

# Postoperative C-reactive protein measurement predicts the severity of complications following surgery for colorectal cancer

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## Abstract

**Purpose** Studies have shown that postoperative serum C-reactive protein (CRP) measurement may be useful in predicting the type of complication, infective or otherwise, following surgery for colorectal cancer. It may be that the magnitude of the postoperative CRP is also associated with the severity of the complication. The aim of the present study was to examine the relationship between daily postoperative CRP concentrations and Clavien-Dindo complication grade.

**Patients and methods** Data was recorded prospectively for patients undergoing elective, potentially curative, surgery for colorectal cancer in two hospitals between January 2011 and January 2013,  $n=241$ . All patients had daily CRP measurement following surgery for the first four postoperative days. Complications were retrospectively classified by Clavien-Dindo grade.

**Results** Of the 241 patients, the majority were male (59 %) and were over 65 years old (69 %). The majority had colonic (86 %) and node negative (65 %) disease. One hundred nineteen patients (49 %) developed a complication, and 28 (12 %) of these were Clavien-Dindo grade 3, 4 or 5. Median and established threshold CRP concentrations on postoperative days 2 (>190 mg/L), 3 (>170 mg/L) and 4 (>125 mg/L) were directly associated with an increase in the Clavien-Dindo grade (all  $p<0.001$ ).

**Conclusion** There was a direct association between exceeding established postoperative day 2, 3 and 4 CRP thresholds and

the severity of complications defined by the Clavien-Dindo grade.

**Keywords** Colorectal cancer · C-reactive protein · Postoperative complication · Clavien-Dindo

## Introduction

Colorectal cancer is the fourth most common cancer in the UK [1]. Although long-term outcome is mostly related to stage at initial presentation, studies have shown that postoperative complications, and in particular anastomotic leak, have a negative impact on both short- and long-term survival [2].

There have been two recent meta-analyses (Warschkow et al. 2012, Singh et al. 2014) including more than 2000 patients which have shown the utility of postoperative serum CRP measurement in the early diagnosis of postoperative infective complications and anastomotic leak after colorectal surgery [3, 4]. The thresholds for CRP on postoperative days 2, 3 and 4 of approximately 190 mg/L, 170 mg/L and 125 mg/L, respectively, have been consistently reported to predict the development of infective complications. Serum albumin has also been investigated, and a concentration below 25 g/L on postoperative day 3 has been reported to be associated with the development of infective complications after surgery for colorectal cancer [5].

An alternative approach is to classify the severity of the complication based upon the intervention required to treat it [6]. A recent retrospective study (Selby et al. 2014) with a small cohort of 127 patients who had undergone elective colorectal cancer surgery used the Clavien-Dindo classification of postoperative complications and reported that the severity of a complication increased with the magnitude of the postoperative day 3 CRP [7].

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The aim of the present study was to examine the relationship between the established postoperative serum CRP and albumin thresholds for the development of infective complications and the severity of complications as defined by the Clavien-Dindo classification following elective surgery for colorectal cancer.

## Patients and methods

### Patients

This observational study included patients who underwent elective, potentially curative resection for histologically confirmed colorectal cancer in two hospitals between January 2011 and January 2013. Patients who underwent emergency surgery, who received neoadjuvant chemotherapy or radiotherapy or who had existing inflammatory conditions, e.g. inflammatory bowel disease and the systemic vasculitides, were excluded.

All patients received prophylactic antibiotics and venous thromboprophylaxis prior to the induction of anaesthesia as per hospital policy. On each postoperative day, patients were clinically assessed and had blood samples, including serum CRP and albumin, obtained as standard until discharged. Further postoperative investigation and intervention was at the discretion of the patient's surgical team who were not blind to serum CRP or albumin results.

### Methods

All data was collected prospectively in a database, anonymised and was subsequently analysed. Recorded information included patient demographics, tumour site, TNM Classification of Malignant Tumours (TNM) stage (AJCC), surgical approach, complications and preoperative and postoperative serum CRP measurements. Data regarding the nature, severity and management of complications was retrospectively categorised using the Clavien-Dindo scale. Any uncertainties were addressed by review of electronic and/or physical case notes. This study was approved as part of surgical audit.

Serum concentrations of CRP (mg/L) were measured using an autoanalyzer (Architect; Abbot Diagnostics, Maidenhead, UK) with a lower detectable limit of 0.2 mg/L as was serum albumin (normal range 35–50 g/L).

The validated Clavien-Dindo classification [8], rather than defining the complication itself assigns a value from 0 (no complication) to 5 (death) based on the intervention required to treat the complication (Table 1).

The preoperative modified Glasgow Prognostic Score (mGPS), which is associated with cancer-specific survival

independent of disease stage [9], was calculated in patients for whom preoperative serum CRP and albumin were available.

The neutrophil lymphocyte ratio (NLR), which is associated with cancer-specific survival independent of disease stage [10], was also calculated for each patient for whom preoperative neutrophil and lymphocyte counts were available.

### Statistical analysis

Categorical data regarding patient characteristics were compared using the chi-squared test. Data regarding postoperative CRP were non-normally distributed and are presented as medians and ranges. Medians of multiple groups were compared using the Kruskal-Wallis test. The magnitude of CRP by each postoperative day was displayed as 95 % confidence intervals of the median. In all tests, a two-sided *p* value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS version 21 for Windows (Chicago, IL, USA).

## Results

In total, 241 patients were included in the study. One hundred forty-two (59 %) were male, and 166 (69 %) were over 65 years old. Most had colonic (86 %) and node negative (65 %) disease. Eleven patients (5 %) had metastatic disease at the time of surgery, of whom seven had synchronous hepatectomy to treat liver metastases. The remaining four were referred to other specialities for curative surgical management of their metastatic disease following their colorectal surgery. One hundred twelve (46 %) patients had laparoscopic surgery with a further 11 (5 %) having an initial laparoscopic approach but requiring conversion to open surgery.

Of the 241 patients, a complication occurred in 119 (49 %) as shown in Table 2. The majority of complications required minimal postoperative intervention and fell into Clavien-Dindo grades 1 (22, 9 %) and 2 (69, 28 %). Complications in fewer patients required more significant action with Clavien-Dindo grade 3 representing surgical or radiological intervention (15, 6 %) and 4 of critical care requirement or organ failure (6, 3 %). Death (Clavien-Dindo grade 5) occurred in seven patients (3 %). Of the 119 complications, 94 (79 %) were due to either surgical site (65) or remote site (29) infection and the remaining 25 (21 %) were non-infective complications.

The relationship between the severity of complication and the perioperative serial CRP is shown in Fig. 1. In both cases, there was little difference in the median preoperative and first postoperative day CRP. Those who developed a complication then sustained a higher median CRP from postoperative day 2 onward.

**Table 1** Clavien-Dindo postoperative complication scale (Dindo et al. 2004)

Clavien-Dindo grade	Description
0	No complication
1	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Acceptable therapeutic regimens are drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
2	Requiring pharmacological treatment with drugs other than such allowed for grade 1 complications
3	Requiring surgical, endoscopic or radiological intervention
3A	Intervention not under general anaesthesia
3B	Intervention under general anaesthesia
4	Life-threatening complication requiring ICU management including CNS complications
4A	Single organ dysfunction (including dialysis)
4B	Multi-organ dysfunction
5	Death

Table 3 shows patients' perioperative characteristics when grouped by Clavien-Dindo grade 0 (no complication), grade 1 to 2 and 3 to 5 complications. No significant difference was found in age group, gender, TNM stage or tumour site. A significantly higher proportion of patients who suffered a Clavien-Dindo grade 3 to 5 complication underwent open surgery (16 %) compared to those who underwent laparoscopic surgery (7 %,  $p=0.001$ ). A significantly greater proportion of patients who suffered a Clavien-Dindo grade 3 to 5 complication had an mGPS score of 2 (44 %) than those who experienced a grade 1 to 2 (19 %) or no complication (17 %,  $p=0.02$ ). Preoperative NLR was not significantly associated with the different Clavien-Dindo classification groups.

When compared between Clavien-Dindo grade groups 0, 1 to 2 and 3 to 5 (Table 3), there was a significant difference in median CRP on postoperative day 2 (123 vs. 176 vs. 234 mg/L,  $p<0.001$ ), day 3 (118 vs. 208 vs. 251 mg/L,  $p<0.001$ ) and day 4 (98 vs. 161 vs. 243 mg/L,  $p<0.001$ ). When compared between Clavien-Dindo grade groups 0, 1 to 2 and 3 to 5, the established postoperative day 2 CRP threshold of 190 mg/L was exceeded by 19, 44 and 61 %, respectively, ( $p<0.001$ ). When compared between Clavien-Dindo grade groups 0, 1 to 2 and 3 to 5, the established postoperative day 3 CRP threshold of 170 mg/L was exceeded by 26, 64 and 81 %, respectively, ( $p<0.001$ ). When compared between Clavien-Dindo

grade groups 0, 1 to 2 and 3 to 5, the established postoperative day 4 CRP threshold of 125 mg/L was exceeded by 42, 64 and 86 %, respectively, ( $p<0.001$ ).

When compared between Clavien-Dindo grade groups 0, 1 to 2 and 3 to 5 (Table 3), there was a significant difference in median albumin on postoperative day 2 (28 vs. 27 vs. 24 g/L,  $p<0.001$ ), day 3 (28 vs. 26 vs. 23 g/L,  $p<0.001$ ) and day 4 (27 vs. 25 vs. 23 g/L,  $p<0.001$ ). When compared between Clavien-Dindo grade groups 0, 1 to 2 and 3 to 5, the established postoperative day 3 albumin threshold of 25 g/L was breached by 23, 48 and 64 %, respectively ( $p<0.001$ ).

## Discussion

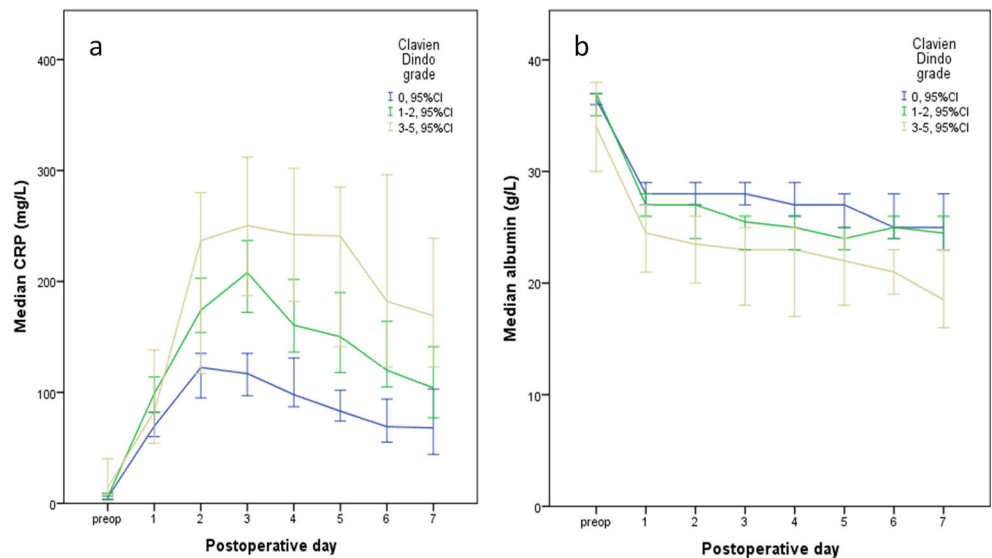
The results of the present study demonstrate that established postoperative serum CRP and albumin thresholds as measured on days 2, 3 and 4 following elective surgery for colorectal cancer can not only be used to predict the type but also the severity of postoperative complications, as defined by the Clavien-Dindo scale. In particular, those patients who required significant surgical or radiological intervention, ITU admission or who died (grades 3 to 5) exceeded those thresholds previously defined for the development of infective complications.

In the present study, the proportions of patients in Clavien-Dindo grades 1 to 5 were similar (49 %) to those in Selby and colleague's paper (43 %) as were the proportions in grades 3 to 5 at 12 and 11 %, respectively [7], although the present study had almost double the number of patients. Similarly, Selby and coworkers included only elective operations for colorectal cancer; however, it was not clear whether they included patients who had undergone neoadjuvant treatment nor was there data regarding the site of tumours or whether patients underwent laparoscopic surgery.

**Table 2** Frequency of complication by Clavien-Dindo grade

Clavien-Dindo grade	N	%
0	122	51 %
1	22	9 %
2	69	28 %
3	15	6 %
4	6	3 %
5	7	3 %
Total	241	100 %

**Fig. 1 a** Perioperative CRP (mg/L) in those without complication (Clavien-Dindo grade 0) and in those with grade 1–2 and 3–5 complication. **b** Perioperative serum albumin (g/L) in those with Clavien-Dindo grade 0, 1 to 2 and 3 to 5 complications



In the present study, approximately half of the patients underwent laparoscopic surgery. It was of interest that fewer patients who underwent laparoscopic surgery developed Clavien-Dindo grade 3 to 5 complications when compared to open surgery. Given that laparoscopic surgery is recognised to generate a smaller systemic inflammatory response than

open surgery [11–13], the present results would suggest that there is a causal relationship between the magnitude of the surgical trauma and the severity of complications following surgery for colorectal cancer. Further work investigating the relationship between the magnitude of the postoperative systemic inflammatory response and the severity of

**Table 3** Patient characteristics by Clavien-Dindo complication grade

Characteristic	All	Clavien-Dindo complication grade			
		0 <sup>a</sup>	1–2 <sup>b</sup>	3–5 <sup>c</sup>	<i>p</i>
Age (<65/65–74/>74)	75/74/92	40/37/45	29/29/33	6/8/14	0.695
Gender (male/female)	142/99	65/57	58/33	19/9	0.183
TNM stage (I/II/III/IV)	58/99/73/11	27/57/34/4	24/32/32/3	7/10/7/4	0.135
Site (colon/rectum)	209/32	110/12	75/16	24/4	0.254
Preop mGPS (0/1/2)	152/20/46	84/7/19	56/11/16	12/2/11	0.02
Preop NLR (<5/>5)	202/33	102/17	77/12	23/4	0.98
Approach (open/lap)	129/112	50/72	59/32	20/8	<0.001
POD2 CRP (median, range, mg/L)	147 (12–454)	123 (12–317)	176 (34–454)	234 (57–321)	<0.001
POD3 CRP (median, range, mg/L)	158 (11–601)	118 (11–316)	208 (35–601)	251 (109–246)	<0.001
POD4 CRP (median, range, mg/L)	143 (21–528)	98 (21–346)	161 (25–528)	243 (67–403)	<0.001
POD2 CRP >190 mg/L (no/yes)	151/77	92/22	48/38	11/17	<0.001
POD3 CRP >170 mg/L (no/yes)	120/105	84/30	31/54	5/21	<0.001
POD4 CRP >125 mg/L (no/yes)	84/114	50/36	30/54	4/24	<0.001
POD2 albumin (median, range, g/L)	27 (11–38)	28 (16–38)	27 (12–38)	24 (11–38)	<0.001
POD3 albumin (median, range, g/L)	26 (9–40)	28 (15–40)	26 (12–34)	23 (9–33)	<0.001
POD4 albumin (median, range, g/L)	25 (10–38)	27 (16–38)	25 (10–32)	23 (11–30)	<0.001
POD3 albumin <25 g/L (no/yes)	134/80	82/25	43/39	9/16	<0.001

*mGPS* preoperative modified Glasgow Prognostic score (0=CRP<10 mg/L, 1=CRP≥10 mg/L and albumin ≥35 g/L, 2=CRP≥10 mg/L and albumin <35 g/L), *NLR* preoperative neutrophil lymphocyte ratio, *POD* postoperative day

<sup>a</sup> 0=No complication

<sup>b</sup> 1–2=Complication requiring minor intervention

<sup>c</sup> 3–5=Complication requiring significant intervention

complications in patients undergoing surgery for colorectal cancer is warranted.

The use of the postoperative systemic inflammatory response as evidenced by CRP measurement in colorectal cancer surgery to detect infectious complications has been applied successfully to other cancer surgery [14–16] and to surgery for benign conditions [17]. It may be that the findings of the present study can also be applied to surgery for other cancers and benign disease. If so, the implications for surgery are profound, providing for the first time an objective postoperative therapeutic target. Moreover, complications of increasing severity may also lead to poorer long-term outcomes, although only a small number of studies have examined this in the context of the Clavien-Dindo classification [18]. It remains to be determined whether strategies to reduce the magnitude of the systemic inflammatory response in the perioperative period will also reduce the severity of postoperative complications.

The main limitation of the present study was the relatively small number of patients examined, particularly with regard to those with Clavien-Dindo grade 3 to 5 complications, although the proportion of patients in each grade was similar to that in Selby and colleague's report in 127 patients [7]. Using the Clavien-Dindo system may lead to some bias as surgeons, anaesthetists and ward staff may manage a given case or complication differently from one another. The surgical teams caring for each patient were not blind to the postoperative CRP or albumin concentration as it was used as a part of routine clinical care and may have guided, in part, the patient management on which the Clavien-Dindo definitions depend. The present work requires external validation.

In summary, there was a direct association between the postoperative systemic inflammatory response, as evidenced by serum CRP and albumin, and the severity of complications following surgery in patients with colorectal cancer.

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