Preoperative C-Reactive Protein as A Predictor of Postoperative Complications in Patients Undergoing Surgery for Colorectal Neoplasia

Sufana Alsaif
University College Dublin  https://orcid.org/0000-0002-8037-965X

Aílín C Rogers
Royal Marsden Hospital

Priscilla Pua
Penang Medical College: RCSI & UCD Malaysia Campus

Paul T Casey
University College Dublin - National University of Ireland: University College Dublin

Geoff G Aherne
University College Dublin - National University of Ireland: University College Dublin

Ann E Brannigan
Mater Private Dublin: Mater Private Hospital

Jurgen J Mulsow
Mater Misericordiae University Hospital

Conor J Shields
Mater Misericordiae University Hospital

Ronan A Cahill (ronan.cahill@ucd.ie)
Mater Misericordiae University Hospital

Research

Keywords: Colorectal cancer, Inflammatory markers, C-reactive protein, Postoperative complications, Clavien-Dindo

DOI: https://doi.org/10.21203/rs.3.rs-96106/v1

License: © This work is licensed under a Creative Commons Attribution 4.0 International License.  Read Full License
Abstract

**Background:** Inflammatory markers are measured following colorectal surgery to detect postoperative complications. However, the association of these markers preoperatively with subsequent postoperative course has not yet been usefully studied.

**Aim:** The aim of this study is to assess the ability of preoperative C-reactive protein (CRP) and other inflammatory marker measurements in the prediction of postoperative morbidity after elective colorectal surgery.

**Methods:** This retrospective study catalogues 218 patients undergoing elective, potentially curative surgery for colorectal neoplasia. Preoperative laboratory results of the full blood count (FBC), C-reactive protein (CRP) and carcinoembryonic antigen (CEA) were recorded. Multivariable analysis was performed to examine preoperative variables against 30-day postoperative complications by type and grade (Clavien-Dindo (CD)), adjusting for age, sex, BMI, smoking status, medical history, open versus laparoscopic operation, and tumor characteristics.

**Results:** Elevated preoperative CRP (≥ 5 mg/L) was significantly predictive of all-cause mortality, with an OR of 17.0 (p < 0.001) and was the strongest factor to predict a CD morbidity grade ≥ 3 (OR 41.9, p < 0.001). Other factors predictive of CD morbidity grade ≥ 3 included smoking, elevated preoperative platelet count and elevated preoperative neutrophil-lymphocyte ratio (OR 15.6, 8.6 and 6.3 respectively, all p < 0.05). CRP values above 5.5 mg/L were indicative of all-cause morbidity (AUC=0.871), and values above 17.5 mg/L predicted severe complications (AUC=0.934).

**Conclusions:** Elevated preoperative CRP predicts increased postoperative morbidity in this patient cohort. The results herein aid risk and resource stratification and encourage preoperative assessment of inflammatory propensity besides simple sepsis exclusion.

Introduction

Inflammatory markers are routinely measured in patients following colorectal surgery to monitor progress alongside clinical parameters. Postoperative C-reactive protein (CRP) levels is particularly useful for the detection of significant postoperative complications. While some physiological derangement is expected following operative intervention, absolute levels of inflammatory markers above expected thresholds, prolonged elevations or a second rise after an initial decline all encourage further investigation or intervention. This allows for early identification and correction of potential complications, or confident discharge of those with uncomplicated clinical courses. Limited resources, whether related to in-hospital environment (i.e. high dependency care utilization) or services (e.g. advanced radiological imaging), may be better correctly deployed and fitted to those most likely to benefit, thus optimizing effort, expenditure and outcome.

Levels of inflammatory markers may be elevated before surgery in the presence of an infection, morbidities such as atherosclerosis, or inactivity in a patient presenting for planned operation. An elevation in full blood cell (FBC) count, its constituent neutrophil, lymphocyte and platelet counts, and CRP is also induced by colorectal neoplasia itself, especially in the context of its metabolic consequences which include sarcopenia and cachexia. The importance of systemic mediators in oncological outcome is underlined by the modified Glasgow Prognostic Score (mGPS), which relates high CRP (> 10 mg/L) to cancer recurrence and reduced 5-year survival. It may be the case that systemic inflammation predisposes patients to immunological dysfunction with short and intermediate infectious, inflammatory and oncological consequences. Patients in a pre-existing pro-inflammatory state are primed for an augmented inflammatory response in the event of additional provocation such as surgery. Despite the presence of considerable data regarding inflammatory mediation, little study to date has examined the propensity for preoperative inflammatory markers to relate to early postoperative complications, with most work presently directed towards their use as snapshot indicators rather than as reflectors of biological balance throughout the perioperative period.

This clinical study was performed to test the hypothesis that elevated preoperative inflammatory markers, particularly CRP, in patients without overt sepsis, may signify a complicated early postoperative course following elective colorectal resection. Such markers may thereby act as early risk stratification tools for patients potentially facing clinical deviation from expected trajectories.

Methods

**Inclusion and exclusion criteria**

Patients who underwent elective, potentially curative resection for colorectal neoplasia in our institution, the Mater Misericordiae University Hospital, between January 2009 and December 2016 were included for analysis. Cases of dysplastic tumors were also included and adjusted for in the analysis. Patients with second cancers and inflammatory bowel disease and those that underwent neoadjuvant chemotherapy or radiation therapy were excluded from the study, in addition to those admitted with fever or overt sepsis. Patients without any laboratory data or postoperative outcome documentation were excluded from analysis, while those with incomplete datasets were included in the relevant subcategory analysis only.

**Patient management**

Patients planned for elective surgery in our institution routinely complete a full diagnostic work-up, which includes computerized tomography of the chest, thorax and abdomen for staging as well as clinical review by senior members of the surgical service, gastroenterology, and general medicine. Following diagnostic work-up, patients attend a preoperative assessment clinic where they are examined by a senior member of the anesthetic and critical care service. Hematological and biochemical testing and, when indicated, electrocardiography and echocardiography are also completed. Results are reviewed and patients with treatable co-morbidity are triaged for specific clinical care. Those with normal investigations, those with abnormal blood tests without overt clinical
correlate (and so without ready correction), and those with conditions that cannot be further optimized but whom are judged suitable for operation all proceed to surgery.

Data interpretation

The blood profiles of patients reviewed for this study were obtained within the time period after diagnosis and before the operation. All patients routinely have FBC measured while some have CRP and carcinoembryonic antigen (CEA) checked as part of their oncological staging and general work-up. The inflammatory markers included for analysis are CRP, white blood cell count (WBC), platelets, neutrophils, lymphocytes, platelets-to-lymphocyte ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR). Hemoglobin (Hb) was also included. Other patient-related factors recorded were age, gender, body mass index, and smoking status. Preoperative comorbidities recorded include diabetes in addition to any defined cardiovascular, respiratory, renal and/or autoimmune disease known to preexist or detected on work-up. Surgical technique was classified as laparoscopic or open, the latter including conversions to open. Tumor site was classified into right-sided (cecum, ascending, and transverse), left-sided (descending and sigmoid), and rectal. In patients with malignant tumors, pathological tumor stage, nodal status and differentiation were recorded.

All 30-day postoperative outcomes and management were recorded prospectively for departmental audit, including categorization into affected system (i.e. respiratory, urinary, neurological, cardiovascular) and Clavien-Dindo classification grading to signify complication severity. Various systemic and surgical site complications were recorded. Systemic complications include thromboembolism, urinary, renal, respiratory, cardiovascular, and neurological complications. Surgical site complications, both superficial and deep, include ileus, anastomotic leakage, and wound infection, dehiscence or hemaition.

Statistical techniques

Continuous variables were presented as means with their standard deviations (σ) in tabular form. Preoperative and intraoperative values were transformed into categorical variables. For example, inflammatory markers were classified as normal or abnormal according to standard laboratory values. Though we used a cut-off of above 5 mg/L to denote CRP elevation, we also ran regression analysis using a cutoff of 10mg/L to assess the validity of this threshold as used in the mGPS scoring system. Univariable analysis was performed using chi square analysis or Fisher’s exact test where appropriate, with these variables examined against all listed postoperative complications and Clavien-Dindo grades. Multivariable analysis included only variables scoring p ≤ 0.25 in the univariable analysis, and was performed using binary logistic regression analysis and expressed as odds ratios (OR). A ROC curve was plotted of CRP against a) the presence and b) the severity of a postoperative complication. Optimal cut-off values of CRP were determined using the Youden index. All analyses were performed using SPSS (SPSS, Version 20. Armonk, NY). Results were considered statistically significant where the two-tailed p-value was less than 0.05.

Results

During the time period, 198 patients underwent surgical resection for colorectal cancer and 20 likewise for colorectal dysplasia (total n = 218). Over 80% of these operations were performed laparoscopically. Patient demographics and tumor characteristics are shown in Table 1A, with most cancers located on the left-side, the majority being node-negative and moderately differentiated. Complete data was available on all patients regarding operation type and approach, tumor characteristics and postoperative complications. All patients underwent preoperative hematological testing. However, only a proportion had CRP (63.8%, n = 139) and CEA (78.4%, n = 171) measured prior to surgery. There was no significant difference in morbidities between the cohort who underwent preoperative CEA or CRP testing versus those who did not (Appendix 1). Almost half of patients had a postoperative complication, with 18.8% (n = 41) graded as a Clavien-Dindo grade ≥ 3, requiring surgical intervention (Table 1C). Mean preoperative laboratory values are reported in Table 1B. Mean CRP in this group of patients presenting for elective colorectal resection was 18.7 mg/L (σ 34.1), with 48.3% having a CRP ≥ 5 mg/L and 30.2% ≥ 10 mg/L.

Predictors of postoperative morbidity were analyzed using logistic regression analysis, with elevated preoperative CRP being the strongest factor to consistently achieve significance in multivariable analysis for morbidity (Table 3). Preoperative CRP ≥ 5 mg/L was the only factor significantly predictive of all-cause mortality, with an OR of 17.0 (p < 0.001) and was the strongest factor to predict a Clavien-Dindo morbidity grade ≥ 3 (OR 41.9, p < 0.001). Other factors predictive of Clavien-Dindo morbidity grade ≥ 3 included smoking, elevated preoperative platelet count, and elevated preoperative neutrophil-lymphocyte ratio (OR 15.6, 8.6, and 6.3 respectively, all p < 0.05).

In particular, both patients with an elevated preoperative CRP and patients who smoke were likely to have renal (OR 17 and 15.7 respectively, both p < 0.05) and respiratory (OR 10.5 and 5.6 respectively, both p < 0.05) postoperative complications. An elevated neutrophil count was associated with postoperative respiratory complications (OR 7, p < 0.05). Unsurprisingly, an open surgical approach was linked to postoperative sepsis (OR 11.5, p = 0.05), and an elevated preoperative platelets count was linked to postoperative thromboembolism as well as neurological complications (OR 14.1 and 54.4 respectively, both p < 0.05).

When the CRP cut-off of 10 mg/L was incorporated into the analysis, CRP remained the preoperative factor most predictive for morbidity with the highest ORs among all inputted variables. However, CRP lost significance for the ability to predict all-cause morbidity. All other examined factors failed to consistently predict postoperative morbidity.

ROC Curve calculations indicated the diagnostic ability of CRP in the prediction of any postoperative complication (CD 1–5) and severe complications (CD 3–5). Area under the curve (AUC) is 0.871 and 0.934 for any and severe complications, respectively. Youden index cut-off values of CRP after which a patient is more likely to have any complication was 5.5 mg/L and the value after which a patient is more likely to have a severe postoperative complication, i.e. CD ≥ 3, was 17.5 mg/L (Fig. 1).

Discussion
Routine preoperative and postoperative care in major elective colorectal surgery includes measurement of blood tests for the identification of baseline and subsequent trends in physiological derangement induced by surgery. In this way, minor and major complications can be diagnosed early, arousing suspicion before clinical symptoms. On this account, prompt management can minimize adverse outcomes. Standard hematological markers such as WCC or neutrophils are relatively weak prognosticators in this regard and hence additional biomarker screening should be performed including CRP. CRP is an acute phase protein with a short half-life (19 hours), synthesized by the liver in a non-specific response to a variety of provocations mediated via proinflammatory cytokines, such as interleukin-6. Its levels rise in response to trauma, infection, ischemia and malignancy. Although not commonly recommended in guidelines related to preoperative work-up, CRP is nonetheless quite commonly ordered as part of oncological staging, and elevated levels in patients without obvious acute malady presenting for and proceeding with elective surgery have been previously reported. Irrespective of this, in most clinical settings only the postoperative CRP levels are followed and most recent clinical research focuses on single postoperative measurements triggering intervention. This frequently occurs without referencing preoperative levels, under the assumption that they are normal in patients presenting for elective surgery. The current study demonstrates that almost half of patients undergoing elective colorectal resection will have a preoperative CRP ≥ 5 mg/L, and nearly a third will be ≥ 10 mg/L.

Systemic inflammation, besides concomitant sepsis and inflammatory pathology, is independently associated with cancer. Standard practice has been to rule gross sepsis prior to surgery, through clinical evaluation and baseline FBC. The absence of overt infection on preoperative blood tests may formerly have reassured. However, the results herein suggest that even a subtle rise in preoperative CRP may warrant stratifying patients into a higher risk group. While preoperative levels of CRP have been examined in other elective surgery scenarios, its association with postoperative complications has been variable, although often only examined with respect to single end-points. Here, we have looked more broadly across the spectrum of morbidity encountered and found correlations worthy of future prospective study. The strong association with CRP with CD grade ≥ 3 morbidity may indicate its use as a clinical tool in the context of preoperative assessment.

Baseline inflammatory mediator levels therefore may predict complications, but yet they themselves can be moderated by preoperative prehabilitation programs. Patients with cardiovascular disease are known to have elevated systemic inflammatory mediators that are responsive to exercise training.

Recent research show that patients presenting for surgery for colorectal cancer can significantly engage with and benefit from preoperative exercise even for short intervals. Improved postoperative outcomes have been demonstrated in some studies, pointing to a possible shared mechanism or marker of inflammatory mediators. Other interventions could include nutrition and microbiome ecology, even if specific anti-inflammatory pharmacology is avoided due to potential wound healing complications. Interestingly in the latter regard, recent work has linked single perioperative steroid usage as part of anesthetic induction with improved postoperative sequence.

The biggest limitation of this study is its retrospective nature, which serves a purpose only in exploring a hypothesis to help its evaluation ahead of a prospective study for proper elucidation and determination. It does not prove causative or mechanistic relationships. In particular, the fact that only a subgroup of patients had CRP measured, and the finding that this biomarker was the most powerfully associated with postoperative complication, suggests that some other factor or variable, unidentified in this audit, may underlie the two correlates. This, however, seems unlikely given that a majority of patients had this test performed, all underwent elective surgery soon after preoperative clinical assessment (suggesting no clinically overt condition present) and that we could find no significant difference between the cohorts in this experience with and without CRP measurement.

**Conclusions**

This study demonstrates that elevated preoperative CRP (≥ 5 mg/L) is a strong predictor of all-cause mortality, and further elevation (CRP ≥ 17.5 mg/L) predicts severe postoperative complications as depicted in Clavien-Dindo grades 3–5. Other strong predictors of severe postoperative complications are smoking, an elevated preoperative platelet count, and an elevated preoperative neutrophil-lymphocyte ratio.

In particular, both patients with an elevated preoperative CRP and patients who smoke were likely to have renal and respiratory postoperative complications. An elevated neutrophil count was associated with postoperative respiratory complications. Unsurprisingly, an open surgical approach was linked to postoperative sepsis, and an elevated preoperative platelets count was linked to postoperative thromboembolism and neurological complications.

Our findings suggest that routinely measuring CRP of patients at the time of preoperative assessment may notably assist risk stratification. The concept of an inflammatory continuum bridging preoperative and postoperative timeframes should be built into other studies to confirm this finding and explain causative, downstream effectors.

**Declarations**

**Ethics**

This study was approved as an audit by the Mater Misericordiae University's Ethics Committee.

**Consent for publication**

Not applicable

**Availability of data and materials**

The datasets generated and analyzed in our study are available from the first author on reasonable request.
Competing interests
The authors declare that they have no competing interests.

Funding
The authors did not receive funding for this study.

Authors’ contributions
Sufana Alsaif, Ailín Rogers, and Ronan Cahill designed the study. Sufana Alsaif, Priscilla Pua, Paul Casey, and Geoff Aherne obtained the data. Sufana Alsaif and Ailín Rogers analyzed the data. Ann Brannigan, Jurgen Muslow, and Conor Shields helped draft and revise the manuscript. All the authors read and approved the final manuscript.

Acknowledgments
None

References
1. McSorley ST, Khor BY, MacKay GJ, Horgan PG, McMillan DC. Examination of a CRP first approach for the detection of postoperative complications in patients undergoing surgery for colorectal cancer: A pragmatic study. Medicine (Baltimore) 2017;96(7): e6133.
2. McSorley ST, Watt DG, Horgan PG, McMillan DC. Postoperative Systemic Inflammatory Response, Complication Severity, and Survival Following Surgery for Colorectal Cancer. Ann Surg Oncol 2016;23(9): 2832-2840.
3. Platt JJ, Ramanathan ML, Crosbie RA, Anderson JH, McKee RF, Horgan PG, McMillan DC. C-reactive protein as a predictor of postoperative infective complications after curative resection in patients with colorectal cancer. Ann Surg Oncol 2012;19(13): 4168-4177.
4. McDermott FD, Heeney A, Kelly ME, Steele RJ, Carlson GL, Winter DC. Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks. The British journal of surgery 2015;102(5): 462-479.
5. Fedewa MV, Hathaway ED, Ward-Ritacco CL. Effect of exercise training on C reactive protein: a systematic review and meta-analysis of randomised and non-randomised controlled trials. Br J Sports Med 2017;51(8): 670-676.
6. Alizadeh Dehnavi R, de Roos A, Rabelink TJ, van Pelt J, Wensink MJ, Romijn JA, Tamsma JT. Elevated CRP levels are associated with increased carotid atherosclerosis independent of visceral obesity. Atherosclerosis 2008;200(2): 417-423.
7. Martinez BK, White CM. The Emerging Role of Inflammation in Cardiovascular Disease. Ann Pharmacother 2018;52(8): 801-809.
8. Coussens LM, Werb Z. Inflammation and cancer. Nature 2002;420(6917): 860-867.
9. Proctor MJ, Morrison DS, Talwar D, Balmer SM, O’Reilly DS, Foulis AK, Horgan PG, McMillan DC. An inflammation-based prognostic score (mGPS) predicts cancer survival independent of tumour site: a Glasgow Inflammation Outcome Study. Br J Cancer 2011;104(4): 726-734.
10. Dolan RD, Lim J, McSorley ST, Horgan PG, McMillan DC. The role of the systemic inflammatory response in predicting outcomes in patients with operable cancer: Systematic review and meta-analysis. Sci Rep 2017;7(1): 16717.
11. Cole DS, Watts A, Scott-Coombes D, Avades T. Clinical utility of peri-operative C-reactive protein testing in general surgery. Ann R Coll Surg Engl 2008;90(4): 317-321.
12. Gaudino M, Nasso G, Andreotti F, Minniti G, Iacoviello L, Donati M, Schiavello R, Possati G. Preoperative C-reactive protein level and outcome following coronary surgery. Eur J Cardiothorac Surg 2002;22(4): 521-526.
13. Zajonz D, Brand A, Lycke C, Ozkurtul O, Theopold J, Spieg J, van Pelt J, Wensink MJ, Romijn JA, Tamsma JT. Elevated CRP levels are associated with increased carotid atherosclerosis independent of visceral obesity. Atherosclerosis 2008;200(2): 417-423.
14. Xiang D, Xing H, Tai H, Xie G. Preoperative C-Reactive Protein as a Risk Factor for Postoperative Delirium in Elderly Patients Undergoing Laparoscopic Surgery for Colon Carcinoma. Biomed Res Int 2017;2017: 5635640.
15. Trepanier M, Minnella EM, Paradis T, Awasthi R, Keneva P, Schwartzman K, Carli F, Fried GM, Feldman LS, Lee L. Improved Disease-free Survival After Prehabilitation for Colorectal Cancer Surgery. Ann Surg 2019;270(3): 493-501.
16. Heger P, Probst P, Wiskemann J, Steindorf K, Diener MK, Mihaljevic AL. A Systematic Review and Meta-analysis of Physical Exercise Prehabilitation in Major Abdominal Surgery (PROSPERO 2017 CRD42017080366). J Gastrointest Surg 2019.
17. McSorley ST, Roxburgh CSD, Horgan PG, McMillan DC. The Impact of Preoperative Dexamethasone on the Magnitude of the Postoperative Systemic Inflammatory Response and Complications Following Surgery for Colorectal Cancer. Ann Surg Oncol 2017;24(8): 2104-2112.

Tables
Table 1
1A: Patient demographics and tumor data
1B: Preoperative hematological and biochemical profile of patients
### A

| Variable                      | n (%)  |
|-------------------------------|--------|
| Age > 65                      | 147 (67.4) |
| Male                          | 136 (62.4)  |
| BMI ≥ 30                      | 43 (29.9)  |
| **Preoperative comorbidity**  |        |
| Cardiovascular                | 65 (29.8)  |
| Respiratory                   | 44 (20.2)  |
| Renal                         | 43 (19.7)  |
| Diabetes                      | 34 (15.6)  |
| Autoimmune                    | 31 (14.2)  |
| Smoker                        | 30 (16.3)  |
| Laparoscopic                  | 176 (80.7) |

### B

| Laboratory value | \( \bar{x} \) | \( \sigma \) | Missing |
|------------------|--------------|--------------|---------|
| Hb (g/dL)        | 12.4         | 2.1          | 1       |
| WBC \((x10^9/L)  | 7.4          | 2.2          |         |
| Platelets \((x10^9/L) | 273   | 82.6        | 2       |
| Neutrophils \((x10^9/L) | 4.8   | 1.9         | 2       |
| Lymphocytes \((x10^9/L) | 1.5   | 0.6         | 2       |
| PLR              | 208          | 125.2        | 4       |
| NLR              | 4.0          | 4.5          | 2       |
| CRP \((mg/L)     | 18.7         | 34.1         | 79      |
| CEA \((ng/mL)    | 8.4          | 24.7         | 47      |

### C

| Variable          | n (%) | Clavien-Dindo Grade |
|-------------------|-------|---------------------|
| Ileus             | 13 (6.0) | 0 111 (50.9) |
| Wound infection   | 8 (3.7)  | 1 52 (23.9) |
| Wound dehiscence  | 3 (1.4)  | 2 14 (6.4)  |
| Hernia            | 7 (3.2)  | 3 12 (5.5)  |
| Anastomotic leak  | 6 (2.8)  | 4 27 (12.4) |
| Sepsis            | 7 (3.2)  | 5 2 (0.9)   |
| Embolism          | 8 (3.7)  |  |
| Urinary           | 16 (7.3) |  |
| Renal             | 16 (7.3) |  |
| Respiratory       | 25 (11.5) |  |
| Cardiovascular    | 21 (9.6) |  |
| Neurological      | 9 (4.1)  |  |
### Table 2
Univariable analysis for postoperative complications

| Variable                  | OR (p-value) |
|---------------------------|--------------|
| Ileus                     | 0.7 (0.608)  |
| Wound infection/dehiscence| 1.0 (0.968)  |
| Anastomotic leak           | 1.2 (0.819)  |
| Sepsis                    | 0.5 (0.284)  |
| Embolism                  | 2.2 (0.220)* |
| Renal complication         | 2.8 (0.060)* |
| Resp complication          | 3.1 (0.060)* |
| Cardiovascular             | 4.0 (0.16)*  |
| Respiratory               | 1.2 (0.862)  |
| Renal                     | 1.0 (0.981)  |
| Diabetes                  | 1.8 (0.443)  |
| Autoimmune tumours         | 3.2 (0.174)* |
| Malignant tumours          | 2.5 (0.269)  |
| Rectal tumours             | 2.6 (0.198)* |
| Open approach**           | 2.7 (0.063)* |
| Haemoglobin < 10 g/dl*     | 1.7 (0.269)  |
| WCC < 4 x 10^9/L           | 2.1 (0.396)  |
| WCC > 11 x 10^9/L         | 0.7 (0.713)  |
| Platelet < 150 x 10^9/L   | 1.0 (0.982)  |
| Platelet > 400 x 10^9/L   | 0.9 (0.923)  |
| Lymphocytes < 1 x 10^9/L  | 1.0 (0.981)  |
| Lymphocytes > 5 x 10^9/L  | 1.2 (0.821)  |
| Neutrophils < 2 x 10^9/L  | 1.2 (0.821)  |
| Neutrophils > 8 x 10^9/L  | 1.2 (0.821)  |
| PLR < 61                  | 1.2 (0.821)  |
| PLR > 239                 | 1.2 (0.821)  |

Results expressed as odds ratios (OR) with p values in brackets. Variables with p values < 0.25 at univariable analysis were denoted ** and included for multivariate analysis. Variables with null values in contingency tables for univariate analysis, OR was not calculated and Fishers exact test used for p value and insertion to multivariate analysis.
### Univariable analysis

|                  | OR (p-value) |
|------------------|--------------|
|                  |              |
| **NLR < 0.83**   | (0.999)      |
|                  | (0.999)      |
|                  | (0.999)      |
|                  | (0.999)      |
|                  | (0.999)      |
|                  | (0.999)      |
|                  | (0.999)      |
| **NLR > 3.92**   |              |
|                  | 1.5 (0.523)  |
|                  | 2.4 (0.172)* |
|                  | 4.8 (0.051)* |
|                  | 0.9 (0.908)  |
|                  | 1.4 (0.664)  |
|                  | 3.2 (0.020)* |
|                  | 2.3 (0.044)* |
|                  | 1.8 (0.198)* |
|                  | 3.0 (0.094)  |
| **CRP ≥ 5 mg/L** | 2.2 (0.356)  |
|                  | 1.6 (0.593)  |
|                  | 5.7 (0.079)* |
|                  | 0.052*       |
|                  | 0.024*       |
|                  | 15.4 (0.001)*|
|                  | 4.5 (0.007)* |
|                  | 7.6 (0.003)* |
|                  | (0.052)*     |
| **CRP ≥ 10 mg/L**| 2.4 (0.281)  |
|                  | 1.0 (0.008)* |
|                  | 10.1 (0.014)*|
|                  | 1.1 (0.002)* |
|                  | 10.1 (0.014)*|
|                  | 16.9 (0.001)*|
|                  | 10.4 (0.000)*|
|                  | 3.6 (0.021)* |
|                  | 1.1 (0.000)  |
| **CEA ≥ 3 ng/mL**| 1.1 (1.000)  |
|                  | 0.2 (0.123)* |
|                  | 0.3 (0.373)  |
|                  | 1.1 (0.872)  |
|                  | 1.5 (0.575)  |
|                  | 1.6 (0.406)  |
|                  | 1.0 (0.935)  |
|                  | 1.5 (0.425)  |
|                  | 3.0 (0.254)  |
| **T stage ≥ 4**  | 2.3 (0.213)* |
|                  | (0.999)      |
|                  | 4.7 (0.073)* |
|                  | 1.1 (0.931)  |
|                  | (0.600)      |
|                  | 1.0 (0.987)  |
|                  | 1.1 (0.876)  |
|                  | 2.7 (0.076)* |
|                  | 2.0 (0.414)  |
| **Node positive**| 0.3 (0.123)* |
|                  | 2.2 (0.254)  |
|                  | 2.6 (0.294)  |
|                  | 2.3 (0.276)  |
|                  | 1.0 (0.997)  |
|                  | 0.8 (0.725)  |
|                  | 0.8 (0.672)  |
|                  | 1.2 (0.667)  |
|                  | 2.2 (0.254)  |
| **Moderate/poorly differentiated** | 3.4 (0.220)* |
|                  | 0.6 (0.437)  |
|                  | 0.4 (0.351)  |
|                  | 1.8 (0.587)  |
|                  | 0.9 (0.876)  |
|                  | 0.8 (0.705)  |
|                  | 1.3 (0.670)  |
|                  | 0.4 (0.034)* |
|                  | 0.6 (0.438)  |

Results expressed as odds ratios (OR) with p values in brackets. Variables with p values < 0.25 at univariable analysis were denoted "*" and included for multivariate analysis. Variables with null values in contingency tables for univariate analysis, OR was not calculated and Fishers exact test used for p value and insertion to multivariate analysis. **versus laparoscopic

**BMI** – body-mass index (kg/m²). **WCC** – white cell count. **PLR** – platelet/lymphocyte ratio. **NLR** – neutrophil/lymphocyte ratio.
Table 3  
Multivariable analysis for postoperative complications (CRP cut-off ≥ 5 mg/L)

|                  | Ileus | Wound infection/dehiscence/hernia | Anastomotic leak | Sepsis | Embolism | Renal complication | Resp complication | Cardio complication | Neut con |
|------------------|-------|-----------------------------------|-------------------|--------|----------|-------------------|-------------------|----------------------|---------|
| Age ≥ 65         |       |                                   |                   |        |          |                   |                   |                       |         |
| Male sex         |       |                                   |                   |        |          |                   |                   |                       |         |
| BMI ≥ 30         |       |                                   |                   |        |          |                   |                   |                       |         |
| Smoker           |       |                                   |                   |        |          | 15.7 (0.003)*     | 5.6 (0.016)*       |                       |         |
| Cardiovascular   |       |                                   |                   |        |          | 13.9 (0.05)*      |                   |                       |         |
| Respiratory      |       |                                   |                   |        |          |                   |                   |                       |         |
| Renal            |       |                                   |                   |        |          | 18.0 (0.032)*     |                   |                       |         |
| Diabetes         |       |                                   |                   |        |          |                   |                   |                       |         |
| Autoimmune       |       |                                   |                   |        |          |                   |                   |                       |         |
| Malignant tumours|       |                                   |                   |        |          |                   |                   |                       |         |
| Rectal tumours   |       |                                   |                   |        |          | 60.4 (0.017)*     |                   |                       |         |
| Open approach**  |       |                                   |                   |        |          | 11.5 (0.05)*      |                   |                       |         |
| Haemoglobin < 10 g/dl* |   |                                   |                   |        |          |                   |                   |                       |         |
| WCC < 4 × 10⁹/L  |       |                                   |                   |        |          |                   |                   |                       |         |
| WCC > 11 × 10⁹/L |       |                                   |                   |        |          |                   |                   |                       |         |
| Platelet < 150 × 10⁹/L |   |                                   |                   |        |          |                   |                   |                       |         |
| Platelet > 400 × 10⁹/L |   |                                   |                   |        |          | 14.1 (0.014)*     |                   | 54.5 (0.03)         |         |
| Lymphocytes < 1 × 10⁹/L | 0.3  |                                   |                   |        |          | 0.3 (0.030)*      |                   |                       |         |
| Lymphocytes > 5 × 10⁹/L |       |                                   |                   |        |          |                   |                   |                       |         |
| Neutrophils < 2 × 10⁹/L |       |                                   |                   |        |          |                   |                   |                       |         |
| Neutrophils > 8 × 10⁹/L |       |                                   |                   |        |          | 7.0 (0.031)*      |                   |                       |         |
| PLR < 61         |       |                                   |                   |        |          |                   |                   |                       |         |
| PLR > 239        |       |                                   |                   |        |          |                   |                   |                       |         |
| NLR < 0.83       |       |                                   |                   |        |          |                   |                   |                       |         |
| NLR > 3.92       |       |                                   |                   |        |          |                   |                   |                       |         |
| CRP ≥ 5 mg/L     |       |                                   |                   |        |          | 17.0 (0.013)*     | 10.5 (0.007)*      |                       |         |
| CEA ≥ 3 ng/mL    |       |                                   |                   |        |          |                   |                   |                       |         |
| T stage ≥ 4      |       |                                   |                   |        |          |                   |                   |                       |         |
| Node positive    |       |                                   |                   |        |          |                   |                   |                       |         |
Multivariable analysis

| Moderate/poorly differentiated |

- Italic – less than three variables significant at univariable analysis so no multivariable analysis performed
Table 3
b: Multivariable analysis for postoperative complications (CRP cut-off ≥ 10 mg/L)

| Outcome | OR (p-value) |
|---------|--------------|
| Age ≥ 65 | 5.0 (0.049) |
| Male sex | |
| BMI ≥ 30 | |
| Smoker | 5.2 (0.030) |
| Cardiovascular | 34.3 (0.005) |
| Respiratory | |
| Renal | |
| Diabetes | |
| Autoimmune | |
| Malignant tumours | 0.1 (0.038) |
| Rectal tumours | 32.0 (0.022) |
| Open approach** | |
| Haemoglobin < 10 g/dL* | |
| WCC < 4 g/L | |
| WCC > 11 g/L | |
| Plt < 150 | |
| Plt > 400 | 13.8 (0.015) |
| Lymphocytes < 1 | |
| Lymphocytes > 5 | |
| Neutrophils < 2 | |
| Neutrophils > 8 | |
| PLR < 61 | |
| PLR > 239 | |
| NLR < 0.83 | |
| NLR > 3.92 | |
| CRP ≥ 10 mg/L | 13.1 (0.002) |
| CEA ≥ 2 ng/mL | |
| T stage ≥ 4 | |
| Node positive | |
| Moderate/poorly differentiated | 0.1 (0.029) |