Int J Colorectal Dis (2011) 26:1405–1413
DOI 10.1007/s00384-011-1262-0

ORIGINAL ARTICLE

Diagnostic accuracy of C-reactive protein and white blood cell counts in the early detection of inflammatory complications after open resection of colorectal cancer: a retrospective study of 1,187 patients

Rene Warschkow · Ignazio Tarantino · Michael Torzewski · Franziska Näf · Jochen Lange · Thomas Steffen

Accepted: 10 June 2011 / Published online: 24 June 2011

Abstract
Purpose Although widely used, there is a lack of evidence concerning the diagnostic accuracy of C-reactive protein (CRP) and white blood cell counts (WBCs) in the postoperative period. The aim of this study was to evaluate the diagnostic accuracy of CRP and WBCs in predicting postoperative inflammatory complications after open resection of colorectal cancer.
Methods In this retrospective study, clinical data and the CRP and WBCs, routinely measured until postoperative day 5 (POD 5), were available for 1,187 patients who underwent colorectal cancer surgery between 1997 and 2009. Using the receiver-operating characteristic (ROC) methodology, the diagnostic accuracy was evaluated according to the area under the curve (AUC).
Results Three hundred forty-seven patients (29.2%; 95% CI, 26.7–31.9%) developed various inflammatory complications. Anastomotic leakage occurred in 8.0% (95% CI, 6.1–9.1%) of patients. The CRP level on POD 4 (AUC 0.76; 95% CI, 0.71–0.81) had the highest diagnostic accuracy for the early detection of inflammatory complications. With a cutoff of 123 mg/l, the sensitivity was 0.66 (95% CI, 0.56–0.74), and the specificity was 0.77 (95% CI, 0.71–0.82). The diagnostic accuracy of the WBC was significantly lower compared to CRP.
Conclusion Measurement of CRP on POD 4 is recommended to screen for inflammatory complications. CRP values above 123 mg/l on POD 4 should raise suspicion of inflammatory complications, although the discriminatory performance was insufficient to provide a single threshold that could be used to correctly predict inflammatory complications in clinical practice. WBC measurement contributes little to the early detection of inflammatory complications.
Registered at www.clinicaltrials.gov (NCT01221324)

Keywords C-reactive protein · White blood cell count · Colorectal · ROC

R. Warschkow (✉) · I. Tarantino · F. Näf · J. Lange · T. Steffen
Department of Surgery, Kantonsspital St. Gallen,
9007 St. Gallen, Switzerland
e-mail: rene.warschkow@kssg.ch

R. Warschkow
Institute of Medical Biometry and Informatics,
Department of Medical Biometry, University of Heidelberg,
69120 Heidelberg, Germany

M. Torzewski
Institute of Clinical Microbiology and Immunology,
9007 St. Gallen, Switzerland

Introduction

Septic complications after colorectal resection for cancer are observed in up to 40% [1, 2] of cases and consist mainly of surgical site infections (up to 40%), pulmonary infections (10%) and urinary infections (5%) [3]. Anastomotic leakage is the most feared complication after colorectal cancer resection and is frequently diagnosed late in the postoperative period, after a mean of 13 days [4]. Other inflammatory complications are diagnosed as late as the ninth postoperative day [5]. Although measurements of C-reactive protein (CRP) and white blood cell counts

(WBCs) are performed extensively, there is still a lack of evidence about their diagnostic value in predicting inflammatory complications, and the optimal timing for such measurements after colorectal cancer surgery remains unknown. It has been reported that for patients with inflammatory complications after colorectal surgery, pre-emptive antibiotic therapy may significantly improve outcomes [6]. Furthermore, in sepsis, early goal-directed therapy is essential in improving survival [7]. Therefore, there is a need for the early detection of infectious complications to facilitate the initiation of adequate treatment as soon as possible. Although procalcitonin levels seem to have a higher diagnostic accuracy than CRP in the detection of inflammatory complications, CRP is the most popular and most widely available marker of the acute inflammatory response [6, 8, 9]. Peak serum levels of CRP lag approximately 2 days behind the initiation of an acute systemic inflammatory response, and its half-life of approximately 19 h is short enough to establish CRP as a valuable marker of inflammatory processes [10–12].

The literature on the diagnostic value of CRP and WBCs after colorectal cancer surgery is limited. Based on small heterogeneous patient groups, some studies failed to demonstrate a relevant diagnostic value of CRP in the detection of inflammatory complications [13]. Other studies did not apply the statistically adequate receiver-operating characteristic (ROC) analysis, probably because of the small sample sizes [5, 14]. In other studies, CRP and WBCs were examined only every other day [15]. One recently published study examining a small cohort estimated an optimal cut-off value of 145 mg/l for CRP on postoperative day 4 (POD 4), which yielded a sensitivity of 0.85 and a specificity of 0.86; the WBC was not assessed [16]. Other studies focused on postoperative changes in CRP rather than on absolute values and identified a lack of decline as a prognostic marker of anastomotic leakage [17].

The present study aimed to assess the diagnostic accuracy of absolute CRP and WBC values and their dynamics in the early detection of inflammatory complications from POD 1 to POD 5 in a series of unselected consecutive patients after colorectal cancer resection.

Patients and methods

The study design was retrospective. A computer search of the institutional database identified a total of 1,238 patients with histologically proven colorectal adenocarcinoma who underwent primary colorectal cancer resection between January 1997 and August 2009. All patients routinely received preoperative antibiotic prophylaxis (500 mg metronidazole i.v. and 2,000 mg cefamandole i.v. for 60 min before surgery) and anticoagulation with low-molecular-weight heparin, in accordance with hospital guidelines.

Data collection and definitions

Data on patient demographics, operative details, postoperative mortality, morbidity and histological results were gathered retrospectively from the medical records. Mortality was defined as any death that occurred on or before the 30th postoperative day. Anastomotic leakage was defined as the presence of an intra-abdominal abscess with confirmation by rectal examination, sigmoidoscopy, extravasation of endoluminally administered water-soluble contrast on radiography or computed tomography or confirmation upon return to the operating room. Wound infections and intra-abdominal abscesses that were not related to anastomotic leakages were recorded according to the diagnosis in the medical records or operation protocols. Pneumonia was recorded when explicitly stated as a diagnosis in the medical records or as a radiological finding. Urinary infections, central line infections, *Clostridium difficile* colitis, or other infections were recorded when explicitly stated in the medical records or when there were bacteriological findings, independent of treatment.

CRP and WBC measurement

CRP concentrations were measured using an automated analytical system (Unicel DxC 800, Beckman Coulter, reference range <8 mg/l). WBCs were performed using an automated haematology analyzer (Sysmex XE-5,000, reference range 4–10 G/l). For CRP, the range of measurement was limited to between 3 and 300 mg/l until August 2005. Subsequent to that, the measurement range was extended to between 1 and 500 mg/l. Therefore, all CRP values exceeding 300 mg/l were designated as 300 mg/l, and values lower that 3 mg/l were designated as 3 mg/l.

Statistical analysis and authorization

Statistical analysis was performed using the R environment (http://www.rproject.org). Two-sided p values <0.05 were considered statistically significant. Continuous data are expressed as the mean±standard deviation or interquartile range (IQR), as appropriate. Confidence intervals (95% CI) of binominal proportions were estimated according to a modified Wilson's method [18].

The diagnostic accuracy was evaluated with the area under the curve (AUC), using the ROC methodology [19]. The AUCs were computed using the non-parametric trapezoidal method, and their 95% confidence limits were computed according to method established by DeLong [20]. Cut-off values were estimated by optimizing the Youden index. Nonparametric 95% CIs for the cut-off

values were computed with bootstrapping using the percentile method (1,999 estimates) [21, 22].

The study was approved by the Swiss Federal Expert Commission for Physician Confidentiality and by the institutional ethical review board. It was registered at www.clinicaltrials.gov (NCT01221324).

Results

Exclusion criteria, baseline and outcomes

For all 1,238 patients with open colorectal cancer resection, clinical follow-up data for a minimum of 2 months were available. Of these patients, 51 were excluded from further analysis because of a lack of CRP and WBC measurements until POD 5. Thus, 1,187 patients were available for further analysis. Compared to the included patients, the excluded patients developed pneumonia less often (3.9% versus 10.2%, p=0.001), resulting in significantly fewer inflammatory complications (23.5% versus 29.2%, p=0.024) (Table 1).

Of the 1,187 patients, 26 died (2.2%; 95% CI, 1.5–3.2%). Inflammatory complications occurred in 347 patients (29.2%; 95% CI, 26.7–31.9%), and anastomotic leakage occurred in 89 of the 1,115 patients who received anastomoses (8.0%; 95% CI, 6.1–9.1%). Leakage was diagnosed after a median of 9.0 days postoperatively (IQR, 6–14 days). Patients with inflammatory complications presented with significantly higher ASA stages, showed a significantly higher prevalence of rectal cancer and received stomas more frequently (Table 2).

Table 1 Inflammatory complications in included and excluded patients

	Total N=1,238	Included N=1,187	Excluded N=51	p value[a]
Any infectious complication	359 (29.0%)	347 (29.2%)	12 (23.5%)	0.024
Anastomotic leakage[b]	91 (7.8%)	89 (8.0%)	2 (4.3%)	0.813
Deep abscess[c]	47 (3.8%)	46 (3.9%)	1 (2.0%)	0.504
Wound infection	78 (6.3%)	77 (6.5%)	1 (2.0%)	0.799
Pneumonia	126 (10.2%)	124 (10.4%)	2 (3.9%)	0.001
Urinary tract infection	92 (7.4%)	87 (7.3%)	5 (9.8%)	0.733
Central line infection	41 (3.3%)	39 (3.3%)	2 (3.9%)	0.574
Clostridium difficile colitis	12 (1.0%)	12 (1.0%)	0 (0.0%)	0.591
Other infection [d]	18 (1.5%)	18 (1.5%)	0 (0.0%)	0.923

[a] Chi-squared test

[b] Analysis for anastomotic leakage limited to 1,162/1,115/47 patients with anastomosis

[c] Not related to anastomosis

[d] Cholecystitis, pancreatitis, genital or facial infections

Postoperative course of CRP and WBCs

A total of 951 patients (80.1%) had 2.0±1.0 CRP measurements through POD 5, and 1,183 (99.7%) had 2.8±1.2 WBC measurements through POD 5. Table 3 compares the CRP and WBC values from patients with and without inflammatory complications. In both groups, the highest CRP and WBC values occurred on POD 2. Patients with inflammatory complications had significantly higher CRP values on POD 2 to POD 5. WBC values were significantly higher in patients with inflammatory complications at every time-point except on POD 2.

Diagnostic accuracy of absolute values of CRP and WBCs

Figure 1 presents the ROC plots for the diagnostic accuracy of CRP levels in predicting inflammatory complications between POD 2 and POD 5. CRP measured on POD 4 had the highest diagnostic accuracy. The intrinsic diagnostic accuracy of CRP and WBC values for inflammatory complications is shown in detail in Table 4. Compared to the diagnostic accuracy of WBCs, CRP had a significantly greater AUC on POD 2 (p=0.034), POD 3 (p=0.003) and POD 4 (p<0.001), but not on POD 5 (p=0.415).

The highest diagnostic accuracy was observed for CRP measured on POD 4, with an AUC of 0.76 (95% CI, 0.71–0.81). The statistically optimal cut-off value for CRP to discriminate between patients with and without inflammatory complications on POD 4 was 123 mg/l (95% CI, 94–160 mg/l). Of 103 patients with inflammatory complications, 68 had CRP values above this cutoff, such that the sensitivity was 0.66 (95% CI, 0.56–0.74). In 162 of 211 patients without inflammatory complications, CRP values did not exceed 123 mg/l, yielding a specificity of 0.77 (95% CI, 0.71–0.82). In Fig. 2, the sensitivity and specificity of CRP measurement on POD 4 in predicting inflammatory complications are plotted over the entire range of CRP measurements. The cut-off value for a sensitivity of 90% was estimated to be 56 mg/l (95% CI, 42–70 mg/l); for a specificity of 90%, the cut-off value was 200 mg/l (95% CI, 151–243 mg/l).

Applying the cut-off value of 123 mg/l for CRP on POD 4, the positive predictive value (PPV) was 0.54 (95% CI, 0.48–0.59), and the negative predictive value (NPV) was 0.85 (95% CI, 0.80–0.88) after adjusting for the observed prevalence of 29.2% in the entire study population. For an NPV of 0.90, the corresponding cut-off value was 54 mg/l. In 71 of 314 patients (22.6%), CRP on POD 4 did not exceed this value. Seven of these patients were classified as false negatives, but developed only less serious complica-

Table 2 Baseline data and clinical outcomes

		Total	Inflammatory complications		*p* value
		N=1,187	Yes (*N*=347)	No (*N*=840)	
Age	[years]	66.9±12.1	68.2±12.1	66.4±12.1	0.021[a]
Body mass index	[kg/m^2]	25.6±4.4	25.6±4.5	25.7±4.3	0.643[a]
Gender	Male	729 (61.4%)	218 (62.8%)	511 (60.8%)	0.522[b]
	Female	458 (38.6%)	129 (37.2%)	329 (39.2%)	
ASA stage	I	102 (8.6%)	22 (6.3%)	80 (9.5%)	<0.001[a,c]
	II	750 (63.2%)	204 (58.8%)	546 (65.0%)	
	III	312 (26.3%)	111 (32.0%)	201 (23.9%)	
	IV	19 (1.6%)	9 (2.6%)	10 (1.2%)	
	X	4 (0.3%)	1 (0.3%)	3 (0.4%)	
Cancer	Colon	650 (54.8%)	176 (50.7%)	474 (56.4%)	0.072[b]
Localization	Rectal	537 (45.2%)	171 (49.3%)	366 (43.6%)	
UICC stage	I	244 (20.6%)	75 (21.6%)	169 (20.1%)	0.695[a,c]
	II	324 (27.3%)	88 (25.4%)	236 (28.1%)	
	III	291 (24.5%)	83 (23.9%)	208 (24.8%)	
	IV	281 (23.7%)	94 (27.1%)	187 (22.3%)	
	X	30 (2.5%)	5 (1.4%)	25 (3%)	
Main operation	Ileocoecal resection	4 (0.3%)	0 (0.0%)	4 (0.5%)	0.019[b]
	Right hemicolectomy	256 (21.6%)	72 (20.7%)	184 (21.9%)	
	Transverse colectomy	9 (0.8%)	4 (1.2%)	5 (0.6%)	
	Left hemicolectomy	71 (6.0%)	17 (4.9%)	54 (6.4%)	
	Anterior resection	296 (24.9%)	78 (22.5%)	218 (26.0%)	
	Low anterior resection	428 (36.1%)	135 (38.9%)	293 (34.9%)	
	Total colectomy	41 (3.5%)	14 (4.0%)	27 (3.2%)	
	Abdominoperineal resection	45 (3.8%)	22 (6.3%)	23 (2.7%)	
	Segmental resection	15 (1.3%)	3 (0.9%)	12 (1.4%)	
	Transanal resection	22 (1.9%)	2 (0.6%)	20 (2.4%)	
Operation time	[min]	159.4±72.1	169±78.2	155.4±69	0.011[a]
Ostomy	No	795 (67.0%)	206 (59.4%)	589 (70.1%)	<0.001[b]
	Yes	392 (33.0%)	141 (40.6%)	251 (29.9%)	
Surgery	Elective	1,090 (91.8%)	315 (90.8%)	775 (92.3%)	0.396[b]
	Urgency	97 (8.2%)	32 (9.2%)	65 (7.7%)	
Additional operation	No	894 (75.3%)	258 (74.4%)	636 (75.7%)	0.620[b]
	Yes	293 (24.7%)	89 (25.6%)	204 (24.3%)	
Re-intervention w/in 30 days	No	1,018 (85.8%)	237 (68.3%)	781 (93.0%)	<0.001[b]
	Yes	151 (12.7%)	110 (31.7%)	41 (4.9%)	
Mortality w/in 30 days	No	1,157 (97.5%)	330 (95.1%)	827 (98.5%)	<0.001[b]
	Yes	26 (2.2%)	17 (4.9%)	9 (1.1%)	
Hospitalisation	[days]	20.7±12.2	27.9±16.4	17.6±8.1	<0.001[a]

[a] Mann–Whitney test

[b] Chi-squared test

[c] Analysis without missing values

tions such as pneumonia (*N*=4), urinary tract infections (*N*=3) and a central line infection (*N*=1).

Diagnostic accuracy of increasing CRP and WBCs

In 55 patients, CRP was measured both on POD 3 and POD 4. Increasing CRP values were observed in 9 of 29 patients with inflammatory complications (sensitivity 0.31; 95% CI, 0.17–0.49) and in 1 of 26 patients without inflammatory complications (specificity 0.96; 95% CI, 0.81–0.99). In 52 patients, CRP was measured both on POD 4 and POD 5. Increasing CRP values were observed in 15 of 35 patients with inflammatory complications (sensitivity 0.43; 95% CI, 0.28–0.59) and in 1 of 17 patients without

Table 3 Postoperative course of CRP and WBC

	Total		Inflammatory complications				*p* value[a]
			Yes		No		
	N	Med (IQR)	*N*	Med (IQR)	*N*	Med (IQR)	
CRP [mg/l]							
Preoperatively	562	5.5 (3.0–21.0)	178	7.0 (3.0–36.0)	384	5.0 (3.0–17.0)	0.006
POD 1	131	97.0 (66.0–136.0)	47	105.0 (68.0–148.0)	84	94.5 (65.0–127.5)	0.283
POD 2	256	151.5 (105.5–213.5)	83	187.0 (118.0–248.0)	173	142.0 (96.5–194.5)	<0.001
POD 3	237	141.0 (100.5–213.5)	91	190.0 (124.0–255.0)	146	123.0 (86.0–176.3)	<0.001
POD 4	314	100.5 (52.0–163.8)	103	163.0 (102.0–270.0)	211	78.0 (43.0–120.0)	<0.001
POD 5	298	69.0 (34.0–129.3)	112	94.5 (53.0–200.8)	186	56.5 (28.8–98.3)	<0.001
WBC [G/l]							
Preoperatively	821	6.5 (5.3–8.1)	247	6.9 (5.4–8.7)	574	6.4 (5.2–7.9)	0.031
POD 1	452	8.7 (6.9–10.8)	146	8.9 (7.8–11.3)	306	8.4 (6.8–10.6)	0.032
POD 2	568	8.5 (6.9–10.6)	174	9.1 (7.2–11.1)	394	8.3 (6.9–10.3)	0.025
POD 3	424	7.8 (6.3–10.4)	157	8.3 (6.7–11.3)	267	7.6 (6.2–9.5)	0.005
POD 4	458	7.1 (5.6–9.1)	140	7.6 (5.9–10.4)	318	6.9 (5.5–8.6)	0.005
POD 5	405	7.2 (5.6–9.6)	146	8.6 (6.7–11.2)	259	6.7 (5.3–8.7)	<0.001

[a] Mann–Whitney test

inflammatory complications (specificity 0.94; 95% CI, 0.73–0.99). After adjusting for the prevalence of 29.2% in the study population, increases in CRP between POD 4 and POD 5 were calculated to have a PPV of 0.75 (95% CI, 0.62–0.85) and an NPV of 0.80 (95% CI, 0.67–0.89). Combining the results of the CRP measurement on POD 4 and the increase in CRP from POD 4 to POD 5 did not improve the diagnostic accuracy, regardless of whether the 'believe-the-positive' or the 'believe-the-negative' rule was applied [23].

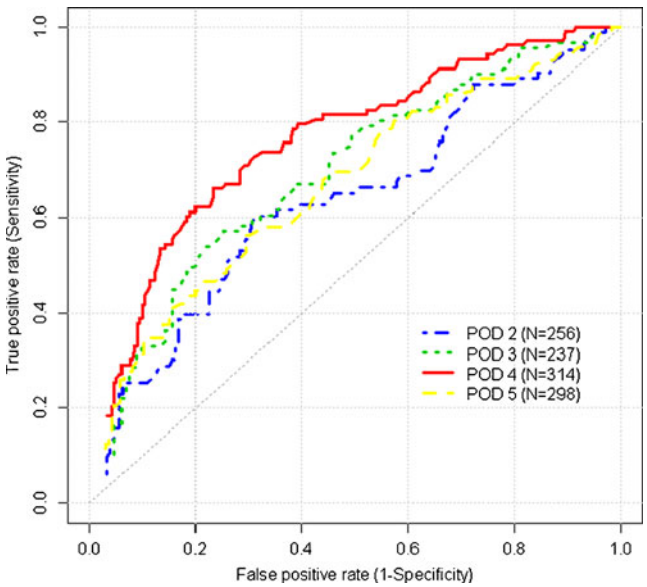

Fig. 1 Empirical ROC plots for diagnostic accuracy of CRP in detecting inflammatory complications at POD 2 to POD 5. The *curves* occur in pairs of sensitivity and false-positive rate (1-specificity) of CRP on PODs 2–5 with AUCs of 0.64, 0.69, 0.76 and 0.67. A perfect marker would have an ROC plot along the *left side* and the *top* of the graph. CRP measured on POD 4 is superior to the other CRP measurement. The ROC plot for CRP on POD 4 does not cross the other plots. All ROC plots are above the *diagonal line*, which is equivalent to classification due to chance with an AUC of 0.5 ('chance diagonal')

In 115 patients, WBC measurements were available on POD 3 and POD 4. Increases in the WBC occurred in 25 of 57 patients with inflammatory complications (sensitivity 0.44; 95% CI, 0.32–0.57) and in 18 of 58 patients without inflammatory complications (specificity 0.69; 95% CI, 0.56–0.79). In 98 patients, WBC measurements were obtained on both POD 4 and POD 5. Increasing WBC levels were observed in 29 of 56 patients with inflammatory complications (sensitivity 0.52; 95% CI, 0.39–0.64) and in 19 of 42 patients without inflammatory complications (specificity 0.55; 95% CI, 0.40–0.69). The PPV was 0.32 (95% CI, 0.24–0.42), and the NPV was 0.73 (95% CI, 0.64–0.81).

Subgroup analysis for anastomotic leakage

In a subgroup analysis, the diagnostic accuracy of CRP and WBC levels in predicting anastomotic leakage was analysed in the 1,115 patients who received anastomoses. Anastomotic leakage was highly correlated with other inflammatory complications; 54 of 89 (60.7%; 95% CI, 50.3–70.2%) patients with anastomotic leakage developed other inflammatory complications. The detailed results for

Table 4 Intrinsic diagnostic accuracy of CRP and WBC for inflammatory complications

	N	Prevalence	Optimal cut-off (95% CI)	TP	FN	TN	FP	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	p_{AUC}
CRP preoperatively	562	31.7%	28 (4–36)	51	127	322	62	0.29 (0.23–0.36)	0.84 (0.80–0.87)	0.56 (0.53–0.60)	0.006
CRP day 1	131	35.9%	123 (51–175)	19	28	62	22	0.40 (0.28–0.55)	0.74 (0.64–0.82)	0.56 (0.46–0.66)	0.283
CRP day 2	256	32.4%	173 (165–248)	50	33	119	54	0.60 (0.49–0.70)	0.69 (0.62–0.75)	0.64 (0.57–0.70)	<0.001
CRP day 3	237	38.4%	185 (122–203)	49	42	114	32	0.54 (0.44–0.64)	0.78 (0.71–0.84)	0.69 (0.63–0.75)	<0.001
CRP day 4	314	32.8%	123 (94–160)	68	35	162	49	0.66 (0.56–0.74)	0.77 (0.71–0.82)	0.76 (0.71–0.81)	<0.001
CRP day 5	298	37.6%	83 (46–161)	63	49	131	55	0.56 (0.47–0.65)	0.70 (0.64–0.77)	0.67 (0.62–0.72)	<0.001
WBC preoperatively	821	30.1%	7.5 (6.0–8.7)	102	145	394	180	0.41 (0.35–0.48)	0.69 (0.65–0.72)	0.55 (0.52–0.58)	0.031
WBC day 1	452	32.3%	7.8 (7.7–8.5)	110	36	130	176	0.75 (0.68–0.82)	0.42 (0.37–0.48)	0.56 (0.52–0.61)	0.032
WBC day 2	568	30.6%	9.2 (8.0–10.5)	86	88	251	143	0.49 (0.42–0.57)	0.64 (0.59–0.68)	0.56 (0.52–0.60)	0.025
WBC day 3	424	37.0%	9.9 (7.3–10.0)	65	92	210	57	0.41 (0.34–0.49)	0.79 (0.73–0.83)	0.58 (0.54–0.63)	0.005
WBC day 4	458	30.6%	9.4 (7.1–9.9)	49	91	261	57	0.35 (0.28–0.43)	0.82 (0.77–0.86)	0.58 (0.54–0.63)	0.005
WBC day 5	405	36.0%	7.1 (6.7–9.9)	102	44	151	108	0.70 (0.62–0.77)	0.58 (0.52–0.64)	0.66 (0.61–0.71)	<0.001

Analysis of receiver-operating characteristic (ROC) curves for inflammatory complications; AUC was estimated non-parametrically with the trapezoidal method

Table provides case loads with CRP/WBC values, prevalence of inflammatory complications, optimal cut-off value maximizing the Youden Index, true-positive (TP), false-negative (FN), true-negative (TN) and false-positive (FP) cases, as well as the sensitivity, and specificity for the cut-off value and p_{AUC} for discrimination between positive and negative cases. Area under the ROC curve (AUC), cuff-off values, sensitivity, specificity and AUC are provided with 95% confidence intervals

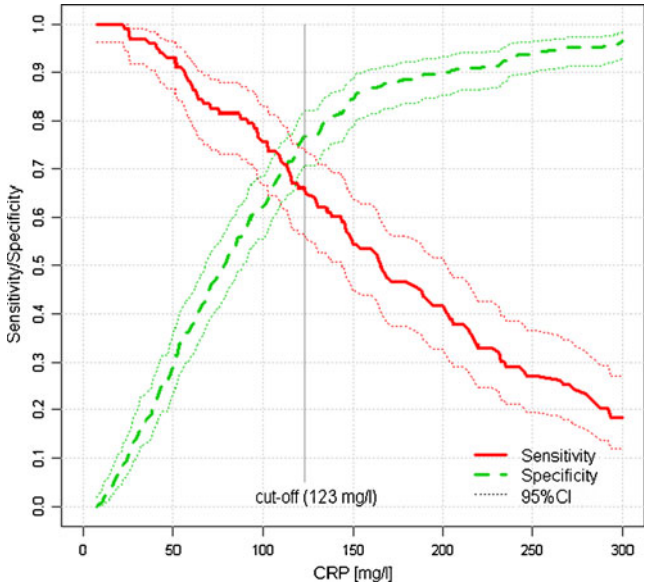

Fig. 2 Sensitivity and specificity of CRP on POD 4 in detecting inflammatory complications

the intrinsic diagnostic accuracy of CRP in detecting anastomotic leakage are provided in Table 5. CRP levels had a significant predictive value for anastomotic leakage on POD 3 to POD 5, but WBC measurements had a significant predictive value for anastomotic leakage on POD 5 only. CRP levels had the highest diagnostic accuracy on POD 4. Applying the cut-off value of 143 mg/l and adjusting for a prevalence of 8%, the PPV on POD 4 was 0.19 (95% CI, 0.14–0.23), and the NPV was 0.97 (95% CI, 0.94–0.99). In Fig. 3, the sensitivity and specificity of CRP measurement on POD 4 in detecting anastomotic leakage are plotted over the entire range of CRP values.

Discussion

The early identification of patients who are at risk for inflammatory complications is undoubtedly of high clinical value. The prevalence of inflammatory complications in this study was as high as 29.2%, with an 8.0% prevalence of anastomotic leakage. The mortality of 2.2% in this study is comparable to the outcomes in other studies [24, 25], and it was significantly higher among patients with inflammatory complications. Consistent with previous reports, leakages were diagnosed after a median of nine postoperative days (IQR, 6–14 days) [4, 5]. As the main finding, CRP measured on POD 4 was the only marker of inflammatory complications and anastomotic leakage that could be rated as moderately accurate, with AUCs of 0.76 and 0.77, respectively [26]. Two other studies found the highest diagnostic accuracy of CRP to be obtained on POD 5, although one of

Table 5 Intrinsic diagnostic accuracy of CRP and WBC for the detection of anastomotic leakage

	N	Prevalence	Optimal cut-off (95% CI)	TP	FN	TN	FP	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	p_{AUC}
CRP preoperatively	530	7.4%	23 (4–67)	15	24	379	112	0.38 (0.25–0.54)	0.77 (0.73–0.81)	0.53 (0.45–0.60)	0.552
CRP day 1	124	8.9%	123 (86–163)	8	3	80	33	0.73 (0.43–0.90)	0.71 (0.62–0.78)	0.65 (0.50–0.81)	0.092
CRP day 2	242	7.9%	174 (101–248)	11	8	138	85	0.58 (0.36–0.77)	0.62 (0.55–0.68)	0.56 (0.43–0.70)	0.360
CRP day 3	226	10.6%	200 (126–241)	14	10	152	50	0.58 (0.39–0.76)	0.75 (0.69–0.81)	0.66 (0.54–0.77)	0.011
CRP day 4	293	8.2%	143 (102–192)	18	6	192	77	0.75 (0.55–0.88)	0.71 (0.66–0.76)	0.77 (0.69–0.84)	<0.001
CRP day 5	278	10.4%	85 (36–175)	20	9	159	90	0.69 (0.51–0.83)	0.64 (0.58–0.70)	0.69 (0.60–0.77)	0.001
WBC preoperatively	773	7.1%	7.6 (3.4–10.2)	23	32	485	233	0.42 (0.30–0.55)	0.68 (0.64–0.71)	0.50 (0.43–0.58)	0.911
WBC day 1	432	7.6%	11.1 (2.5–22.0)	9	24	308	91	0.27 (0.15–0.44)	0.77 (0.73–0.81)	0.52 (0.41–0.63)	0.708
WBC day 2	535	7.9%	10.0 (7.7–11.0)	19	23	343	150	0.45 (0.31–0.60)	0.70 (0.65–0.73)	0.52 (0.43–0.62)	0.608
WBC day 3	401	9.5%	9.8 (6.7–12.1)	17	21	262	101	0.45 (0.30–0.60)	0.72 (0.67–0.77)	0.56 (0.46–0.65)	0.256
WBC day 4	425	8.5%	7.8 (6.9–10.6)	21	15	246	143	0.58 (0.42–0.73)	0.63 (0.58–0.68)	0.58 (0.48–0.68)	0.125
WBC day 5	375	9.3%	7.3 (5.8–9.9)	26	9	182	158	0.74 (0.58–0.86)	0.54 (0.48–0.59)	0.63 (0.54–0.71)	0.014

Analysis of receiver-operating characteristic (ROC) curves for anastomotic leakage; AUC was estimated non-parametrically with the trapezoidal method.

Table provides case loads with CRP/WBC values, prevalence of anastomotic leakage, optimal cut-off value maximizing the Youden Index, true-positive (TP), false-negative (FN), true-negative (TN) and false-positive (FP) cases, as well as the sensitivity, and specificity, for the cut-off value and p_{AUC} for discrimination between positive and negative cases. Area under the ROC curve (AUC), cuff-off values, sensitivity, specificity, and AUC are provided with 95% confidence intervals.

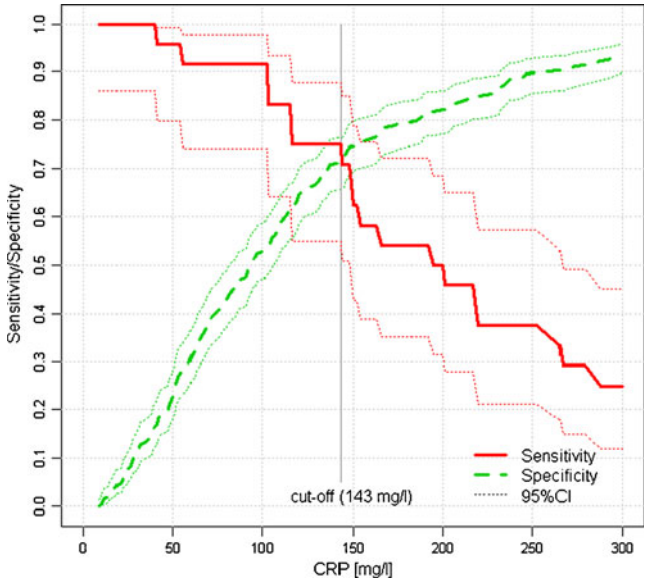

Fig. 3 Sensitivity and specificity of CRP on POD 4 in detecting anastomotic leakage

those studies did not assess CRP on POD 4 [15, 16]. The AUCs were higher than in the present study; however, in one study, patients who had undergone laparoscopic operations were included [16], whereas the other study assessed a heterogeneous patient cohort that included patients with cancer, diverticulitis and Crohn's/ulcerative colitis [15].

Increasing CRP between POD 4 and POD 5 was not sensitive for inflammatory complications, but it was specific. This result is consistent with the findings of another recent study that demonstrated a lack of CRP decline as a strong prognostic marker of anastomotic leakage; however, that study did not apply the statistically adequate ROC analysis [17]. In the present study, WBC values did not contribute substantially to distinguishing between patients with and without inflammatory complications. To our knowledge, there is no other study that directly compares the diagnostic impact of CRP and WBC in detecting inflammatory complications after colorectal surgery.

To derive clinical decisions from CRP values, it is important to know that sensitivity and specificity are inversely related depending on the choice of the cut-off value. Using the statistically estimated 'optimal' cut-off value of 123 mg/l for CRP on POD 4, the sensitivity was 66%, and the specificity was 77% in predicting inflammatory complications; this corresponds to a PPV of 54% and an NPV of 85% after adjustment for a prevalence of 29.2%. The maximal achievable PPV for CRP when applying higher cut-off values was less than 70%. Therefore, the diagnostic accuracy of an increased CRP was not sufficiently high to rule in inflammatory complications in clinical practice [27]. Thus, the present data do not support

the initiation of pre-emptive antibiotic treatment based solely on an elevated CRP on POD 4, as was proposed by Chromik et al. for procalcitonin [6]. In contrast, postoperative estimations of CRP are valuable in ruling out inflammatory complications. For this aim, a clinically defined cut-off value, and not the statistically estimated optimal value, should be applied. To achieve an NPV of 90%, the necessary cut-off value was 54 mg/l. Unfortunately, the evidence from the present retrospective study is not sufficiently strong to provide a distinct cut-off value with the necessary certainty. Such a cutoff should be identified and proven in large prospective studies, and the present results might serve as a benchmark.

According to the present study, in patients with CRP values exceeding 123 mg/l on POD 4, inflammatory complications will develop in approximately every other patient, and a higher CRP indicates a higher risk of inflammatory complications. When in doubt, a urinalysis, thoracic X-ray, ultrasound examination or even a CT scan should be considered in addition to a careful clinical examination. Clinical suspicion may likely arise from an elevated CRP on POD 4, although CRP measurements cannot be used to separate patients into diseased and non-diseased groups; rather, CRP values must be interpreted in the context of the whole clinical picture.

In the present study, 61% of the patients with anastomotic leakage developed other inflammatory complications. Furthermore, CRP is not specific to a particular type of inflammatory complication [12]. Therefore, it seems questionable to use this marker to predict leakages if patients with other inflammatory complications are considered non-diseased. Nevertheless, when using a CRP of 143 mg/l on POD 4 as the cut-off value, the NPV was as high as 97%, and the PPV was 19%. With an NPV of 97%, the development of anastomotic leakage can be ruled out when the CRP value on POD 4 is 143 mg/l or less. PPV is too low to rule in anastomotic leakage [27].

In contrast to most other studies, the overall median hospital stay of 20.7±12.2 days in the present series reflects the current hospital policy in Switzerland, where reimbursement is not yet based on diagnosis-related groups (DRG). Under the special circumstances of this diagnostic study, the long hospital stay is an advantage because the detection rate for complications may be higher. This hypothesis is highlighted by the wide range of complications identified in this study. Implementation of DRG-based reimbursement and fast-track surgery inevitably leads to shorter hospital stays. In such a context, CRP screening on POD 4 might prevent the discharge of patients who may have undetected inflammatory complications.

In interpreting the findings of the present study, it is important to consider that these results are limited to a single centre cohort between 1997 and 2009. Due to the difficulties associated with the retrospective design, this study did not assess the timing of inflammatory complications, except for anastomotic leakage. Various forms of biases are likely to have occurred in the present study, and they may have affected the selection of patients and the diagnostic performance. For instance, postoperative CRP measurements may have influenced the application of diagnostic techniques for detection of postoperative inflammatory complications. However, the retrospective study design allowed for the assessment of a large cohort that was treated according to day-to-day clinical practice. In light of the comparative effectiveness research [28, 29] guidelines, the present study and its clinically relevant approach may help clinicians with their decisions about using CRP as a diagnostic marker in patients who have undergone colorectal cancer resection.

Conclusion

Although the present study used a retrospective design, it confirmed CRP, best measured on POD 4, as a moderately accurate diagnostic marker in the prediction of postoperative inflammatory complications, including anastomotic leakage. CRP values should not be used as a 'black-and-white' decision criterion, as the diagnostic accuracy was insufficient to provide a single threshold that performed sufficiently well to correctly predict inflammatory complications in clinical practice. Interpretation of CRP values must be considered within the whole clinical scenario. Measurement of WBCs contributes little to the early detection of inflammatory complications. If postoperative CRP measurement is to be considered as a routine screen for postoperative inflammatory complications after colorectal cancer surgery, we recommend performing this test on POD 4.

References

1. Velasco E, Thuler LC, Martins CA, Dias LM, Conalves VM (1996) Risk factors for infectious complications after abdominal surgery for malignant disease. Am J Infect Contr 24(1):1–6
2. Nakamura T, Mitomi H, Ihara A, Onozato W, Sato T, Ozawa H, Hatade K, Watanabe M (2008) Risk factors for wound infection after surgery for colorectal cancer. World J Surg 32(6):1138–1141
3. Rovera F, Dionigi G, Boni L, Piscopo C, Masciocchi P, Alberio MG, Carcano G, Diurni M, Dionigi R (2007) Infectious complications in colorectal surgery. Surg Oncol 16(Suppl 1):S121–S124
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(2):254–258
5. Welsch T, Muller SA, Ulrich A, Kischlat A, Hinz U, Kienle P, Buchler MW, Schmidt J, Schmied BM (2007) C-reactive protein as early predictor for infectious postoperative complications in rectal surgery. Int J Colorectal Dis 22(12):1499–1507
6. Chromik AM, Endter F, Uhl W, Thiede A, Reith HB, Mittelkotter U (2006) Pre-emptive antibiotic treatment vs 'standard' treatment

in patients with elevated serum procalcitonin levels after elective colorectal surgery: a prospective randomized pilot study. Langenbecks Arch Surg 391(3):187–194
7. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345(19):1368–1377
8. Sponholz C, Sakr Y, Reinhart K, Brunkhorst F (2006) Diagnostic value and prognostic implications of serum procalcitonin after cardiac surgery: a systematic review of the literature. Crit Care 10 (5):R145
9. Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J (2004) Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. Clin Infect Dis 39(2):206–217
10. Mayer J, Rau B, Gansauge F, Beger HG (2000) Inflammatory mediators in human acute pancreatitis: clinical and pathophysiological implications. Gut 47(4):546–552
11. Mofidi R, Duff MD, Wigmore SJ, Madhavan KK, Garden OJ, Parks RW (2006) Association between early systemic inflammatory response, severity of multiorgan dysfunction and death in acute pancreatitis. Br J Surg 93(6):738–744
12. Pepys MB, Hirschfield GM (2003) C-reactive protein: a critical update. J Clin Invest 111(12):1805–1812
13. Reith HB, Mittelkotter U, Debus ES, Kussner C, Thiede A (1998) Procalcitonin in early detection of postoperative complications. Dig Surg 15(3):260–265
14. Matthiessen P, Henriksson M, Hallbook O, Grunditz E, Noren B, Arbman G (2008) Increase of serum C-reactive protein is an early indicator of subsequent symptomatic anastomotic leakage after anterior resection. Colorectal Dis 10(1):75–80
15. Korner H, Nielsen HJ, Soreide JA, Nedrebo BS, Soreide K, Knapp JC (2009) Diagnostic accuracy of C-reactive protein for intraabdominal infections after colorectal resections. J Gastrointest Surg 13(9):1599–1606
16. Mackay GJ, Molloy RG, O'Dwyer PJ (2011) C-reactive protein as a predictor of postoperative infective complications following elective colorectal resection. Colorectal Dis 13(5):583–587
17. Woeste G, Muller C, Bechstein WO, Wullstein C (2010) Increased serum levels of C-reactive protein precede anastomotic leakage in colorectal surgery. World J Surg 34(1):140–146
18. Agresti A, Coull BA (1998) Approximate is better than "exact" for interval estimation of binomial proportions. Am Stat 52:119–126
19. Hanley JA, McNeil BJ (1982) The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 143(1):29–36
20. DeLong ER, DeLong DM, Clarke-Pearson DL (1988) Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 44 (3):837–845
21. Boos DD (2003) Introduction to the bootstrap world. Stat Sci 18 (2):168–174
22. DiCiccio TJ, Efron B (1996) Bootstrap confidence intervals. Stat Sci 11(3):189–212
23. Pepe MS, Thompson ML (2000) Combining diagnostic test results to increase accuracy. Biostatistics 1(2):123–140
24. Karanicolas PJ, Dubois L, Colquhoun PH, Swallow CJ, Walter SD, Guyatt GH (2009) The more the better?: the impact of surgeon and hospital volume on in-hospital mortality following colorectal resection. Ann Surg 249(6):954–959
25. Richards CH, Leitch FE, Horgan PG, McMillan DC (2010) A systematic review of POSSUM and its related models as predictors of post-operative mortality and morbidity in patients undergoing surgery for colorectal cancer. J Gastrointest Surg 14 (10):1511–1520
26. Greiner M, Pfeiffer D, Smith RD (2000) Principles and practical application of the receiver-operating characteristic analysis for diagnostic tests. Prev Vet Med 45(1–2):23–41
27. Pewsner D, Battaglia M, Minder C, Marx A, Bucher HC, Egger M (2004) Ruling a diagnosis in or out with "SpPIn" and "SnNOut": a note of caution. BMJ 329(7459):209–213
28. Wilensky GR (2006) Developing a center for comparative effectiveness information. Health Aff (Millwood) 25(6):w572–w585
29. Sox HC, Greenfield S (2009) Comparative effectiveness research: a report from the Institute of Medicine. Ann Intern Med 151 (3):203–205