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original article

Early diagnosis of anastomotic leakage after colorectal surgery by the Dutch leakage score, serum procalcitonin and serum C-reactive protein: study protocol of a prospective multicentre observational study by the Italian ColoRectal Anastomotic Leakage (iCral) study group

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SUMMARY: **Early diagnosis of anastomotic leakage after colorectal surgery by the Dutch leakage score, serum procalcitonin and serum C-reactive protein: study protocol of a prospective multicentre observational study by the Italian ColoRectal Anastomotic Leakage (iCral) study group.**

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Background. *Anastomotic leakage (AL) is a dreaded major complication after colorectal surgery. There is no uniform definition of anastomotic dehiscence and leak. Over the years many risk factors have been identified (distance of anastomosis from anal verge, gender, BMI, ASA score) but none of these allows an early diagnosis of AL. The DUtch LeaKage (DULK) score, C reactive protein (CRP) and procalcitonin (PCT) have been identified as early predictors for anastomotic leakage starting from postoperative day (POD) 2-3. The study was designed to prospectively evaluate AL rates after colorectal resections, in order to give a definite answer to the need for clear risk factors, and testing the diagnostic yeld of DULK score and of laboratory markers.*

Methods and analysis. *A prospective enrollment for all patients undergoing elective colorectal surgery with anastomosis carried out from September 2017 to September 2018 in 19 Italian surgical centers. Outcome measures: preoperative risk factors of anastomotic leakage; operative parameters; leukocyte count, serum CRP, serum PCT and DULK score assessment on POD 2 and 3. Primary endpoint is*

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AL; secondary endpoints are minor and major complications according to Clavien-Dindo classification; morbidity and mortality rates; readmission and reoperation rates, length of postoperative hospital stay (Retrospectively registered at ClinicalTrials.gov Identifier: NCT03560180, on June 18, 2018).

Ethics. *The ethics committee of the "Comitato Etico Regionale delle Marche - C.E.R.M." reviewed and approved this study protocol on September 7, 2017 (protocol no. 2017-0244-AS). All the participating centers submitted the protocol and obtained authorization from the local Institutional Review Board.*

KEY WORDS: Anastomotic leakage - Colorectal surgery - Multicenter study - Prospective observational study - Study protocol.

Comment by the Editor-in-Chief

We accepted very favorably the publication of this very interesting polycentric and perspective article, which reports the opinion of many Italian surgeons particularly dedicated to colorectal surgery. We think the article should be considered the stand point on the treated topics within the Italian Surgery, which with many personal and group scientific papers give an important contribution to the knowledge about anastomotic dehiscence in colorectal surgery (Giorgio Di Matteo).

Background

Anastomotic leakage (AL) is a dreaded major complication after colorectal surgery (1). The overall incidence of anastomotic dehiscence and subsequent leaks is 2 to 7% when surgery is performed by experienced surgeons (2-5). The lowest leak rates are found with ileocolic anastomoses (1 to 3%) and the highest occur with coloanal anastomosis (10 to 20%) (6). Leaks usually become apparent between 5 and 7 days postoperatively. Almost half of all leaks occurs after the patient has been discharged, and up to 12% occurs after postoperative day (POD) 30 (4). Late leaks often present insidiously with low-grade fever, prolonged ileus, and nonspecific symptoms attributable to other postoperative infectious complications. Small, contained leaks present later in the clinical course and may be difficult to distinguish from postoperative abscesses by radiologic imaging, making the diagnosis uncertain and underreported.

There is no uniform definition of an anastomotic dehiscence and leak (5). In a review of 97 studies, as an example, 56 different definitions of AL were used (7). The majority of reports defines it using clinical signs, radiographic findings, and intraoperative findings (8, 9). Clinical signs include: pain, fever, tachycardia, peritonitis, purulent or feculent drainage. Radiographic signs include: fluid collections, gas containing collections. Intraoperative findings include: gross enteric spillage, anastomotic disruption.

Risk factors for dehiscence and leak are classified according to the site of the anastomosis (extraperitoneal or intraperitoneal), with a significantly increased risk of anastomotic leak in extraperitoneal versus intraperitoneal anastomoses (6.6 *versus* 1.5%; 2.4% overall) (10).

Major risk factors for extraperitoneal AL include: distance of the anastomosis from the anal verge (anastomoses within 5 cm from anal verge are at the highest risk for AL), anastomotic ischemia, male gender and obesity.

Major risk factors for an intraperitoneal AL include: American Society of Anesthesiologists (ASA) score III to V, emergent surgery, prolonged operative time, hand-sewn ileocolic anastomosis.

Controversial, inconclusive, or pertinent negative associations between the following variables and AL have been reported: neoadjuvant radiation therapy, drains, protective stoma, hand-sewn colorectal anastomosis, laparoscopic procedure, mechanical bowel preparation, nutritional status, perioperative corticosteroids.

Early diagnosis is crucial to treat patients limiting the related mortality. Several clinical items were suggested in order to detect AL as soon as possible: fever, pain, tachycardia, peritoneal purulent or faecal drain, and dynamic ileus (1-5). Moreover, several laboratory markers were proposed, such as leukocytosis, serum procalcitonin (PCT) and C-Reactive Protein (CRP) (11-13). Finally, in 2009 den Dulk et al. (14) proposed a leakage score (DUtch LeaKage, DULK), that considers several items

(fever, heart rate, respiratory rate, urinary production, mental status, clinical conditions, signs of ileus, gastric retention, fascial dehiscence, abdominal pain, wound pain, leukocytosis, CRP, increase of urea or creatinine and nutrition status), to give a score, based on which a subsequent diagnostic and therapeutic strategy is chosen.

Therefore, we planned this study to prospectively evaluate AL rates after colorectal resections, trying to give a definite answer to the need for clear risk factors, and testing the diagnostic yeld of DULK score and laboratory markers.

Methods and analysis

Prospective enrollment from September 2017 to September 2018 in 19 Italian surgical centers. All patients undergoing elective colorectal surgery with anastomosis to be included in a prospective database after written informed consent. A total of more than 1,150 patients is expected based on a mean of 55 cases/year per center (Retrospectively registered at ClinicalTrials.gov Identifier: NCT03560180, on June 18, 2018).

Inclusion criteria

1. Patients submitted to laparoscopic/robotic/open/converted ileo-colo-rectal resection with anastomosis (both intra- and extra-corporeal), including planned Hartmann's reversals
2. American Society of Anesthesiologists' (ASA) class I, II or III
3. Elective surgery
4. Patients' written acceptance to be included in the study.

Exclusion criteria

1. American Society of Anesthesiologists' (ASA) class IV-V
2. Patients with stoma before or at operation
3. Simple stoma closure
4. Transanal procedure
5. Pregnancy
6. Ongoing infection prior to surgery
7. Hyperthermic intraperitoneal chemotherapy for carcinomatosis.

Outcome measures

a) Preoperative risk factors for AL (age, gender, obesity, nutritional status (9, 10), diabetes, cardiovascular disease, renal failure, inflammatory bowel disease, ASA class I-II *vs* III)
b) Operative parameters (approach, procedure, anastomotic technique, length of operation, pT-NM stage)
c) Leukocyte count, serum CRP, serum PCT and DULK score assessment in 2nd and 3rd postoperative day. Minor and major complications according to Clavien-Dindo classification (15, 16).

Endpoints

1. Anastomotic leakage rate
2. Morbidity and mortality rates
3. Readmission and reoperation rates
4. Length of postoperative hospital stay.

Recorded data and follow-up

Potential patient-specific and intraoperative risk factors will be recorded: gender, body mass index, nutritional status according to the Mini Nutritional Assessment short-form (17, 18), surgical indication (cancer, polyps, chronic inflammatory bowel disease, diverticular disease), preoperative albuminemia, use of steroids, renal failure and dialysis, preoperative leukocyte count, CRP, PCT cardiovascular or respiratory disease, American Society of Anesthesia score, bowel preparation (decision made by operating surgeon), laparoscopy or laparotomy, level of anastomosis and technique (mechanical or hand-sewn, intra- or extra-corporeal), operative time, presence of drainage, and perioperative blood transfusions). During the postoperative period, patients will be examined by the attending surgeon daily. Fever (central temperature > 38°C), pulse, abdominal signs, bowel movements, volume and aspect of drainage (if present) will be recorded daily. Leucocyte count, CRP, PCT and Dulk score will be measured in the evening before the operation (in addition to albuminemia) and on postoperative days 2, 3, and 6 (optional). The attending surgeon will make any decision for complementary exams and imaging according to his own criteria. The rate of any complication will be calculated and graded according to Clavien-Dindo (15, 16) including all leaks (independently of clinical significance), wound infection (according to the definitions of the Centers for Disease Control and Prevention and wound culture) (19), pneumonia (clinical symptoms, and physical and radiological examinations), central line infection (positive blood culture), urinary tract infection (positive urine culture with bac-

terial count). All patients will be followed-up in the outpatient clinic up to 6 weeks after discharge from the hospital.

Main endpoint is AL (intended as any deviation from the planned postoperative course related to the anastomosis, or presence of pus or enteric contents within the drains, presence of abdominal or pelvic collection in the area of the anastomosis on postoperative CT scan, performed at the discretion of the attending surgeon, leakage of contrast through the anastomosis during enema or evident anastomotic dehiscence at reoperation for postoperative peritonitis). Thus, all detected leaks will be considered independently of clinical significance. No imaging will be performed routinely in order to search for leakage.

Secondary endpoints are morbidity and mortality rates, readmission and reoperation rates, and postoperative length of stay. All data will be prospectively recorded into Case Report Forms and transmitted to the coordinating center on a monthly basis. Thereafter, all data will be incorporated into a spreadsheet (MS Excel), checking for any discrepancy, that will be addressed and solved through strict cooperation between the promoter, the data manager and the chief investigator of any participating center.

Statistical analysis

All quantitative values will be expressed as mean ± standard deviation, median and range; categorical data with percentage frequencies. Mean values of secondary endpoints will be compared according to the presence or absence of AL using Student's two-sided t test (allowing for heterogeneity of variances) or with a non-parametric Mann-Whitney test. Mean values of DULK score, CRP and PCT levels will also be compared using Student's two-sided t test (allowing for heterogeneity of variances) or with a non-parametric Mann-Whitney test. Both univariate analysis and multivariate analysis will be performed to assess risk factors for leakage and overall complications. The odds ratio (OR) will be presented followed by its 95% confidence interval (95% CI). Areas under the receiver-operating characteristics (ROC) curve will be calculated. For all statistical tests the significant level is fixed at $p < .05$. Multivariate analysis will be performed using logistic models. Statistical analyses will be carried out using STATA software (Stata Corp. College Station, Texas, USA).

Sample size

Considering that the ASA grade (I and II *vs* III) is mostly significant among risk factors for AL (3, 5, 8), an estimation of the OR for AL and ASA grade is equal to 5.6 (20); assuming a confidence interval for the estimation of the OR at 95% and a maximum error equal to 0.04, the required sample size is n=1,062 (about 885 and 177 cases expected in ASA I-II and ASA III, respectively).

Discussion

Anastomotic leak (AL) is one of the most feared complications by colorectal surgeons and the consequences of a late diagnosis can be life threatening (4). The first clinical evidence of anastomotic leaks usually shows between POD 5 and 7, or later when patients have already been discharged (4), especially considering the progressive increase of Enhanced Recovery After Surgery (ERAS) programs with discharge within POD 4-5.

The lack of a uniform definition of AL represents the first crucial bias in comparing studies. In a review, Bruce et al. (7) analyzed 49 lower GI studies and found out that only 29 papers gave a definition of AL and among these, definitions were different. Some considered as ALs only the ones requiring a reoperation; others considered any radiological evidence even if there was no clinical, laboratory or clinical practice modification. AL is usually described with clinical, radiological and intraoperative findings.

Our definition of AL includes all symptomatic leaks. Routine radiological search for leaks was not requested for two reasons: occult leaks do not need a therapeutic adjustment and contrast enemas can facilitate the transformation of an occult leak into a clinically relevant one. Moreover the exclusion of primary stoma patients should give us an actual rate of AL.

Early diagnosis of AL is the main endpoint of this study. In order to do this, we considered a series of risk factors associated with AL in previous studies. ASA score and age are constant risk factors in evaluating surgical outcomes as they are directly related to comorbidities (20) such as diabetes, cirrhosis, and chronic renal failure. ASA IV-V patients were excluded because they have a high mortality and morbidity risk regardless of surgery. Obesity (BMI>30) and a poor nutritional status with low albumin and protein blood levels are associated with a higher risk of complications in colorectal surgery (21, 22). To

evaluate nutritional status, we used the mini nutritional assessment short formula (MNA-SF) (17), a simple, reliable and widely accepted tool (18) that can be used to decide the need for nutritional support prior to surgery in order to decrease the risk of complications.

When analyzing the results we expect a confirmation of the higher risk of AL according to these parameters, including disease type, TNM classification, site of resection, type and site of anastomosis. These results will help define a population of patients with a higher risk of AL but will not allow an early diagnosis.

The DULK score has been suggested for earlier diagnosis of AL. This clinical tool assigns a score that guides the surgeon in decision making (14). It is based on 13 items assessing general clinical conditions, abdominal signs and symptoms, laboratory findings and diet that are assigned each with a value. Total scores > 3 suggests close clinical and imaging evaluation. In the original study the score allowed earlier diagnosis of AL, reducing the delay from 4 days in the control group to 1,5 days, resulting in earlier treatment and lower mortality and morbidity rates related to AL. These results have been confirmed in different studies and some Authors described a higher sensibility and specificity of the score when compared to laboratory findings alone (23). Nevertheless, we must consider the simplicity and reproducibility of this scoring system.

In the last years CRP and PCT serum values have been increasingly used as early markers of septic surgical complications. Ortega-Deballon et al. (12) and Oberhofer et al. (13) showed in two observational studies how high post-operative PCT and CRP blood levels were associated with major complications and suggested that patients with high post-operative values should undergo imaging studies to search for surgical complications. In another study, Giaccaglia et al. (11) showed that low levels of these two biomarkers on POD 3 and 5 were associated with a low risk of developing AL. In a subsequent multicenter investigation, the PREDICS study (24), they strongly suggested to include both CRP and PCT serum levels on POD 3 and 5 in the decision making for patient discharge after colorectal surgery. Although it seemed that adding PCT serum values to PCR could improve the overall accuracy of laboratory markers in early diagnosis of AL (25), a recent meta-analysis (26) failed to confirm this finding, stressing the issue of cost-raising due to the fact that the cost of any serum PCT determination is ten to twenty-fold compared to CRP. Considering the trend in shorter hospital stay showed after implementation of ERAS programs (27), and that clinical manifestations of AL usually appear after POD 5, we decided to collect PCT and CRP values on POD 2 and 3, leaving another determination on POD 6 as an option.

The combination of the Dulk score with serum markers may improve early AL diagnosis. Recruitment was closed on September 30, 2018, as initially planned, with 1,546 cases enrolled.

Ethics and dissemination

The institutional review board of the coordinating center (Comitato Etico Regionale delle Marche - C.E.R.M.) reviewed and approved this study protocol on September 7, 2017 (no. 2017-0244-AS). All the participating centers submitted the protocol and obtained authorization from the local institutional review boards. All the participating investigators discussed and approved this investigation protocol during the first investigator's meeting held in September 2017.

The results of the study are intended to be presented at national and international medical congresses on corresponding fields of interest (colorectal surgery, abdominal surgery). Written publications of the results are planned within surgical journals.

The authorship for written publications was confirmed to all participating investigators, only being granted in the case of substantive contributions to the design, conduct, data analysis, collection and interpretation. After completion of the full study report, anonymized participant-level datasets will be available by contacting the principal investigator.

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Conflicts of interest statement

The Authors have no competing interests to declare.

References

1. Boushey R, Williams LJ. Management of anastomotic complications of colorectal surgery. Uptodate 2018. [https://www.uptodate.com/contents/management-of-anastomotic-complications-of-colorectal-surgery] accessed on September 11, 2018.
2. Slieker JC, Komen N, Mannaerts GH, Karsten TM, Willemsen P, Murawska M, Jeekel J, Lange JF. Long-term and perioperative corticosteroids in anastomotic leakage: a prospective study of 259 left-sided colorectal anastomoses. Arch Surg. 2012;147:447-452.
3. Kingham TP, Pachter HL. Colonic anastomotic leak: risk factors, diagnosis, and treatment. J Am Coll Surg. 2009;208:269-278.
4. Hyman N, Manchester TL, Osler T, Burns B, Cataldo PA. Anastomotic leaks after intestinal anastomosis: it's later than you think. Ann Surg. 2007;245:254-258.
5. Park JS, Choi GS, Kim SH, Kim HR, Kim NK, Lee KY, Kang SB, Kim JY, Lee KY, Kim BC, Bae BN, Son GM, Lee SI, Kang H. Multicenter analysis of risk factors for anastomotic leakage after laparoscopic rectal cancer excision: the Korean laparoscopic colorectal surgery study group. Ann Surg. 2013;257:665-671.
6. Russ A, Kennedy GD. Postoperative complications. In: ASCRS Textbook of Colon and Rectal Surgery. 3rd Edition. Edited by Steele SR, Hull TL, Read TE, Saclarides TJ, Senagore AJ, Whitlow CB. New York: Springer International Publishing; 2016:121-140.
7. Bruce J, Krukowski ZH, Al-Khairy G, Russell EM, Park KG. Systematic review of the definition and measurement of anastomotic leak after gastrointestinal surgery. Br J Surg. 2001;88:1157-1168.
8. Law WI, Chu KW, Ho JW, Chan CW. Risk factors for anastomotic leakage after low anterior resection with total mesorectal excision. Am J Surg. 2000;179:92-96.
9. Lipska MA, Bissett IP, Parry BR, Merrie AE. Anastomotic leakage after lower gastrointestinal anastomosis: men are at a higher risk. ANZ J Surg. 2006;76:579-585.
10. Platell C, Barwood N, Dorfmann G, Makin G. The incidence of anastomotic leaks in patients undergoing colorectal surgery. Colorectal Dis. 2007;9:71-79.
11. Giaccaglia V, Salvi PF, Cunsolo GV, Sparagna A, Antonelli MS, Nigri G, Balducci G, Ziparo V. Procalcitonin, as an early biomarker of colorectal anastomotic leak, facilitates enhanced recovery after surgery. J Crit Care. 2014;29:528-532.
12. Ortega-Deballon P, Radais F, Facy O, d'Athis P, Masson D, Charles PE, Cheynel N, Favre JP, Rat P. C-reactive protein is an early predictor of septic complications after elective colorectal surgery. World J Surg. 2010;34:808-814.
13. Oberhofer D, Juras J, Pavicić AM, Rancić Zurić I, Rumenjak V. Comparison of C-reactive protein and procalcitonin as predictors of postoperative infectious complications after elective colorectal surgery. Croat Med J. 2012;53:612-619.
14. den Dulk M, Noter SL, Hendriks ER, Brouwers MA, van der Vlies CH, Oostenbroek RJ, Menon AG, Steup WH, van de Velde CJ. Improved diagnosis and treatment of anastomotic leakage after colorectal surgery. Eur J Surg Oncol. 2009;35:420-426.
15. 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;240:205-213.
16. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, de Santibañes E, Pekolj J, Slankamenac K, Bassi C, Graf R, Vonlanthen R, Padbury R, Cameron JL, Makuuchi M. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009;250:187-196.
17. Kaiser MJ, Bauer JM, Ramsch C, Uter W, Guigoz Y, Cederholm T, Thomas DR, Anthony P, Charlton KE, Maggio M, Tsai AC, Grathwohl D, Vellas B, Sieber CC, MNA-International Group. Validation of the Mini Nutritional Assessment short-form (MNA-SF): a practical tool for identification of nutritional status. J Nutr Health Aging. 2009;13:782-788.
18. Skipper A, Ferguson M, Thompson K, Castellanos VH, Porcari J. Nutrition screening tools: an analysis of the evidence. JPEN J Parenter Enteral Nutr. 2012;36:292-298.
19. Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections 1992: a modification of CDC definitions of surgical wound infections. Infect Control Hosp Epidemiol. 1992;13:606-608.
20. Bakker IS, Grossmann I, Henneman D, Havenga K, Wiggers T. Risk factors for anastomotic leakage and leak-related mortality after colonic cancer surgery in a nationwide audit. Br J Surg. 2014;101:424-432.
21. Choi HK, Law WL, Ho JWC. Leakage after resection and intraperitoneal anastomosis for colorectal malignancy: analysis of risk factors. Dis Colon Rectum. 2006;49:1719-1725.
22. Biondo S, Parés D, Kreisler E, Ragué JM, Fraccalvieri D, Ruiz AG, Jaurrieta E. Anastomotic dehiscence after resection and primary anastomosis in left-sided colonic emergencies. Dis Colon Rectum. 2005;48:2272-2280.
23. Martin G, Dupré A, Mulliez A, Prunel F, Slim K, Pezet D. Validation of a score for the early diagnosis of anastomotic leakage following elective colorectal surgery. J Visc Surg. 2015;152:4-10.
24. Giaccaglia V, Salvi PF, Antonelli MS, Nigri G, Pirozzi F, Casagranda B, Giacca M, Corcione F, de Manzini N, Balducci G, Ramacciato G. Procalcitonin reveals early dehiscence in colorectal surgery: the PREDICS study. Ann Surg. 2016;263:967-972.
25. Garcia-Granero A, Frasson M, Flor-Lorente B, Blanco F, Puga R, Carratalá A, Garcia-Granero E. Procalcitonin and C-reactive protein as early predictors of anastomotic leak in colorectal surgery: a prospective observational study. Dis Colon Rectum. 2013;56:475-483.
26. Cousin F, Ortega-Deballon P, Bourredjem A, Doussot A, Giaccaglia V, Fournel I. Diagnostic accuracy of procalcitonin and C-reactive protein for the early diagnosis of intra-abdominal infection after elective colorectal surgery: a meta-analysis. Ann Surg. 2016;264:252-256.
27. Ljungqvist O, Scott M, Fearon KC. Enhanced recovery after surgery: a review. JAMA Surg. 2017;152:292-298.