

**Early diagnosis of anastomotic leakage after colorectal surgery: a prospective observational validation study of the Dutch Leakage score, serum procalcitonin and serum CRP: the Italian ColoRectal Anastomotic Leakage (iCRAL) study group.**

**BACKGROUND**

Anastomotic leakage is a dreaded major complication after colorectal surgery [1]. The overall incidence of anastomotic dehiscence and subsequent leaks is 2 to 7 percent when performed by experienced surgeons [2-5]. The lowest leak rates are found with ileocolic anastomoses (1 to 3 percent) and the highest occur with coloanal anastomosis (10 to 20 percent) [6]. Leaks usually become apparent between five and seven days postoperatively. Almost half of all leaks occur after the patient has been discharged, and up to 12 percent occur after postoperative day 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 an anastomotic leak were used [7]. The majority of reports define an anastomotic leak using clinical signs, radiographic findings, and intraoperative findings [8, 9]. The clinical signs include: Pain, Fever, Tachycardia, Peritonitis, Feculent drainage, Purulent drainage. The radiographic signs include: Fluid collections, Gas containing collections. The intraoperative findings include: Gross enteric spillage, Anastomotic disruption.

Risk factors for a dehiscence and leak are classified according to the site of the anastomosis (extraperitoneal or intraperitoneal). A prospective review of 1598 patients undergoing 1639 anastomotic procedures for benign or malignant colorectal disease found a significantly increased

risk of anastomotic leak with extraperitoneal compared with intraperitoneal anastomoses (6.6 versus 1.5 percent; 2.4 percent overall) [10].

Major risk factors for an extraperitoneal anastomotic leak include: The distance of the anastomosis from the anal verge (Patients with a low anterior resection and an anastomosis within 5 cm from the anal verge are the highest risk group for an anastomotic leak), Anastomotic ischemia, Male gender, Obesity.

Major risk factors for an intraperitoneal anastomotic leak include: American Society of Anesthesiologists (ASA) score Grade III to V, Emergent surgery, Prolonged operative time, Hand-sewn ileocolic anastomosis.

Controversial, inconclusive, or pertinent negative associations between the following variables and an anastomotic leak 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. For this reason several clinical items were proposed in literature to detect anastomotic leakage as soon as possible: fever, pain, tachycardia, peritoneal, purulent or faecal drain, and dynamic ileus [1- 5]. Moreover, also 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 consider 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 is chosen a therapeutic strategy.

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

## **METHODS**

Prospective enrollment from September 2017 to November 2018 in 20 Italian surgical centers. All patients undergoing elective colorectal surgery with anastomosis will be included in a prospective database after having provided a written informed consent. A total of more than 1,160 patients is expected based on a mean of 50 cases/year per center.

### **Inclusion criteria**

1. Patients submitted to laparoscopic/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**

1. Preoperative risk factors of anastomotic leakage (age, gender, obesity, state of nutrition [9-10], diabetes, cardiovascular, renal failure, inflammatory bowel disease, ASA class I-II vs III)

2. Operative parameters (approach, procedure, anastomotic technique, time of operation, pTNM stage)
3. Leukocyte count, serum CRP, serum procalcitonin and DULK score assessment in 2<sup>nd</sup> and 3<sup>rd</sup> postoperative day. Minor and major complications according to Clavien-Dindo classification [15, 16]
4. Anastomotic leakage rate
5. Morbidity-Mortality rates
6. 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, surgeon and perioperative blood transfusion(s). 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-ALL 3 – Protocollo dello Studio

Dindo [15, 16] including all leaks (independently of clinical significance), wound infection, pneumonia, central line infection, urinary tract infection. Urinary tract infection will be diagnosed on the basis of positive urine culture with bacterial count. Central line infection will be diagnosed on the basis of positive blood culture. Superficial and deep incisional infections will be diagnosed according to the definitions of the Centers for Disease Control and Prevention and a culture will be performed [19]. Pneumonia will be diagnosed on the basis of clinical symptoms, and physical and radiological examinations. The surgeons will be blinded to the results of the CRP and PCT assays. Patients will be followed-up in the outpatient clinic up to 6 weeks after discharge from the hospital.

Main outcome is anastomotic dehiscence (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 outcomes are morbidity and mortality rates, and postoperative length of stay. All data will be prospectively recorded into CRF 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 chief investigator, data manager and participating center.

### **Statistical Analysis**

Quantitative values will be expressed as mean  $\pm$  standard deviation, median and range; categorical data with percentage frequencies. Mean values of duration of stay will be compared according to the presence or absence of fistulas 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 anastomotic dehiscence [3, 5, 8], an estimation of the OR for anastomotic dehiscence 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).

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Appendix 1 **DULK SCORE [14]**

	<b>Valori Normali</b>	<b>Score</b>	<b>Valori alterati</b>	<b>Score</b>
<b>Febbre</b>	$\leq 38.0^{\circ} \text{C}$	0	$\geq 38.0^{\circ} \text{C}$	1
<b>Frequenza cardiaca</b>	$\leq 100 \text{ bpm}$	0	$\geq 100 \text{ bpm}$	1
<b>Frequenza respiratoria</b>	$\leq 30 \text{ atti/min}$	0	$\geq 30 \text{ atti/min}$	1
<b>Diuresi</b>	$\geq 30 \text{ ml/h o } 700 \text{ ml/die}$	0	$\leq 30 \text{ ml/h o } 700 \text{ ml/die}$	1
<b>Stato mentale</b>	Normale stato mentale	0	Agitazione o Letargia	2
<b>Condizioni cliniche</b>	Stabili o in miglioramento	0	Deterioramento	2
<b>Segni di ileo</b>	No	0	Ileo	2
<b>Ritenzione gastrica</b>	No	0	Ritenzione Gastrica	2
<b>Deiscenza della fascia</b>	No	0	Deiscenza della fascia	2
<b>Dolore addominale o altri non di ferita</b>	No dolore	0	Dolore non della ferita	2
<b>Segni di infezione</b>	No aumento leucociti o PCR	0	Aumento dei leucociti di $\geq 5\%$ o della PCR	1
<b>Funzionalità renale</b>	No aumento Urea o Creatinina	0	Aumento di Urea o Creatinina di $\geq 5\%$	1
<b>Stato nutrizionale</b>	Dieta Normale	0	Enterale/Parenterale Totale	1/2
<b>TOTALE</b>				

## Appendix 2 CLAVIEN-DINDO CLASSIFICATION [15, 16]

**TABLE 1.** Classification of Surgical Complications

### Grade Definition

Grade I Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions

Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside

Grade II Requiring pharmacological treatment with drugs other than such allowed for grade I complications

Blood transfusions and total parenteral nutrition are also included

Grade III Requiring surgical, endoscopic or radiological intervention

Grade IIIa Intervention not under general anesthesia

Grade IIIb Intervention under general anesthesia

Grade IV Life-threatening complication (including CNS complications)\* requiring IC/ICU management

Grade IVa Single organ dysfunction (including dialysis)

Grade IVb Multiorgan dysfunction

Grade V Death of a patient

Suffix “d” If the patient suffers from a complication at the time of discharge (see examples in Table 2), the suffix “d” (for “disability”) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

\*Brain hemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding transient ischemic attacks.

CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

**TABLE 2.** Clinical Examples of Complication Grades

Grades	Organ System	Examples
Grade I	Cardiac	Atrial fibrillation converting after correction of K <sub>+</sub> -level
	Respiratory	Atelectasis requiring physiotherapy
	Neurological	Transient confusion not requiring therapy
	Gastrointestinal	Noninfectious diarrhea
	Renal	Transient elevation of serum creatinine
	Other	Wound infection treated by opening of the wound at the bedside
Grade II	Cardiac	Tachyarrhythmia requiring $\beta$ -receptor antagonists for heart rate control
	Respiratory	Pneumonia treated with antibiotics on the ward
	Neurological	TIA requiring treatment with anticoagulants
	Gastrointestinal	Infectious diarrhea requiring antibiotics
	Renal	Urinary tract infection requiring antibiotics
	Other	Same for I followed by tx with antibiotics for phlegmonous infection
Grade IIIa	Cardiac	Bradyarrhythmia requiring pacemaker implantation in local anesthesia
	Neurological	See grade IV
	Gastrointestinal	Biloma after liver resection requiring percutaneous drainage
	Renal	Stenosis of the ureter after kidney transplantation treated by stenting
Grade IIIb	Other	Closure of dehiscent noninfected wound in the OR under local anesthesia
	Cardiac	Cardiac tamponade after thoracic surgery requiring fenestration
	Respiratory	Bronchopleural fistulas after thoracic surgery requiring surgical closure
	Neurological	See grade IV
	Gastrointestinal	Anastomotic leakage after descendentostomy requiring relaparotomy
	Renal	Stenosis of the ureter after kidney transplantation treated by surgery
	Other	Wound infection leading to eventration of small bowel
	Grade IVa	Cardiac Heart failure leading to low-output syndrome
	Respiratory	Lung failure requiring intubation
	Neurological	Ischemic stroke/brain hemorrhage
Grade IVb	Gastrointestinal	Necrotizing pancreatitis
	Renal	Renal insufficiency requiring dialysis
	Cardiac	Same as for IVa but in combination with renal failure
	Respiratory	Same as for IVa but in combination with renal failure
	Gastrointestinal	Same as for IVa but in combination with hemodynamic instability
	Neurological	Ischemic stroke/brain hemorrhage with respiratory failure
Renal	Same as for IVa but in combination with hemodynamic instability	
Suffix “d”	Cardiac	Cardiac insufficiency after myocardial infarction (IVa–d)
	Respiratory	Dyspnea after pneumonectomy for severe bleeding after chest tube placement (IIIb–d)
	Gastrointestinal	Residual fecal incontinence after abscess following descendentostomy with surgical evacuation. (IIIb–d)
	Neurological	Stroke with sensorimotor hemisindrome (IVa–d)
	Renal	Residual renal insufficiency after sepsis with multiorgan dysfunction (IVb–d)
	Other	Hoarseness after thyroid surgery (I–d)

TIA, transient ischemic attack; OR, operating room.

## Appendix 3 **MNA®** [17]

### Screening

**A Presenta una perdita dell' appetito? Ha mangiato meno negli ultimi 3 mesi? (perdita d'appetito, problemi digestivi, difficoltà di masticazione o deglutizione)**

- 0 = Grave riduzione dell'assunzione di cibo
- 1 = Moderata riduzione dell'assunzione di cibo
- 2 = Nessuna riduzione dell'assunzione di cibo

**B Perdita di peso recente (<3 mesi)**

- 0 = perdita di peso > 3 kg
- 1 = non sa
- 2 = perdita di peso tra 1 e 3 kg
- 3 = nessuna perdita di peso

**C Motricità**

- 0 = dal letto alla poltrona
- 1 = autonomo a domicilio
- 2 = esce di casa

**D Nell' arco degli ultimi 3 mesi: malattie acute o stress psicologici?**

- 0 = sì 2 = no

**E Problemi neuropsicologici**

- 0 = demenza o depressione grave
- 1 = demenza moderata
- 2 = nessun problema psicologico

**F1 Indice di massa corporea (IMC) = peso in kg / (alt ezza in m)<sup>2</sup>**

- 0 = IMC <19
- 1 = 19 ≤ IMC < 21
- 2 = 21 ≤ IMC < 23
- 3 = IMC ≥ 23

SE L' IMC NON E DISPONIBILE, SOSTITUIRE LA DOMANDA F1 CON LA DOMANDA F2.

NON RISPONDERE ALLA DOMANDA F2 SE LA DOMANDA F1 E GIA' STATA COMPLETATA

**F2 Circonferenza del polpaccio (CP in cm)**

- 0 = CP inferiore a 31
- 3 = CP 31 o superiore

### Valutazione di screening (max.14 punti)

**12-14** punti: stato nutrizionale normale

**8-11** punti: a rischio di malnutrizione

**0-7** punti: malnutrito

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