Updates in Surgery (2019) 71:339–347
https://doi.org/10.1007/s13304-018-00612-1

ORIGINAL ARTICLE

Colorectal surgery in Italy: a snapshot from the iCral study group

The Italian ColoRectal Anastomotic Leakage (iCral) study group[1]

Received: 24 October 2018 / Accepted: 28 November 2018 / Published online: 11 February 2019

Abstract

During a recent prospective trial on early diagnosis of anastomotic leakage (AL) after colorectal surgery, we gathered a large database on more than 1500 procedures performed in 19 surgical centers in Italy over a 12-month period. Main purpose of the present paper is to show the epidemiological data about colorectal procedures and anastomotic leakage. Prospective enrollment for all elective colorectal resections with anastomosis (September 2017–September 2018). Primary endpoint was AL; secondary endpoints were morbidity and mortality rates, readmission and reoperation rates, and length of post-operative hospital stay (ClinicalTrials.gov; Identifier: NCT03560180). There were 1546 enrolled cases (56.9% of 2717 total resected cases). The rate of minimally invasive resections was 83.5%. Overall AL rate was 4.92% (76 cases; range per center 0-12.12%). Mean ± SD time to AL diagnosis was 5.95 ± 4.78 days (median 5, range 1-31). Overall morbidity rate was 30.20%, mortality 1.29% (20 cases; range per center 0-3.27), readmission 0.90%, and reoperation 6.92%. Mean ± SD post-operative LOS was 7.89 ± 5.97 days (median 6; range 1-120). AL significantly influenced all other secondary endpoints. This study offers a good snapshot of colorectal resections in Italy. There was a high rate of laparoscopic resections, reflecting the special interest in this kind of surgery by the participating centers. AL, morbidity, mortality, readmission and reoperation rates are compared to those reported in previous population-based studies. Compared to series dealing with open colorectal resections, the time to diagnosis of AL was shortened by several days.

Keywords Anastomotic leakage · Colorectal surgery · Multicenter study · Prospective observational study

Background

Anastomotic leakage (AL) is a dreaded major complication after colorectal surgery [1]. The overall incidence of anastomotic dehiscence and subsequent leaks is 2–7% when surgery is performed by experienced surgeons [2–5]. The lowest leak rates are found with ileocolic anastomoses (1 to 3 percent) and the highest (10 to 20 percent) occur with coloanal anastomosis [6]. Leaks usually become apparent between five and 7 days post-operatively. Almost half of all leaks occur after the patient has been discharged, and up to 12% occur after post-operative day (POD) 30 [4].

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) [7, 8]. 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–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 of AL is crucial to treat patients limiting the related mortality. Several clinical items were suggested to detect AL as soon as possible: fever, pain, tachycardia, peritoneal purulent or fecal drain, and dynamic ileus [1–5]. Moreover, several laboratory markers were proposed, such as

Marco Catarci Principal investigator and promoter.

Members of the iCral study group are listed in the Acknowledgements section at the end of the article.

✉ The Italian ColoRectal Anastomotic Leakage (iCral) study group
marco.catarci@sanita.marche.it

[1] UOC Chirurgia Generale, Ascoli Piceno, Italy

leukocyte count, serum procalcitonin (PCT) and C-reactive protein (CRP) [9–11]. Finally, in 2009 den Dulk et al. [12] 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 yield of DULK score and laboratory markers. Main purpose of the present paper is to show epidemiological data about colorectal procedures and anastomotic leakage.

Table 1 Inclusion and exclusion criteria

Inclusion criteria
Patients submitted to laparoscopic/robotic/open/converted ileo-colo-rectal resection with anastomosis (both intra- and extracorporeal), including planned Hartmann's reversals.
American Society of Anesthesiologists' (ASA) class I, II or III
Elective surgery
Patients' written acceptance to be included in the study.
Exclusion criteria
American Society of Anesthesiologists' (ASA) class IV–V
Patients with stoma before or at operation
Simple stoma closure
Transanal procedure
Pregnancy
Ongoing infection prior to surgery
Hyperthermic intraperitoneal chemotherapy for carcinomatosis.

Methods

Prospective enrollment was carried out from September 2017 to September 2018 in 19 Italian surgical centers (Fig. 1). All patients undergoing elective colorectal surgery with anastomosis were included in a prospective database after written informed consent. The study protocol was registered at ClinicalTrials.gov (Identifier: NCT03560180) and published elsewhere [13]. Inclusion and exclusion criteria are reported in Table 1.

Potential patient-specific and intraoperative risk factors for AL were recorded: gender, body mass index (BMI), nutritional status according to the Mini Nutritional Assessment short-form [14, 15], surgical indication (cancer, polyps, chronic inflammatory bowel disease, diverticular disease, other), chronic liver disease, perioperative administration

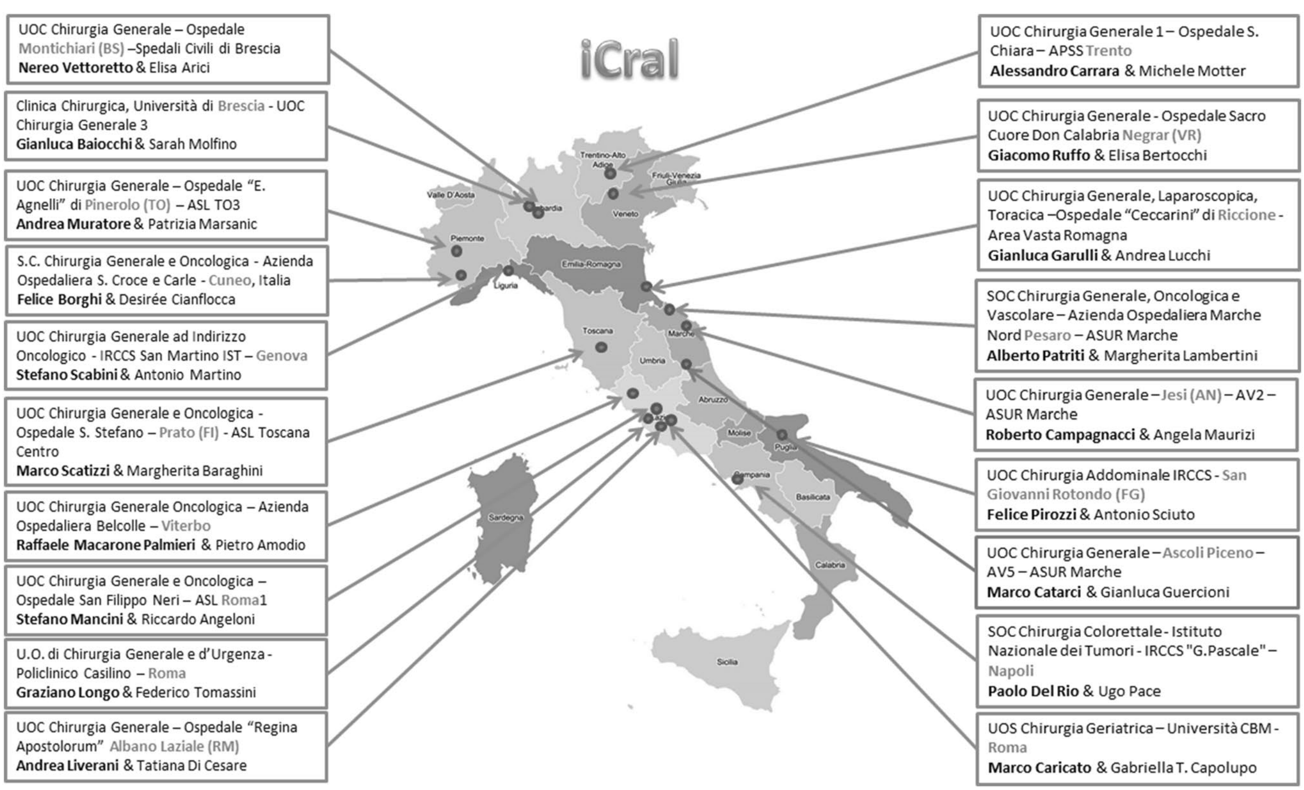

Fig. 1 Italian ColoRectal Anastomotic Leakage (iCral) study group: participating centers, and local chief and co-investigators

of steroids, renal failure and dialysis, American Society of Anesthesia (ASA) score, laparoscopy or laparotomy or converted approach, level of anastomosis and technique (mechanical or hand-sewn, intra- or extracorporeal), operative time, and perioperative blood transfusions. During the post-operative period, patients were examined by the attending surgeon daily. Fever (central temperature > 38 °C), pulse, abdominal signs, bowel movements, volume and aspect of drainage (if present) were recorded daily. Any decision for complementary exams and imaging was made according to the attending surgeon's own criteria. Any complication was calculated and graded according to Clavien–Dindo [16, 17] including all leaks (independently of clinical significance), wound infection (according to the definitions of the Centers for Disease Control and Prevention, and wound culture [18]), pneumonia (clinical symptoms, and physical and radiological examinations), central line infection (positive blood culture), and urinary tract infection (positive urine culture with bacterial count). All patients were followed up in the outpatient clinic up to 6 weeks after discharge from the hospital.

Primary endpoint was AL (intended as any deviation from the planned post-operative course related to the anastomosis, or the presence of pus or enteric contents within the drains if present, the presence of abdominal or pelvic collection in the area of the anastomosis on post-operative 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 post-operative peritonitis). Thus, all detected leaks were considered independently of clinical significance. No imaging was routinely performed to search for leakage.

Secondary endpoints were morbidity and mortality rates, readmission and reoperation rates, and post-operative length of stay (LOS). All data were prospectively recorded into case report forms and transmitted to the coordinating center on a monthly basis. Thereafter, all data were incorporated into a spreadsheet (MS excel), checking for any discrepancy that was addressed and solved through strict cooperation between the promoter, the data manager and local investigators of any participating center.

Statistical analysis

All quantitative values were expressed as mean ± standard deviation (SD), median and range, and categorical data with percentage frequencies. Mean values of secondary endpoints were 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. For all statistical tests the significant level was fixed at $p < 0.05$. Statistical analyses were carried out using STATA software (Stata Corp. College Station, Texas, USA). Estimated sample size was calculated considering ASA grade

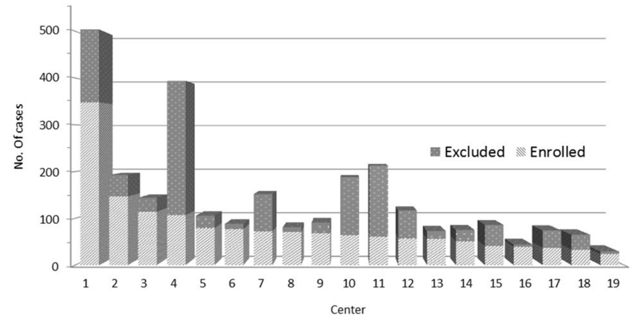

Fig. 2 Patient accrual per single center (*Y* axis: no. of cases)

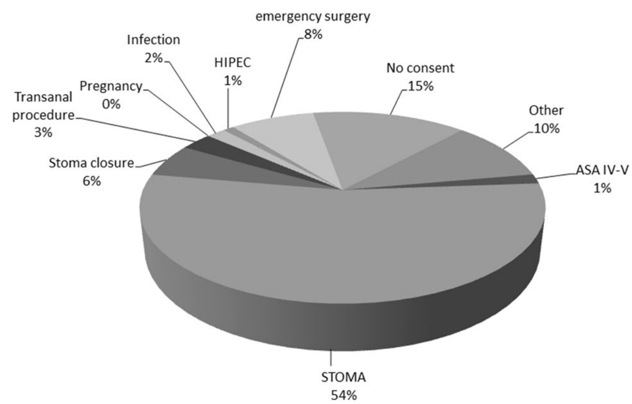

Fig. 3 Causes of exclusion in 1171 cases

(I and II vs. III) as mostly significant among risk factors for AL [3, 5, 19, 20]; an estimation of the OR for AL and ASA grade is equal to 5.6 [19]; assuming a confidence interval for the estimation of the OR at 95% and a maximum error equal to 0.04, the required sample size was $n = 1062$ (about 885 and 177 cases expected in ASA I–II and ASA III, respectively).

Results

After a mean accrual period of 11.52 months (median 12; range 7–14), 1546 patients submitted to colorectal resection and anastomosis were enrolled in the study (Fig. 2), out of a total of 2717 resections (56.9%) performed in the same period. Reasons for exclusion are reported in Fig. 3. Male to female ratio was 0.84. Mean ± SD age was 64.41 ± 16.59 years (median 68; range 18–94). Mean ± SD BMI was 25.27 ± 4.31 kg/m^2 (median 24.89; range 14.86–44.98). Mean ± SD nutritional score (MNA-SF) was 12.44 ± 1.91 (median 13; range 2–14), with 46 (2.91%) cases of clear malnutrition (score 2–7), and 297 cases (19.21%) suspected for malnutrition (score 8–11). Other risk factors for AL are reported in Table 2. Most

Table 2 Risk factors for anastomotic leakage

Risk factors	Pattern	No.	%
ASA class	I–II	1.063	68.76
	III	483	31.24
Diabetes mellitus	No	1.364	88.23
	Yes	182	11.77
Chronic renal failure	No	1.482	95.86
	Yes	64	4.14
Dialysis	No	1.544	99.87
	Yes	2	0.13
Perioperative steroids	No	1.510	97.67
	Yes	36	2.33
Neoadjuvant therapy	No	1.516	98.05
	Yes	30	1.95
Pre-operative blood transfusions	No	1.440	93.14
	Yes	106	1.96
Intra- and post-operative blood transfusions	No	1.395	90.23
	Yes	151	9.77
Chronic liver disease	No	1.537	99.42
	Yes	9	0.58

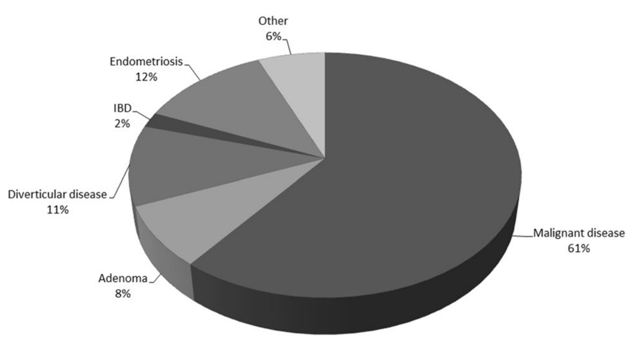

Fig. 4 Indications for surgery in 1546 enrolled cases (*IBD* inflammatory bowel disease)

common indication for surgery was neoplastic disease (1064 cases; 68.81%) followed by other indications (Fig. 4). The overall rate of minimally invasive approach was 83.5%, right colectomy being the most commonly performed operation (Table 3). The rate of minimally invasive approach and of conversion per single center is reported in Fig. 5. There were 28 (1.81%) associated procedures, mostly liver resections, cholecystectomy, wedge urinary bladder resection and adnexectomy. Nearly 88% of the anastomoses (1354 cases) was performed with a stapler, mostly (976 cases, 63.13%) intracorporeally. The details concerning the anastomosis according to the type of procedure are reported in Table 4. Mean ± SD duration of surgery was 178.88 ± 77.13 min (median 160; range 30–510). Mean ± SD distance of the anastomosis from the anal margin (available in 513 left/anterior resections and Hartmann reversals) was 9.37 ± 3.11 cm (median 9; range 0.5–35).

Table 3 Type of operation

Approaches	No.	%
Open	255	16.49
Laparoscopic/robotic	1196	77.36
Converted	95	6.15
Operation		
Right colectomy	533	34.47
Extended right colectomy	75	4.85
Transverse colectomy	31	2.00
Left colectomy	444	28.72
Splenic flexure colectomy	47	3.04
Anterior resection	358	23.15
Hartmann reversal	31	2.00
(Sub)total colectomy	16	1.03
Other	11	0.7

Overall AL rate was 4.92% (76 cases; range per center 0–12.12%). Median time to diagnosis of AL was on POD 5, while 85% of AL was diagnosed within POD 8 (Fig. 6). AL diagnosis was reached through CT scan with water-soluble contrast enema in 30 cases (39.5%), through clinical judgement in 23 cases (30.3%), through CT scan with i.v. contrast in 22 cases (28.9%) and through endoscopy in one case.

A total of 632 perioperative complications (556 excluding AL) were recorded in 467 (440 excluding AL) patients (overall morbidity rate 30.20%). Minor complications (Clavien–Dindo grade I–II) were 447 (70.72%) and major complications (Clavien–Dindo grade III–IVb) were 185 (29.28%). The spectrum and grading of perioperative complications are reported in Table 5. Overall operative mortality rate was 1.29% (20 cases; range per center 0–3.27%). There were 14 readmissions (0.90%), and 107 reoperations (6.92%). Mean ± SD post-operative LOS was 7.89 ± 5.97 days (median 6; range 1–120). Mean post-operative LOS per single center is reported in Fig. 7. AL significantly influenced all other secondary endpoints (Table 6).

Discussion

The Italian Colorectal Anastomotic Leakage study group (iCral) is a spontaneous aggregation of general surgeons with specific interest in colorectal resections. It is composed of two general surgery units in university hospitals, three specialized colorectal units in research hospitals, four general surgery units in district hospitals and nine general surgery units in general hospitals (Fig. 1) that are broad spectra of nearly all kind of surgical units performing colorectal resections in our country, far from pretending

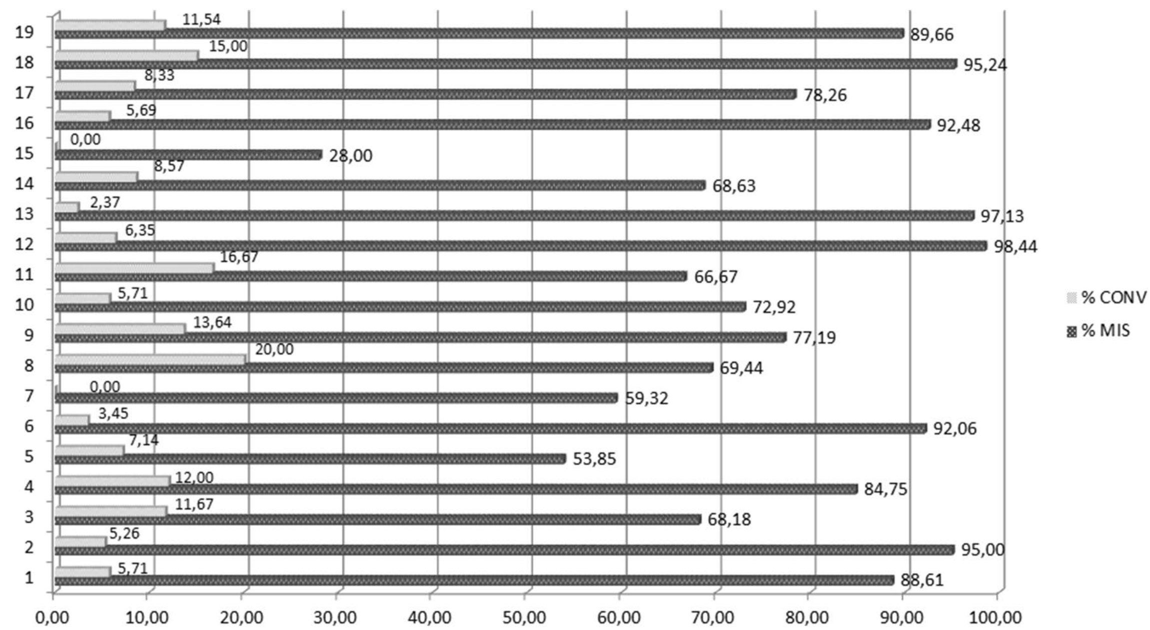

Fig. 5 Rates of minimally invasive surgery (% MIS) and of conversion to open surgery (% CONV) per single center

Table 4 Type of anastomosis according to the type of procedure

Operations	Anastomosis								
	Manual no. (%)	Stapled no. (%)	Intra no. (%)	Extra no. (%)	E–E no. (%)	E–S no. (%)	S–E no. (%)	S–S iso no. (%)	S–S ani no. (%)
Right colectomy	133 (21.9)	475 (78.1)	265 (43.6)	343 (56.4)	–	36 (5.9)	16 (2.6)	469 (77.2)	87 (14.3)
Transverse colectomy	14 (45.2)	17 (54.8)	7 (32.2)	24 (67.8)	9 (29.1)	–	2 (6.5)	17 (54.8)	3 (9.6)
Left colectomy	21 (4.7)	423 (95.3)	353 (79.5)	91 (20.5)	388 (87.4)	12 (2.7)	32 (7.2)	10 (2.3)	2 (0.4)
Splenic flexure colectomy	15 (31.9)	32 (68.1)	14 (29.8)	33 (70.2)	11 (23.4)	2 (4.2)	7 (14.9)	24 (51.1)	3 (6.4)
Anterior resection and HR	4 (1.0)	385 (99.0)	330 (84.8)	59 (15.2)	360 (92.5)	6 (1.6)	22 (5.6)	1 (0.3)	–
Other	5 (18.5)	22 (81.5)	7 (25.9)	20 (74.1)	6 (22.2)	1 (3.7)	9 (33.3)	10 (37.1)	1 (3.7)
Total	192 (12.4)	1354 (87.6)	976 (63.1)	570 (36.9)	774 (50.1)	57 (3.7)	88 (5.7)	531 (34.3)	96 (6.2)

Intra intracorporeal, *Extra* extracorporeal, *E–E* end-to-end, *E–S* end-to-side, *S–E* side-to-end, *S–S iso* side-to-side isoperistaltic, *S–S ani* side-to-side anisoperistaltic, *HR* Hartmann reversal

it to be comprehensive of all the actual situations about colorectal surgery in Italy. The actual rate of resections per year outweighted the expected one (2717 consecutive resections; mean ± SD per center 143 ± 120.38; median 91; range 29–504). One possible source of bias is the exclusion of 1171 cases (44.1%), mainly because of the necessity of a diverting stoma at operation (Fig. 3), but the study was primarily designed to evaluate the diagnostic yield of serum biomarkers for AL, and including proximally diverted anastomoses has already been demonstrated as a significant source of confounding bias for this purpose [21]. Neoplastic disease remains the most common indication for surgery (Fig. 4), followed by diverticular and other benign diseases [22]. We recorded an unexpected very high rate (83%) of minimally invasive resections (mostly laparoscopic, with a small percentage of robotic resections). This finding is

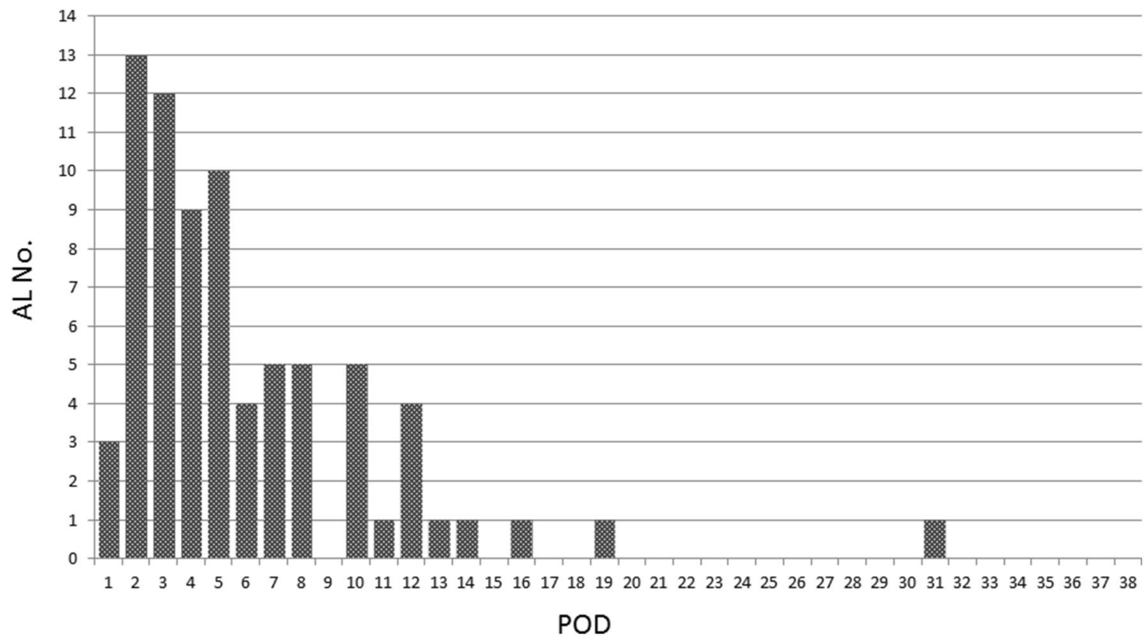

Fig. 6 Time to diagnosis of anastomotic leakage (AL) per post-operative day (POD)

Table 5 Spectrum and grading of perioperative complications

Complication types	Grade I	Grade II	Grade IIIa	Grade IIIb	Grade IVa	Grade IVb	Total no. (%)
Anastomotic leak	–	–	1	69	–	6	76 (4.92)
Surgical site infection	37	26	–	–	–	–	63 (4.08)
Abdominal bleeding	–	–	1	10	2	1	14 (0.90)
Trocar/wound site bleeding	1	2	–	3	–	–	6 (0.38)
Abdominal collection/abscess	1	5	8	2	–	–	16 (1.03)
Deep wound dehiscence	–	–	–	5	–	–	5 (0.32)
Intestinal obstruction	2	–	–	7	–	–	9 (0.58)
Anastomotic bleeding	4	7	20	–	–	–	31 (2.00)
Small bowel perforation	1	–	–	4	–	–	5 (0.32)
Acute mesenteric ischemia	–	–	–	2	–	–	2 (0.13)
Cardiac dysfunction	9	19	1	–	2	3	34 (2.22)
Pneumonia and pulmonary failure	8	49	1	–	2	1	61 (3.96)
Neurologic (TIA, stroke)	2	2	1	–	–	–	5 (0.32)
DVT/Pulmonary embolism	–	3	–	–	–	–	3 (0.19)
Renal failure	10	3	–	–	5	4	22 (1.42)
Anemia	5	60	–	–	–	–	65 (4.20)
Fever	4	24	1	–	–	–	29 (1.87)
Urinary tract infection	3	18	–	–	–	–	21 (1.36)
Urinary retention	9	6	1	–	–	–	16 (0.71)
Paralytic ileus	41	41	–	–	–	–	82 (5.30)
Acute peptic ulcer/erosive gastritis	–	2	1	–	–	–	3 (0.19)
Other	22	19	–	10	–	11	62 (4.01)
Total	159	288	36	112	11	26	632 (100)

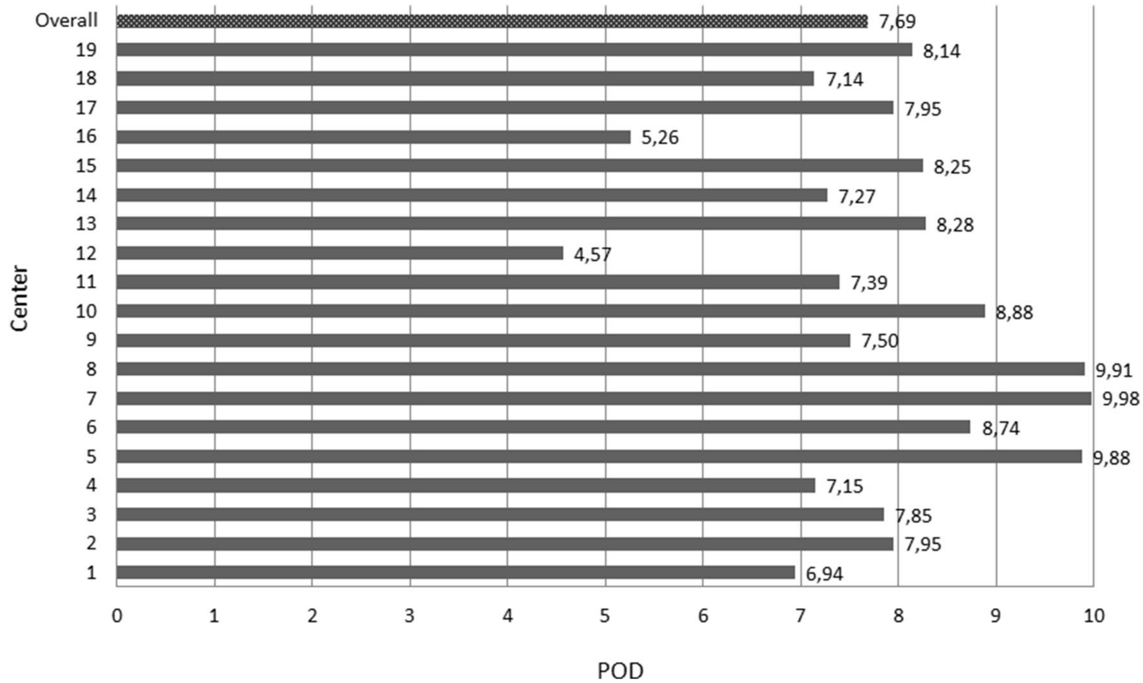

Fig. 7 Mean post-operative length of stay (LOS) per single center

Table 6 Secondary endpoints according to the presence/absence of AL

Endpoints	AL (no. = 76)	no AL (no. = 1470)	*p*
Other Morbidity rate (no.; %)	49; 64.47	391; 26.59	<0.0001
Clavien–Dindo I–II	29; 38.16	311; 21.15	<0.0008
Clavien–Dindo III–IV	20; 26.31	80; 5.44	<0.0001
Mortality rate (no.; %)	6; 7.89	14; 0.95	0.0003
Readmission rate (no.; %)	4; 5.26	10; 0.68	0.0041
Reoperation rate (no.; %)	69; 90.79	38; 2.58	< 0.0001
Post-operative LOS (days; mean ± SD)	21.06 ± 5.66	7.21 ± 3.95	< 0.0001

strikingly different from that available online concerning colorectal resections in Italy for cancer in 2016: most recent available data (2016) from PNE-AGENAS (Piano Nazionale Esiti—Agenzia Nazionale Servizi Sanitari), a nationwide database, show penetration rates of laparoscopic procedures for colorectal cancer ranging at 35.4% for colon resections and at 42.6% for rectal resections [23]. Possibly, such a high rate reflects the special interest in this kind of surgery by the participating centers. Concerning the anastomosis (Table 4), this study confirms a high rate (87.6%) of stapled anastomoses, highest (99.0%) in colorectal and lowest (54.8%) in transverse resections, a prevalence (63.1%) of intracorporeal vs. extracorporeal anastomoses, highest (84.8%) in colorectal and lowest (25.9%) in other resections (mostly total colectomies). Side-to-side isoperistaltic anastomosis is the most frequently performed anastomotic fashioning in right (77.2%), transverse (54.8%) and splenic flexure (51.1%) colectomies, whereas end-to-end colorectal anastomosis is most frequently performed in left colectomies (87.4%) and anterior resections/Hartmann reversals (92.5%).

We recorded 76 cases of AL (4.92%), including all symptomatic leaks. Routine radiological search for AL was not requested per protocol for two reasons: clinically occult leaks do not need a therapeutic adjustment and contrast enemas can facilitate the transformation of an occult leak into a clinically relevant one [3, 7]. Therefore, subclinical AL was not systematically diagnosed, which may underestimate the AL rate. On the other hand, patients with derivative stoma were excluded and, for this reason, subclinical ALs were probably rare. As a consequence, nearly all the detected leaks required a reoperation, representing nearly two-thirds of the indications for reoperation (Table 5). These figures are comparable to those previously reported in population-based studies [6, 19, 24, 25], with the only exception being the timing of diagnosis of AL: in previous series based on open colorectal resections [4], the mean time to AL diagnosis was after

12.7 days, median POD 8, with 85% of AL diagnosis within POD 21; in our series, mean was 5.9 days, median POD 5, with 85% of AL diagnosis within POD 8 (Fig. 6); nearly all AL cases were diagnosed by clinical signs and confirmed by CT scan with i.v. contrast or contrast enema. We strongly think that this finding is influenced by two factors: (1) the study, as reported above, was designed to test clinical and serological markers for AL diagnosis, and, therefore, this could have called a particular attention to the issue of AL diagnosis; (2) the high rate of minimally invasive resections could have "shifted" earlier to the clinical appearance of AL. Considering the raising penetration of enhanced recovery programs (ERPs) in colorectal surgery [26–28], this finding deserves particular attention. Median post-operative LOS in this series (6 days) was lower than that (8 days) reported in national database in 2016 [23]. Exclusion of diverting stoma and ASA > III patients and of urgent cases may be the main reason for this finding, the other being partial or full implementation of an ERP in four out of 19 participating centers (374/1546 cases treated along an ERP with adherence variable from 50 to 80%), also reflected in a significantly lower mean post-operative LOS (Fig. 7).

In any case, this study confirms that AL remains a strong negative determinant of early outcomes after colorectal resection: it significantly increases the morbidity, mortality, readmission and reoperation rates, while significantly prolonging post-operative LOS (Table 5). The iCral study group is now moving towards thorough analysis of clinical and biochemical markers and risk factors for AL diagnosis as planned, while launching a new prospective study (iCral2) designed to test AL rates against the adherence to ERPs.

Acknolwedgements Members of The Italian ColoRectal Anastomotic Leakage (iCral) study group and authors are: Marco Catarci Principal investigator and promoter (General Surgery Unit, Ospedale "C. e G. Mazzoni", ASUR Marche AV5 Via degli Iris snc, 63100 Ascoli Piceno, Italy), Giacomo Ruffo (General Surgery Unit, Sacro Cuore Hospital, Negrar, VR, Italy), Felice Borghi (Department of Surgery, Santa Croce e Carle Hospital, Cuneo, Italy), Alberto Patriti (Department of Surgery, Marche Nord Hospital, Pesaro e Fano, PU, Italy), Paolo Delrio (Colorectal Surgical Oncology, National Cancer Institute - IRCCS - G. Pascale Foundation, Naples, Italy), Marco Scatizzi (General and Oncologic Surgery Unit, Santo Stefano Hospital, Prato, FI, Italy), Stefano Mancini (General and Oncologic Surgery Unit, San Filippo Neri Hospital, Rome, Italy), Gianluca Garulli (General Surgery Unit, "Ceccarini" Hospital, Riccione, RN, Italy), Alessandro Carrara (Department of Surgery, Santa Chiara Hospital, Trento, Italy), Felice Pirozzi (Abdominal Surgery Unit, Casa Sollievo della Sofferenza Hospital, San Giovanni Rotondo, FG, Italy), Stefano Scabini (General and Oncologic Surgery Unit, National Cancer Center "San Martino", Genoa, Italy), Andrea Liverani (General Surgery Unit, Regina Apostolorum Hospital, Albano Laziale, RM, Italy), Gianluca Baiocchi (General Surgery Unit 3, University and Spedali Civili of Brescia, Brescia, Italy), Roberto Campagnacci (Department of Surgery, "C. Urbani" Hospital, Jesi, AN, Italy), Andrea Muratore (General Surgery Unit, "E. Agnelli" Hospital, Pinerolo, TO, Italy), Graziano Longo (General Surgery Unit, Policlinico Casilino, Rome, Italy), Marco Caricato (Geriatric Surgery Unit, Policlinico Campus BioMedico, Rome, Italy), Raffaele Macarone Palmieri (General and Oncologic Surgery Unit, Belcolle Hospital, Viterbo, Italy), Nereo Vettoretto (General Surgery Unit, Spedali Civili of Brescia, Montichiari, BS, Italy), Marcello Ceccaroni (Gynecology Unit, Sacro Cuore Hospital, Negrar, VR, Italy), Paolo Ciano (General Surgery Unit, Ospedale "C. e G. Mazzoni", ASUR Marche AV5 Via degli Iris snc, 63100 Ascoli Piceno, Italy), Elisa Bertocchi (General Surgery and Gynecology Units, Sacro Cuore Hospital, Negrar, VR, Italy), Desirée Cianflocca (Department of Surgery, Santa Croce e Carle Hospital, Cuneo, Italy), Margherita Lambertini (Department of Surgery, Marche Nord Hospital, Pesaro e Fano, PU, Italy), Ugo Pace (Colorectal Surgical Oncology, National Cancer Institute - IRCCS - G. Pascale Foundation, Naples, Italy), Maddalena Baraghini (General and Oncologic Surgery Unit, Santo Stefano Hospital, Prato, FI, Italy), Lorenzo Pandolfini (General and Oncologic Surgery Unit, Santo Stefano Hospital, Prato, FI, Italy), Riccardo Angeloni (General and Oncologic Surgery Unit, San Filippo Neri Hospital, Rome, Italy), Andrea Lucchi (General Surgery Unit, "Ceccarini" Hospital, Riccione, RN, Italy), Giacomo Martorelli (General Surgery Unit, "Ceccarini" Hospital, Riccione, RN, Italy), Giuseppe Tirone (Department of Surgery, Santa Chiara Hospital, Trento, Italy), Michele Motter (Department of Surgery, Santa Chiara Hospital, Trento, Italy), Antonio Sciuto (Abdominal Surgery Unit, Casa Sollievo della Sofferenza Hospital, San Giovanni Rotondo, FG, Italy), Antonio Martino (General and Oncologic Surgery Unit, National Cancer Center "San Martino", Genoa, Italy), Andrea Pierre Luzzi (General and Oncologic Surgery Unit, National Cancer Center "San Martino", Genoa, Italy), Tatiana di Cesare (General Surgery Unit, Regina Apostolorum Hospital, Albano Laziale, RM, Italy), Sarah Molfino (General Surgery Unit 3, University and Spedali Civili of Brescia, Brescia, Italy), Angela Maurizi (Department of Surgery, "C. Urbani" Hospital, Jesi, AN, Italy), Patrizia Marsanic (General Surgery Unit, "E. Agnelli" Hospital, Pinerolo, TO, Italy), Federico Tomassini (General Surgery Unit, Policlinico Casilino, Rome, Italy), Simone Santoni (General Surgery Unit, Policlinico Casilino, Rome, Italy), Gabriella Teresa Capolupo (Geriatric Surgery Unit, Policlinico Campus BioMedico, Rome, Italy), Pietro Amodio (General and Oncologic Surgery Unit, Belcolle Hospital, Viterbo, Italy), Elisa Arici (General Surgery Unit, Spedali Civili of Brescia, Montichiari, BS, Italy), Benedetta Ruggeri (Clinical Governance Unit, "C. e G. Mazzoni" Hospital, Ascoli Piceno, Italy), Gianluca Guercioni (General Surgery Unit, Ospedale "C. e G. Mazzoni", ASUR Marche AV5 Via degli Iris snc, 63100 Ascoli Piceno, Italy).

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. Medtronic SI® Italy gave liberal and unconditioned economic support for the organization of the first, second and third investigator meetings, held in Milan, Italy, on September 2017 and June 2018, and in Rome on October 2018, respectively.

Compliance with ethical standards

Conflicts of interest The authors have no competing interests to declare.

Ethical approval 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. After completion of the full study report, anonymized participant-level datasets will be available upon reasonable request by contacting the principal investigator.

Informed consent Informed consent was obtained (in written form) by all the participants in the study.

References

1. Boushey R, Williams LJ (2018) Management of anastomotic complications of colorectal surgery. Uptodate [https://www.uptodate.com/contents/management-of-anastomotic-complications-of-colorectal-surgery]. Accessed 11 Sept 2018
2. Slieker JC, Komen N, Mannaerts GH, Karsten TM, Willemsen P, Murawska M, Jeekel J, Lange JF (2012) Long-term and perioperative corticosteroids in anastomotic leakage: a prospective study of 259 left-sided colorectal anastomoses. Arch Surg 147:447–452
3. Kingham TP, Pachter HL (2009) Colonic anastomotic leak: risk factors, diagnosis, and treatment. J Am Coll Surg 208:269–278
4. Hyman N, Manchester TL, Osler T, Burns B, Cataldo PA (2007) Anastomotic leaks after intestinal anastomosis: it's later than you think. Ann Surg 245:254–258
5. Bruce J, Krukowski ZH, Al-Khairy G, Russell EM, Park KG (2001) Systematic review of the definition and measurement of anastomotic leak after gastrointestinal surgery. Br J Surg 88:1157–1168
6. 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 (2013) Multicenter analysis of risk factors for anastomotic leakage after laparoscopic rectal cancer excision: the Korean laparoscopic colorectal surgery study group. Ann Surg 257:665–671
7. Russ A, Kennedy GD (2016) Postoperative complications. In: Steele SR, Hull TL, Read TE, Saclarides TJ, Senagore AJ, Whitlow CB (eds) ASCRS textbook of colon and rectal surgery, 3rd edn. Springer, New York, pp 121–140
8. Platell C, Barwood N, Dorfmann G, Makin G (2007) The incidence of anastomotic leaks in patients undergoing colorectal surgery. Colorectal Dis 9:71–79
9. Giaccaglia V, Salvi PF, Cunsolo GV, Sparagna A, Antonelli MS, Nigri G, Balducci G, Ziparo V (2014) Procalcitonin, as an early biomarker of colorectal anastomotic leak, facilitates enhanced recovery after surgery. J Crit Care 29:528–532
10. Ortega-Deballon P, Radais F, Facy O, d'Athis P, Masson D, Charles PE, Cheynel N, Favre JP, Rat P (2010) C-reactive protein is an early predictor of septic complications after elective colorectal surgery. World J Surg 34:808–814
11. Oberhofer D, Juras J, Pavicić AM, Rancić Zurić I, Rumenjak V (2012) Comparison of C-reactive protein and procalcitonin as predictors of postoperative infectious complications after elective colorectal surgery. Croat Med J 53:612–619
12. den Dulk M, Noter SL, Hendriks ER, Brouwers MA, van der Vlies CH, Oostenbroek RJ, Menon AG, Steup WH, van de Velde CJ (2009) Improved diagnosis and treatment of anastomotic leakage after colorectal surgery. Eur J Surg Oncol 35:420–426
13. Benedetti M, Pergolini I, Ciano P et al (2019) 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 observational validation study by the Italian ColoRectal Anastomotic Leakage (iCral) study group. G Chir 40:20–25
14. 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 (2009) Validation of the mini nutritional assessment short-form (MNA-SF): a practical tool for identification of nutritional status. J Nutr Health Aging 13:782–788
15. Skipper A, Ferguson M, Thompson K, Castellanos VH, Porcari J (2012) Nutrition screening tools: an analysis of the evidence. JPEN J Parenter Enteral Nutr 36:292–298
16. Dindo D, Demartines N, Clavien PA (2004) Classification of surgical complications. A new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 240:205–213
17. 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 (2009) The Clavien–Dindo classification of surgical complications: 5-year experience. Ann Surg 250:187–196
18. Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG (1992) CDC definitions of nosocomial surgical site infections 1992: a modification of CDC definitions of surgical wound infections. Infect Control Hosp Epidemiol 13:606–608
19. Bakker IS, Grossmann I, Henneman D, Havenga K, Wiggers T (2014) Risk factors for anastomotic leakage and leak-related mortality after colonic cancer surgery in a nationwide audit. Br J Surg 101:424–432
20. Choi HK, Law WL, Ho JWC (2006) Leakage after resection and intraperitoneal anastomosis for colorectal malignancy: analysis of risk factors. Dis Colon Rectum 49:1719–1725
21. Sciuto A, Merola G, De Palma GD, Sodo M, Pirozzi F, Bracale UM, Bracale U (2018) Predictive factors for anastomotic leakage after laparoscopic colorectal surgery. World J Gastroenterol 24:2247–2260
22. Gessler B, Eriksson O, Angenete A (2017) Diagnosis, treatment, and consequences of anastomotic leakage in colorectal surgery. Int J Colorectal Dis 32:549–556
23. Agenzia Nazionale per i Servizi Sanitari Regionali. Piano Nazionale Esiti Ed. 2017. URL http://pne2017.agenas.it/. Accessed 19 Sept 2018
24. Frasson M, Flor-Lorente B, Rodríguez JL, Granero-Castro P, Hervás D, Alvarez Rico MA, Brao MJ, Sánchez González JM, Garcia-Granero E, ANACO Study Group (2015) Risk factors for anastomotic leak after colon resection for cancer: multivariate analysis and nomogram from a multicentric, prospective, national study with 3193 patients. Ann Surg 262:321–330
25. Midura EF, Hanseman D, Davis BR, Atkinson SJ, Abbott DE, Shah SA, Paquette IM (2015) Risk factors and consequences of anastomotic leak after colectomy: a national analysis. Dis Colon Rectum 58:333–338
26. Ljungqvist O, Scott M, Fearon KC (2017) Enhanced recovery after surgery: a review. JAMA Surg 152:292–298
27. Brescia A, Tomassini F, Berardi G, Sebastiani C, Pezzatini M, Dall'Oglio A, Laracca GG, Apponi F, Gasparrini M (2017) Development of an enhanced recovery after surgery (ERAS) protocol in laparoscopic colorectal surgery: results of the first 120 consecutive cases from a university hospital. Updates Surg 69:359–365
28. Braga M, Beretta L, Pecorelli N, Maspero M, Casiraghi U, Borghi F, Pellegrino L, Bona S, Monzani R, Ferrari G, Radrizzani D, Iuliani R, Bima C, Scatizzi M, Missana G, Guicciardi MA, Muratore A, Crespi M, Bouzari H, Ceretti AP, Ficari F, PeriOperative Italian Society Group (2018) Enhanced recovery pathway in elderly patients undergoing colorectal surgery: is there an effect of increasing ages? Results from the perioperative Italian Society Registry. Updates Surg 70:7–13