INDEX COPERNICUS INTERNATIONAL

ORIGINAL ARTICLE

Risk factors and inflammatory predictors for Anastomotic Leakage following Total Mesorectal Excision with defunctioning stoma

Rybakov Evgeny[1], Shelygin Yuri[1,2], Tarasov Mikhail[1], Sukhina Marina[1], Zarodniuk Irina[1], Alexeev Mikhail[1,2], Chernyshov Stanislav[1]

[1]State Scientific Centre of coloproctology, Moscow, Russia
[2]Russian Medical Academy of Continuous Professional Education

Article history: Received: 20.01.2018 Accepted: 24.04.2018 Published: 30.06.2018

ABSTRACT:

Background: This study aims to examine the factors involved in anastomotic leak (AL) following low anterior resection and total mesorectal excision (LAR-TME) and to determine the usefulness of early measurement of the inflammatory biomarkers C-Reactive Protein (CRP) and Procalcitonin (PCT).

Methods: One hundred patients undergoing LAR-TME with proximal diverting stoma were analysed between 2013 and 2016. Postoperative CRP and PCT levels were measured on the 3rd and 6th postoperative days.

Results: There were 11 clinical leaks with a negative impact in univariate analysis on AL of male gender, larger and stenotic tumours, intraoperative blood loss > 200 mL, need for perioperative blood transfusion, postoperative anaemia and operating time exceeding 180 minutes. Upon multivariate analysis, only perioperative blood transfusion was an independent AL risk factor. Recorded CRP was higher in AL patients when compared with non-AL cases on both the 3rd postoperative day (152.4 mg/L vs 93 mg/L, respectively; P < 0.0001) and the 6th postoperative day (130.5 mg/L vs 68.2 mg/L; P < 0.0001). PCT levels also significantly differed between AL and non-AL cases on the 3rd postoperative day (0.5 ng/mL vs 0.2 ng/mL, respectively; P < 0.0001) and the 6th postoperative day (1.16 ng/mL vs 0.1 ng/mL, respectively; P < 0.0001). Both CRP and PCT showed high negative predictive values (NPV) for the diagnosis of AL on both postoperative days.

Conclusion: Following low restorative proctectomy, high NPV of CRP and PCT measurements for the diagnosis of anastomotic leaks may assist decision-making for early hospital discharge.

KEYWORDS: Anastomotic Leak; Low Anterior Resection; C-Reactive Protein; Procalcitonin; Biomarkers

Acknowledgments: We thank Professor Andrew Zbar for his critical review of the manuscript.

INTRODUCTION

Anastomotic leak (AL) following colorectal surgery can be a devastating adverse postoperative event, with an incidence variably reported at between 3 and 39%, overall (1). Systematic analyses have identified the number of patient, disease and surgeon related factors implicated in AL (2 - 4). The long-term consequences of AL following rectal or anal anastomosis include an overall worse functional outcome (5) the occasional need for permanent stoma and potentially higher local recurrence rate in those cases performed for rectal carcinoma (6). Early diagnosis and treatment of AL is crucial in reducing the likelihood of such an unfavourable outcome or the structural sequelae such as fistula, sinus formation and stricture, each of which can seriously impact the patient's quality of life (7).

Analysis of the potential risk factors controlling AL after total mesorectal excision will affect operative decision-making including, most importantly, the utilisation of temporary diverting stoma. Many existing studies examining these variables are limited by the retrospective nature of their design and by considerable heterogeneity concerning both the definition of AL itself and the range of its managements once diagnosed (8). In the current era of fast-track protocols of management following colorectal anastomoses, significant delays in the diagnosis of a potentially life-threatening AL will also substantially increase the length of hospital stay, along with hospital re-admission rates and overall cost (9). The expected inflammatory response following colorectal surgery has led some groups to focus on specific postoperative inflammatory markers as early predictors for AL (10). One example is C-reactive protein (CRP), an acute-phase serum reactant induced by an up-regulated postoperative cascade of pro-inflammatory cytokines. In this respect, meta-analyses have shown a high positive and negative predictive value of an elevated CRP in the early postoperative period for broad infectious complications following colorectal surgery (11) as well as for the specific prediction of AL (12). Procalcitonin (PCT) has emerged as a sensitive marker for the diagnosis and monitoring of sepsis (13) and has been shown to have a high negative predictive value for AL in the early postoperative period (14). The aims of this study are to define the risk factors for AL in an unselected cohort of patients undergoing restorative low proctectomy with covering proximal diversion following total mesorectal excision (TME) and to examine the diagnostic value of postoperative CRP and PCT measurements in the prediction of AL.

MATERIALS AND METHODS

Ethical permission was obtained from the local hospital ethics committee for the conduct and analysis of the study with prospective collation of data and blood sampling. Data for analysis from 100 unselected patients undergoing low anterior resection with total mesorectal excision (LAR-TME) were obtained between January

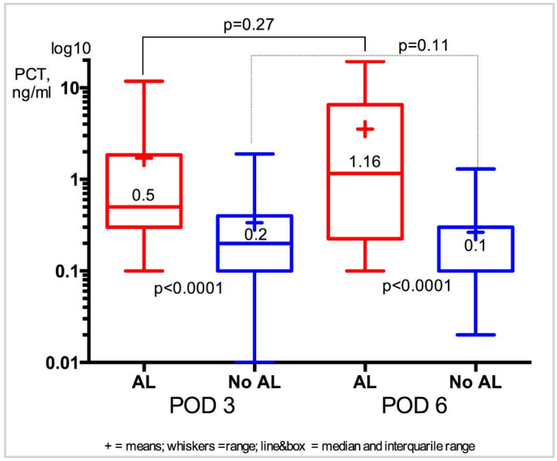

Fig. 1. Comparison of mean CRP values in AL and non-AL populations on the 3rd and 6th postoperative days.

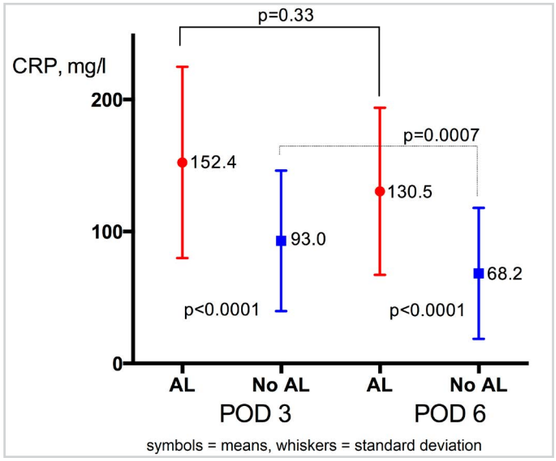

Fig. 2. Comparison of median concentration of PCT in AL and non-AL populations on the 3rd and 6th postoperative days.

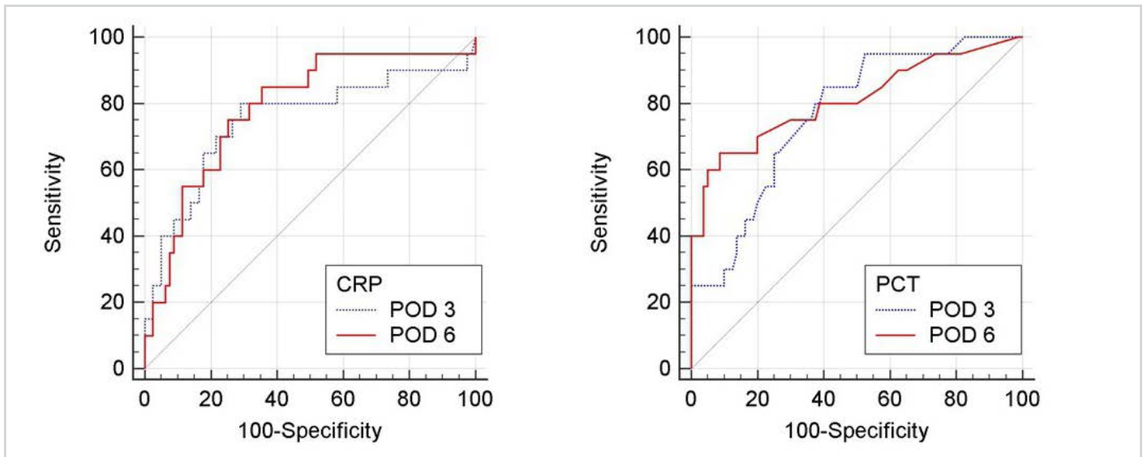

Fig. 3. Receiver operating characteristic (ROC) curves for C-Reactive Protein (mg/L) (Left-hand image) and Procalcitonin – PCT (ng/mL) (Right-hand image) for diagnosis of anastomotic leakage (AL) on the 3rd and 6th postoperative days.

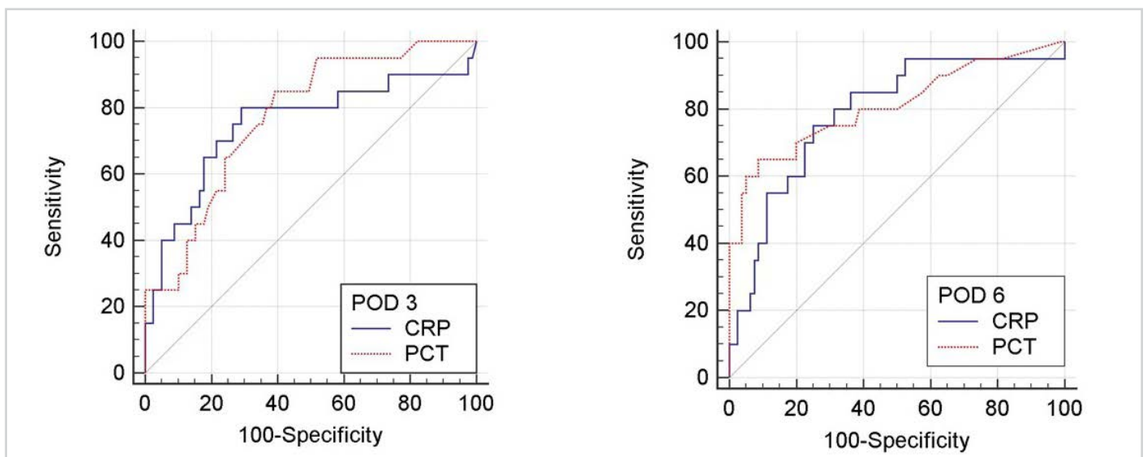

Fig. 4. Comparative receiver operating characteristic (ROC) curves for C-Reactive Protein (mg/L) and Procalcitonin – PCT (ng/mL) for diagnosis of anastomotic leakage (AL) on the 3rd (Left-hand image) and 6th (Right-hand image) postoperative days.

Tab. I. Characteristics of Study Population.

PARAMETER	RESULT
Mean age ± SD years	62.4 ± 9.2
Sex, n (%) Male Female	 46 (46.0) 54 (54.0)
Median BMI (range) kg/m²	26.0 (18.4-39.4)
Smokers, n (%) ¥	32 (32.0)
Preoperative chemoradiation, n (%)	27 (27.0)
Tumour histology, n (%) Carcinoma Adenoma	 88 (88.0) 12 (12.0)
Tumour stage TNM* Stage 0 pT0N0M0 Stage I pT1-2N0M0 Stage II pT3-4N0M0 Stage III pT1-4N1-2M0 Stage IV pT1-4N0-2M1	 2 (2.3) 22 (25.0) 33 (37.5) 24 (27.3) 7 (7.9)
Obstructing tumor, n (%)	23 (23.0)
Median operation time (range) min	153 (90 – 420)
Surgical approach, n (%) Open Laparoscopic	 88 (88.0) 12 (12.0)
Mobilisation of splenic flexure, n (%)	43 (43.0)
Type of preventive stoma, n (%) Transversostomy Ileostomy	 65 (65.0) 35 (35.0)
Type of colorectal anastomosis, n Straight Side-to-end	 81 (81.0) 19 (19.0)
Reinforcement of anastomosis	31 (36.0)
On-table lavage in LBO	9 (9.0)
Transfusion of blood components	17 (17.0)

*Percentage is calculated from the number of Adenocarcinomas (n=88)
¥ Mean smoking = 17.2 packs of cigarettes per annum
Legend: BMI – Body Mass Index, LBO – Large Bowel Obstruction, SD – Standard deviation

Tab. II. Postoperative Complications (16).

TYPE OF COMPLICATION	CLAVIEN – DINDO GRADE	N (%)*
Prolonged lymphorrhea ¥ (> 10 days)	I	1 (1.0)
Prolonged ileus (>5 days)	II	18 (18.0)
C. difficile colitis	II	11 (11.0)
Reactive pleural effusion	IIIa	1 (1.0)
Urinary retention	IIIa	7 (7.0)
Peristomal abscess	IIIa	1 (1.0)
Small bowel obstruction	IIIb	2 (2.0)
Incisional	IIIb	1 (1.0)
Anastomosis leakage (Grade B)	IIIa	**7 (7.0)**
Anastomosis leakage (Grade C)	IIIb	**4 (4.0)**
Generalised peritonitis	IVb	3 (3.0)
Death	V	2 (2.0)

*Percentage calculated from 100 patients
¥ Prolonged lymph drainage via drain following extended pelvic lymphadenectomy
ϥ Surgical site infection- subfascial abscess

2014 and December 2016 from the registry of the State Scientific Centre of Coloproctology Moscow. Low anastomoses were defined as those performed < 6 cm. from the anal verge as measured by rigid rectoscopy. Standard preoperative work-up included rigid proctoscopy plus biopsy, full colonoscopy, thoracoabdominal CT scanning and pelvic magnetic resonance imaging (MRI). Tumours unable to be negotiated by the colonoscope were labelled as incipiently obstructive. Where appropriate, neoadjuvant treatment was employed with an average radiation dose of 40cGy combined with intravenous 5-Fluorouracil or Capecitabine. Anastomoses were performed either as low end-to-end or as side-to-end configured reconstruction using a combination of a CONTOUR® Curved Cutter Stapler (Ethicon, NJ USA) for transection, with anastomosis construction utilising either a 29-mm CDH or a 31-mm EEA™ (Covidien) stapler. Where deemed appropriate, anastomoses were reinforced with interrupted 3/0 Vicryl sutures inserted on the transection end of either circular or linear staple lines. Proximal diversions were performed in all the analysed cases either utilising a transverse colostomy or a loop ileostomy.

Consensus definition and grading (A, B and C) of AL reported by the International Study Group of Rectal Cancer (15) was used. The clinical symptoms of AL used included frank signs of peritonitis, the presence of enteric-type discharge from a drain or via the wound, clinical evidence of rectovaginal fistula and/or dehiscence of the anastomotic line detected either by digital rectal examination or by endoscopy. If the postoperative period was entirely uneventful, a routine water-soluble contrast enema (Gastrografin® Bracco Russia) was performed on the 7th postoperative day. All other postoperative complications were recorded in accordance with the Clavien –Dindo classification (16).

Blood samples obtained by venepuncture for plasma PCT concentration measurement were centrifuged at 3000 rpm within 30 minutes of collection. Both PCT and CRP measurements were recorded for the 3rd and the 6th postoperative days. Procalcitonin levels were measured using the mini VIDAS® LUMItest PCT kit (Brahms Diagnostica BioMérieux SA, France) which employed an immunoluminometric assay in accordance with the manufacturer's instructions (detection limit 0.05 ng/mL). In the test, a dual antigen-antibody system is used which binds to two different PCT sites where luminescence after binding is measured with in-built software calculation by the automated Berilux Analyser 250 (Behring Diagnostics, Marburg Germany). C-reactive protein (CRP) levels were evaluated by ELISA (CX5PRO Beckman Coulter, USA) using a biotinylated detection antibody and an Avidin-Horseradish Peroxidase conjugate according to the manufacturer's instructions. The optical density (OD) of the reaction was measured spectrophotometrically at 450 nm with calculation of the CRP by comparison to a standard OD curve (Sensitivity 0.1 mg/L).

STATISTICAL ANALYSIS

Data were recorded onto Excel spreadsheets with analysis using SPSS 22.0 (Chicago, Ill.) and GraphPad Prism 6.0 (La Jolla, CA) software programs. Numerical variables were tested for normality distribution by the D'Agostino-Pearson transformation test with means (+ SD) and medians (+ range) presented where appropriate for normal and non-normal data, respectively. The unpaired t-test or the Mann-Whitney U test were used as appropriate for comparisons, with categorical variables compared using the Chi-square or Fisher's exact test where indicated. Odds ratios with 95% confidence intervals were calculated as an evaluation of the impact of individu-

Tab. III. Risk factors of anastomotic leakage (Univariate and Multivariate Analysis).

PARAMETER	AL (%)	OR	95%CI	P (UVA)	P (MVA)
Age ≤62 years >62 years	11/54 (20) 9/46 (20)	1.01	0.39–2.83	1.00	
Sex male female	15/46 (32.6) 5/54 (9.3)	4.74	1.57–14.35	**0.005**	0.61
Smoking yes no	8/32 (28) 12/68 (18.8)	1.56	0.56–4.29	0.43	
BMI (kg/m²) ≥30 <30	2/10 (20) 18/90(20)	1.00	0.20–5.12	1.00	
Preoperative CRT yes no	6/27 (22.2) 14/73 (19.2)	1.20	0.41–3.54	0.78	
Tumour histology Carcinoma Adenoma	18/91 (19.8) 2/9 (22.2)	0.84	0.17–4.51	1.00	
Tumour stage pTNM o, II III, IV	9/48 (18.8) 11/43 (25.6)	1.83	0.68–4.92	0.46	
Tumour size, cm ≥ 4.0 < 4.0	18/56(32.1) 2/44(4.5)	9.94	2.16–45.73	**0.0007**	0.96
Obstructing tumour yes no	11/23(47.8) 9/77(11.6)	6.93	2.34–20.26	**0.0005**	0.09
Height of tumour over DL, cm ≤ 6.0 > 6.0	10/35(28.6) 10/65 (15.4)	2.20	0.81–5.96	0.13	
Preoperative Haemoglobin g/L ≤90 >90	1/7 (14.3) 19/93 (20.4)	2.05	0.22–19.48	1.00	
Preoperative albumin, g/L <35 ≥35	1/6 (16.6) 19/94 (20.2)	0.79	0.09–7.16	1.00	
Operating time, min ≥180 <180	11/35 (31.4) 9/65 (18.1)	2.85	1.05-7.77	**0.048**	0.37
Intraoperative blood loss, ml ≥200 <200	15/54 (27.8) 5/46 (10.9)	3.15	1.05–9.50	**0.045**	0.15
Splenic flexure mobilisation yes no	13/57 (22.3) 7/43 (16.3)	1.52	0.55–4.21	0.46	
High-tie of IMA yes no	3/15 (20) 17/85 (20)	1.00	0.25–3.94	1.00	
Anastomosis straight side-to-end	14/81 (17.3) 6/19 (31.5)	0.45	0.15–1.00	0.20	
Reinforcement of anastomosis yes no	3/36 (8.3) 17/64 (26)	0.15	0.07–0.3	**0.002**	0.21
Circular stapler diameter, mm 29 31	5/36 (13.9) 15/64 (23.4)	0.58	0.19–1.78	0.43	
On-table lavage for LBO yes no	16/86 (18.6) 4/14(28.6)	0.62	0.16–2.06	0.47	
Type of preventive stoma, Transversostomy Ileostomy	7/35 (20) 7/65 (10.8)	2.07	0.66–6.48	0.24	
Transfusion of blood components yes no	10/27(37.0) 10/73 (13.7)	3.71	1.33–10.35	**0.02**	**0.034**
Haemoglobin on POD3 g/L ≤90 >90	4/11(36.4) 16/89 (17.8)	2.61	0.69–9.98	0.22	
Albumin on POD3, g/L <35 ≥35	19/82(23.2) 1/18 (5.6)	3.71	1.33–10.35	0.11	

Legend: UVA – Univariate analysis, MVA – Multivariate analysis AL – Anastomotic Leak, OR – Odds ratio, CI – Confidence intervals, POD – Postoperative day(s), LBO – Large bowel obstruction, IMA – Inferior mesenteric artery, CRT – Chemoradiation, BMI – Body mass index

al risk factors with a multivariate analysis conducted to determine their statistical independence. Logistic regression was then used on independent variables for comparison. Receiver operating characteristic (ROC) curves were generated creating sensitivity/specificity pairs for varying decision thresholds of both biomarkers on the 3rd and the 6th postoperative days with the calculation of positive (PPV) and negative predictive values (NPV) and relative areas under the curve (AUC). P values <0.05 were considered significant.

RESULTS

Table I shows the demographic characteristics of the study cohort, which included 54 females (mean age 62.4± 9.2 years). Over one--quarter of the cases underwent neoadjuvant therapy with 23% described as obstructing or near-obstructing tumours. Nine cases underwent on-table colonic lavage for complete or incipient obstruction with 17 receiving perioperative transfusion. 81 patients underwent straight colorectal anastomosis with 19 patients having a Baker-style side-to-end restorative proctectomy and 31 patients requiring anastomotic suture line reinforcement. In 7 cases, synchronous non-anatomical wedge resections of hepatic metastases were performed. Table II outlines the postoperative Clavien-Dindo classification for the patient cohort with 58 complications occurring overall in 27 of the cases. The majority of complications were Grade I or II in nature requiring basic pharmacological interventions and simple non-operative therapies. There were 2 patients presenting with an early adhesive small bowel obstruction who required repeat laparotomy and adhesiolysis. One case required a second laparotomy because of retraction of the ileostomy with localised peritonitis. This latter patient required drainage, peritoneal lavage and refashioning of the stoma. There were two postoperative deaths. In one case, there was a significant leak from the stump end of a side-to-end anastomosis with concomitant pelvic sepsis. Repeat laparotomy performed on the 9th postoperative day with anastomotic resection and exteriorisation was unsuccessful with the patient dying of multi-organ failure. In the other case, the patient developed multi-organ failure and generalised sepsis most likely originating from a deep wound infection in the absence of either clinical or radiological signs of an AL.

Water-soluble contrast enema detected contrast extravasation in 9 patients whose postoperative course was uneventful and in no case where there was a demonstrable radiological leak in the absence of clinical features suggestive of an AL, was there any therapeutic requirement. A clinically significant AL developed in 11 patients, 7 of whom had a Grade B complication and 4 of whom were Grade C in type. Of the Grade B cases, all were managed successfully with intravenous antibiotics and with trans-anal, trans--anastomotic drainage and irrigation. Two of the Grade C patients underwent anastomotic resection with Hartmann procedure of the rectal stump and an end colostomy. The other 2 cases underwent a repeat laparotomy with abdominal lavage and intra-peritoneal drainage only without the need for dismantling of the anastomosis.

Table III shows the results of univariate analysis of factors implicated in postoperative AL development. There is a significant negative impact of male gender (OR=4.74, 95% CI 1.57 – 14.35; P=0.005) and measured Haemoglobin < 90 g/l on the 3rd postoperative day (OR=2.60, 95% CI 1.07 – 9.98; P=0.04). Equally, a tumour size exceeding 4 cm in maximal diameter (OR=9.94, 95% CI 2.16 – 45.73; P=0.0007) and the presence of an incipiently or frankly obstructing tumour (OR=6.93, 95% CI 2.34 – 20.26; P=0.0005), significantly increased the risk of postoperative AL. Other factors which increased the likelihood of AL included those cases where there was > 200 mL of intra-operative blood loss (OR=3.15, 95% CI 1.05 – 9.50; P=0.045), patients receiving perioperative blood or blood product transfusion (OR=10.43, 95% CI 3.24 – 33.61; P=0.02) and those where the operative time exceeded 180 minutes (OR=2.85, 95% CI 1.05 – 7.77; P=0.048).

By contrast, the relative risk for AL was substantially lowered in those cases undergoing anastomotic staple line suture reinforcement (OR=0.15, 95% CI 0.03-0,07; P=0.002). Age, BMI, a history of smoking, preoperative anaemia, tumour histology or stage, a high-tie of the inferior mesenteric artery, splenic flexure mobilisation or anastomotic type did not impact the likelihood of postoperative AL. All significant variables were placed into a multivariate analysis with only the presence of a perioperative blood transfusion remaining a significant independent variable implicated in postoperative AL (OR=3.71, 95% CI 1.33-10.35; P=0.034).

Figure 1 shows a box and whisker plot for CRP measurement on the 3rd and 6th postoperative days where the median CRP at both time periods was significantly higher in the AL group when compared with the non-AL group (P < 0.0001). There was less of a decrease in CRP between the time periods in AL cases (152.4 mg/L vs. 130.5 mg/L; P=0.33) when compared with a significant reduction in CRP over time in those cases without AL (93 mg/L vs 68.2 mg/L; P =0.0007). The plot of median PCT concentrations during postoperative time periods (Figure 2) shows a significant difference between AL and non-AL cases on both the 3rd (0.5 ng/mL vs 0.2 ng/mL, respectively; P < 0.0001) and the 6th (1.16 ng/mL vs 0.1 ng/mL; P < 0.0001) postoperative days. In non-AL cases, there is a slight fall in PCT concentration over time, whereas PCT level rises by the 6th postoperative day in patients with AL, although this increase was not statistically significant.

Figure 3 shows ROC curves generated for CRP and PCT on both postoperative days. For CRP, there was a cut-off of 120 mg/L for the diagnosis of AL on the 3rd postoperative day with a sensitivity/specificity pairing of 75% and 75%, respectively (P < 0.0001). On the 6th postoperative day, the CRP cut-off was 96 mg/L with a sensitivity/specificity pairing of 80% and 71%, respectively (P=0.0007). AL cut-off for PCT was calculated at 2.4 ng/mL on the 3rd postoperative day resulting in a sensitivity/specificity pairing of 85% and 60%, respectively. PCT cut-off for diagnosis of AL decreased by the 6th postoperative day down to 0.7 ng/mL resulting in a sensitivity/specificity pairing of 65% and 91%, respectively. Both CRP and PCT demonstrated a particularly high NPV for the diagnosis of AL on the 3rd postoperative day (92.3% vs 94.2%, respectively) as well as on the 6th postoperative day (93.4% vs 91.3%, respectively). The comparative area under the curve (AUC) estimates between CRP and PCT was similar (Figure 4) where on the 3rd postoperative day,AUC for CRP was 0.75 and that for PCT was 0.77 (P=0.75). Comparative AUCs on the 6th postoperative day for CRP and PCT were 0.77 and 0.75, respectively (P=0.8).

DISCUSSION

A number of studies have examined the principal factors implicated in AL following LAR-TME (17-20) as well as the clinical va-

lue of diverting stoma (21, 22). Our rate of symptomatic leakage (11%) is in line with other reports (19, 20, 23), with Tortorelli et al. (20) also reporting an adverse effect on AL with perioperative blood transfusion, and Bertelsen et al. (17) with perioperative blood loss. The expanded use of minimally invasive techniques for LAR-TME will also significantly impact upon the amount of perioperative blood loss and may indirectly affect AL risk. Male gender in particular, as has been reported in our study, is associated with a greater risk of AL in line with other reports (17, 24), where it has been independently suggested that a more selective decision for temporary protective stoma can be made in female cases (25). Similar to our study, there has been no report of a deleterious effect on the integrity of low rectal anastomoses imposed by preoperative radiation or by neoadjuvant chemoradiation (26). Smokers had a higher risk of AL upon univariate analysis but this disappeared in multivariate analysis. Others have reported similar findings where Sorensen and colleagues have suggested that prolonged preoperative cessation of smoking is likely to have a beneficial impact (27, 28).

In general, the decision for temporary protective stoma is not made independently of anastomotic height. The principal risk factor for AL is the distance of anastomosis from the anal verge where the lower the anastomosis, the greater the risk (17, 18, 20, 23). Utilisation of stoma reduces the risk for reoperation after anastomosis as well as clinical consequences of the leak and ultimately chances of permanent stoma. Its use does not, however, eliminate the likelihood of AL itself (29). Debate is continued, concerning the best type of proximal diversion; namely loop ileostomy vs transverse colostomy. Trial data are conflicting, where in some randomised controlled trials comparing the two techniques, there is an advantage concerning the reported incidences of stoma-related complications and the need for surgical revision for either loop ileostomy (30) or alternatively, for transverse colostomy (31).

Findings similar to ours, concerning the pro-inflammatory biomarker CRP have been reported by Zawadski et al. (32) but with slightly higher discriminatory values for AL in their study by the 3rd postoperative day. An almost identical level of CRP and its postoperative timing and sensitivity for the diagnosis of AL was recently reported by Scepanovic et al (33). Several studies have compared CRP at different time points following colorectal surgery (12) where Cousin et al. (34) found a greater discrimination with CRP for AL diagnosis by the 5th postoperative day. Such timing might be too late, however, for surgical teams, which discharge their patients earlier than this time point as part of their policy of fast-track surgery. This approach would favour the use of a specific exclusionary threshold rather than an expected decrement in the biomarker used where it has been suggested that absolute values might be more accurate than the kinetics of a measurable trend (35). Studies would suggest also that a too early measurement of markers like CRP could limit diagnostic accuracy, where there is an initial postoperative generic 'inflammatory noise' that reduces both the specificity and PPV of any given test. The usefulness of such a biomarker as suggested in our study is then in the exclusion of the diagnosis of AL and is therefore best reflected in its NPV.

The dynamics of postoperative Procalcitonin (PCT) are slightly different to those of CRP, with similar findings as in our study (14, 34). Early elevation of measurable PCT (on the first or second postoperative days, for example), will be non-specific and reflect bacterial contamination or translocation secondary to bowel preparation. The PREDICS study (14) noted higher PCT levels on the 5th postoperative day than were found in our study on the 6th postoperative day, with Zawadski et al. (32) also showing higher early PCT levels in their AL cases than noted in our study. Some authors have found that PCT adds no diagnostic value for an AL (14, 35) whereas others have suggested that it is a better AL predictor when compared with CRP (36).

There are several limitations to our study. Firstly, its retrospective nature (despite prospective accumulation of data), confers a bias in reporting the incidence of postoperative complications. The prevalence of AL in our patients is in keeping with other reports, however, suggesting that there has not been an AL overestimation or a selection bias. Lack of clinician blinding to elevated biomarkers may have, however, led to a more intensive investigation of these cases creating an additional reporting bias. Once biomarkers have been chosen for clinical use in the diagnosis of AL, despite differences in their postoperative kinetics, the timing of assays appears to be as critical as is the consensus cut-off value. In this setting, NPV for an agreed cut-off level needs to be sufficiently high to be effective in deciding about postoperative hospital discharge. By contrast, the measurement of novel agents such as calprotectin, intestinal fatty acid binding protein and peritoneal fluid cytokines (10, 37) will rely on acceptable PPV values in order to judge their effectiveness as markers for the diagnosis of AL and to guide operative re-intervention. The kinetics of CRP and PCT following rectal resection and anastomosis will also most likely significantly differ between open and minimally invasive approaches and these varying postoperative stress responses will need to be determined in future studies.

REFERENCES:

1. Buchs N.C., Gervaz P., Secic M., Mugnier-Konrad B., Morel P.: Incidence, consequences, and risk factors for anastomotic dehiscence after colorectal surgery: a prospective monocentric study. Int. J. Colorectal Dis. 2008; 23: 265–270.
2. Shogan B.D., Carlisle E.M., Alverdy J.C., Umanskiy K.: Do we really know why colorectal anastomoses leak? J. Gastrointest. Surg. 2013; 17: 1698–1797.
3. Pommergaard H.C., 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: 662–671.
4. Ho Y-H., Ashour M.A.T.: Techniques for colorectal anastomosis. World J. Gastroenterol. 2010; 16: 1610–1621.
5. Nesbakken A., Nygaard K., Lunde O.C.: Outcome and late functional results after anastomotic leakage following mesorectal excision for rectal cancer. Br. J. Surg. 2001; 88:400–404.
6. Sammour T., Hayes I.P., Jones I.T., Steel M.C., Faragher I., Gibbs P.: Impact of anastomotic leak on recurrence and survival after colorectal cancer surgery: a BioGrid Australia analysis. A.N.Z. J. Surg. 2016. Doi: 10.1111/ans.13648.
7. Ashburn J.H., Stocchi L., Kiran R.P., Dietz D.W., Remzi F.H.: Consequences of anastomotic leak after restorative proctectomy for cancer: effect on long-term function and quality of life. Dis. Colon Rectum. 2013; 56: 275–280.
8. Blumetti J., Abcarian H.: Management of low colorectal anastomotic leak. World J. Gastrointest. Surg. 2015; 7: 378–383.
9. Hyman N., Manchester T.L., Osler T., Burns B., Cataldo P.A.: Anastomotic leaks after intestinal anastomosis: It's later than you think. Ann. Surg. 2007; 245: 2548
10. Reisinger K.W., Poeze M., Hulsewé K.W., van Acker B.A. et al.: Accurate prediction of anastomotic leakage after colorectal surgery using plasma markers for intestinal damage and inflammation. J. Am. Coll. Surg. 2014; 219: 744–751.
11. Warschkow R., Beutner U., Steffen T., Muller S.A., Schmied B.M., Guller U. et al.: Safe and early discharge after colorectal surgery due to C-reactive protein: a diagnostic meta-analysis of 1832 patients. Ann. Surg. 2012; 256: 245–250.
12. Singh P.P., Zeng A.S.L., Srinivasa S., Lemanu D.P., Connolly A.B., Hill A.G.: Systematic review and meta-analysis of use of serum C-reactive protein levels to predict anastomotic leak after colorectal surgery. Br. J. Surg. 2014; 101: 339–346.
13. Limper M., de Kruif M.D., Duits A.J. et al. : The diagnostic role of procalcitonin and other biomarkers in discriminating infectious from non-infectious fever. J. Infect. 2010; 60: 409–416.
14. Giaccaglia V., Salvi P.F., Antonelli M.S., Nigri G., Pirozzi F. et al.: Procalcitonin reveals early dehiscence in colorectal surgery: The PREDICS study. Ann Surg 2016; 263: 967–972.
15. Rahbari N.N., Weitz J., Hohenberger W., Heald R.J., Moran B. 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: 339–351.
16. Dindo D., Demartines N., Clavien P.A.: Classification of surgical complication: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann. Surg. 2004; 240: 205–213.
17. Bertelsen C.A., Andreasen A.H., Jørgensen T., Harling H. Danish Colorectal Cancer Group. Anastomotic leakage after anterior resection for rectal cancer: risk factors. Colorectal. Dis. 2010; 12: 37–43.
18. Chambers W.M., Mortensen N.J.: Postoperative leakage and abscess formation after colorectal surgery. Best Practice Res. Clin. Gastroenterol. 2004; 18: 865–880.
19. Eberl T., Jagoditsch M., Klingler A., Tschmelitsch J.: Risk factors for anastomotic leakage after resection for rectal cancer. Am. J. Surg. 2008; 196: 592–598.
20. Tortorelli A.P., Alfieri S., Sanchez A.M., Rosa F., Papa V. et al.: Anastomotic leakage after anterior resection for rectal cancer with mesorectal excision: Incidence, risk factors and management. Am. Surgeon. 2015; 81: 41–47.
21. Dehni N., Schlegel R.D., Cunningham C. et al.: Influence of a defunctioning stoma on leakage rates after low colorectal anastomosis and colonic J pouch--anal anastomosis. Br. J. Surg. 1998; 85: 1114–1117.
22. Marusch F., Koch A., Schmidt U. et al.: Value of a protective stoma in low anterior resections for rectal cancer. Dis. Colon Rectum. 2002; 45: 1164–1171.
23. Eriksen M.T., Wibe A., Norstein J. et al.: Anastomotic leakage following routine mesorectal excision for rectal cancer in a national cohort of patients. Colorectal Dis. 2005; 07: 51–57.
24. Law W-L., Chu K-W., Ho J.W.C., ChanC-W.: Risk factors for anastomotic leakage after low anterior resection with total mesorectal excision. Am. J. Surg. 2000; 179: 92–96.
25. Lipska M.A., Bissett I.P., Parry B.R., Merrie A.E.H.: Anastomotic leakage after lower gastrointestinal anastomosis: men are at higher risk. A.N.Z. J. Surg. 2006; 76: 579–585.
26. Nisar P.J., Lavery I.C., Kiran R.P.: Influence of neoadjuvant radiotherapy on anastomotic leak after restorative resection for rectal cancer. J. Gastrointest. Surg. 2010; 16: 1750–1757.
27. Sorensen L.T., Jorgensen T., Kirkeby L.T. et al.: Smoking and alcohol abuse are major risk factors for anastomotic leakage in colorectal surgery. Br. J. Surg. 1999; 86: 927–931.
28. Sorensen L.T., Jorgensen T.: Short-term pre-operative smoking cessation intervention does not affect postoperative complications in colorectal surgery: a randomized clinical trial. Colorectal Dis. 2003; 5: 347–352.
29. Wu S.W., Ma C.C., Yang Y.: Role of protective stoma in low anterior resection for rectal cancer: a meta-analysis. World J. Gastroenterol. 2014; 20: 18031–18037.
30. Edwards D.P., Leppington-Clarke A., Sexton R. et al.: Stoma-related complications are more frequent after transverse colostomy than loop ileostomy: a prospective randomised clinical trial. Br. J. Surg. 2001; 88: 360–363.
31. Law W.L., Chu K.W., Choi H.K.: Randomised clinical trial comparing loop ileostomy and loop transverse colostomy for faecal diversion following total mesorectal excision. Br. J. Surg. 2002; 89: 704–708.
32. Zawadski M., Czarnecki R., Rzaca M., Obuszko Z., Velchuru V.R.: C-reactive protein and procalcitonin predict anastomotic leaks following colorectal cancer resections – a prospective study. Videosurg. Miniinv. 2015; 10: 567–573.
33. Scepanovic M.S.. Kovacevic B., Cijan V., AnticA. et al.: C-reactive protein as an early predictor for anastomotic leakage in elective abdominal surgery. Tech. Coloproctol. 2013; 17: 541–547.
34. 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.
35. Facy O., Paquette B., Orry D. et al.: Diagnostic accuracy of inflammatory markers as early predictors of infection after elective colorectal surgery. Results from the IMACORS study. Ann. Surg. 2016; 263: 961–966.
36. Takakura Y., Hinoi T., Egi H., Shimomura M., Adachi T. et al.: Procalcitonin as a predictive marker for surgical site infection in elective colorectal cancer surgery. Langenbecks Arch. Surg. 2013; 398: 833–839.
37. Hyšpler R., Tichá A., Kaška M., Žaloudková L., Plíšková L., Havel E, Zadák Z.: Markers of perioperative bowel complications in colorectal surgery patients. Dis. Markers. 2015. Doi: 10.1155/2015/428535.

Word count: 2910 Page count: 8 Tables: 3 Figures: 4 References: 37

DOI: 10.5604/01.3001.0011.8169 Table of content: https://ppch.pl/issue/11207

Copyright: Copyright © 2018 Fundacja Polski Przegląd Chirurgiczny. Published by Index Copernicus Sp. z o. o. All rights reserved.

Competing interests: The authors declare that they have no competing interests.

The content of the journal „Polish Journal of Surgery" is circulated on the basis of the Open Access which means free and limitless access to scientific data.

This material is available under the Creative Commons - Attribution 4.0 GB. The full terms of this license are available on: http://creativecommons.org/licenses/by-nc-sa/4.0/legalcode

Corresponding author: Evgeny Rybakov, State Scientific Centre of coloproctology, Saliama Adila 2, Moscow, 123423, phone +7 916 1405308, fax +7 499 199 0409, e-mail erybakov@gmail.com, ORCID 0000-0002-3919-906

Cite this article as: Rybakov E., Shelygin Y., Tarasov M., Sukhina M. Zarodniuk I., Alexeev M., Chernyshov S,; Risk factors and inflammatory predictors for Anastomotic Leakage following Total Mesorectal Excision with defunctioning stoma; Pol Przegl Chir 2018: 90 (3): 25-32