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Moyes, L.H. and Leitch, E.F. and McKee, R.F. and Anderson, J.H. and Horgan, P.G. and McMillan, D.C. (2009) *Preoperative systemic inflammation predicts postoperative infectious complications in patients undergoing curative resection for colorectal cancer*. *British Journal of Cancer*, 100 (8). pp. 1236-1239. ISSN 0007-0920

<http://eprints.gla.ac.uk/7680/>

Deposited on: 14 October 2009

**Pre-operative systemic inflammation predicts post-operative infectious complications in patients undergoing curative resection for colorectal cancer**

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Running title: Systemic inflammation and postoperative complications in colorectal cancer

Keywords: Colorectal cancer, surgery, Glasgow Prognostic Score, infectious complications.

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**Abstract:**

The presence of systemic inflammation prior to surgery, as evidenced by the Glasgow Prognostic Score (mGPS), predicts poor long term survival in colorectal cancer. The aim was to examine the relationship between the pre-operative mGPS and the development of post-operative complications in patients undergoing potentially curative resection for colorectal cancer. Patients (n=455) who underwent potentially curative resections between 2003 and 2007 were assessed consecutively and details recorded in a database. The majority of patients presented for elective surgery (85%), were over the age of 65 years (70%), male (58%), deprived (53%), had TNM stage I/ II disease (61%) and had pre-operative haemoglobin (56%), white cell count (87%) and mGPS 0 (58%) in the normal range. Following surgery 86 (19%) patients developed a post-operative complication; 70 (81%) of which were infectious complications. On multivariate analysis, peritoneal soiling ( $p<0.01$ ), elevated pre-operative white cell count ( $p<0.05$ ) and mGPS ( $p<0.01$ ) were independently associated increased risk of developing a post-operative infection. In elective patients, only the mGPS (OR 1.75, 95%CI 1.17-2.63,  $p=0.007$ ) was significantly associated with increased risk of developing a post-operative infection. Pre-operative elevated mGPS predicts increased post-operative infectious complications in patients undergoing potentially curative resection for colorectal cancer.

## **Introduction**

Colorectal cancer remains the second most common cause of cancer death in Western Europe (Cancerstats, 2004, [www.cancerresearchuk.org](http://www.cancerresearchuk.org)). Despite advances in surgical techniques, perioperative care and adjuvant chemoradiotherapy, overall survival remains poor with only 50% patients surviving five years after potentially curative resection (McArdle and Hole, 2002).

Whilst tumour stage has been the main basis of predicting long term survival in patients undergoing surgery for cancer it is now recognized that post-operative complications contribute to poor cancer specific survival (Rizk et al., 2004; Khuri et al., 2005; McArdle et al., 2005; Law et al., 2007). In particular, McArdle and coworkers (2005) reported that in a prospective cohort of 2,235 patients undergoing potentially curative resection for colorectal cancer, the post-operative complication of anastomotic leakage was associated with poorer cancer specific survival, independent of Dukes stage. Law and coworkers (2007) reported similar results in 1,657 patients who underwent curative resection for colorectal cancer.

The basis of this observation is not clear. It has been postulated that the presence of an enhanced systemic inflammatory response may be responsible (McArdle et al., 2005) since the systemic inflammatory response, as evidenced by an elevated C-reactive protein concentration, has been shown to be associated with poor cancer specific survival, independent of tumour stage (Nielsen et al., 2000; McMillan et al., 2003; Crozier et al., 2006). Studies have shown that elevated C-reactive protein concentrations in the post-operative period may predict an increased chance of post-operative infection (Welsch et al., 2007) and anastomotic leakage (Matthiessen et al., 2008). An initial appraisal might suggest that early post-operative infection initially declares

itself as a rise in C-reactive protein before overt clinical infection develops and this infection causes decreased long term survival. However, it has been reported that the pre-operative, but not the immediate post-operative, elevated C-reactive protein concentrations are associated with cancer specific survival (Crozier et al., 2007).

With respect to the measurement of the systemic inflammatory response the combination of C-reactive protein and albumin (Glasgow Prognostic Score, mGPS) has been shown to improve the prediction of cancer specific survival in a variety of common solid tumours (McMillan et al., 2008) including primary operable colorectal cancer (McMillan et al., 2007; Ishizuka et al., 2007). To our knowledge the relationship between the pre-operative systemic inflammatory response and post-operative complications has not been previously examined.

The hypothesis underlying the present study was that a pre-operative systemic inflammatory response, as evidenced by the mGPS, may be an underlying host characteristic that predisposes to post operative infection in patients undergoing potentially curative resection for colorectal cancer.

## **Patients and methods**

### Patients

Patients with histologically proven colorectal cancer who, on the basis of laparotomy findings and/or preoperative abdominal computed tomography, were considered to have undergone a potentially curative resection and had routine laboratory measurement of white cell counts, albumin and C-reactive protein, between January 2003 and October 2007 at Glasgow Royal Infirmary were prospectively included in the study. The antibiotic regimen was based on 1g of second generation cephalosporin and 500mg metronidazole at induction of general anaesthesia. No other antibiotics were normally given. Three consultant surgeons (Anderson, Horgan and McKee) performed the majority of the operations (79%). The surgical approach was open in all cases.

Patients were assessed consecutively and their details recorded in our colorectal cancer database. The tumours were staged according to the TNM criteria (AJCC, 2002). Patients who had pre-operative clinical evidence of infection or other inflammatory conditions were excluded from the study. 23 patients were excluded based on these criteria.

The extent of deprivation was defined using the Carstairs deprivation index (Carstairs and Morris, 1991). This is an area based measure derived from the 2001 census, using the postcode of residence at diagnosis, which divides the score into a seven-point index. For illustrative purposes, the results are presented by amalgamating the seven categories into three groups: affluent (categories 1 and 2), intermediate (categories 3–5) and deprived (categories 6 and 7). The Carstairs deprivation index has been extensively utilised in cancer patients and is particularly appropriate for use in the central belt of Scotland (Hole and McArdle, 2002).

Patients were assessed for the following complications: infectious (wound infection, intra-abdominal abscess, anastomotic leak, pneumonia and septicaemia) and non infectious (cardiac events encompassing acute coronary syndrome and acute myocardial infarction, and pulmonary embolism). The criteria used to define infectious complications were the same as that previously described (Ytting et al., 2005). (1) Wound infection was defined as the presence of pus, either discharged spontaneously or requiring drainage. Wound infection included a subgroup of patients with perineal infection, following abdomino-perineal resection of the rectum. (2) Intra-abdominal abscess was verified by either surgical drainage or by ultrasonographically guided aspiration of pus. (3) Anastomotic leakage was defined as radiologically verified fistula to bowel anastomosis or diagnosed by relaparotomy. (4) Pneumonia was defined by fever above 38.5°C and a positive X-ray, and requirement of antibiotic treatment. (5) Septicaemia was defined by clinical symptoms combined with a positive blood culture.

Nonsymptomatic or minor urinary tract infection was not recorded, and therefore only included if complicated by septicaemia.

The study was approved by the Research Ethics Committee, Royal Infirmary, Glasgow.

### Blood parameters

Routine pre-operative laboratory measurements of white cell count, albumin and C-reactive protein concentration were carried out. The coefficient of variation for these methods, over the range of measurement, was less than 10% as established by routine quality control procedures.

The mGPS was constructed as previously described (McMillan et al., 2007). Briefly, a normal albumin (>35g/l) and normal C-reactive protein (<10mg/l) scores 0, with an elevated C-reactive protein scoring 1 and an elevated C-reactive protein together with a low albumin scoring 2.

### Statistics

Data are presented as median (range). Grouping of the variables was carried out using standard thresholds. Comparisons between groups of patients were carried out using the Mantel–Haenszel ( $X^2$ ) test for trend as appropriate. Logistic regression analysis was used to examine the effect of variables on the development of post-operative infection. Analysis was performed using SPSS software (SPSS for Windows Version 15.0, SPSS Inc, Chicago, IL, USA).



## Results

The relationship between the pre-operative systemic inflammatory response (mGPS) and clinicopathological characteristics in patients (n= 455) who underwent curative surgery for colorectal cancer is shown in Table 1. The majority of patients were over the age of 65 years (70%), were male (58%), were deprived (53%) and presented for elective surgery (85%). The majority of patients presented with colonic tumours (60%), had T3-4 disease (81%), had no nodal involvement (61%) and had TNM stage I/ II disease (61%). The majority of patients had pre-operative haemoglobin (56%), white cell count (87%) and mGPS 0 (58%) in the normal range.

Following surgery 86 (19%) patients developed a post-operative complication; 70 (81%) of which were infectious complications. The 16 non-infectious events were pulmonary embolism (n=1), myocardial infarction (n=6), acute coronary syndrome (n=5), acute onset atrial fibrillation (n=4). The 70 infectious events were septicaemia (n=6), pneumonia (n=33), anastomotic leak (n=14), intra-abdominal collection (n=2) and wound infection (n=15).

An elevated mGPS was associated with deprivation ( $p<0.05$ ), emergency presentation ( $p<0.001$ ), peritoneal soiling ( $p\leq 0.01$ ), colonic tumours ( $p<0.001$ ), advanced tumour stage ( $p<0.01$ ), low haemoglobin ( $p<0.001$ ), high white cell count ( $p<0.001$ ) and post-operative infections ( $p<0.01$ ).

The relationship between clinicopathological characteristics, systemic inflammatory response and post-operative infections in patients undergoing surgery for colorectal cancer is shown in Table 2. On binary logistic regression analysis, deprivation ( $p<0.10$ ), emergency presentation ( $p<0.001$ ), peritoneal soiling ( $p=0.001$ ), elevated pre-operative white cell count ( $p<0.001$ ), C-reactive protein ( $p<0.001$ ), albumin ( $p<0.001$ ) and mGPS ( $<0.001$ ) were associated

with increased risk of developing a post-operative infection. On multivariate analysis, peritoneal soiling ( $p<0.01$ ), elevated pre-operative white cell count ( $p<0.05$ ) and mGPS ( $p<0.01$ ) were independently associated increased risk of developing a post-operative infection.

When only those patients who presented electively were considered in the analysis ( $n=385$ ), on binary logistic regression analysis, only the mGPS (OR 1.75, 95%CI 1.17-2.63,  $p=0.007$ ) was significantly associated with increased risk of developing a post-operative infection.

## **Discussion**

The results of the present study show that the pre-operative systemic inflammatory response, as evidenced by the mGPS, was independently associated with an increased risk of post-operative infectious complications in patients undergoing potentially curative resection for colorectal cancer. This relationship persisted after patients with an emergency presentation were excluded from the logistic regression analysis. Given that post-operative infections are relatively common in patients undergoing surgery for colorectal cancer and are associated with increased hospital stay and treatment costs, it may be that the simple routinely available pre-operative measurement of the mGPS will be clinically useful in identifying patients at high risk of developing infectious complications.

The basis of the independent relationship between an elevated mGPS before surgery and post-operative infections in patients with primary operable colorectal cancer is not clear. A plausible explanation is that an elevated mGPS may reflect compromised cell-mediated immunity as C-reactive protein is associated with lymphopenia (Nozoe et al., 2000; Leitch et al., 2007) and an impaired T-lymphocytic response (Canna et al., 2005) in patients with colorectal tumours. Alternatively, C-reactive protein is also associated with components of the innate immune system including complement, and this response may also be compromised (DuClos and Mold, 2004; Ytting et al., 2006). Also, an mGPS of 2, based as it is on the presence of an ongoing systemic inflammatory response and hypoalbuminaemia, reflects the loss of lean tissue and protein (McMillan et al., 1998; McMillan et al., 2001) which is likely to further compromise immune function. Therefore, the results of the present study suggest that compromised immune function may occur before surgery and influences post-operative infectious complications.

It was of interest that, in the present study, an elevated pre-operative white cell count was also independently associated with increased risk of post-operative infectious complications. However, the white cell count was strongly associated with mGPS and compared with the mGPS, the significance of its association weakened on multivariate analysis. Furthermore, in those patients who presented electively, white cell count was no longer significantly associated with post-operative infection. This would support the routine use of the mGPS to identify patients at increased risk of developing infectious complications. However, it remains to be determined whether the pre-operative systemic inflammatory response may be moderated and whether such moderation may reduce post-operative infectious complications.

In summary, the results of the present study indicate that a simple inflammation-based prognostic score identifies patients at increased risk of developing infectious complications following potentially curative resection for colorectal cancer.

### **Acknowledgements**

We gratefully acknowledge the interest and encouragement of Mr Ian G Finlay and Professor Colin S McArdle, Royal Infirmary, Glasgow.

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Table 1. The relationship between the pre-operative systemic inflammatory response (mGPS) and clinicopathological characteristics in patients undergoing potentially curative surgery for colorectal cancer (n= 455).

		mGPS 0 n= 259 (%)	mGPS 1 n= 130 (%)	mGPS 2 n= 66 (%)	p-value
Age	<65 years	88 (34)	28 (28)	22 (33)	0.283
	65-74 years	88 (34)	46 (35)	18 (27)	
	≥75 years	83 (32)	48 (37)	26 (40)	
Sex	Female	98 (38)	62 (48)	30 (46)	0.102
	Male	161 (62)	68 (52)	36 (54)	
Deprivation	Affluent (1, 2)	15 (6)	1 (1)	2 (3)	0.014
	Intermediate (3, 4, 5)	118 (46)	53 (40)	24 (36)	
	Deprived (6, 7)	126 (48)	76 (59)	40 (61)	
Presentation	Elective	245 (95)	100 (77)	40 (61)	<0.001
	Emergency	14 (5)	30 (23)	26 (39)	
Peritoneal soiling					
	None or serous fluid	256 (98%)	126 (97%)	61 (92%)	0.010
	Local pus	2 (1%)	4 (3%)	4 (6%)	
	Free pus or faeces	1 (1%)	0 (0%)	1 (2%)	
Tumour site	Colon	128 (49)	93 (72)	54 (82)	<0.001
	Rectum	131 (51)	37 (28)	12 (18)	
Tumour	T1	24 (9)	3 (2)	0 (0)	<0.001
	T2	48 (19)	9 (7)	4 (6)	
	T3	128 (49)	69 (53)	33 (50)	
	T4	59 (23)	49 (38)	29 (44)	
Nodal involvement	N0	164 (63)	75 (58)	37 (56)	0.148
	N1	72 (28)	34 (26)	22 (33)	
	N2	23 (9)	21 (16)	7 (11)	
TNM stage	I	63 (24)	10 (8)	4 (6)	0.001
	II	102 (39)	68 (52)	33 (50)	
	III	94 (37)	52 (40)	29 (44)	
Haemoglobin	≥12g/dl	180 (70)	64 (49)	11 (17)	<0.001
	<12g/dl	79 (30)	66 (51)	55 (83)	
White cell count	<8.5x10 <sup>9</sup> /l	191 (74)	63 (49)	26 (39)	<0.001
	8.5-11.0x10 <sup>9</sup> /l	52 (20)	42 (32)	24 (37)	
	>11x10 <sup>9</sup> /l	16 (6)	25 (19)	16 (24)	
Complications	None	223 (86)	105 (81)	41 (62)	0.004
	Infectious	25 (10)	21 (16)	24 (36)	
	Non-infectious	11 (4)	4 (3)	1 (2)	



Table 2. The relationship between the studied variables and post-operative infection in patients undergoing potentially curative surgery for colorectal cancer (n= 455).

	Univariate Odds ratio (95% CI)	p-value	Multivariate Odds ratio (95% CI)	p-value
Age (<65/ 65-74/ ≥75 years)	1.01 (0.74-1.38)	0.961		
Sex (Female/ Male)	1.26 (0.74-2.12)	0.395		
Deprivation (1-2/ 3-5/ 6-7)	1.51 (0.94-2.42)	0.089		0.335
Presentation (Elective/ Emergency)	3.52 (1.96-6.32)	<0.001		0.058
Peritoneal soiling (None or serous fluid/ Local pus/ Free pus or faeces)	7.17 (2.35-21.86)	0.001	4.91 (1.60-15.08)	0.005
Tumour site (Colon/ Rectum)	1.02 (0.61-1.72)	0.935		
Tumour (T1/ T2/ T3/ T4)	1.19 (0.86-1.64)	0.295		
Nodal involvement (N0/ N1/ N2)	0.99 (0.68-1.43)	0.942		
TNM stage (I/ II/ III)	0.97 (0.68-1.38)	0.844		
Haemoglobin (≥12/ <12g/dl)	1.53 (0.92-2.55)	0.104		
White cell count (<8.0/ 8.5-11.0/ >11x10 <sup>9</sup> /l)	1.95 (1.41-2.72)	<0.001	1.46 (1.01-2.11)	0.043
C-reactive protein (≤10/ >10mg/l)	2.79 (1.64-4.74)	<0.001		
Albumin (≥35/ <35g/l)	3.14 (1.80-5.48)	<0.001		
mGPS (0/ 1/ 2)	2.28 (1.64-3.16)	<0.001	1.76 (1.22-2.55)	0.003