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Early prediction of adverse events in enhanced recovery based upon
the host systemic inflammatory response

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Abstract

Aim: Early identification of patients experiencing post-operative complications is imperative for successful management. C reactive protein (CRP) is a non-specific marker of inflammation used in many specialties to monitor patient condition. The role of CRP measurement early in the elective postoperative colorectal patient is unclear, particularly in the context of enhanced recovery [ERAS].

Methods: 533 consecutive patients who underwent elective colorectal surgery between October 2008 and October 2010 within an established ERAS programme were studied. Patients were separated into a development group of 265 patients and a validation group of 268 patients by chronological order. CRP and white cell count [WCC] were added to a prospectively maintained ERAS database. The primary outcome of the study was all adverse events [including infective complications, post-operative organ dysfunction and prolonged length of stay] during the initial hospital admission. Significant predictors for adverse events on univariate analysis were submitted to multivariate regression analysis and the resulting model applied to the validation group. The validity and predictive accuracy

of the regression model was assessed using ROC Curve/ Area under Curve analysis.

Results: CRP levels greater than 150 on post-operative day 2 and a rising CRP on day 3 were independently associated with all adverse events during the hospital admission. A weighted model was applied to the validation group yielding an AUC of 0.65 [95%CI 0.58-0.73] indicating, at best, modest discrimination and predictive accuracy for adverse events.

Conclusion: Measurement of CRP in patients after elective colorectal surgery in the first few days after surgery within ERAS can assist in identifying those at risk of adverse events and a prolonged hospital stay. A CRP value of >150 on day 2 and a rising CRP on day 3 should alert the surgeon to an increased likelihood of such events.

What is new in this paper?

The study assesses the association between CRP levels in the early postoperative period and all adverse events in a large elective colorectal patient population treated within an enhanced recovery programme indicating that CRP as an independent predictor.

Introduction

C reactive protein (CRP) is a liver derived protein produced by the acute phase response and is a non-specific marker of inflammation [1,2]. It is produced within 4-6 hours of injury and peaks at 36-60 hours after injury, quickly falling once the inflammatory stimulus is removed due to its short half-life. [3] CRP has been studied within the pathophysiology of colorectal cancer and inflammatory bowel disease. In colorectal cancer, elevated pre-operative CRP is associated with poorer disease-specific and overall survival that is independent of Dukes' stage in those undergoing potentially curative surgery. [4,5,6] Within the context of inflammatory bowel disease, the association of CRP with a diagnosis of Crohn's disease and with ulcerative colitis has been known since the 1980s. [7-11].

The role of CRP has been related to infective adverse events rather than to other postoperative adverse events. Several studies have focused on the role of postoperative CRP in predicting outcome concentrating on infective complications, especially post-operative intra-abdominal sepsis. "Infective" complications in these studies have been broadly categorized [including anastomotic leakage] in a predominantly open surgery population. In three small studies, a serum CRP value of over 190 on day 3 or 125 or 145 on day 4, respectively has been reported to be significantly associated with an increased

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incidence of sepsis [12-14]. Others have reported that elevated CRP is associated with an increased likelihood of developing parastomal infection after emergency surgery for colonic obstruction [15]. However, within enhanced recovery we would anticipate that many patients would be suitable for discharge after 3 or 4 days and assessing CRP beyond these time-points potentially redundant. Should an ERAS patient remain in hospital beyond 3 or 4 days then by implication an adverse event may be in evolution. Earlier prediction would therefore be beneficial.

Early identification of any complication is imperative for successful management and current clinical assessment methods e.g. MEWS [Modified Early Warning Score] are helpful although documentation and implementation can be extremely variable. [16-18] Interpretation of clinical observations can also become subjective when perceived within the context of anxiety or poorly controlled pain. It would therefore be beneficial to recognize and use additional markers to objectively identify at-risk post-operative patients to enable earlier detection, and potentially reduce morbidity. The association of CRP to outcome after elective major colorectal surgery is still unclear. No evidence exists currently for its validity in an Enhanced Recovery Programme. To identify, at the earliest opportunity, those at risk of adverse events and a prolonged hospital stay would assist in planning in-patient care.

This study aimed to determine the relevance of CRP measurement early in the post-operative period after elective colorectal surgery within an established Enhanced Recovery programme that uses laparoscopy as the favoured modality for primary resection.

Method

Patient characteristics

533 consecutive patients who underwent elective colorectal surgery within an established ERAS programme in a tertiary referral centre between October 2008 and October 2010 were studied. Patients were separated by chronological order into a development group of 265 [2008-2009] patients and a validation group of 268 [2009-2010] patients (Figure 1.). Data reflect all outcomes in the first 30 days after surgery.

ERAS database

All patients within the hospital's ERAS programme are prospectively entered into a multidimensional database that records multiple pre, intra and post-operative factors. Blood results including WCC and CRP are checked routinely during the first three post-operative days within the ERAS protocol and thereafter according to a patient's progress. WCC was assessed preoperatively but CRP was not. Values for CRP and WCC for post-operative days 1 to 3 [and days 4 and 5 according to clinical need] were added retrospectively to the database. The outcome of interest was all adverse events during the initial hospital stay (including infective complications, post-operative organ

dysfunction and length of stay (LOS); prolonged LOS ≥ 6 days). Routinely, all total mesorectal resections and ileo-anal pouch operations were defunctioned with a loop stoma. All primary rectal resections are offered laparoscopy as the first-line approach.

Patients were categorised according to whether a rectal resection [+/- colon] or colonic resection [+/- small bowel] was performed in relation to CRP measurements on postoperative days 1 to 4. Similar categorization according to operative approach and postoperative CRP levels on days 1 to 4 was performed.

Statistical analysis

In the development group significant associations with all adverse events during the initial hospital admission were assessed on univariate analysis. Assuming non-Normal data distribution, categorical data were compared using Chi-square test and continuous data using Mann-Whitney and Kruskal-Wallis tests.

To determine a suitable 'cut-off' level for CRP measurements to predict all adverse events, the development group was subjected to Receiver-Operator Characteristic (ROC) Curve analysis to determine the optimal specificity and sensitivity to predict adverse events on postoperative days 1 to 4.

Significant associations [$p < 0.05$] on univariate analysis were submitted to multivariate logistic regression analysis to identify independent predictors of adverse events. Independent predictors were then used to produce both proper linear model [based on Beta weights] and unit

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weighted models for adverse events with 'goodness-of-fit' assessed using Hosmer-Lemeshow test. A higher p value indicated a better fit for the resulting predictive model. The models were applied to the validation group and ROC Curve analysis was used to assess the effectiveness of the regression models in predicting adverse events by measuring the area under the curve [AUC]. A poor predictive accuracy would yield a value of 0.50-0.65; a modest accuracy 0.65-0.75; good accuracy 0.75-0.85; excellent accuracy 0.85-1.00. SPSS (Version 14.0) software was used for all analyses with significance as $p < 0.05$.

Results

The development and validation group demographic data were similar and are displayed in Table 1.

Development group

The median length of hospital stay for the development group was 5 days [IQR 3-7]. The laparoscopy subgroup length of stay was 4 days [IQR 3-6]. The median stay for open surgery was 7 days [IQR 5-9]; In the presence of any adverse event a significant difference in initial hospital stay was identified between groups [no adverse event: median 5 days [IQR 4-6 days]; adverse event[s] 9 days [IQR 7-14] [$p=0.0005$]

Adverse event[s] occurred in 40.8% of the group. The most frequent complication was post-operative nausea and vomiting [single or multiple episodes; NOT requiring NG intubation] in 23.9%, with the most

common complication after discharge being an infective complication [of any type] in 8.6%. Infective complications during the primary admission occurred in 6.7% and included surgical site infection in 3.5%; Urinary tract infection in 1.2%; Chest infection in 3.7%. Urinary retention occurred in 2.0%; Cardiovascular complications occurred in 1.6% and overall, readmission within 30 days was required in 10.6% of the group. No DVT or PTEs were identified. Clinical anastomotic leak rate requiring re-operation was 2.8%. . The adverse event rate based upon the surgical approach was 37% for laparoscopic; 65% for converted procedures; 53.4% for open operations and 33.3% for peristomal/ stoma reversals.

Data for WCC and CRP on postoperative days 1 to 3 were incomplete in 18 patients leaving 247 patients with complete CRP data for days 1 to 3. Only 88 patients [33%] had CRP checked on post-operative day 4. Data for day 4 should therefore be interpreted with caution.

The profile of median CRP values in the first 4 postoperative days for all patients and those with and without postoperative adverse events is shown in Figure 2. Except for the first [$p=0.171$] and fourth [$p=0.422$] postoperative days, significant differences in CRP levels existed on day 2 [$p=0.0005$] and day 3 [$p=0.0005$] between groups.

CRP data were further assessed using ROC Curve analysis. An association between CRP level and adverse event[s] with optimal sensitivity and specificity [the curve "shoulder"] was identified with a CRP >150 on day 2 and CRP >120 on day 3 [Figure 3.] CRP

Accepted Article

measurements in the development group were recategorised with CRP level > 150 or below on postoperative day 2 and with a CRP >120 or below on postoperative day 3. On univariate analysis, significant differences in adverse events and length of stay were found between CRP categories. An adverse event [OR 4.0 (95%CI 2.00-7.98)] or prolonged initial hospital stay [OR 2.5 (95%CI 1.52-4.22)] was more likely with a CRP > 150 on day 2. Similarly with a CRP > 120 on day 3, adverse events [OR 2.9 (95%CI 1.41- 5.87)] and prolonged initial hospital stay [OR 2.9 (95%CI 1.53- 5.57)] were more likely.

The trend in CRP measurements was also assessed. For example, a CRP falling on postoperative day 3 was associated with a reduced likelihood of adverse event[s] [OR 0.31 (95%CI 0.16-0.62)] or prolonged hospital stay [OR 0.44 (95%CI 0.23-0.86)]. Where CRP was increasing on postoperative day 3 the median hospital stay was 7 days [IQR 5-11], conversely a fall in CRP on day 3 was associated with a median hospital stay of 5 days [IQR 4-7]; $p=0.017$.

The effect of categorising patients by rectal or colonic resection and the impact of surgical approach in relation to CRP is recorded in table 2. The association with adverse events is also assessed. No significant differences in CRP level existed between colon or rectal resections on days 1 to 4. On days 2 and 3 significant differences existed in CRP levels in patients with an adverse event. Days 1 and 4 were not significantly associated with differences in CRP levels in colon or rectal resection patients and adverse events. On postoperative days 1 and 2 CRP

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levels were significantly elevated in open surgery and converted procedures compared to laparoscopic resections. No significant differences in CRP levels existed between peristomal procedures/stoma reversals and laparoscopic resections.

Validation group

Univariate predictors for adverse events were identified and multivariate regression models were produced [table 3.] The 'goodness-of-fit' of the models was satisfactory [Hosmer-Lemeshow test; $p=0.695$]. Using both unit-weighted and proper linear regression models applied to the validation group the Area Under the Curve [AUC] was determined. At best, a modest discrimination and predictive accuracy was identified using the regression models: AUC 0.65 [95%CI 0.56-0.71]

Discussion

CRP is a non-specific marker of inflammation that rises with the insult of surgery but its predictive validity for adverse events remains unclear. This study assessed a population of elective major colorectal surgery patients treated within an enhanced recovery programme favouring laparoscopy for primary resection. We find that both the absolute values and the trend in CRP postoperatively can be used to identify patients at risk of postoperative adverse events at an earlier stage than in other similar studies. Multivariate regression analysis indicated that a CRP level > 150 on day 2 and a rising CRP on day 3 were independent

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predictors of adverse outcome and this finding might alert clinicians at an early phase in the postoperative period of impending adverse events and a potentially prolonged hospital stay. Conversely it may provide some reassurance where CRP is low and/ or falling in the first few postoperative days that early discharge is suitable. This is of importance as we attempt to permit earlier discharge of ERAS patients without incurring high readmission rates with adverse events; in this way CRP levels may be used to confirm that a patient is “safe” for discharge in conjunction with other discharge targets within an ERAS pathway. This may be particularly useful in informing discharge decisions for those who progress most rapidly through the ERAS pathway. Nevertheless, although CRP was an independent predictor of adverse events, the regression model generated produced only modest discrimination in predicting adverse events. It is therefore likely that in addition to CRP measurement, other factors including clinical scoring systems should be considered when attempting more accurate early prediction and identification of adverse events.

It is interesting to note that in different clinical scenarios such as acute pancreatitis that a CRP > 150 at 48 hours has prognostic value. Studies report similar AUC of 0.68 [0.56-0.80] [19]. Whether adverse events result from an exaggerated host response or the host response is exaggerated in the presence of an adverse event or reflects a combination is not clear from this study. Whether a generalised host response in any different injury situation that produces a CRP level >

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150 at 48 hours reflects poorer host outcome is also unclear. We noted that the surgical approach was associated with a higher CRP level with increased magnitude of invasion; with highest levels in patients undergoing open surgery or a laparoscopic converted to open procedure although significant differences between groups were identified only in the first and second postoperative days. However, the surgical approach was not an independent predictor of adverse events although the large proportion of laparoscopic resections may have influenced this finding.

CRP values may be used to assist postoperative management, potentially identifying adverse events early in their evolution before they become clinically apparent or when clinical signs are subtle; a value above 150 on day 2 being the earliest objective measure, and that a trend in CRP that continues to rise implies another source of inflammation is driving higher CRP levels. In comparison, based on our results, white cell count [WCC] cannot be reliably used to predict adverse events.

Just as any clinical assessment parameter should not be used in isolation, neither should the CRP value. This study suggests that CRP may be useful in generating an accurate analysis of the condition of the postoperative elective colorectal patient in combination with clinical assessment: adding an objective measure onto an often-subjective clinical assessment. Independent validation of our study findings is required before routine measurement of CRP can be

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regarded as a useful objective measure upon which we can inform decision-making. However, it appears that it has a more valid role than measuring WCC, that is likely to be assessed daily in the post-operative period in most UK surgical units. Whether a combination of Day 2 CRP level with existing clinically based early-warning systems will produce more refined identification of potential adverse events remains to be established and should be further tested in the Enhanced Recovery population. Whether our results are applicable to Enhanced Recovery services that offer predominantly open surgery also remains to be established. Assessing whether the post-operative CRP level can be used to justify postoperative imaging or its deferral where clinical uncertainty exists would also be of merit.

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Conflict of interest

None; the authors have no further commercial association or financial disclosures to declare.

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Figure 1. Study design.

Table 1. Development and Validation Group Demographics

Demographics	Development Group		Validation Group	
	n	%	N	%
Age	57 [IQR 43-68]	-	58 [IQR 47-70]	-
Primary LOS [days]	5 [IQR 4-8]		5 [IQR 4-8]	
Primary stay adverse event[s]	111	40.8%	114	42.4%
Prolonged length of stay [≥ 6 days]	112	42.2%	120	44.6%
Reoperation in 30 days	17	6.4%	17	6.3%
Rectal resection [+/- colon]	86	32.5%	98	36.4%
Colon resection [+/- small bowel]	129	48.7%	125	56.1%
Stoma procedure alone	50	18.9%	46	17.1%
Surgical approach				
Laparoscopic	162	61.1%	173	64.3%
Open	58	21.9%	38	14.1%
Converted	20	7.9%	22	8.0%
Through stoma	24	9.4%	36	13.4%

Figure 2. Postoperative CRP values

Figure 3. ROC Curve Analysis for optimal CRP "cut-off"

Table 2. CRP levels, resection type and surgical approach

		CRP & Postoperative day			
		Day 1	Day 2	Day 3	Day 4
All rectal resections [+/- colon]		90 [IQR 58-150]	154 [IQR 75-213]	112 [IQR 64-228]	103 [IQR 52-200]
All colon resections [+/- small bowel]		82 [IQR 51-134]	100 [IQR 159-215]	143 [IQR 82-211]	113 [IQR 63-200]
		P=0.811	P= 0.612	P=0.515	P=0.608
All rectal resections [+/- colon]					
	Adverse event[s]	93 [IQR 35-163]	213 [IQR 115-289]	208 [IQR 68-320]	135 [IQR 66-212]
	No adverse event	87 [IQR 62-145]	131 [IQR 72-172]	88 [IQR 53-140]	93 [IQR 48-128]
		P=0.599	P=0.008	P=0.028	P=0.124
All colon resections [+/- small bowel]					
	Adverse event[s]	106 [IQR 50-150]	184 [IQR 126-185]	184 [IQR 96-232]	133 [IQR 67-218]
	No adverse event	75 [IQR 52-124]	132 [IQR 80-195]	108 [IQR 65-186]	87 [IQR 48-183]
		P=0.302	P=0.023	P=0.019	0.136
All laparoscopic resections		73 [IQR 43-110]	143 [IQR 76-196]	115 [IQR 66-200]	94 [IQR 52-184]
		P values are crosstabulations with all laparoscopic resections			
Open procedure		101 [IQR 62-196]	175 [IQR 126-283]	141 [IQR 86-257]	129 [IQR 91-224]
		P=0.006	P=0.002	P=0.085	P=0.104
Converted to open procedures		136 [IQR 94-217]	198 [IQR 123-260]	184 [IQR 83-286]	178 [IQR 51-227]
		P=0.006	P= 0.013	P=0.098	P=0.231
Through stoma/ stoma reversal		51 [IQR 34-72]	110 [IQR 93-193]	88 [IQR 69-152]	N/A
		P=0.067	0.974	0.540	

Significant associations are in bold

Table 3. Univariate and multivariate analysis

Variable	Univariate analysis		Multivariate analysis	
	Adverse Event[s]		Adverse Event[s]	
	P	OR [95%CI]	P	OR [95%CI]
Colon/ Rectal resection	0.117	1.56 [95%CI 0.89-2.73]		
Operation type	0.693			
Complex major/ major/ intermediate	0.325			
New stoma	0.392	0.79 [95%CI 0.48-1.34]		
Operation approach	0.021		0.096	
ASA [I-IV]	0.408			
Age	0.821			
Patient Weight [kg]	0.661			
Prolonged LOS > 6 days]	0.0005	5.4 [95%CI 3.2-9.12]		
Day 1 CRP	0.171			
Day 2 CRP	0.0005			
Day 3 CRP	0.0005			
Day 4 CRP	0.422			
Day 2 CRP > 150	0.0005	3.99 [95%CI 2.00-7.98]	0.007	3.5[95%CI 1.4-8.8]
Day 3 CRP > 120	0.003	2.88 [95%CI 1.41-5.87]	0.082	
Day 3 CRP trend [up/ down]	0.001	2.28 [95%CI 1.67-3.12]	0.002	5.1[95%CI 1.8-14.1]
Pre-op WCC	0.073			
Day 1 WCC	0.500			
Day 2 WCC	0.154			
Day 3 WCC	0.461			
Day 4 WCC	0.345			
Abdominal drain	0.398	0.77 [95%CI 0.42-1.41]		
Epidural used	0.428			
Intraoperative crystalloid [mls]	0.018			
Intraoperative colloid [mls]	0.479			
Intraoperative blood [mls]	0.773			
Intraoperative Doppler	0.980	0.99 [95%CI 0.57-1.72]		
New stoma	0.392	0.79 [95%CI 0.48-1.34]		
Day 1 oral fluid intake	0.415			
Day 2 oral fluid intake	0.319			
Day 3 oral fluid intake	0.181			

Significant associations are in bold