STUDY PROTOCOL | CONFIDENTIAL FILE

DoubleCheck

Enhanced perioperative care for improving outcomes after colorectal resection by implementation of best practice for the prevention of anastomotic leakage: protocol for a multicenter open-label trial with historical controls

Principal Investigator Ferrara, Italy
Prof. C. Feo
Department of Surgery, Ospedale del Delta, Lagosanto, Ferrara, Italy

Principal Investigator Amsterdam UMC, The Netherlands
Dr. F. Daams
Gastrointestinal surgeon, Department of Surgery, Amsterdam University Medical Centers, Location VUmc, Amsterdam, The Netherlands

Trial coordinator
Drs. B T Bootsma
PhD student, Department of Surgery, Amsterdam University Medical Centers, Location VUmc, Amsterdam, The Netherlands

Amsterdam UMC
Universitair Medische Centra

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Ferrara

Abstract

Background

Colorectal anastomotic leakage (CAL) remains a severe complication. Recent research has identified several modifiable perioperative CAL risk factors, suggesting that the intraoperative condition plays an important role in CAL development. Aim of this study is to successfully implement an enhanced perioperative care protocol, focusing on optimizing the intraoperative condition of the patient to minimalize exposure to CAL risk factors. Secondly, this study will investigate whether implementation of this new guideline results in a better intraoperative condition and a decreased CAL rate.

Methods

This study will be performed using an open-label multicenter design with historical cohort in nine participating hospitals. We aim to include 1600 adult patients that underwent a colorectal resection with creation of a primary anastomosis. The patients in the intervention group will be treated according to an enhanced perioperative care protocol focusing on optimizing the intraoperative condition of the patient and thereby minimalize exposure to 6 known modifiable independent intraoperative risk factors: anemia, hypothermia, epidural anesthesia, vasopressor drug administration, incorrect antibiotic prophylaxis and hyperglycemia. The control group consists of 1592 historical patients that were treated with standard perioperative practice. Compliance to the study protocol, the patient's intraoperative condition and exposure to modifiable intraoperative risk factors, 30-day CAL and other postoperative complications will be measured.

Discussion

The strength of this study is the combination of implementing an enhanced perioperative practice protocol in patients undergoing colorectal resection and the evaluation on the intraoperative condition and effect on CAL rate in actual practice.

Trial registration

Clinical Trials Registry: ClinicalTrials.gov NCT05250882

Background

Colorectal anastomotic leakage (CAL) remains a severe complication following surgery with a reported incidence of 3-19% worldwide. It often results in a decreased health related quality of life as leakage can result in re-operation with chance of a permanent stoma. Hospital costs are increased by a prolonged stay, admission to the intensive care unit and reinterventions. CAL after colon or rectal cancer surgery also adversely impacts oncological prognosis as various studies have shown CAL to be associated with an increased risk of local recurrence and poor cancer-specific survival(1-3).

CAL risk factor investigation has been the focus of many studies. Several patient-related risk factors have been identified such as age, body mass index, comorbidity and smoking(4, 5). These factors are mostly static and not modifiable. Recently published research however has shown risk factors that are modifiable(6, 7). A large, multicenter, observational study including 1592 patients that underwent colorectal surgery identified several modifiable CAL risk factors: preoperative anemia, intraoperative hypothermia, intraoperative hyperglycemia, intraoperative use of vasopressor drugs, epidural analgesia, incorrect or lack of antibiotic prophylaxis, intraoperative fecal contamination and duration of surgery. Most interesting, when none of these risk factors were present, the CAL rate was significantly lower(6).

Adequate perioperative management appears to be important for improving outcomes of patients undergoing colorectal resection. It is of great importance to set strict perioperative goals and to optimize the intraoperative status of the patient. However, up to now, this is not a part of the standard care and no protocols exists. Aim of this proposed open-label multicenter trial, the Double Checks study, is to educate clinicians in this topic by implementing a best practice protocol to optimize the intraoperative condition and minimalize the exposure to the abovementioned modifiable risk factors of CAL. Secondly, the study will investigate whether implementation of this new enhanced perioperative care guideline results in a better intraoperative condition and a decreased CAL rate as compared to current practice.

Methods

The present study is a multicenter open-label clinical trial with historical controls. Nine medical centers in the Netherlands will participate in this study. The objective of this study is to successfully implement an enhanced perioperative care protocol in several hospitals and to evaluate the effect on the patient's intraoperative condition and the effect on colorectal anastomotic leakage rate.

Hypothesis

Our hypothesis in the study are as follows:

- The Double Check enhanced perioperative care bundle may successfully be implemented at the participating hospitals with a good acceptability
- The Double Check enhanced perioperative care bundle will improve the intraoperative condition of the patient compared to the intraoperative condition that measured while treating patients with standard care (the LekCheck study cohort)(6)
- The Double Check intervention bundle will have a decreasing effect on CAL compared to the historical standard care group (LekCheck study cohort)(6) and compared to registered CAL rates of the participating hospitals from 2018-2021.

Design

This new form of standard care will be implemented in Dutch hospitals that also participated in our previous study, the Lek Check study(6).

Primary and secondary outcomes

The primary outcome of the study is the intraoperative condition of the patient measured by exposure to the modifiable intraoperative CAL risk factors of interest in this study: anemia, hypothermia, hyperglycemia, use of vasopressor drugs and epidural anesthesia.

The secondary variables of interest are 30-day CAL and other postoperative morbidity, 30-day mortality, reintervention rate, duration of hospital stay, critical care admission and re-admission rate. CAL is defined as a grade B or C according to the ISREC classification(8).

Patient selection and methods

The intended population for this study consists of all consecutive patients undergoing colorectal surgery with creation of a primary anastomosis that are treated at the department of surgery of the hospitals participating in the study. The following inclusion and exclusion criteria will be used:

Inclusion criteria

- Age 18 and above
- Bowel (small intestine/colon/rectal) resection with creation of a primary anastomosis
- Ability to give informed consent

Exclusion criteria

- The need for emergency surgery
- Scheduled operation concerning a reoperation for complications from recent surgery (within 3 months after the initial procedure).
- The inability to read or understand informed consent material

Patients will be informed and provided with written information about the study in the outpatient clinic by the treating physician. Patients will be asked to participate in the study and need to give written informed consent, solely for the use of their medical information and medical files. The choice whether to participate or not in this study has no consequences for the care the patient will receive. A patient will be treated in the same way as all other patients, even if he/she decides not to participate in this study. Whether a patient receives care according to the current standard care or according to the new standard enhanced perioperative Double Check guideline depends on when the hospital will switch to the new standard care. This is independent of the patient's choice to participate in the study or not.

Investigational treatment

The Double Check enhanced perioperative care bundle exists out of interventions applicable without the introduction of new material to the operating room, on top of usual care. The Double Check interventions are listed in figure 1. The protocol is based on the results of our previous large, multicenter, international observational cohort study(6), systematic literature analyses, an inventory in current protocols on perioperative care and expert opinion. Consensus is reached with colorectal surgeons from all participating centers. The final protocol was reviewed critically by experts in the field of colorectal surgery before implementation. This quality improvement intervention does not include or investigate any new products or additional materials that are not already present and in use in the participating hospitals.

The purpose of the protocol is optimizing the intraoperative condition of the patient and thereby minimalize exposure to 6 known modifiable independent intraoperative risk factors: anemia, hypothermia, epidural anesthesia, vasopressor drug administration, incorrect antibiotic prophylaxis and hyperglycemia.

The following interventions are part of the Double Check enhanced perioperative care bundle:

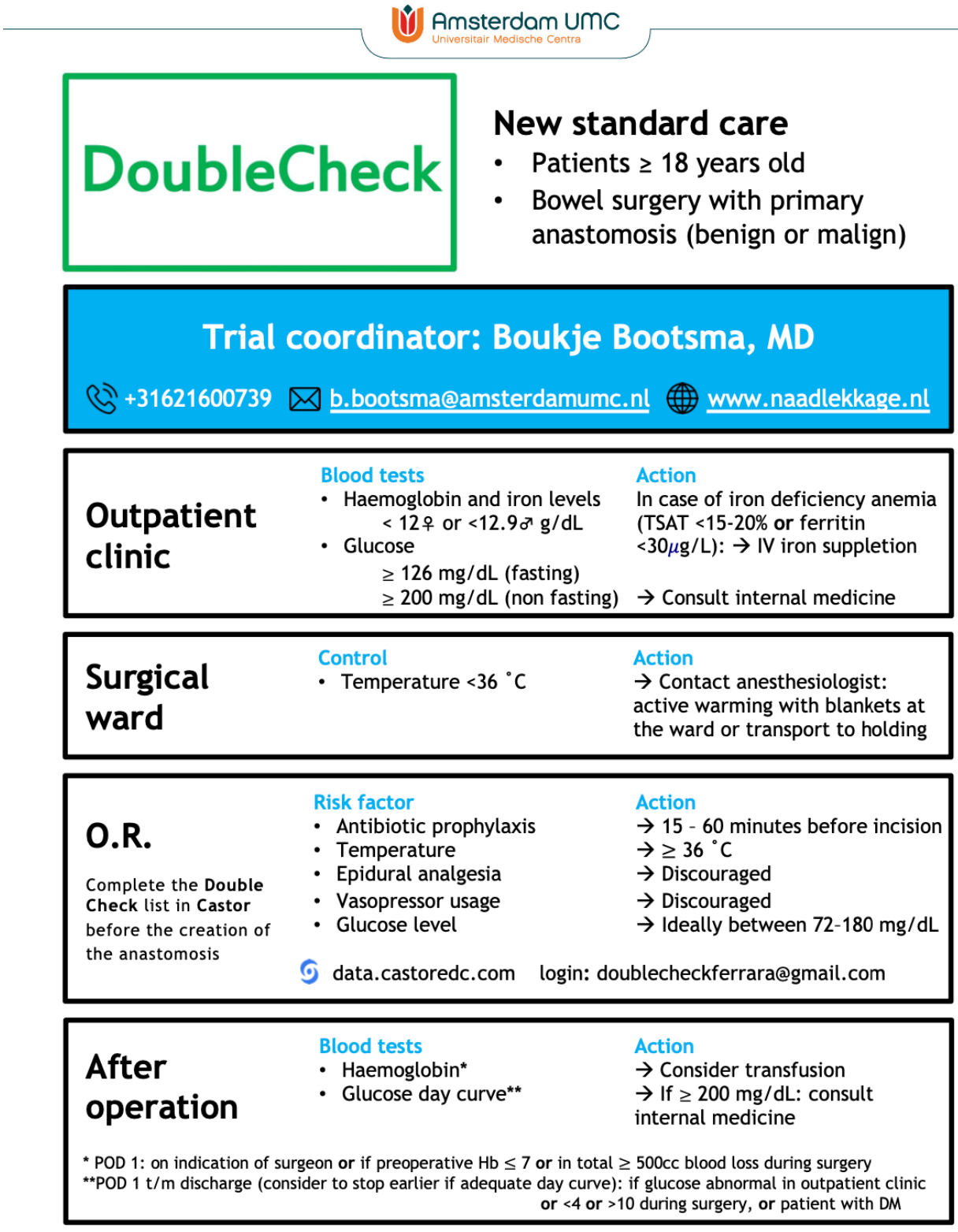
- *Treatment of preoperative anemia*: patients with a proven iron deficiency anemia (hemoglobin level <7.5 mmol/L for women and <8.0 mmol/L for men [< 12♀ or <12.9♂ g/dL] and TSAT <15-20% or ferritin <30μg/L) will receive intravenous iron infusion in the weeks prior to the operation. The dosage is adjusted for the patient's weight and hemoglobin level. Hemoglobin levels will be remeasured after iron infusion therapy.
- *Perioperative blood glucose management*: in the preoperative period at the out-patient clinic, blood glucose level and HbA1c level will be measured. In case of hyperglycemia *[*≥ 126

mg/dL (fasting) *or* ≥ 200 mg/dL (non fasting)] and/or elevated HbA1c level, internal medicine physician will be consulted for potential diagnosis and treatment of diabetes mellitus. Intraoperatively, blood glucose levels will be measured. A value between 4-10 mmol/L is considered as optimal. However, evidence is lacking on intraoperative glucose management, therefore no guideline for intraoperative glucose management is given and the decision to treat hyperglycemia is left to the discretion of the anesthesiologist during the procedure. Postoperatively, daily blood glucose levels will be measured in all patients with diabetes mellitus or patients that had hyperglycemia intraoperatively. Hyperglycemia should be treated in accordance with the diabetic consultant nurse or physician.

- *Normothermia:* the core temperature is aimed at ≥ 36°C. Preoperatively at the surgical ward on the day of the procedure, the nurse will measure the temperature and if this < 36°C, the patient will be transferred to the holding room for active warming therapy with forced air warming or pre-warmed blankets. Intraoperatively the temperature will be measured continuously. Postoperatively, warming should be continued if the patient's temperature is < 36°C until adequate body temperature is achieved.
- *Antibiotic prophylaxis*: intravenous antibiotic prophylaxis should be given within 15-60 minutes before incision as a single-dose administration to all patients.
- *Avoid unnecessary vasopressor drug administration*: if not necessary to maintain adequate mean arterial blood pressure, vasopressor drug administration is discouraged. In a significant amount of the patients in the LekCheck study, we registered that vasopressor drugs were administered and could actually have been stopped at the point of completing the LekCheck list and thus were administrated longer than necessary. We strongly encourage anesthesiologists to control more frequently whether it is still necessary to administer the vasopressor(s) and, if not, to stop the administration in order to limit its potential CAL risk-increasing effect during the operation.
- *Avoid epidural anesthesia:* epidural anesthesia is discouraged in patients undergoing laparoscopic surgery. An alternative analgesic technique is preferred.

At all times, the care team is permitted to amend any of the interventions in both groups to guarantee safe anesthesia and surgery.

Figure 1


Amsterdam UMC
Universitair Medische Centra
DoubleCheck
New standard care
• Patients ≥ 18 years old
• Bowel surgery with primary anastomosis (benign or malign)
Trial coordinator: Boukje Bootsma, MD
+31621600739 b.bootsma@amsterdamumc.nl www.naadlekkage.nl
Outpatient clinic
Blood tests
• Haemoglobin and iron levels
< 12♀ or <12.9♂ g/dL
• Glucose
≥ 126 mg/dL (fasting)
≥ 200 mg/dL (non fasting)
Action
In case of iron deficiency anemia (TSAT <15-20% or ferritin <30μg/L): → IV iron suppletion
→ Consult internal medicine
Surgical ward
Control
• Temperature <36 ˚C
Action
→ Contact anesthesiologist: active warming with blankets at the ward or transport to holding
O.R.
Complete the Double Check list in Castor before the creation of the anastomosis
Risk factor
• Antibiotic prophylaxis
• Temperature
• Epidural analgesia
• Vasopressor usage
• Glucose level
Action
→ 15 - 60 minutes before incision
→ ≥ 36 ˚C
→ Discouraged
→ Discouraged
→ Ideally between 72-180 mg/dL
data.castoredc.com login: doublecheckferrara@gmail.com
After operation
Blood tests
• Haemoglobin*
• Glucose day curve**
Action
→ Consider transfusion
→ If ≥ 200 mg/dL: consult internal medicine
* POD 1: on indication of surgeon or if preoperative Hb ≤ 7 or in total ≥ 500cc blood loss during surgery
**POD 1 t/m discharge (consider to stop earlier if adequate day curve): if glucose abnormal in outpatient clinic or <4 or >10 during surgery, or patient with DM
castor Patient registration: data.castoredc.com
Double Check trial: Enhanced perioperative care for improving outcomes after colorectal resection: implementation of best practice for the prevention of anastomotic leakage

Control: current practice

Perioperative care according to usual practice. Current practice was left to the discretion of the local clinicians. Historical controls from our previously conducted LekCheck study (6) will be used as replacement of a control arm. The LekCheck study is a prospective observational study, that aimed to evaluate the intraoperative condition of patients undergoing colorectal surgery and evaluate the relation with these intraoperative parameters with CAL. The study group consisted of 1562 adult patients that underwent colorectal surgery with primary anastomosis 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, local perfusion and oxygenation, contamination and surgery related factors. This study identified 7 perioperative potentially modifiable risk factors for CAL: preoperative anemia, intraoperative hypothermia, intraoperative hyperglycemia, intraoperative use of vasopressor drugs, epidural analgesia, incorrect or lack of antibiotic prophylaxis, intraoperative fecal contamination and duration of surgery.

Measurements

The following main study parameters are gathered for this study:

- The intraoperative condition of the patient: during the procedure, at the time of creation of the anastomosis, the following parameters will be measured as the anesthesiologist/assistant anesthetic nurse/operation-assistant will fill in the 'Double Check list' in consultation with the operating surgeon: preoperative hemoglobin level, temperature, glucose level, correct administration of antibiotic prophylaxis, vasopressor administration, use of epidural anesthesia.
- Compliance to the protocol: measuring if every step was followed and if not, reason for violation of the protocol. The answers to these questions will be gathered at the end of the study by provided information from the hospitals and questions asked to the participating physicians. Additionally, questions will be asked to the participating centers and the local head investigators. The number of protocol violations will be compared.

The following secondary parameters will be measured:

- CAL: defined as a grade B or C according to the ISREC-classification(8).
    - Grade A: anastomotic leakage requiring no active therapeutic intervention
    - Grade B: Anastomotic leakage requiring active therapeutic intervention but manageable without re-laparotomy
    - Grade C: Anastomotic leakage requiring re-laparotomy
- Complications other than CAL: defined as any adverse event occurring in the postoperative period until 30 days after surgery and graded according to the Dindo–Clavien classification(9). Clavien grade I–II were considered as minor and grade IIIa to IVb as major complication.

- 30-day mortality, length of hospital stay, length of intensive care unit stay, 30-day readmission rate

The following other demographic and clinical data will be collected to measure the association with the abovementioned outcome parameters:

- Age, sex, body mass index, American Society of Anesthesiologists (ASA) Score, co-morbid disease(s) and type(s), history of smoking, type of cancer, stage of cancer, TNM classification, type of neo-adjuvant therapy, postoperative pathology, pathologic diagnosis, resection margin in case of malignancy, TMN stadium in case of malignancy, type of surgical intervention, type of surgery (laparoscopic, open), conversion, type of anastomosis, type of surgeon, additional organ or vascular resections, operative time, intra- operative blood loss, mean saturation, mean arterial pressure, intraoperative fluid administration, preoperative bowel preparation, time in theatre, type of analgesia, intraoperative event, creation of a stoma.

Data collection, management and analysis

All anonymized information gathered in the study will be stored in a Castor database at the Amsterdam UMC, location VU Medical Center. All hospital specific data is stored at a specific place on the local server. The database is protected with passwords and only the study coordinator will have full access to the database. Participating hospitals will only have access to add data from their own participating patients. The data will stored for 15 years after the study is officially closed.

Statistical analysis

The primary and secondary outcomes will be compared between the control group and the intervention group using a logistic regression model. Dichotomous and categorical values will be analyzed using the Pearson's Chi-square test or Fisher's exact test. For parametric and non-parametric continuous parameters, the Student's t-test and Mann-Whitney U test will be used. For all tests, a two sided p-value of ≤ 0.05 will be considered as statistically significant. Statistical analysis will be performed using SPSS version 28 for Windows and Mac (SPSS, Chicago, Illinois, USA).

Ethical approvals

The trial protocol and additional papers, including consent for and patient information sheet have been approved by the Medical Ethics Review Committee of VU University Medical Center (METC-VUmc) and the Medical Ethics Review Committee of Maastricht University Medical Center (METC-MUMC+) and have been declared exempt from the Medical Research Involving Human Subjects Act (WMO) (approval number: METC-VUmc 2020.0634). This study will be performed in accordance with the ethical standards in the 1964 Declaration of Helsinki. Informed consent will be gathered for all participating patients.

Study oversight and monitoring

Amsterdam UMC, location VUmc will be the coordinating center for the Double Check trial and will also provide the study coordinator. Every participating hospital will provide a local research coordinator for their hospital. The Double Check study has been declared exempt from the Medical Research Involving Human Subjects Act (WMO) and will therefore not have an interim analysis, auditing trial conduct, or data monitoring board. Relevant protocol amendments will be communicated to all participating hospitals, the funding party, and the ethical committee.

Dissemination of results

Dissemination of the study results will be through journal publications and presentation at stakeholder and scientific meetings. A group authorship will be set up and used for the publication of the report of the Double Check study. All authors should have contributed to: the design of the study; or the inclusion of patients; or collection or analysis of data of the study; and with drafting or revising the article. The research coordinators from the participating hospitals will be offered participation in the group authorship.

Discussion

This publication presents an implementation study with the use of an open-label, multicenter design with historical cohorts for the use of an enhanced perioperative care protocol in patients undergoing colorectal resection. This study will be used to implement the protocol in several hospitals. In addition, this study aims to answer the question whether the enhanced perioperative care protocol improves the intraoperative condition of the patient and minimalizes exposure to risk factors of CAL and if it will decrease CAL rate.

A limitation of this study is the choice of an open-label design with historical controls instead of a randomized controlled trial. This design was chosen, as after the results of the previous LekCheck trial(6), we did not want to wait before the enhanced perioperative care protocol could be implemented. Performing a randomized trial with creating another control group first, would only have taken more time and seemed ambiguous, as we already had a perfect control group, namely the LekCheck cohort(6). We believe this is a historical control group of high quality, as it consists of patients that were treated for the same indications, the design of the study was the same and the measured intraoperative parameters and outcome parameters were the same as for this current study. The standard care in the participation hospitals has not changed after the LekCheck study(6). Therefore, the only difference between the historical cohort and the Double Check study group, will be the intervention, and time. This time bias that is caused by this design is the second limitation of this study. We try to overcome this limitation, by additionally analyzing the hospital specific CAL rates of the period of time between the historical cohort and the start of the Double Check study and compare these with the CAL rate of this current Double Check study, next to the comparison of the CAL rate with the historical cohort CAL rate.

Strengths of this study is the fact that it is an implementation study in combination with a comparative study and the pragmatic nature of the study, that leads to a clear and easy protocol to use for every hospital. We hope the results of this study will be used for the implementation of the enhanced perioperative care protocol in patients undergoing colorectal surgery nationally, as an addition to the current ERAS guidelines.

References

1. Koedam TWA, Bootsma BT, Deijen CL, van de Brug T, Kazemier G, Cuesta MA, et al. Oncological Outcomes After Anastomotic Leakage After Surgery for Colon or Rectal Cancer: Increased Risk of Local Recurrence. Ann Surg. 2020.
2. Wang S, Liu J, Wang S, Zhao H, Ge S, Wang W. Adverse Effects of Anastomotic Leakage on Local Recurrence and Survival After Curative Anterior Resection for Rectal Cancer: A Systematic Review and Meta-analysis. World J Surg. 2017;41(1):277-84.
3. Mirnezami A, Mirnezami R, Chandrakumaran K, Sasapu K, Sagar P, Finan P. Increased local recurrence and reduced survival from colorectal cancer following anastomotic leak: systematic review and meta-analysis. Ann Surg. 2011;253(5):890-9.
4. McDermott FD, Heeney A, Kelly ME, Steele RJ, Carlson GL, Winter DC. Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks. Br J Surg. 2015;102(5):462-79.
5. Pommergaard HC, Gessler B, Burcharth J, Angenete E, Haglind E, Rosenberg J. Preoperative risk factors for anastomotic leakage after resection for colorectal cancer: a systematic review and meta-analysis. Colorectal Dis. 2014;16(9):662-71.
6. Huisman DE, Reudink M, van Rooijen SJ, Bootsma BT, van de Brug T, Stens J, et al. LekCheck: A Prospective Study to Identify Perioperative Modifiable Risk Factors for Anastomotic Leakage in Colorectal Surgery. Ann Surg. 2022;275(1):e189-e97.
7. van Rooijen SJ, Huisman D, Stuijvenberg M, Stens J, Roumen RMH, Daams F, 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.
8. Rahbari NN, Weitz J, Hohenberger W, Heald RJ, Moran B, Ulrich A, et al. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. Surgery. 2010;147(3):339-51.
9. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205-13.