Original article

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Anastomotic leakage after elective colorectal surgery: a prospective multicentre observational study on use of the Dutch leakage score, serum procalcitonin and serum C-reactive protein for diagnosis

The Italian ColoRectal Anastomotic Leakage (iCral) Study Group*

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Background: **The purpose of this study was to test use of the Dutch leakage score (DLS), serum C-reactive protein (CRP) and serum procalcitonin (PCT) in the diagnosis of anastomotic leakage (AL) after elective colorectal resection in a prospective observational study.**

Methods: **Patients undergoing elective colorectal resection with anastomosis in 19 centres were enrolled over a 1-year period from September 2017. The DLS and CRP and PCT levels were evaluated on postoperative day (POD) 2, POD3 and POD6. Statistical analysis, including determination of the area under the receiver operating characteristic (ROC) curve (AUC), was performed for the primary endpoint of AL; secondary endpoints were morbidity and mortality rates (ClinicalTrials.gov identifier: NCT03560180).**

Results: **Among 1546 patients enrolled, the AL rate was 4·9 per cent. Morbidity and mortality rates were 30·2 and 1·3 per cent respectively. With respect to AL, DLS performed better than CRP and PTC levels on POD2 and POD3 (AUC 0·75 and 0·84), whereas CRP levels were documented with better AUC values on POD6 (AUC 0·81). Morbidity was poorly predicted, whereas mortality was best predicted by PCT on POD2 (AUC 0·83) and by DLS on POD3 and POD6 (AUC 0·87 and 0·98 respectively). Overall, the combination of positive PCT, CRP and DLS values resulted in a probability of AL of 21·3 per cent on POD2, 33·4 per cent on POD3, and 47·1 per cent on POD6. However, the combination of their negative values excluded AL in 99·0 per cent of cases on POD2, 99·3 per cent on POD3, and 99·2 per cent on POD6.**

Conclusion: **DLS and CRP level are good positive and excellent negative predictors of AL; the addition of PCT improved the predictive value for diagnosis of AL.**

*Members of the iCral Study Group are co-authors of this article and may be found under the heading Collaborators

Funding information
No funding

Paper accepted 27 January 2020
Published online in Wiley Online Library (www.bjsopen.com). **DOI:** 10.1002/bjs5.50269

Introduction

Anastomotic leakage (AL) is a major complication after colorectal surgery[1], with a reported incidence ranging from 2 to 7 per cent when surgery is performed by experienced surgeons[2–7]. To limit the clinical consequences of this major complication (high reoperation rate, increased morbidity and mortality rates, and possibly worse long-term outcome), AL should be detected and treated as soon as possible. Fever, pain, tachycardia, peritoneal purulent or faecal drain, and dynamic ileus have commonly been suggested as clinical signs of AL[1–7]. These signs and others were grouped into a clinical score (Dutch leakage score, DLS)[8], useful for a specific diagnostic and therapeutic algorithm.

Moreover, several laboratory markers have been proposed, such as leucocyte count, serum procalcitonin (PCT) and C-reactive protein (CRP) levels[9–11]. In a recent prospective multicentre investigation[12], both CRP and PCT serum levels on postoperative day (POD) 3

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Table 1 Basal and postoperative values of C-reactive protein, procalcitonin and Dutch leakage score according to the endpoints

	Anastomotic leakage			Morbidity			Mortality		
	Yes	No	*P*†	Yes	No	*P*†	Yes	No	*P*†
CRP									
Basal	10·32(28·43)	10·76(22·42)	0·544	14·35(28·79)	9·16(19·67)	0·003	25·35(40·35)	10·54(22·57)	0·009
POD2	176·51(126·69)	109·01(68·01)	< 0·001	143·57(89·08)	96·49(61·79)	< 0·001	201·22(83·91)	111·27(72·61)	< 0·001
POD3	212·29(111·94)	98·61(71·51)	< 0·001	143·83(94·95)	86·45(61·12)	< 0·001	209·33(109·22)	102·80(76·51)	< 0·001
POD6*	156·06(89·11)	61·36(57·81)	< 0·001	97·79(78·71)	45·67(41·17)	< 0·001	192·66(74·43)	67·94(65·05)	0·001
PCT									
Basal	0·11(0·21)	0·13(0·40)	0·648	0·14(0·35)	0·12(0·41)	0·089	0·31(1·00)	0·13(0·38)	0·265
POD2	5·65(12·04)	1·36(3·26)	< 0·001	2·81(6·59)	1·03(2·37)	< 0·001	12·49(19·06)	1·45(3·58)	< 0·001
POD3	5·56(11·05)	0·94(2·54)	< 0·001	2·24(5·86)	0·67(1·56)	< 0·001	11·39(19·56)	1·03(2·76)	< 0·001
POD6*	4·12(6·19)	0·86(5·89)	0·002	1·87(8·15)	0·52(3·31)	< 0·001	12·70(12·93)	1·02(5·83)	0·002
DLS									
Basal	0·39(0·89)	0·25(0·72)	0·123	0·36(0·89)	0·21(0·65)	0·001	1·20(1·91)	0·24(0·69)	< 0·001
POD2	3·48(2·79)	1·53(1·39)	< 0·001	2·35(2·06)	1·31(1·12)	< 0·001	4·55(3·48)	1·59(1·48)	< 0·001
POD3	4·07(3·08)	1·15(1·31)	< 0·001	2·25(2·22)	0·87(0·90)	< 0·001	5·62(3·93)	1·24(1·46)	< 0·001
POD6*	3·40(3·51)	0·87(1·22)	< 0·001	1·79(2·22)	0·50(0·61)	< 0·001	7·64(4·40)	1·01(1·47)	< 0·001

Values are mean(s.d.). *Data available for 566 patients. CRP, C-reactive protein; PCT, procalcitonin; DLS, Dutch leakage score. †Mann–Whitney *U* test.

and POD5 were strongly suggested to be included in decision-making for patient discharge after colorectal surgery. It is still controversial whether adding PCT to CRP improves the overall accuracy of laboratory markers in the early diagnosis of AL[13,14]; a recent meta-analysis[15] failed to confirm any added value of PCT, stressing the issue of increased costs as determination of serum PCT concentration is 4–20-fold more expensive than estimation of CRP level.

Little is known about the diagnostic accuracy of the combination of clinical and laboratory markers for the diagnosis of AL, or whether the addition of the DLS to CRP and PCT may improve early AL diagnosis. A previous small (100 patients) single-centre series[16] identified cumulative (POD1–4) area under the receiver operating characteristic curve (AUC) values at 0·8357 for DLS, 0·8035 for CRP and 0·7188 for PCT. This study was conducted to evaluate AL prospectively after colorectal resection, aiming to determine the specificity and sensitivity of DLS, CRP and PCT.

Methods

A 1-year prospective observational study was conducted from September 2017 in 19 Italian centres. The study protocol (ClinicalTrials.gov NCT03560180) was registered and published beforehand[17,18]. Briefly, all consecutive patients undergoing elective colorectal surgery with anastomosis were enrolled following written informed consent. Patients were included if undergoing elective minimally invasive (laparoscopic or robotic) or open/converted ileocolorectal resection with intracorporeal or extracorporeal anastomosis, including Hartmann reversal. Exclusion criteria were: ASA grade IV–V; patients with a stoma before or at operation; stoma reversal without resection; transanal resection; pregnancy; ongoing infection before surgery; and hyperthermic intraperitoneal chemotherapy (HIPEC) for carcinomatosis.

CRP, PCT and DLS[8] were measured before surgery and on POD2, POD3 and (optional) POD6.

Postoperative clinical examination was conducted daily by the surgical team for the following signs: fever (above 38°C), pulse rate, abdominal pain, bowel movements, volume and aspect of drainage (if present). Any complementary investigation was decided according to the attending surgeon's own criteria, and imaging was not performed routinely to detect leakage.

All complications were registered according to the Clavien–Dindo classification[19,20], including leak, wound infection[21], pneumonia, central line and urinary tract infection. Follow-up was conducted in the outpatient clinic for up to 6 weeks after discharge.

The primary endpoint was AL, defined as any deviation from the planned postoperative course related to the anastomosis, presence of pus or enteric fluid in drains or an abdominal/pelvic collection in the area of the anastomosis on CT, contrast leakage through the anastomosis during administration of an enema, or anastomotic dehiscence at reoperation for postoperative peritonitis.

Secondary endpoints were morbidity and mortality rates. Readmissions and reoperations were also recorded, as

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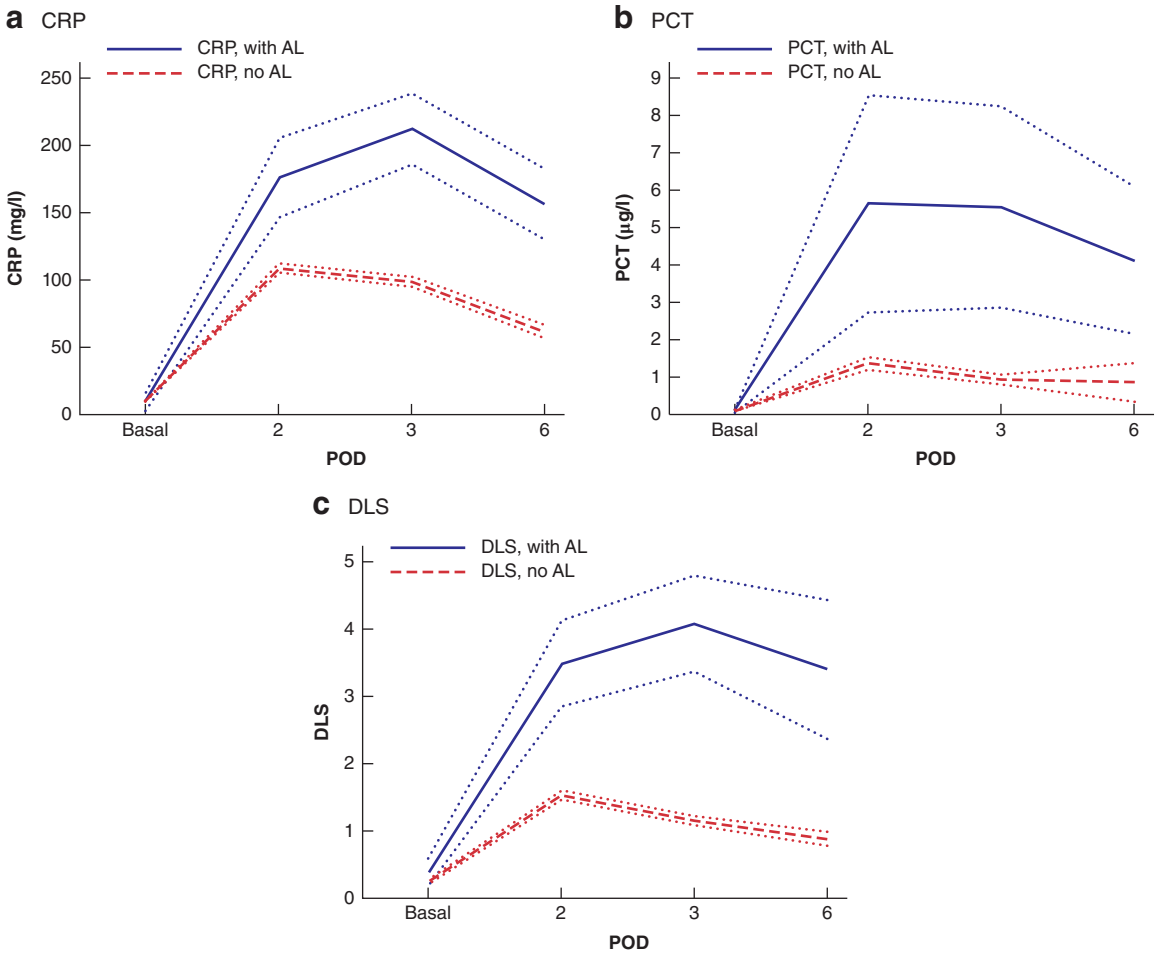
Fig. 1 Basal and postoperative C-reactive protein, procalcitonin and Dutch leakage score values according to the presence or absence of anastomotic leakage



a C-reactive protein (CRP), **b** procalcitonin (PCT) and **c** Dutch leakage score (DLS). Mean values are shown with 95 per cent confidence intervals. AL, anastomotic leakage; POD, postoperative day.

was postoperative length of hospital stay. All data were recorded prospectively, transmitted to the coordinating centre monthly, and incorporated into a spreadsheet. Any discrepancy was checked and addressed.

The ethics committee of the Comitato Etico Regionale delle Marche reviewed and approved the study protocol on 7 September 2017 (protocol number 2017-0244-AS). All participating centres submitted the protocol and obtained authorization from the local institutional review board.

Statistical analysis

As the presence of comorbidities is one of the most significant risk factors for AL[3,5,22,23], the estimated sample size was calculated on the basis of an estimated odds ratio of 5·6[22] for ASA grade I–II *versus* grade III; assuming a 95 per cent c.i. for the estimation and a maximum error of 0·04, the required sample size was 1062. Quantitative values are expressed as mean(s.d.) or median values, with ranges and 95 per cent c.i.. Categorical data are shown with percentage frequencies. Differences in continuous variables were analysed with the Mann–Whitney *U* test.

AUC values were calculated for DLS, CRP and PCT on POD2, POD3 and POD6 for all endpoints; values of 0·7–0·8 were considered acceptable, 0·8–0·9 as excellent, and those above 0·9 as outstanding[24]. Differences in AUC values were analysed with the χ^2 test. With respect to the primary endpoint of AL, optimal cut-off points for DLS,

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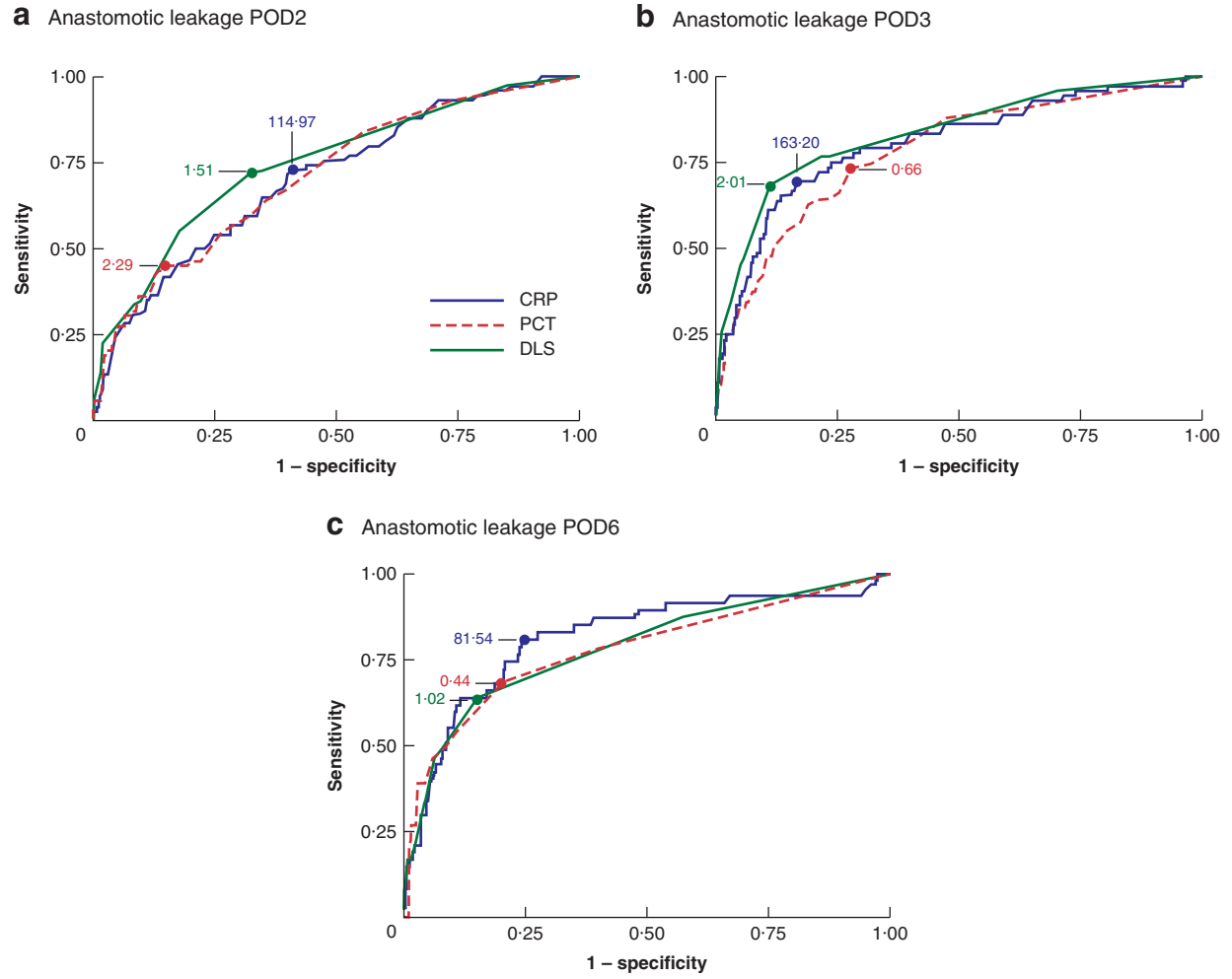
Fig. 2 Areas under the receiver operating characteristic (ROC) curve for anastomotic leakage for C-reactive protein, procalcitonin and the Dutch leakage score on postoperative days 2, 3 and 6



a Postoperative day (POD) 2, **b** POD3 and **c** POD6. Optimal cut-off values for C-reactive protein (CRP; mg/l), procalcitonin (PCT; μg/l) and the Dutch leakage score (DLS) are indicated.

CRP and PCT were obtained by applying Youden's index (sensitivity + specificity – 1), choosing AUC values where the index was maximal.

Negative (NPVs) and positive (PPVs) predictive values were also calculated. All patients with AL as defined above and with values of the three potential predictors (DLS, CRP and PCT) above the cut-off point were considered to be true positives, and all patients without AL and with potential predictor values below the cut-off point were considered true negatives. A logistic regression model was built using the presence or absence of AL as the dependent variable, and CRP, PCT and DLS values equal to or less than, or greater than their respective cut-offs as explanatory factors. Using logistic transformation of the linear predictors, the probability of AL related to different combinations of predictor values was determined.

For all statistical tests the significance level was fixed at $P < 0{\cdot}050$. Statistical analyses were carried out using STATA® software (StataCorp, College Station, Texas, USA).

Results

From September 2017 to September 2018, 1546 patients were enrolled in the study from a total of 2717 resections performed. Reasons for exclusion of 1171 patients were:

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Table 2 Receiver operating characteristic (ROC) curve analysis

	AUC	Optimal cut-off value*	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	*P*‡
Anastomotic leakage							
POD2							0·451
CRP	0·706 (0·637, 0·773)	114·97	73·0	59·0	08·3	97·7	
PCT	0·712 (0·642, 0·782)	2·29	45·0	85·3	13·1	96·9	
DLS	0·747 (0·682, 0·812)	1·51	72·4	67·3	10·3	97·9	
POD3							0·481
CRP	0·807 (0·744, 0·868)	163·20	69·4	83·4	17·5	98·2	
PCT	0·784 (0·723, 0·854)	0·66	73·1	72·2	9·2	98·2	
DLS	0·836 (0·777, 0·893)	2·01	68·5	88·8	23·8	98·2	
POD6†							0·894
CRP	0·815 (0·738, 0·891)	81·54	80·9	75·4	23·0	97·7	
PCT	0·780 (0·704, 0·874)	0·44	68·3	80·0	22·0	96·8	
DLS	0·786 (0·705, 0·865)	1·02	63·8	85·0	27·8	96·3	
Morbidity							
POD2							0·915
CRP	0·661 (0·630, 0·692)	114·97	61·0	65·4	43·1	79·6	
PCT	0·666 (0·636, 0·699)	0·29	74·3	50·5	39·5	81·8	
DLS	0·667 (0·636, 0·697)	1·51	56·2	74·7	49·1	79·8	
POD3							0·764
CRP	0·688 (0·657, 0·718)	104·23	61·1	68·9	46·6	80·0	
PCT	0·684 (0·654, 0·716)	0·26	69·1	59·3	42·7	81·4	
DLS	0·721 (0·691, 0·750)	1·51	50·2	87·3	63·7	79·8	
POD6†							0·462
CRP	0·567 (0·517, 0·615)	57·34	70·9	42·3	28·4	81·8	
PCT	0·518 (0·461, 0·567)	1·34	94·7	10·7	33·0	81·3	
DLS	0·532 (0·480, 0·582)	0·03	63·1	42·7	35·2	70·1	
Mortality							
POD2							0·340
CRP	0·807 (0·680, 0·932)	126·93	88·6	64·2	2·3	99·8	
PCT	0·829 (0·703, 0·954)	1·01	81·3	70·5	3·0	99·7	
DLS	0·823 (0·704, 0·942)	2·52	72·2	81·0	4·3	99·6	
POD3							0·251
CRP	0·793 (0·667, 0·918)	128·22	83·3	70·4	3·3	99·7	
PCT	0·843 (0·719, 0·963)	1·06	75·0	77·7	3·6	99·6	
DLS	0·869 (0·759, 0·979)	2·02	82·4	86·3	6·7	99·8	
POD6†							0·072
CRP	0·913 (0·754, 1·000)	107·09	100	80·6	5·3	100	
PCT	0·954 (0·801, 1·000)	0·897	100	86·8	5·4	100	
DLS	0·978 (0·894, 1·000)	3·51	100	94·5	18·4	100	

Values in parentheses are 95 per cent confidence intervals. *Values are mg/l for C-reactive protein (CRP) and μg/l for procalcitonin (PCT). †Data available for 566 patients. AUC, area under the receiver operating characteristic curve; PPV, positive predictive value; NPV, negative predictive value; POD, postoperative day; DLS, Dutch leakage score. ‡χ^2 test (comparison of AUC values).

stoma before or at operation, 53·9 per cent; refusal of consent, 14·7 per cent; urgent or emergency procedure, 8·0 per cent; stoma closure without resection, 5·6 per cent; transanal procedure, 3·0 per cent; ongoing infection, 1·8 per cent; ASA grade IV–V, 1·6 per cent; HIPEC, 1·0 per cent; and other reason (pregnancy, inability to complete all data requested in the case report form), 10·3 per cent. Preliminary epidemiological data have been published in a previous report[18]. Overall, neoplastic disease accounted for 68·8 per cent of the resections, and minimally invasive surgery was employed in 83·5 per cent of procedures.

Seventy-six patients (4·9 per cent) reported AL, with a mean(s.d.) time to diagnosis of 5·94(4·97) (range 1–31) days. Diagnosis was reached by CT with

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Table 3 Logistic regression analysis for the presence of anastomotic leakage according to the optimal cut-off point for the three predictors

	Coefficient	s.e.	*Z*	*P*
POD2				
CRP	0·920	0·297	3·09	0·002
PTC	0·895	0·271	3·30	0·001
DLS	1·520	0·292	5·20	< 0·001
Constant	−4·640	0·307	−15·11	< 0·001
POD3				
CRP	1·553	0·322	4·83	0·001
PTC	1·046	0·329	3·18	0·001
DLS	2·214	0·297	7·46	< 0·001
Constant	−5·005	0·309	−16·20	< 0·001
POD6				
CRP	1·482	0·465	3·19	0·001
PTC	1·474	0·415	3·55	< 0·001
DLS	1·705	0·401	4·25	< 0·001
Constant	−4·775	0·413	−10·98	< 0·001

POD, postoperative day; CRP, C-reactive protein; PTC, procalcitonin; DLS, Dutch leakage score.

Table 4 Probability of the presence or absence of anastomotic leakage according to combinations of predictor values in relation to their optimal cut-off points

	Probability of AL (%)					
	POD2		POD3		POD6	
Combination*	**PPV**	**NPV**	**PPV**	**NPV**	**PPV**	**NPV**
CRP>, PCT>, DLS>	21·3	78·7	33·4	66·6	47·1	52·9
CRP>, PCT≤, DLS>	10·0	90·0	15·0	85·0	17·0	83·0
CRP≤, PCT>, DLS>	9·8	90·2	14·8	85·2	16·9	83·1
CRP>, PCT>, DLS≤	5·6	94·4	5·8	94·2	14·0	86·0
CRP≤, PCT≤, DLS>	4·2	95·8	5·2	94·8	4·4	95·6
CRP>, PCT≤, DLS≤	2·4	97·6	1·9	98·1	3·6	96·4
CRP≤, PCT>, DLS≤	2·3	97·7	1·9	98·1	3·6	96·4
CRP≤, PCT≤, DLS≤	1·0	99·0	0·7	99·3	0·8	99·2

*>, Indicates value above optimal cut-off point; ≤, indicates value equal to or less than optimal cut-off point. AL, anastomotic leakage; POD, postoperative day; PPV, positive predictive value; NPV, negative predictive value; CRP, C-reactive protein; PCT, procalcitonin; DLS, Dutch leakage score.

water-soluble contrast enema (30 patients, 39 per cent) or intravenous contrast (22, 29 per cent), clinical evaluation (23, 30 per cent) and endoscopy (1 patient, 1 per cent). The degree of severity of AL was Clavien–Dindo grade IIIa in one patient (1 per cent), grade IIIb in 69 patients (91 per cent), and grade IVb in six (8 per cent).

The overall morbidity rate was 30·2 per cent, and included 447 grade I–II and 185 grade III–IVb complications[18]. The operative mortality rate was 1·3 per cent. Fourteen patients were readmitted to hospital, and 107 (6·9 per cent) required reoperation. The mean(s.d.) duration of postoperative hospital stay was 7·89(5·97) (median 6, 95 per cent c.i. 7·59 to 8·19, range 1–120) days.

Basal and postoperative values of CRP, PCT and DLS according to the endpoints are shown in *Table 1* and *Fig. 1*.

With respect to AL, DLS performed better than CRP and PTC (highest AUC value) on POD2 and POD3, whereas CRP level had better sensitivity and specificity curves on POD6 (*Fig. 2*). Morbidity was predicted poorly by all laboratory values and clinical score, whereas mortality was predicted best by PCT on POD2 and by DLS on POD3 and POD6. No differences between AUCs were statistically significant (*Table 2*).

Logistic regression confirmed the statistical significance of all the three predictors with regard to AL (*Table 3*). The probability of AL according to CRP, PCT and DLS values below or above their cut-off points are shown in *Table 4*. The maximal PPVs (all predictor values above the cut-off points) were 21·3 per cent on POD2, 33·4 per cent on POD3, and 47·1 per cent on POD6. The maximal NPVs (all predictor values equal to or less than cut-off points, last row) were 99·0, 99·3 and 99·2 per cent on POD2, POD3 and POD6 respectively.

Discussion

This multicentre prospective study has demonstrated that the combination of laboratory markers and clinical scoring system allows the exclusion of AL in the early postoperative period (NPV 99·0 per cent on POD2).

The main potential source of bias in this prospective study was the exclusion of 1171 patients (43·1 per cent), mainly due to the presence of a diverting stoma (53·9 per cent of exclusions), in the evaluation of the diagnostic yield of clinical and serum biomarkers for AL[25]. Another possible confounder was the recorded proportion of minimally invasive resections (83·5 per cent), which was higher than that reported (40–46·7 per cent) in the same period in a nationwide database[26]. This finding probably reflects the exclusion of urgent resections and the particular interest in colorectal resection and minimally invasive surgery in participating centres.

AL was detected in 76 patients (4·9 per cent), well within the range (2·7–10 per cent) reported previously in large cohort studies[22,27–30]. The mean time to diagnosis of AL was 5·94 days (median POD5), compared with 12·7 days (median POD8) in open colorectal resections[4]. It remains difficult to establish whether this was actually earlier diagnosis, as the use of both clinical and serological markers for

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AL diagnosis in the present study may have focused special attention on this diagnosis, or whether this was simply an earlier appearance of AL due to the high rate of minimally invasive resections (earlier return of bowel function compared with open surgery). In any case, this finding deserves particular attention when considering the increasing use of enhanced recovery programmes in colorectal surgery[31,32].

With regard to laboratory markers, significant differences in postoperative values were observed in patients with AL and those without. Both CRP and PCT levels showed their typical course as acute-phase proteins induced by the systemic inflammation response, peaking at POD2 (PCT) and at POD3 (CRP), as reported previously[10–14,33].

Different clinical scoring systems for early diagnosis of AL have been suggested[8,34], externally validated[16] and further modified[35]. Although not statistically significant as a predictor of AL, the clinical score (DLS) appeared to be the best predictor of AL on POD2 and POD3. This score was devised to reduce the delay in the diagnosis of AL and related mortality; it was originally based[8] on 11 easily accessible and recordable clinical parameters and on two laboratory tests (a 5 per cent increase in leucocytes or CRP, and a 5 per cent increase in blood urea or creatinine), with scores ranging from 0 to 20 (cut-off 4), and then simplified and revalidated using three clinical parameters and one laboratory test (CRP levels above 250 mg/l), with scores ranging from 0 to 4 (cut-off 1), maintaining the same diagnostic accuracy[35]. In the present study protocol[17], the original DLS was applied.

The addition of PCT to DLS and CRP improved both the cumulative PPV and NPV of tests for the presence or absence of AL. However, PCT was the best predictor of mortality on POD2 (AUC 0·829; cut-off 1·01 μg/l; NPV 0·997), confirming its role in patients with ongoing sepsis[36]. Although previous studies[14,15] suggested that PCT should not be used routinely as a biochemical marker for early diagnosis of AL after elective colorectal surgery, owing to its poor cost-effectiveness, the combined use of DLS, CRP and PCT on POD2 and POD3 may be useful to predict or exclude patients with clinically severe AL and potentially uncontrolled sepsis and death.

Collaborators

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Acknowledgements

Medtronic SI® Italy provided liberal and unconditional economic support for the organization of three investigator meetings, held in Milan, Italy, in September 2017 and June 2018, and in Rome, Italy, in October 2018.
Disclosure: The authors declare no conflict of interest.

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