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LekCheck: A Prospective Study to Identify Perioperative Modifiable Risk Factors for Anastomotic Leakage in Colorectal Surgery

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Objective: To assess potentially modifiable perioperative risk factors for anastomotic leakage in adult patients undergoing colorectal surgery.

Summary Background Data: Colorectal anastomotic leakage (CAL) is the single most important denominator of postoperative outcome after colorectal surgery. To lower the risk of CAL, the current research focused on the association of potentially modifiable risk factors, both surgical and anesthesiological.

Methods: A consecutive series of adult patients undergoing colorectal surgery with primary anastomosis was enrolled from January 2016 to December 2018. Fourteen hospitals in Europe and Australia prospectively collected perioperative data by carrying out the LekCheck, a short checklist carried out in the operating theater as a time-out procedure just prior to the creation of the anastomosis to check perioperative values on 1) general condition 2) local perfusion and oxygenation, 3) contamination, and 4) surgery related factors. Univariate and multivariate logistic regression analysis were performed to identify perioperative potentially modifiable risk factors for CAL.

Results: There were 1562 patients included in this study. CAL was reported in 132 (8.5%) patients. Low preoperative hemoglobin (OR 5.40, $P < 0.001$), contamination of the operative field (OR 2.98, $P < 0.001$), hyperglycemia (OR 2.80, $P = 0.003$), duration of surgery of more than 3 hours (OR 1.86, $P = 0.010$), administration of vasopressors (OR 1.80, $P = 0.010$), inadequate timing of preoperative antibiotic prophylaxis (OR 1.62, $P = 0.047$), and application of epidural analgesia (OR, 1.81, $P = 0.\ 014$) were all associated with CAL.

Conclusions: This study identified 7 perioperative potentially modifiable risk factors for CAL. The results enable the development of a multimodal and multidisciplinary strategy to create an optimal perioperative condition to finally lower CAL rates.

Keywords: anastomotic leakage, colorectal surgery, modifiable risk factor, perioperative care

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Over the recent years, improved surgical techniques and enhanced recovery programs, early detection and treatment and higher surgeon caseloads have been proven effective to decrease the incidence and reduce the consequences of colorectal anastomotic leakage (CAL).[1,2] In addition, several preoperative, intraoperative, and postoperative risk factors for CAL have been identified.[3–5] Despite these advances, CAL remains a severe complication following surgery with a reported incidence ranging from 3 to 19%

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worldwide.[3] Leakage often results in a reoperation leading to a decreased health related quality of life and often a permanent stoma. Consequently, it increases hospital stay and health expenditures. CAL after colorectal surgery for cancer has a negative impact on the prognosis with regard to local recurrence and reduced survival rates.[6–9]

The exact risk factors of CAL remain unclear. Previous studies have revealed that patient-related factors, such as male gender and higher American Society of Anesthesiologist (ASA) score, are associated with CAL.[4,10–13] Also, intra-operative factors, such as operative time, and blood loss, are associated with higher leakage rates.[13] These risk factors, however, are mostly static and non-modifiable. Recently, it has been suggested that some risk factors for CAL can actually be modified, as intraoperative temperature, blood pressure, and glucose levels may also contribute to the development of CAL.[14–17] However, it is still unknown what the optimal values for these factors are during perioperative care.

The prognostic value of potentially modifiable perioperative risk factors for CAL has not yet been examined. This is the first international prospective multicenter registration study where perioperative data is collected just prior to the creation of the anastomosis during colorectal surgery. We aimed to analyze the association between perioperative potentially modifiable risk factors and CAL.

METHODS

Study Design and Patient Population

Fourteen hospitals in the Netherlands, 1 hospital in Belgium, 1 in Italy and 1 hospital in Australia participated in the LekCheck study collecting data from January 2016 to December 2018. Adult patients undergoing surgery with the formation of a primary anastomosis for malign or benign indications were included. A multifactorial intra-operative checklist, the LekCheck, was designed in 2016 by surgeons from 2 Dutch hospitals (VU Medical Center in Amsterdam and Máxima Medical Center in Veldhoven) and was supported by the Dutch Taskforce Colorectal Anastomotic Leakage (Acknowledgements). The study was approved by the Ethics Committee of the participating medical centers and all patients provided informed consent.

Data Collection

The LekCheck contained 4 main topics including modifiable and nonmodifiable factors: 1) general condition of the patient (hemoglobin level, temperature, glucose, antibiotic prophylaxes), 2) local perfusion and oxygenation (blood loss, blood transfusion, oxygen saturation, mean arterial pressure, urine production, fluid suppletion, subjective clinical assessment of perfusion), 3) contamination, and 4) surgery related factors (duration of surgery, surgical procedure, approach, configuration, anastomotic technique and location, administration of vasopressors, intraoperative events, suture reinforcement, stoma type, surgeon fit to perform). All LekCheck items were prospectively collected by carrying out an additional time-out procedure in the operating theater just prior to the creation of the anastomosis during which both the surgeon and anesthesiologist were present. Baseline characteristics such as sex, age, body mass index (BMI), ASA classification score, diabetes, intoxications (smoking, alcohol use, steroid use), benign or malignant disease, detection by screening program, distance of the tumor to the anal verge, neoadjuvant therapy, and the Tumor-Node-Metastasis (TNM) stage according to the American Joint Committee on Cancer,[18] were recorded. Data of the presence of CAL, the diagnosis and treatment were determined and collected prospectively with a follow-up of 30 days postoperatively.

TABLE 1. Perioperative Modifiable Factors and Their Cut-off Values for Optimal Intraoperative Condition

Variable	Cut-off Values
Temperature	<36°
Glucose	>109.8 mg/dL
Antibiotic prophylaxes	<15 or >60 min prior incision
Administration of vasopressors	Yes
Hemoglobin	Male <10.5 g/dL Female <9.7 g/dL
Blood loss	>100 mL
Blood transfusion	Yes
Oxygen saturation	<95%
Mean arterial pressure	<60 mm Hg
Fluid administration	>1000 cc/h
Fecal contamination	Yes
Application of epidural analgesia	Yes
Duration of surgery	>3 h
Intraoperative event	Yes

Adapted from van Rooijen et al: Intraoperative modifiable risk factors of colorectal anastomotic leakage: Why surgeons and anesthesiologists should act together. *Int J Surg*. 2016.[16]

DEFINITIONS

Potentially modifiable LekCheck factors and their cut-off values for optimal intraoperative condition were extracted from a previously published review by our research group (Table 1).[16] LekCheck values were dichotomized in order to create a composite score. Temperature below 36 degrees Celsius was considerate low. Hyperglycemia was defined as a glucose level above 109.8 mg/dL. Adequate timing of the administration of antibiotic prophylaxes was within 15 to 60 minutes prior to incision. Administration of vasopressors, the requirement of blood transfusion and the application of epidural analgesia were all classified as yes/no. A low preoperative hemoglobin (Hb) was defined by a concentration of less than 10.5 g/dL in males and less than 9.7 g/dL in females. Blood loss was collected by blood from suction bottles and/or drainage bags and was defined as 100 mL or more. An oxygen saturation below 95% was considerate low. A low mean arterial pressure (MAP) was defined by 60 mm Hg or lower. Suboptimal intraoperative fluid management was defined by the administration of 1000 mL or more per hour. Prolonged surgery was considered 3 hours or more. Contamination was subjectively measured (yes/no), surgeons were instructed to report contamination as more than normal when the operated field was contaminated more than the regular loss of bowel content during a colorectal resection without bowel preparation. Intraoperative events were scored as yes/no and included: hypoxic events, hypertension, hypercarbia, bradycardia, hypotension, embolism, reanimation, more extensive resection than planned, serosa lesions, bladder and ureteral injuries, intraoperative bleeding, splenectomy or bleeding. Anastomotic location above the level of the peritoneal reflection was classified as colonic, below as rectal. Leakage was defined according to Reisinger: "clinically relevant anastomotic leakage is defined as extra luminal presence of contrast fluid on contrast-enhanced CT scans and/or leakage when relaparotomy was performed, requiring reintervention or treatment."[19]

Statistical Analysis

Data were analyzed with Statistical Package for the Social Sciences software (SPSS 25-0, SPSS, Chicago, IL). First, descriptive statistics were used to analyze baseline characteristics. A 90% completeness of the LekCheck was considered successful, allowing

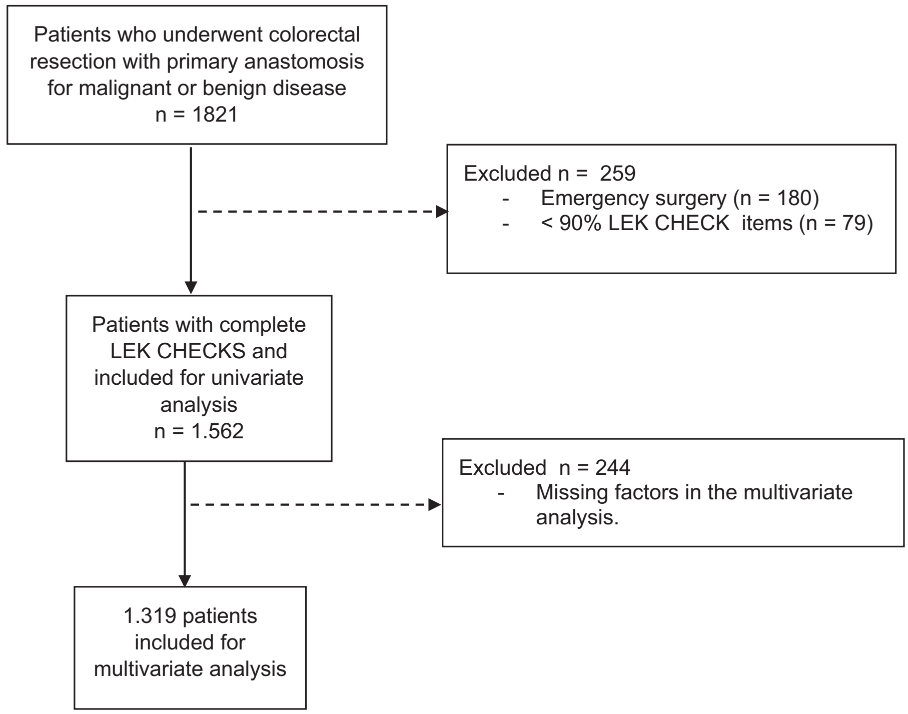

FIGURE 1. Flow diagram of study selection.

a maximum of 2 variables as missing data. Categorical variables are expressed as proportions (%). Differences between patients with and without CAL were tested with Pearson's χ^2 test. Continuous variables are expressed as mean (standard deviation) or medians (interquartile range) depending on skewness. Differences between continuous variables were tested with the Student *t* test (normal distribution) or the Mann–Whitney *U* test (skewed distribution). *P* values < 0.05 were considered statistically significant.

Logistic regression analyses with CAL as primary outcome were performed to analyze associations with LekCheck factors. First, the associations were tested for single factors in a univariate analysis. Second, significant LekCheck factors ($P < 0.10$) were analyzed in a multivariate model, adjusting for other variables (baseline and surgery related) that differed significantly between patients with and without CAL. We performed a subgroup analysis to analyze patients according to anastomotic location (colon and rectum). In the multivariate logistic regression analysis 2-sided *P* values < 0.05 were considered statistically significant. Results are reported as odds ratios (OR) and 95% confidence intervals (CIs).

RESULTS

The LekCheck was performed in 1821 patients. Seventy-nine patients were excluded from the analysis due to incompleteness of data in the checklists (<90% complete) and for this study, 180 patients were excluded due to emergency surgery. A flowchart of the inclusion is shown in Figure 1.

Baseline Characteristics

Cohort characteristics of the included patients for both groups (with and without anastomotic leakage) are summarized in Table 2. Of the 1562 included patients, 799 (51%) were male and the median age was 69 (range 21–95 yrs). Patients with CAL were significantly more often men (62% vs. 50%, $P = 0.009$), were more frequently ASA score ≥ 3 (34% vs. 24%, $P = 0.009$) and had diabetes mellitus more often (22% vs. 14%, $P = 0.017$). Furthermore, significantly more long-term smokers (>15 pack years) were present in the leakage group (31% vs. 2%, $P = 0.011$). If a tumor was present, the mean distance of the tumor to the anal verge was smaller in patients with CAL (12 vs. 15 cm, $P = 0.009$).

Surgical Characteristics

The 1562 procedures that were performed were: 140 (9%) subtotal colectomies, 168 (11%) left colectomies, 526 (34%) right colectomies, 26 (2%) transverse colonic resections, 303 (20%) sigmoid resections, 349 (22%) rectum resections, and 50 (3%) reversals of Hartmann's procedures (Table 3). The mean duration of surgery was significantly longer in patients with CAL (186 vs. 156 min, $P < 0.000$). A higher leakage rate was seen following a primarily open approach versus laparoscopic procedures (13% vs. 7.7%, $P = 0.007$). Likewise, if an intraoperative event occurred, the CAL rate increased (14% vs. 7.5%, $P = 0.001$). The distribution of type of anastomosis (end-to-end, end-to-side, side-to-end, side-to-side) can be found as supplemental data in Table 5, http://links.lww.com/SLA/C26.

Outcome

While 214 (13.7%) patients had a clinical suspicion, CAL was confirmed in 132 patients (8.4%). The median time interval between surgery and the diagnosis of CAL was 5 days (IQR 3–8). The length of hospital stay was longer in the leakage group (20 vs. 6 d, $P < 0.001$). The overall 30-day mortality rate was 1.3% (21 of 1562), which was significantly worse in patients with CAL (5.6% vs. 0.9%, $P = 0.001$).

Thirty-two (24%) of the 132 leakage patients, got some form of nonoperative treatment such as antibiotics (17%), insertion of a drain (8%), or both (6%). In total, 90 patients had a reintervention, among them: 4 (3%) patients received suture reinforcement of the anastomosis, 24 (18%) patients were treated by a deviating stoma alone, 37 (28%) patients by dismantling the anastomosis and installing a stoma and in 25 (19%) patients a complete new anastomosis

TABLE 2. Baseline Characteristics of Patient Population (n = 1562)

Variable	Anastomotic Leakage (n = 132)		No Anastomotic Leakage (n = 1430)		*P* Value
		Missing		Missing	
Sex (male)	81 (62%)		718 (50%)		**0.009**
Age (yrs)*	71 (21–91)		68 (23–95)		0.162
< 70	64 (48%)		759 (53%)		
≥ 70	68 (52%)		663 (47%)		
Body mass index ≥ 30 kg/m^2	27 (20%)		241 (17%)		0.212
ASA classification					**0.009**
< 3	87 (66%)		1075 (76%)		
≥ 3	45 (34%)		343 (24%)		
Diabetes mellitus	29 (22%)		204 (14%)	n = 12	**0.017**
Intoxications					
Current smoker	18 (14%)	n = 5	169 (12%)	n = 70	0.326
Pack years ≥ 15 yrs	40 (31%)	n = 4	301 (22%)	n = 43	**0.011**
Alcohol intake ≥ 3 units/d	14 (10%)	n = 4	121 (9%)	n = 2	0.244
Steroid use (excl. inhalers)	4 (4%)		36 (3%)	n = 14	0.449
Disease				n = 6	0.157
Malignant	113 (85%)		1163 (82%)		
Benign	19 (15%)		261 (18%)		
Diagnosed by screening program	48 (42%)	n = 18	476 (39%)	n = 238	0.361
Neoadjuvant therapy		n = 3		n = 74	0.195
None	111 (86%)		1192 (88%)		
5 × 5 radiotherapy	10 (8%)		92 (7%)		
Chemotherapy	3 (2%)		30 (2%)		
Chemoradiotherapy	5 (4%)		42 (3%)		
Distance of tumor from AV <15 cm	37 (29%)	n = 6	267 (19%)	n = 22	**0.005**
Pathological TNM stage		n = 21		n = 284	0.158
I (T1–2N0M0)	52 (47%)		407 (36%)		
II (T3–4N0M0)	23 (21%)		324 (28%)		
III (T1–4N1–2M0)	27 (24%)		352 (31%)		
IV (T1–4N1–2M1)	9 (8%)		63 (6%)		

Data are presented as number (%) unless stated otherwise.
*Data are presented as medians (range).
AV indicates anal verge. A $P < 0.05$ was considered statistically significant.
Bold numbers are statistically significant.

was created. Treatment with an Endo-Sponge occurred in 10 (7.5%) patients after rectum resections.

Risk Factors of Colorectal Anastomotic Leakage

Regarding the potentially modifiable factors low temperature, hyperglycemia, inadequate timing of preoperative antibiotic prophylaxis, administration of vasopressors, low preoperative haemoglobin, fluid supplementation of >1000 mL per hour, contamination of the operative field, application of epidural analgesia, duration of surgery of more than 3 hours, and intraoperative event were associated factors of CAL in the univariate analyses (Table 4). The multivariate analysis revealed the following independent associated factors for CAL: low preoperative hemoglobin (OR 5.40, 95% CI 2.94–9.95, $P < 0.001$), contamination of the operative field (OR 2.98, CI 1.55–5.75, $P < 0.001$), hyperglycemia (OR 2.80, 95% CI 1.44–5.58, $P = 0.003$), duration of surgery of more than 3 hours (OR 1.86, 95% CI 1.18–2.95, $P = 0.010$), administration of vasopressors (OR 1.80, 95% CI 1.13–2.73, $P = 0.010$), epidural analgesia (OR, 1.81, 95% CI 1.15–2.84, $P = 0.014$), and inadequate timing of preoperative antibiotic prophylaxis (OR 1.62, 95% CI 1.03–2.55, $P = 0.047$).

Subgroup Analyses (Anastomotic Location)

When colonic and rectal anastomoses were separately analyzed in multivariate analyses, associated factors for leakage of colonic anastomoses were low preoperative hemoglobin (OR 5.23, $P < 0.001$), contamination of the operative field (OR 4.03, $P < 0.001$), administration of vasopressors (OR 1.69, $P = 0.04$), hyperglycemia (OR 3.36, $P = 0.009$), and application of epidural analgesia (OR 2.08, $P = 0.011$). For rectal anastomoses, the following factors were significant: low preoperative hemoglobin (OR 5.02, $P = 0.019$), administration of vasopressors (OR 3.45, $P = 0.012$), and inadequate timing of preoperative antibiotic prophylaxis (OR 2.66, $P = 0.026$).

Subjective Clinical Assessment of Perfusion

When the operating surgeon was asked to rate the local perfusion of the anastomosis on a scale from 4 to 10, the median score of the leakage group was 8 compared to a 9 for patients without CAL. The occurrence of CAL was significantly higher in patients rated with an ≤ 7 or lower ($P < 0.001$) (Fig. 2).

Relation Between Numbers of Risk Factors and Anastomotic Leakage

The median number of the abovementioned 7 potentially modifiable risk factors for leakage was 3 in the leakage group compared to 2 in the nonleakage group ($P < 0.001$). In patients without any risk factors, the incidence of CAL was 2% versus 38% in patients with 6 risk factors present (Fig. 3).

DISCUSSION

This prospective multicenter study identified 7 perioperative potentially modifiable risk factors for CAL. Although no causal relationship has been demonstrated with this study, the patients in

TABLE 3. Surgery Related Factors and Risk for Anastomotic Leakage

Variable	Anastomotic Leakage (n = 132)	Missing	No Anastomotic Leakage (n = 1430)	Missing	*P* Value
Duration of surgery (min)	186 (32–385)	n = 4	153 (29–483)	n = 60	**0.000**
Surgical procedure					0.189
Subtotal colectomy	13 (9%)		127 (91%)		
Left hemicolectomy	16 (10%)		152 (90%)		
Right hemicolectomy	29 (5%)		497 (95%)		
Low anterior resection	37 (13%)		250 (87%)		
Sigmoid resection	30 (10%)		273 (90%)		
Transverse colon resection	1 (4%)		25 (96%)		
Rectum resection	4 (6%)		58 (94%)		
Reversal of Hartmann	2 (4%)		48 (96%)		
Surgical approach		n = 1		n = 15	**0.007**
Open	31 (23%)		209 (15%)		
Laparoscopy	90 (69%)		1132 (80%)		
Laparoscopy with conversion	10 (8%)		74 (5%)		0.223
Anastomotic location					**0.009**
Colon	91 (69%)		1123 (79%)		
Rectum	41 (31%)		307 (21%)		
Anastomotic configuration		n = 5		n = 40	**0.005**
End-to-end	35 (28%)		276 (20%)		
End-to-side	11 (7%)		94 (7%)		
Side-to-end	37 (30%)		304 (22%)		
Side-to-side	44 (35%)		716 (51%)		
Suture reinforcement	42 (32%)	n = 2	547 (40%)	n = 49	0.163
Anastomotic technique		n = 11		n = 123	0.189
Hand sewn	20 (17%)		272 (21%)		
Stapled	100 (82%)		997 (76%)		
Hand sewn and stapled	1 (1%)		38 (3%)		
Stoma type					0.082
Ileostomy	15 (94%)		103 (89%)		
Colostomy	1 (6%)		13 (11%)		
Goal directed therapy	29 (22%)	n = 1	277 (20%)	n = 40	0.307
Urine production in 1 h (mL)	95 (0–1180)		97 (0 – 1280)		0.395
Seniority of surgeon					0.189
Consultant surgeon	114 (86%)		1186 (82%)		
Fellow/register	18 (14%)		244 (17%)		
Fit to perform	119 (100%)	n = 13	1347 (99%)	n = 81	0.844

Data are presented as number (%) or as medians (range) for categorical and continuous variables, respectively. n is number of inclusions if due to missing data this deviates from total. Intraoperative events include: hypoxic events, hypertension, hypercarbia, bradycardia, hypotension, embolism, reanimation, more extensive resection than planned, serosa lesions, bladder and ureteral injuries, intraoperative bleeding, splenectomy or bleeding). A $P < 0.05$ was considered statistically significant.

Bold numbers are statistically significant.

whom none of these risk factors were present (11% of our study population) had a remarkable low leakage rate of 2% versus 38% in patients with 6 risk factors present. Therefore, we do hypothesize that an integrated approach by both the surgical and anesthesiological teams to optimize the patient's perioperative condition might possibly lead to a decrease of CAL.

The present study showed an overall CAL rate of 8.5% (colon 7.5% vs. rectum 12%), a mortality rate of patients with CAL of 5.6% and a significantly longer length of hospital stay of 14 days in the leakage group. This is in concordance with the existing evidence of the leakage rates reported in previous studies and the Dutch national colorectal audit.[9,11,13,20]

With a prevalence of 6% in our overall study population, a low preoperative hemoglobin was the single most important contributor to CAL (OR 5.4, $P < 0.001$). This underlines the importance to optimize hemoglobin concentration as early as possible in the preoperative period. In order to achieve normohemoglobinemia in clinical practice, a multidisciplinary efficient approach is needed for early detection and treatment of anemia.[21–23] Preoperative suboptimal haemoglobin levels are mostly correctable in the preoperative phase and recent studies have shown that intravenous iron therapy increases hemoglobin level in case of iron deficiency anemia. Two major randomized controlled trials (RCT) in progress analyzing perioperative morbidity and mortality after active management of preoperative anemia should provide the answer whether this increase in hemoglobin level actually correlates with a reduction in complications.[24–26]

Perioperative hyperglycemia is clinically highly relevant since it was seen in 73% of our study population, that, interestingly enough, consisted of only 19% of patients with diabetes. Ziegler et al in 2012 suggested similar results concerning hyperglycemia.[27] Previously, a large cohort study also suggested that among nondiabetic patients, those with perioperative hyperglycemia have an increased risk of complications.[28] Whether perioperative hyperglycemia is caused by (undiagnosed) diabetes or surgical metabolic stress remains unclear.[29] However, except for protocols of cardiovascular surgery trials, strict intraoperative glycemic control regimens in surgical care are lacking. Although the present study does not show that optimization of glucose levels decreases the incidence of CAL, at the very least this parameter can be used for the prediction of the risk of a CAL. Next to this preoperative plasma concentrations of glycosylated hemoglobin (Hb)A1c could be used to identify

TABLE 4. Distribution of Modifiable LekCheck Factors and Logistic Regression Analyses for Colorectal Anastomotic Leakage

		Univariate Analysis*		Multivariate Analysis†	
Variable	**No. (%)**	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**
Temperature					
≥ 36 °	1229 (80%)	1		1	
< 36 °	306 (20%)	1.78 (1.16–2.74)	**0.008**	1.39 (0.85–2.29)	0.186
Glucose (mg/dL)					
≤ 109.8	39 (27%)	1		1	
> 109.8	1082 (73%)	2.79 (1.53–5.07)	**<0.001**	2.8 (1.44–5.58)	**0.003**
Antibiotics prophylaxes					
15–60 min	1102 (73%)	1		1	
< 15 or > 60 min	399 (27%)	2.08 (1.40–3.10)	**<0.001**	1.62 (1.03–2.55)	**0.037**
Administration of vasopressors					
No	928 (62%)	1		1	
Yes	579 (38%)	1.93 (1.30–2.87)	**<0.001**	1.8 (1.13–2.73)	**0.012**
Hemoglobin (g/dL)					
Male ≥ 10.5, female ≥ 9.7	1366 (94%)	1		1	
Male < 10.5, female < 9.7	92 (6%)	4.80 (2.80–8.23)	**<0.001**	5.4 (2.94–9.95)	**<0.001**
Blood loss (mL)					
≤ 100	1058 (69%)	1			
> 100	484 (31%)	1.06 (0.71–1.58)	0.753		
Blood transfusion					
No	1527 (98%)	1			
Yes	35 (2%)	1.44 (0.23–2.78)	0.745		
Oxygen saturation					
≥ 95%	1441 (94%)	1			
< 95%	86 (6%)	1.24 (0.59–2.59)	0.558		
Mean arterial pressure (mm Hg)					
≥ 60	1496 (98%)	1			
< 60	32 (2%)	0.92 (0.21- 3.94)	0.800		
Fluid administration (mL/h)					
≤ 1000	936 (76%)	1		1	
> 1000	303 (24%)	0.56 (0.33–0.96)	0.037	0.65 (0.34–1.24)	0.191
Fecal contamination					
No	1407 (94%)	1		1	
Yes	89 (6%)	4.04 (2.31–67.04)	**<0.001**	2.98 (1.55–5.75)	**<0.001**
Epidural analgesia					
No	1011 (67%)	1		1	
Yes	487 (33%)	2.31 (1.56–3.40)	**<0.001**	1.81 (1.15–2.84)	**0.010**
Duration of surgery (h)					
≤ 3	1052 (70%)	1		1	
> 3	446 (30%)	2.19 (1.48–3.24)	**0.000**	1.86 (1.18–2.95)	**0.007**
Intraoperative event*					
No	1344 (86%)	1		1	
Yes	218 (14%)	1.94 (1.23–3.05)	**0.004**	1.15 (0.66–1.99)	0.622

*Adjusted for: sex, American Society of Anesthesia score (ASA) ≥ 3, diabetes, pack years ≥ 15, distance of tumor from anal verge <15 cm, and anastomotic location.
†Adjusted for: sex, American Society of Anesthesia score (ASA) ≥ 3, diabetes, pack years ≥ 15, distance of tumor from anal verge <15 cm, anastomotic location and configuration, stoma type and surgical approach.
Bold values have been found statistically significant ($P < 0.05$).

patients at higher risk of deprived glycaemic control resulting in increased rates of postoperative complications.[30]

Contamination of the operative field was an independent risk factor for CAL, which is in accordance with previous studies that show its role in surgical site infections.[31] Although prevention of contamination is not always possible, intraoperative awareness could lead to significant decrease of its presence. Other means to reduce contamination might be the debated perioperative selective decontamination (SDD) of the digestive tract. A meta-analysis by Roos et al[31] reported a significantly lower incidence of CAL in patients who received prophylactic SDD (3.3%) versus the control group (7.4%). On the other hand, a recently published study showed no effect of SDD on the CAL rate.[32]

Confirming the extensive amount of evidence on its influence on infectious complications, inadequate preoperative (<15 min or >60 min prior to surgery) antimicrobial therapy was also found to be a significant contributing factor to CAL.[33,34] The finding that such variety in timing of administration exists, accentuates that adherence to protocols is often challenging in daily practice.

Administration of vasopressors during surgery also showed to be an independent risk factor for CAL. This might be caused by vasoconstriction and ischemic effects of the vasopressor drugs at the anastomotic site.[35] Despite frequent perioperative use of these drugs, the exact role of vasopressors on the anastomotic healing process is not well studied in the literature. Interestingly, our results revealed that intraoperative mean arterial pressure rates did not differ significantly between patients with and without CAL. In line with this are the results found in a large study by Babazade et al, showing no clinical effect of intraoperative hypotension on the risk of infection after colorectal surgery.[36] However, in that study as in ours, the mean

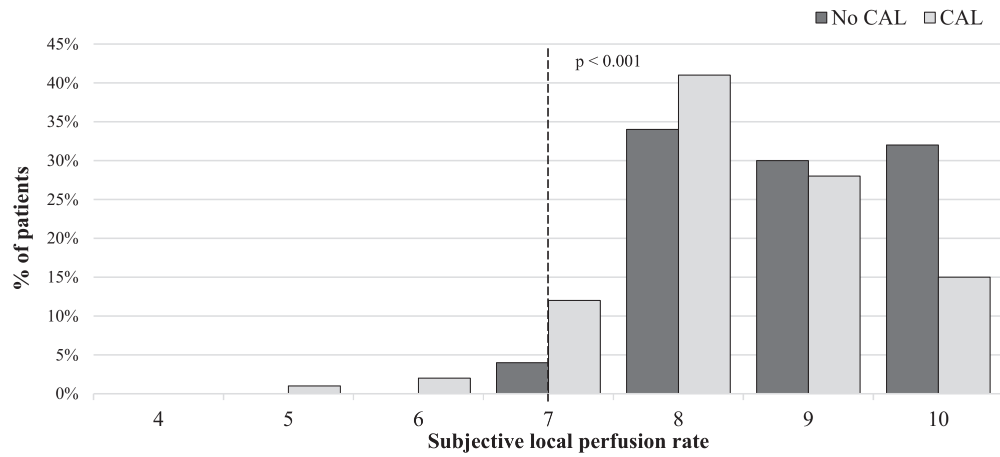

FIGURE 2. Differences in subjective local perfusion rates given by surgeons between patients without colorectal anastomotic leakage (CAL) (Dark colored bars, n = 1366) versus patients with CAL (Light colored bars, n = 125).

arterial pressure rate was only collected intraoperatively, which does not allow us to draw conclusion of its effect in case of prolonged hypotension.

In the present study, patients who received intraoperative epidural analgesia were at almost a 2-fold higher risk of developing a CAL. When analyzing open resections separately, 18% of the patients receiving intraoperative epidural analgesia developed CAL compared to 8% of the patients receiving other forms of analgesia ($P = 0.015$). In laparoscopic surgery, this difference was not seen (10% vs. 8%, $P = 0.378$). Existing evidence about the effect of epidural analgesia on CAL is controversial.[17] Sympathetic activity and intestinal perfusion are important issues in this, however poorly understood.[37] A meta-analysis in 2001 did not show an impaired or increased risk on CAL.[38] The use of epidural analgesia remains equivocal and future research should focus on this topic to draw more valid conclusions.

As also reported in previous studies, nonmodifiable perioperative factors such as male gender,[7,12] ASA greater than 2,[11] a history of smoking,[39] shorter distance of the tumor to anal verge[9,12] and open surgery[5] were all significantly related to a higher CAL rate in our study. Contradictory to other studies, a significant association between current smoking and anastomotic leakage was not found.[3] Smoking, and several other preoperative factors that were not analyzed in the current study (eg, malnutrition, physical performance, psychological coping), enable preoperative risk prediction and are valuable in targeted multimodal prehabilitation programs.[40] Prehabilitation should play a crucial role in future research focussing on optimization of suboptimal perioperative conditions. The LekCheck should not be inseparable from but rather be in accordance with preoperative optimization initiatives.

Several limitations of the current study are worth mentioning. The risk factors were collected by means of a 1-off intraoperative

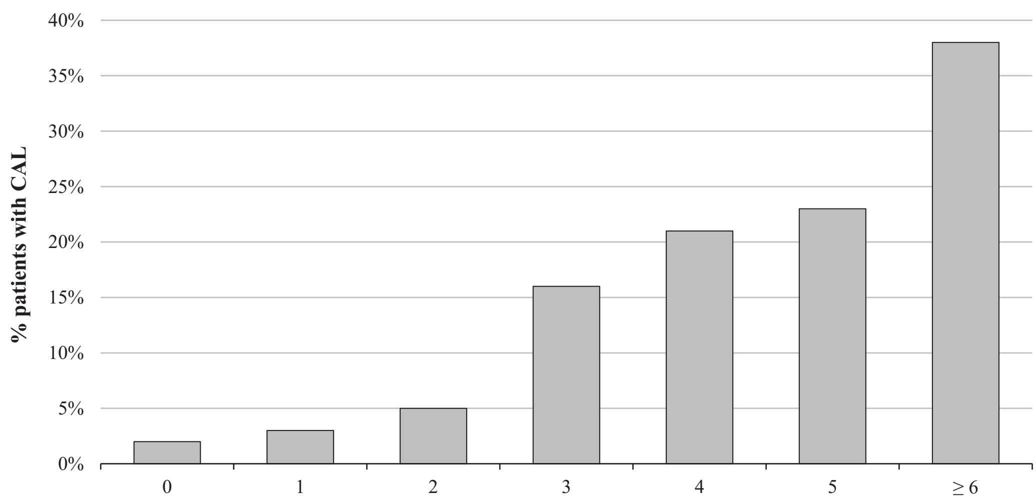

FIGURE 3. Percentage of patients with colorectal anastomotic leakage (CAL) related to the amount of perioperative potentially modifiable risk factors (low preoperative hemoglobin, contamination of the operative field, hyperglycemia, duration of surgery of more than 3 h, administration of vasopressors, inadequate timing of preoperative antibiotic prophylaxis, and application of epidural analgesia).

checklist. Since this is a snapshot of the actual situation at the time of the anastomosis, we do not have the data on the duration of the parameters collected such as the duration of vasopressor use or the duration of hypotension before its correction. Next to this, we are unaware of whether efforts were taken to optimize items prior or after the LekCheck during the final stage of the study when the operative teams became more aware of the risk factors scored. Checklists have a potentially beneficial effect on the measured outcome, due to the debated Hawthorne-effect. Inclusion numbers per hospital were too small to relate an observed reduction of present LekCheck factors to an actual decrease in CAL. Finally, it is important to point out that there is much debate about the definition of CAL since around the globe there is no generally accepted definition. We used Reisinger's definition,[19] although we know that this definition is quite strict and therefore we may have missed some anastomotic leaks in our analysis.

CONCLUSION

This study revealed 7 potentially modifiable intraoperative risk factors for CAL. This study shows that during optimal intraoperative conditions the incidence of CAL is very low. The LekCheck is a useful warning tool to identify suboptimal intraoperative conditions during colorectal surgeries. Future research should focus on modifying these suboptimal conditions by collaboration between the anesthesiologist and the surgeon. This is the subject of an ongoing multicenter study.

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