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

Daitlin E. Huisman, MD, Muriël Readink, MD, van Rooijen, MD, PhD; Boukje T. Bootsma, MD; Tim van de Brug, PhD; Jurres Stens, MD; Wim Bleeker, MD
Laurents P. S. Stassen, MD, PhD; Audrey Jongen, MD, PhD; Carlo V. Feo, MD, FACS; Simone Targa, MD; Niels Komen, MD, PhD; Hidde M. Kroon, MD, PhD
Tarik Sammour, MBCHB, PhD, FRACS; Emmanuel A. G. L. Lagaee, MD; Aaltbert K. Talsma, MD
Johannes A. Wegdam, MD; Tammo S. de Vries Reilingh, MD; Bob van Wely, MD
Marie J. van Hoogstraten, MD; Dirk J. A. Sonneveld, MD; Sanne C. Veltkamp, MD
Emiel G. G. Verdaasdonk, MD, PhD; Rudi M. H. Roumen, MD
Gerrit D. Slooter, MD, PhD; and Freek Daams, MD

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

Summary Background Data: Anastomotic colorectal 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 general condition 2 local perfusion and oxygenation, contamination, and surgery related factors. Univariate and multivariate logistic regression analysis was performed to identify potentially modifiable perioperative 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 5.60, P = 0.001), 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

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). In addition, several preoperative, intraoperative, and postoperative risk factors for CAL have been identified. Despite these advances, CAL remains a severe complication following surgery with a reported incidence ranging from 3 to 19% critically examined the manuscript, provided suggestions for improvement and contributed to new insights: “Wim Bleeker, Laurens P.S. Stassen, Audrey Jongen, Carlo V. Feo, Simone Targa, Niels Komen, Hidde M. Kroon, Tarik S, Emmanuel A.G.L. Lagaee, Aaltbert K. Talsma, Johannes A. Wegdam, Tammo S. de Vries Reilingh, Bob van Wely, Marie J. van Hoogstraten. Dirk J.A. Sonneveld, Sanne C. Veltkamp, Emiel G.G. Verdaasdonk, Rudi M.H. Roumen, Gerrit D. Slooter, Freek Daams.”

All authors above have given final approval or the version to be published. The authors report no conflicts of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal’s Web site (www.annalsofsurgery.com).

This is an open access article distributed under the terms of the Creative Commons Attribution-No Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Copyright © 2020 The Author(s). Published by Wolters Kluwer Health, Inc.

Annals of Surgery • Volume 275, Number 1, January 2022
www.annalsofsurgery.com | e189
worldwide.\textsuperscript{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.\textsuperscript{4–9} 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.\textsuperscript{1,10–13} Also, intra-operative factors, such as operative time, and blood loss, are associated with higher leakage rates.\textsuperscript{1,5} 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.\textsuperscript{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 malignant or benign indications were included. A multifactorial intraoperative 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 (Acknowledgments). 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,\textsuperscript{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.

| Variable          | Cut-off Values |
|-------------------|----------------|
| Temperature       | <36°C          |
| 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.\textsuperscript{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).\textsuperscript{16} LekCheck values were dichotomized in order to create a composite score. Temperature below 36 degrees Celsius was considered 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 considered 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, embo- lism, reanimation, more extensive resection than planned, serosa lesions, bladder and ureteral injuries, intraoperative bleeding, sple-nectomy 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.”\textsuperscript{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...
Patients who underwent colorectal resection with primary anastomosis for malignant or benign disease  
\[n = 1821\]

Excluded  \[n = 259\]
- Emergency surgery (\(n = 180\))
- < 90% LEK CHECK items (\(n = 79\))

Patients with complete LEK CHECKS and included for univariate analysis  
\[n = 1,562\]

Excluded  \[n = 244\]
- Missing factors in the multivariate analysis.

1,319 patients included for multivariate analysis

**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 \(\chi^2\) 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 (\(P \leq 0.10\)) 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 \(\geq 3\) (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, and 50 (3%) 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 instal-ling 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 |
|---------------------------------|-------------------------------|-----------------------------------|---------|
| Sex (male)                      | 81 (62%)                      | 718 (50%)                         | 0.009   |
| Age (yrs)                       |                               |                                   |         |
| < 70                            | 71 (21–91)                    | 68 (23–95)                        | 0.162   |
| ≥ 70                            | 64 (48%)                      | 759 (53%)                         |         |
| Body mass index ≥ 30 kg/m²      | 27 (20%)                      | 241 (17%)                         | 0.212   |
| ASA classification              |                               |                                   |         |
| < 3                             | 87 (66%)                      | 1075 (76%)                        | 0.009   |
| ≥ 3                             | 45 (34%)                      | 343 (24%)                         |         |
| Diabetes mellitus               | 29 (22%)                      | 204 (14%)                         | 0.017   |
| Intoxications                   |                               |                                   |         |
| Current smoker                  | 18 (14%)                      | n = 5                             | 0.326   |
| Pack years ≥ 15 yrs             | 40 (31%)                      | n = 4                             | 0.011   |
| Alcohol intake ≥ 3 units/d      | 14 (10%)                      | n = 4                             | 0.244   |
| Steroid use (excl. inhalers)    | 4 (3%)                        | 36 (3%)                           | 0.449   |
| Disease                         |                               |                                   |         |
| Malignant                       | 113 (85%)                     | 1163 (82%)                        |         |
| Benign                          | 19 (15%)                      | 261 (18%)                         |         |
| Diagnosed by screening program  | 48 (42%)                      | n = 18                            | 0.361   |
| Neoadjuvant therapy             | n = 3                         | 476 (39%)                         | 0.195   |
| None                            |                                |                                   |         |
| 5 × 5 radiotherapy              | 10 (8%)                       | 92 (7%)                           |         |
| Chemotherapy                    | 3 (2%)                        | 30 (2%)                           |         |
| Cherenbroatherapy               | 5 (4%)                        | 42 (3%)                           |         |
| Distance of tumor from AV <15 cm| 37 (29%)                      | n = 6                             | 0.005   |
| Pathological TNM stage          | n = 21                        | 267 (19%)                         | 0.158   |
| I (T1–2N0M0)                    | 52 (47%)                      | 407 (36%)                         |         |
| II (T3–4N0M0)                   | 23 (18%)                      | 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 2.65, 95% CI 1.13–2.37, 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) | No Anastomotic Leakage (n = 1430) | 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 hemicolecotomy               | 16 (10%)                      | 152 (90%)                         |         |
| Right hemicolecotomy              | 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                 |                               |                                   | 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         |                               |                                   | 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%)                      | 547 (40%)                         | 0.163   |
| Anastomotic technique             |                               |                                   | 0.189   |
| Hand sewn                         | 20 (17%)                      | 272 (21%)                         |         |
| Stapled                           | 100 (82%)                     | 997 (76%)                         |         |
| Hand sewn and stapled             | 1 (1%)                        | 38 (3%)                           | 0.082   |
| Stoma type                        |                               |                                   |         |
| Ileostomy                         | 15 (94%)                      | 103 (89%)                         |         |
| Colostomy                         | 1 (6%)                        | 13 (11%)                          |         |
| Goal directed therapy            | 29 (22%)                      | 277 (20%)                         | 0.307   |
| Urine production in 1 h (mL)      | 95 (0–1180) n = 1             | 97 (0 – 1280) n = 40              | 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%)                        | 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.
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 al31 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

| Variable                        | Univariate Analysis | Multivariate Analysis |
|---------------------------------|---------------------|-----------------------|
|                                 | OR (95% CI)         | P Value               |
|                                 | OR (95% CI)         | P Value               |
| Temperature                     |                     |                       |
| ≥ 36 °C                         | 1                   | 1                     |
| < 36 °C                         | 1.78 (1.16–2.74)    | 0.008                 |
| Glucose (mg/dL)                 |                     |                       |
| ≤ 109.8                         | 1                   | 1                     |
| > 109.8                         | 2.79 (1.53–5.07)    | <0.001                |
| Antibiotics prophylaxes         |                     |                       |
| 15–60 min                       | 1                   | 1                     |
| < 15 or > 60 min                | 2.08 (1.40–3.10)    | <0.001                |
| Administration of vasopressors  |                     |                       |
| No                              | 1                   | 1                     |
| Yes                             | 1.93 (1.30–2.87)    | <0.001                |
| Hemoglobin (g/dL)               |                     |                       |
| Male ≥ 10.5, female ≥ 9.7       | 1                   | 1                     |
| Male < 10.5, female < 9.7       | 4.80 (2.80–8.23)    | <0.001                |
| Blood loss (mL)                 |                     |                       |
| ≤ 100                           | 1                   | 1                     |
| > 100                           | 1.06 (0.71–1.58)    | 0.753                 |
| Blood transfusion               |                     |                       |
| No                              | 1                   | 1                     |
| Yes                             | 1.44 (0.23–2.78)    | 0.745                 |
| Oxygen saturation               |                     |                       |
| ≥ 95%                           | 1                   | 1                     |
| < 95%                           | 1.24 (0.59–2.59)    | 0.558                 |
| Mean arterial pressure (mm Hg)  |                     |                       |
| ≥ 60                            | 1                   | 1                     |
| < 60                            | 0.92 (0.21–3.94)    | 0.800                 |
| Fluid administration (mL/h)     |                     |                       |
| ≤ 1000                          | 1                   | 1                     |
| > 1000                          | 0.56 (0.33–0.96)    | 0.037                 |
| Fecal contamination             |                     |                       |
| No                              | 1                   | 1                     |
| Yes                             | 4.04 (2.31–67.04)   | <0.001                |
| Epidural analgesia              |                     |                       |
| No                              | 1                   | 1                     |
| Yes                             | 2.31 (1.56–3.40)    | <0.001                |
| Duration of surgery (h)         |                     |                       |
| ≤ 3                             | 1                   | 1                     |
| > 3                             | 2.19 (1.48–3.24)    | 0.000                 |
| Intraoperative event            |                     |                       |
| No                              | 1                   | 1                     |
| Yes                             | 1.94 (1.23–3.05)    | 0.004                 |

1Adjusted for: sex, American Society of Anesthesia score (ASA) ≥ 3, diabetes, pack years ≥ 15, distance of tumor from anal verge <15 cm, and anastomotic location.

2Adjusted 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).
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. Sympathetic activity and intestinal perfusion are important issues in this, however poorly understood. A meta-analysis in 2001 did not show an impaired or increased risk on CAL. 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, ASA greater than 2, a history of smoking, shorter distance of the tumor to anal verge and open surgery 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. 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. 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
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 become 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, 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.

ACKNOWLEDGMENTS

This research project was supported by the Taskforce Anastomotic Leakage, the Netherlands. The taskforce made contributions to the conception and design of the project. The members are as follows: M. Aren, MD, PhD, W.A. Benneman, Prof Dr, MD, PhD, W. Bleeker, MD, H.D. de Boer, MD, PhD, G.S.A. Boersena, MD, PhD, B.T. Bootma BSc, W.A. Borstlap, MD, PhD, J.W.A. Bosmans, MD, PhD, N. Bouvy, Prof Dr, MD, PhD, F.J.C. van den Broek, MD, PhD, W.J.A. Broekelman, M. Daams, MD, PhD, J.W. Dekker, MD, PhD, M. den Dulk, MD, PhD, I.F. Faneyte, MD, PhD, H. van Goor, Prof Dr, MD, PhD, M.J.P.M. Goaert, MD, PhD, F. van de Graaf, MD, W.M.U. van Grevenstein, MD, PhD, K. Havenga, MD, PhD, B. van den Hevel, MD, PhD, D.E. Huisman, MSc, PhD candidate, A. Jongen, MD, A.G., R.E. Klahbers, MD, PhD, N. Komen, MD, PhD, H.M. Kron, MD, PhD, J.F. Lange, Prof Dr, MD, PhD, E.A.G.L. Luque, MD, T. Lubbers, MD, PhD, A.J.G. Maaskant-Braat, MD, PhD, J. Melenhorst, MD, PhD, Menon, MD, C. Molenaar, PhD candidate, L. de Nee, MD, PhD, K. Peeters, MD, PhD, V.D. Plat, MSc, PhD candidate, M. Readink, PhD candidate, S.J. van Rootvijt, MD, PhD, R.M.H. Roumen, MD, PhD, J. Schoonderoord, MD, B. Smeets, MD, PhD, G.D. Slooter, MD, PhD, D.J.A. Sonneveld, MD, C.L., M. Sosef, MD, PhD, R. Sparreboom, MD, PhD candidate, E.J. Spillenaar Bilgen, MD, A.K. Talma, MD, S.C. Velkamp, MD, J.A. Wegdam, MD, B. van Wely, MD, S. Yauw, MD, PhD.

REFERENCES

1. Sciuto A, Merola G, De Palma GD, et al. Predictive factors for anastomotic leakage after laparoscopic colorectal surgery. World J Gastroenterol. 2016;22:2247–2250.
2. Daams F, Luyer M, Lange JF. Colorectal anastomotic leakage: aspects of prevention, detection and treatment. World J Gastroenterol. 2013;19:2293–2297.
3. McDermott FD, Heeney A, Kelly ME, et al. Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks. Br J Surg. 2015;102:462–479.
4. Pomergaard HC, Gessler B, Burchardt J, et al. Preoperative risk factors for anastomotic leakage after resection for colorectal cancer: a systematic review and meta-analysis. Colorectal Dis. 2014;16:662–671.
5. Telem DA, Chiu EH, Nguyen SQ, et al. Risk factors for anastomotic leak following colorectal surgery: a case-control study. Arch Surg. 2010;145:37–46.
6. Mirnezami A, Mirnezami R, Chandrakumaran K, et al. Increased local recurrence and reduced survival from colorectal cancer following anastomotic leak: systematic review and meta-analysis. Ann Surg. 2011;253:809–899.
7. Walker KG, Bell SW, Rickard MJ, et al. Anastomotic leakage is predictive of diminished survival after potentially curative resection for colorectal cancer. Ann Surg. 2004;240:255–259.
8. McArdle CS, McMillan DC, Hole DJ. Impact of anastomotic leakage on long-term survival of patients undergoing curative resection for colorectal cancer. Br J Surg. 2005;92:1150–1154.
9. Boccia MA, Buettner PG, Rozen WM, et al. Risk factors and outcomes for anastomotic leakage in colorectal surgery: a single-institution analysis of 1576 patients. World J Surg. 2011;35:186–195.
10. Mileski WJ, Joehr R, Rege RV, et al. Treatment of anastomotic leakage following low anterior colon resection. Arch Surg. 1988;123:968–971.
11. Bakker IS, Grossmann I, Henneman D, et al. Risk factors for anastomotic leakage and leak-related mortality after colonic cancer surgery in a nationwide audit. Br J Surg. 2014;101:42–32.
12. Park JS, Choi GS, Kim SH, et al. Multicenter analysis of risk factors for anastomotic leakage after laparoscopic colorectal cancer excision: the Korean laparoscopic colorectal surgery study group. Ann Surg. 2013;257:665–671.
13. Dekker JW, Liefers GJ, de Moel van Otterloo JC, et al. Predicting the risk of anastomotic leakage in left-sided colorectal surgery using a colon leakage score. J Surg Res. 2011;166:27.
14. Kawada K, Hasegawa S, Hida K, et al. Risk factors for anastomotic leakage after laparoscopic low anterior resection with DST anastomosis. Surg Endosc. 2014;28:2988–2999.
15. Fowler AJ. A review of recent advances in perioperative patient safety. Ann Med Surg (Lond). 2013;2:10–14.
16. van Rooijen SJ, Huisman D, Stuijvenberg M, et al. Intraoperative modifiable risk factors of colorectal anastomotic leakage: why surgeons and anesthesiologists should act together. Int J Surg. 2016;36(Pt A):183–200.
17. Bardram L, Funch-Jensen P, Jensen P, et al. Recovery after laparoscopic colonic surgery with epidural analgesia, and early oral nutrition and mobilisation. Lancet. 1995;345:763–764.
18. Edge SB, Compton CC. The American joint committee on cancer; the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol. 2010;17:1471–1474.
19. Reisinger KW, Poeze M, Hulswede KW, et al. Accurate prediction of anastomotic leakage after colorectal surgery using plasma markers for intestinal damage and inflammation. J Am Coll Surg. 2014;219:744–751.
20. Van Leersum NJ, Snijders HS, Henneman D, et al. The Dutch Surgical Colorectal Audit. Eur J Surg Oncol. 2013;39:1063–1070.
21. Mynster T, Nielsen HJ. The impact of storage time of transfused blood on perioperative outcomes. Transfusion. 2013;53:10–18.
22. Monstyr T, Nielsen HI. The impact of storage time of transfused blood on postoperative infectious complications in colorectal cancer surgery. Scan J Gastroenterol. 2006;35:212–217.
23. Lee MR, Hong CW, Yoon SN, et al. Risk factors for anastomotic leakage after resection for rectal cancer. Hepatogastroenterology. 2006;53:682–686.
24. Moran M, Ozmen MM, Durzan AP, et al. The effect of erythropoietin on healing of obstructive vs nonobstructive left colonic anastomosis: an experimental study. World J Emerg Surg. 2007;2:13.
25. Munoz M, Acheson AG, Auerbach M, et al. Randomized controlled trial comparing ferric(III)carboxymaltose infusion with oral iron supplementation in the treatment of preoperative anemia in colorectal cancer patients. BMC Surg. 2015;15:7–6.
26. Munting KE, Klein AA. Optimisation of pre-operative anemia in patients before elective major surgery: why, when, and how? Anaesthesia. 2019;74(suppl 1):49–57.
27. Ziegler MA, Catto JA, Riggs TW, et al. Risk factors for anastomotic leak and mortality in diabetic patients undergoing colectomy: Analysis from a state-wide surgical quality collaborative. Arch Surg. 2012;147:600–605.
28. Kotagal M, Symons RG, Hirsch IB, et al. Perioperative hyperglycemia and risk of adverse events among patients with and without diabetes. Ann Surg. 2015;261:97–103.

© 2020 The Author(s). Published by Wolters Kluwer Health, Inc.
29. Levy N, Dhatariya K. Pre-operative optimisation of the surgical patient with diagnosed and undiagnosed diabetes: A practical review. *Anaesthesia*. 2019;74(suppl 1):58–66.

30. Gustafsson UO, Thorell A, Soop M, et al. Haemoglobin A1c as a predictor of postoperative hyperglycemia and complications after major colorectal surgery. *Br J Surg*. 2009;96:1358–1364.

31. Roos D, Dijksman LM, Tijssen JG, et al. Systematic review of perioperative selective decontamination of the digestive tract in elective gastrointestinal surgery. *Br J Surg*. 2013;100:1579–1588.

32. Abis GSA, Stockmann HBAC, Bonjer HJ, et al. Randomized clinical trial of selective decontamination of the digestive tract in elective colorectal cancer surgery (SELECT trial). *Br J Surg*. 2019;106:355–363.

33. Abis GS, Stockmann HB, van Egmond M, et al. Selective decontamination of the digestive tract in gastrointestinal surgery: Useful in infection prevention? A systematic review. *J Gastrointest Surg*. 2013;17:2172–2178.

34. Kiran RP, Murray AC, Chiuazan C, et al. Combined preoperative mechanical bowel preparation with oral antibiotics significantly reduces surgical site infection, anastomotic leak, and ileus after colorectal surgery. *Ann Surg*. 2015;262:41–45.

35. Zakrison T, Nascimento BA Jr, Tremblay LN, et al. Perioperative vasopressors are associated with an increased risk of gastrointestinal anastomotic leakage. *World J Surg*. 2007;31:1627–1634.

36. Babazade R, Yilmaz HO, Zimmerman NM, et al. Association between intraoperative low blood pressure and development of surgical site infection after colorectal surgery: A retrospective cohort study. *Ann Surg*. 2016;266:1058–1064.

37. Freise H, Van Aken HK, et al. Risks and benefits of thoracic epidural anaesthesia. *Br J Anaesth*. 2011;107:859–868.

38. Holte K, Kehlet H. Epidural anaesthesia and analgesia: effects on surgical stress responses and implications for postoperative nutrition. *Clin Nutr*. 2002;21:199–206.

39. Kim MJ, Shin R, Oh HK, et al. The impact of heavy smoking on anastomotic leakage and stricture after low anterior resection in rectal cancer patients. *World J Surg*. 2011;35:2806–2810.

40. van Rooijen S, Carli F, Dalton S, et al. Multimodal prehabilitation in colorectal cancer patients to improve functional capacity and reduce postoperative complications: the first international randomized controlled trial for multimodal prehabilitation. *BMC Cancer*. 2019;19:98.