https://doi.org/10.1097/00000542-199206000-00006
32. Rollins KE, Javanmard-Emamghissi H, Acheson AG, Lobo DN. (2019) The role of oral antibiotic preparation in elective colorectal surgery: A meta-analysis. Ann Surg 270: 43-58. https://doi.org/10.1097/SLA.0000000000003145
33. Koskenvuo L, Lehtonen T, Koskensalo S, et al. (2019) Mechanical and oral antibiotic bowel preparation versus no bowel preparation for elective colectomy (MOBILE): A multicentre, randomised, parallel, single-blinded trial. Lancet 394: 840-8. https://doi.org/10.1016/S0140-6736(19)31269-3
34. Qadan M, Gardner SA, Vitale DS, Lominadze D, Joshua IG, Polk HC Jr. (2009) Hypothermia and surgery: immunologic mechanisms for current practice. Ann Surg 250: 134-40. https://doi.org/10.1097/SLA.0b013e3181ad85f7
35. Billeter AT, Hohmann SF, Druen D, Cannon R, Polk HC Jr. (2014) Unintentional perioperative hypothermia is associated with severe complications and high mortality in elective operations. Surgery 156: 1245-52. https://doi.org/10.1016/j.surg.2014.04.024
36. Gustafsson UO, Scott MJ, Hubner M, et al. (2019) Guidelines for perioperative care in elective colorectal surgery: Enhanced Recovery After Surgery (ERAS®) Society Recommendations: 2018. World J Surg 43: 659-95. https://doi.org/10.1007/s00268-018-4844-y

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.