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Post-operative neutrophil–lymphocyte ratio predicts complications following colorectal surgery☆

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Abstract *Introduction:* The neutrophil–lymphocyte ratio (NLR) correlates with serial organ dysfunction scores in colorectal surgical patients in critical care units. We hypothesised that the NLR on the first day after an elective colorectal resection would identify patients at increased risk of subsequent complications.
Methods: With Ethics Committee approval, 100 patients were recruited to a prospective cohort study. Pre-operative test results and the full blood count on the first post-operative day were noted for all patients. The development of any pre-defined post-operative complications was recorded.
Results: Elective colorectal resection was associated with an increase in mean NLR from 3.5 to 11.6 ($p < 0.001$). Thirty patients developed at least one predefined complication. Patients with an NLR $\geq$9.3 on the first post-operative day had a significantly greater risk of complications (likelihood ratio 2.12; 95% confidence interval 1.366–3.253). Twenty-two patients had a white cell count $\geq$11 on the first post-operative day but this was not associated with a significantly increased risk of complications (likelihood ratio 1.94; 95% confidence interval 0.94–3.9).
Conclusion: NLR $\geq$9.3 on the first post-operative day is associated with an increased risk of complications. This simple derivation of routinely available data helps to identify patients at high-risk of complications, allowing targeted preventive measures.

Introduction

Post-operative complications are more common following major gastroenterological surgery compared to other surgical specialities, resulting in increased resource utilisation.[1] About one-third of patients undergoing colorectal surgery develop a post-operative complication.[2] Surgical intervention is associated with a systemic inflammatory

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response, characterised by fever, metabolic and immunologic changes[3–6] and tissue repair. The inflammatory response is characterised by an increase in circulating neutrophil levels accompanied by a fall in circulating lymphocyte levels.[7,8] The neutrophil–lymphocyte ratio (NLR) provides a simple index of the systemic inflammatory response and resulting immunosuppression. It correlates with organ dysfunction scores and clinical course in critically ill patients.[9] Thus, NLR could provide a simple method to identify patients at high-risk of post-operative complications. We aimed to determine if the neutrophil–lymphocyte ratio on the first post-operative day identifies patients at increased risk of complications following elective open colorectal surgery.

Methods

Consecutive patients over 18 years of age undergoing elective, open large bowel resection were recruited to a prospective, cohort study. The study was conducted during 2005 in the colorectal unit of a 600-bed district general hospital in the United Kingdom. The unit comprises three consultant colorectal surgeons and performs approximately 130 colorectal resections each year. All patients received care according to the usual practice of the responsible consultant surgeon. Each patient received one dose of prophylactic antibiotics at induction, usually cefuroxime and metronidazole. Urinary catheters were routinely used. Epidural insertion was at the discretion of the responsible anaesthetist. Active warming was used throughout each procedure. Thromboembolic prophylaxis was used in all patients, comprising anti-thrombotic stockings and subcutaneous enoxaparin. All participants provided written informed consent. The study was approved by an NHS Research Ethics Committee.

Post-operatively, each patient was reviewed daily for the development of pre-defined complications. The following complications were recorded: wound infection (erythema, discharge, pyrexia, wound culture positive for pathogenic organism); chest infection (cough, sputum, pyrexia, signs on chest auscultation or chest x-ray); urinary tract infection (positive pathogenic urine or catheter specimen culture, pyrexia); intra-abdominal collection (confirmed radiologically or at laparotomy); other infective complication (any other infective complication associated with pyrexia, leucocytosis and positive cultures, e.g. line infection); pulmonary oedema (tachycardia, tachypnoea, crepitations on auscultation, oxygen saturation less than 95% on room or pulmonary congestion on chest x-ray, responding promptly to diuretic administration); myocardial infarction (ST segment elevation or new Q-waves on electrocardiogram confirmed by internal physician or elevated serum troponin I levels); pulmonary embolus (high probability ventilation/perfusion scan or positive CT pulmonary angiogram); new-onset arrhythmias (any rhythm other than sinus confirmed on a 12-lead electrocardiogram); renal failure (requiring renal replacement therapy).

Full blood counts were performed pre-operatively and on the first post-operative day for all patients as part of their routine care. All full blood counts were performed in the West Suffolk Hospital Haematology Laboratory by staff blinded to the study. The NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. The pre- and post-operative NLR and total white cell counts (WCC) were recorded for all patients.

The statistical analysis was performed using Statsdirect 2.4.1 (Statsdirect Ltd., UK). All *p*-values are two sided and significance was set at the 5% level. Continuous data were compared by the Student *t*-test and Mann–Whitney *U*-test as appropriate. Categorical data were compared by the

Table 1 Pre-operative characteristics in patients with and without complications

Variable	Complications ($n = 30$)	No complications ($n = 70$)	*p*
Age (years)	74 (66.9–80.1)	72 (63.1–77.3)	0.25
Male gender	17	37	0.89
Rectal surgery	19	26	0.03
Diabetic	3	5	0.64
Respiratory disease	7	6	0.06
Ischaemic heart disease	11	6	0.001
Cerebrovascular disease	1	4	0.99
Inflammatory bowel disease	3	2	0.19
Diverticular disease	6	13	0.99
Colorectal cancer	25	61	0.62
Smoker	6	7	0.2
Previous abdominal surgery	14	29	0.63
Use of purgative bowel preparation	21	52	0.66
Pre-operative laboratory values			
Sodium (mmol/dl)	140.2 (3.45)	140 (2.76)	0.76
Potassium (mmol/dl)	4.27 (0.46)	0.34	0.9
Urea (mmol/dl)	5.8 (1.89)	5.7 (1.59)	0.81
Creatinine (mmol/dl)	84 (22.9)	85 (20.7)	0.73
White cell count	8.04 (1.99)	7.75 (2.04)	0.51
Neutrophil–lymphocyte ratio	3.97 (2.16)	3.28 (1.87)	0.11

Table 2 Intra-operative variables in patients with and without complications

Variable	Complications ($n = 30$)	No complications ($n = 70$)	p
Duration of anaesthesia (min)	202 (70.9)	165 (63.6)	0.01
CVP line use	14	26	0.37
Epidural use	28	60	0.21
Lowest systolic blood pressure (mmHg)	81 (9.8)	82 (9.5)	0.66
Hypotension (systolic blood pressure <90 mmHg for 10 min)	16	25	0.1
Maximum heart rate (beats/min)	86 (16.3)	80 (15.5)	0.07
Blood loss (ml)[a]	400 (0 to 985)	0 (0 to 200)	0.0001
Fluid balance (ml)	3382 (1015.2)	3267 (1197.9)	0.65

[a] Median (interquartile range).

Fisher exact or chi-square tests. All data are presented as mean (standard deviation), unless otherwise stated. Receiver operating characteristic (ROC) curves were constructed for post-operative NLR and WCC in order to determine the optimal cut-off values for predicting post-operative complications. The distribution of complications between groups above and below the cut-off value was then compared and likelihood ratios calculated. In order to determine whether post-operative NLR is an independent predictor of complications, a multiple logistic regression model was constructed. Factors with a p-value of 0.1 or less in a univariate analysis were entered into the model.

Results

During 2005, 100 patients (54 male) were recruited. Their mean age was 69.7 years (95% confidence interval 67.1—72.4). The majority of patients (86) underwent surgery for colorectal cancer. Of these, 45 patients had rectal tumours. The remaining 14 patients underwent open large bowel resection for a variety of benign conditions (9 diverticulosis, 5 inflammatory bowel disease). Pre-defined complications occurred in 30 patients (8 wound infection, 1 catheter infection, 4 intra-abdominal sepsis, 7 chest infection, 6 other infective, 3 pulmonary oedema, 8 arrhythmias and 1 renal failure). Some developed more than one post-operative complication. Patients who developed a complication were more likely to have a history of respiratory or ischaemic heart disease (Table 1). Rectal surgery was associated with a higher complication rate. The complications group underwent longer procedures with greater blood loss and a higher maximum intra-operative heart rate (Table 2).

There were no differences in pre-operative white cell counts or neutrophil—lymphocyte ratios (Table 1). However, patients who went on to develop post-operative complication had a higher NLR on the first post-operative day (Table 3). ROC curve analysis of NLR suggested that a cut-off of 9.3 was the optimal value for predicting complications, with an area under the curve of 0.66. This cut-off point produced a sensitivity of 0.66 (95% CI 0.47—0.83) and a specificity of 0.69 (95% CI 0.56—0.79). ROC curve analysis for post-operative WCC identified an optimal cut-off of 11 for predicting post-operative complications (area under the curve 0.51). Sensitivity at this point was 0.33 (95% CI 0.173—0.528) and specificity was 0.81 (95% CI 0.703—0.897). Likelihood ratios are compared between NLR and WCC in Table 4.

A multivariate logistic regression model was constructed to determine whether post-operative NLR was independent of complications. The least significant variable was dropped from each iteration of the model until all remaining variables were significant at the 5% level. Only a history of ischaemic heart disease, intra-operative blood loss and post-operative serum potassium values retained significance in the final model.

Discussion

The neutrophil—lymphocyte ratio is a simple index of the systemic inflammatory response. Previous work from our unit has shown that the NLR correlates with medium term survival in patients with colorectal cancer.[10] Pre-procedural NLR also predicts long-term survival among patients undergoing percutaneous coronary intervention.[11] However, the value of post-procedural NLR is unclear.

Table 3 Laboratory values on the first post-operative day

Variable	Complications ($n = 30$)	No complications ($n = 70$)	p
Sodium (mmol/dl)	138 (3.14)	138 (3.66)	0.85
Potassium (mmol/dl)	4.3 (0.44)	4.04 (0.39)	0.003
Urea (mmol/dl)	5.18 (1.98)	4.46 (1.53)	0.06
Creatinine (mmol/dl)	83 (30.5)	76 (20.6)	0.26
Total white cell count	9.7 (4.33)	9.4 (3.71)	0.76
Neutrophil—lymphocyte ratio	14.3 (9.11)	10.5 (8.85)	0.05

Table 4 Likelihood ratios at the optimal cut-off values for NLR and WCC

	Complications (*n*, %)	No complications (*n*, %)	Likelihood ratio (95% CI)
NLR ≥9.3	20 (66)	22 (31)	
NLR <9.3	10 (33)	48 (69)	2.12 (1.366—3.253)
WCC ≥11	10 (33)	11 (16)	
WCC <11	20 (66)	59 (84)	1.03 (0.939—3.902)

Various attempts have been made to identify chemical markers that predict an increased risk of post-operative complications following colorectal surgery. Procalcitonin and complement C3a levels in the first 24 h following elective colorectal surgery correlate with the presence of the systemic inflammatory response syndrome (SIRS).[12] However, the predictive value of these markers is disputed[12,13] while the relationship between the presence of SIRS and subsequent complications is also unclear.[14] ROC curve analyses were not performed to identify optimal cut-off values. In addition, these markers are expensive and availability is limited outside research programmes.

White cell counts and C-reactive protein levels are widely available in many healthcare systems. Unfortunately, both white cell and CRP levels display non-specific increases following surgery. Levels are about the same in patients with SIRS and those without.[12] As a result, both post-operative white cell count and CRP levels have minimal predictive value in identifying high-risk patients. This is in keeping with the low observed sensitivity for white cell count in our series. The area under the curve for white cell count was only 0.51, barely above the 'line of no significance'.[15] Our data suggest that post-operative NLR may be more useful. A previous study found that NLR correlated with sequential organ dysfunction scores.[9] However, the study cohort was restricted to intensive care patients and included some critically ill non-surgical patients. Our series was restricted to a cohort of elective colorectal patients only, attenuating the effect of patient heterogeneity.

The current study has several limitations. There is some heterogeneity within the cohort, as we included patients undergoing surgery for inflammatory bowel disease and diverticulosis as well as cancer. The underlying diagnosis had no apparent effect on the complication rate but the sample size is small. Post-operative NLR did not retain significance in a multivariate model. However, this is also likely to be a reflection of the small sample size. Post-operative NLR was a significant predictor of complications in the univariate analysis. It is easily derived from routinely available data. Patients with an NLR of 9.3 or above on the first day after elective colorectal surgery appear to have an increased risk of complications. A much larger series is required to determine whether NLR is an independent predictor. In the meantime, this observation may facilitate early, targeted intervention.

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