Association of pretreatment neutrophil–lymphocyte ratio and outcome in emergency colorectal cancer care

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ABSTRACT

INTRODUCTION The association between the neutrophil–lymphocyte ratio (NLR) and outcome in elective colorectal cancer surgery is well established; the relationship between NLR and the emergency colorectal cancer patient is, as yet, unexplored. This paper evaluates the predictive quality of the NLR for outcome in the emergency colorectal cancer patient.

MATERIALS AND METHODS A total of 187 consecutive patients who underwent emergency surgery for colorectal cancer were included in the study. NLR was calculated from the haematological tests done on admission. Receiver operating characteristic analyses were used to determine the most suitable cut-off for NLR. Outcomes were assessed by mortality at 30 and 90 days using stepwise Cox proportional hazards regression.

RESULTS An NLR cut-off of 5 was found to have the highest sensitivity and specificity. At 30 days, age and time from admission to surgery were associated with increased mortality; a high NLR was associated with an increased risk of mortality in univariate but not multivariate analysis. At 90 days, age, NLR, time from admission to surgery and nodal status were all significantly associated with increased mortality on multivariate analysis.

CONCLUSIONS Pre-operative NLR is a cheap, easily performed and useful clinical tool to aid prediction of outcome in the emergency colorectal cancer patient.

KEYWORDS

Neutrophil – Lymphocyte – Colorectal cancer

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Introduction

Colorectal cancer is the fourth most common cancer in England, accounting for over 33,000 newly diagnosed cancer cases in 2014.¹ Those patients who present as emergencies have been shown to have more advanced disease and inferior outcomes when compared with their elective counterparts.²

England has a high rate of emergency presentation compared with other equivalent-income countries and this is associated with poor rates of disease survival, especially in the first year after diagnosis.^{3–6} Many of these deaths occur in the first three months after diagnosis⁷ and it has been suggested that the poor short-term survival rates in England may be related to high numbers of early postoperative deaths.^{8,9} Reliable and inexpensive markers of prognosis, particularly in relation to the probability of survival from major operative intervention, may aid clinicians in selecting those most likely to benefit from surgery. This may subsequently improve early survival from emergency surgery for colorectal cancer in England.

One potential such marker is the neutrophil–lymphocyte ratio (NLR). In 2001, Zahorec noted that critically ill patients in intensive care exhibited a marked neutrophilia in conjunction with a severe lymphocytopenia. The ratio between these two variables was termed the NLR, which was shown to reflect systemic inflammation and to have prognostic implications.¹⁰ Numerous studies have investigated the association between the NLR and outcome in elective colorectal cancer care, with a clear negative correlation between a high NLR and postoperative outcome.^{11–16} Almost all these studies exclude emergency patients, however, in an attempt to reduce variation. Recently, studies have found that NLR is strongly associated with short-term outcomes in other acute surgical emergencies, suggesting that NLR is not just a long-term outcome prediction tool.^{17–19}

Despite this finding, the role of the NLR in predicting outcome in the emergency colorectal cancer patient remains unexplored. This study therefore aims to use a retrospective cohort analysis of those patients presenting acutely at our institution to assess the role of the NLR in predicting outcomes at 30 and 90 days postoperatively in

the emergency colorectal cancer patient, to help in identifying whether NLR can assist in the selection of the most appropriate candidates for surgery.

Materials and methods

Through interrogation of the electronic patient database held at St. James' University Hospital, Leeds, a total of 248 consecutive patients who underwent emergency surgery for colorectal cancer between January 2008 and December 2014 were identified. Only those patients who did not present acutely, did not undergo operative intervention or who did not have on-admission blood tests were excluded.

Data with regard to essential clinical and pathological parameters (age, sex, comorbidities and previous colorectal surgery) were collected. Comorbidities were summarised using the Charlson Comorbidity Index.²⁰ Further information regarding type of admission (acute/elective) and surgical intervention (procedure) was collected. Date of admission and surgery were used to calculate the time from admission to surgery (time of decision to operate was not available). Surgical variables were collected from the surgeon's report and included the procedure undertaken, surgical access route (open or laparoscopic) and tumour location.

Haematological variables of the neutrophil and lymphocyte count on admission were recorded. These variables were then converted to the NLR via simple division of the absolute neutrophil count by the absolute lymphocyte count. Postoperative histological data were retrieved from histopathology reports, and included tumour, node and metastasis stage, Dukes' stage and the maximum tumour diameter.

Outcomes were measured by overall survival at 30 and 90 days. The survival time was calculated as the number of days from the date of surgery to the date of death, as recorded in the patient's record. Reason for death was not

Table 1 Patient demographics for the 187 patients in the sample who underwent surgery.

Parameter	Demographic ^b
Age (years) ^a	74 (IQR 64–80)
Sex:	
Male	94 (50.3)
Female	93 (49.7)
Charlson Index ^a	4 (IQR 2–7)
Reason for admission:	
Obstruction	134 (71.7)
Perforation	44 (23.5)
Appendicitis	6 (3.2)
Intussusception	2 (1.1)
Ischaemic bowel	1 (0.5)
Time from admission to surgery (days) ^a	2 (IQR 1–4)
Time from surgery to discharge (days) ^a	12 (IQR 7–23)
Mortality at 30 days	26 (13.9)
Mortality at 90 days	40 (21.4)
Dukes' score:	
A	5 (2.7)
B	72 (38.5)
C	68 (36.3)
D	42 (22.5)
Procedure type:	
Open	117 (62.6)
Laparoscopic	53 (28.3)
Laparoscopic converted to open	10 (5.4)
Endoscopic	7 (3.7)
Tumour location:	
Caecum	48 (25.7)
Sigmoid colon	43 (23.0)
Ascending colon	26 (13.9)
Descending colon	26 (13.9)
Rectum	15 (8.0)
Transverse colon	13 (6.9)
Rectosigmoid	11 (5.9)
Appendix	5 (2.7)

^a Averages displayed are the median.

^b Percentages are shown in parenthesis unless otherwise stated.

included in the analysis as the information was absent from the electronic records.

Statistical analysis was performed using Stata 14 software. A *P* value less than 0.05 was classed as statistically significant, with all confidence intervals reported at the

95% level. The optimal dichotomisation point for the NLR was calculated using receiver operating characteristic (ROC) curve analysis and the application of the Youden's index to identify the point with maximum sensitivity and specificity. The relationship between NLR and other clinicopathological variables was evaluated using nonparametric tests (Pearson's chi squared test/Mann-Whitney test) due to the skewed distribution of the NLR variable. Survival analysis was graphically assessed using Kaplan-Meier survival curves, with significance of difference tested by the log-rank test. Cox proportional hazards regression was used for both univariate and stepwise multivariate analysis, with the threshold for multivariate analysis set at $P = 0.05$.

Results

Of the 248 consecutive patients who presented acutely and received urgent surgical intervention, 51 patients were excluded due to receiving elective surgery that was incorrectly coded. A further 10 who did not have a full blood count (FBC) taken on admission were also excluded (Fig 1). The remaining 187 patients were entered into the study (Table 1); 162 patients had their tumour resected (86.6%), 18 received a defunctioning stoma (9.6%) and 7 were stented endoscopically (3.8%). At 30 and 90 days post-surgery, 26 (13.9%) and 40 (21.4%) patients had died, respectively. The maximum tumour diameter was unavailable for 36 (19.3%) of the 187 patients included for analysis.

ROC curve analysis was performed to identify the ideal cut-off point for the NLR as a predictor for overall survival at both 30 and 90 days (Fig 2). At 30 days, an NLR of 5.0 had the highest sensitivity (73.1%) and specificity (49.7%), whereas at 90 days an NLR of 5.5 had the highest sensitivity (65.0%) and specificity (53.7%). Patients were subsequently dichotomised at a cut-off of 5, as this value maximised sensitivity without overly compromising specificity.

Thereafter, the dichotomised patients were categorised as those with a low NLR (< 5) and those with a high NLR

(≥ 5 ; Table 2). Patients with a high NLR had increased mortality at both 30 and 90 days (19.0%, $P = 0.031$, and 27%, $P = 0.046$, respectively). The median age was higher in the high NLR group (75 years) compared with the low NLR (71 years) but this was not statistically significant ($P = 0.246$). More patients with a high NLR were admitted with perforation (30.0%) compared with the low NLR group (14.9%) but, again, the difference was not significant ($P = 0.077$). Mortality at 90 days in those presenting with perforation was similar between the low and high groups, at 3 (23.1%) patients and 8 (25.8%) patients, respectively. No other significant differences were seen between gender ($P = 0.165$), comorbidities ($P = 0.305$), procedure type ($P = 0.539$), intervention performed ($P = 0.538$), cancer location ($P = 0.152$), tumour staging (Table 2) or time from admission to surgery ($P = 0.988$).

Kaplan-Meier curves were plotted to compare estimated survival between those with a low and a high NLR (Fig 3). An NLR of 5 or above was associated with a poorer prognosis over the first 90 days post-surgery ($P = 0.044$, log-rank). 19 (73.0%) deaths at 30 days were in the high NLR group, while 27 (67.5%) deaths at 90 days occurred in the high NLR group.

Univariate and multivariate analysis using Cox proportional hazards was performed with outcome measured by mortality at both 30 and 90 days post-surgery (Tables 3 and 4). At 30 days, older patients (hazard ratio, HR, 1.065, $P = 0.004$) and time from admission to surgery (HR 1.060, $P = 0.004$) were the only significant predictors of inferior outcomes on both univariate and multivariate analysis. NLR was significant at univariate analysis (HR 2.454, $P = 0.042$) but fell short on multivariate analysis (HR 2.245, $P = 0.069$).

At 90 days, age (HR 1.065, $P < 0.001$) and time from admission to surgery (HR 1.082, $P < 0.001$) remained significant again on both univariate and multivariate analysis. In addition, NLR (HR 2.436, $P = 0.014$) and node staging (HR 2.020, $P = 0.001$) were also significant on both univariate and multivariate analysis. Although Charlson Index, Dukes'

Table 2 The clinicopathological characteristics of the low and high neutrophil-lymphocyte ratio groups.

Parameter	Neutrophil-lymphocyte ratio				P-value
	Low < 5 (n = 87)		High ≥ 5 (n = 100)		
	(n)	(%)	(n)	(%)	
Median age (years)	71 (IQR 63–80)		75 (IQR 65–80)		0.246
Sex:					0.165
Male	39	44.8	55	55.0	
Female	48	55.2	45	45.0	
Reason for admission:					0.077
Obstruction	70	80.4	64	64.0	
Perforation	13	14.9	31	30.0	
Appendicitis	2	2.3	4	4.0	
Intussusception	1	1.2	1	1.0	
Ischaemic bowel	1	1.2	0	0	
Mortality at 30 days	7	8.0	19	19.0	0.031 ^a
Mortality at 90 days	13	14.9	27	27.0	0.046 ^a
Median Charlson Index	4 (IQR 2–7)		4 (IQR 3–7)		0.305
T stage:					0.595
1	1	1.2	1	1.0	
2	2	2.3	2	2.0	
3	29	33.3	23	23.0	
4	55	63.2	74	74.0	
N stage:					0.865
0	37	42.5	40	40.0	
1	22	25.3	29	29.0	
2	28	32.2	31	31.0	
M stage:					0.371
0	70	80.5	75	75.0	
1	17	19.5	25	25.0	
Dukes' score:					0.351
A or B	37	42.5	40	40.0	
C or D	50	57.5	60	60.0	
Procedure type:					0.539
Open or converted to open	56	64.4	71	71.0	
Laparoscopic	26	29.9	27	27.0	
Endoscopic	5	5.7	2	2.0	
Operative intervention:					0.338
Resection	75	86.2	87	87.0	
Defunctioning stoma	7	8.0	11	11.0	
Stent Insertion	5	5.8	2	2.0	
Return to theatre	8	9.2	11	11.0	0.684

Table 2 The clinicopathological characteristics of the low and high neutrophil–lymphocyte ratio groups.

Parameter	Neutrophil–lymphocyte ratio				P-value
	Low < 5 (n = 87)		High ≥ 5 (n = 100)		
	(n)	(%)	(n)	(%)	
Cancer location:					0.152
Caecum	25	28.7	23	23.0	
Sigmoid	16	18.4	27	27.0	
Rectum	6	6.9	9	9.0	
Other	40	46.0	41	41.0	

^a Significant.
IQR, interquartile range.

score and presence of metastases showed significance on univariate analysis, these measures failed to reach significance in the multivariate model.

Discussion

This study found that emergency colorectal cancer patients with a high preoperative NLR (defined as ≥ 5) had higher mortality rates at 90 days compared with those with a preoperative NLR of less than 5. To our knowledge, this is the first study to explore the relationship between preoperative NLR and outcome in patients with colorectal cancer who present as an emergency.

Within both univariate and multivariate analysis, NLR, age, nodal status and time from admission to surgery proved to be significant predictors of poorer outcomes at 90 days postoperatively. These findings support that of

previous studies that have observed a higher NLR to be significantly correlated with worse outcomes in patients with colorectal cancer undergoing elective surgery.^{11,13,14} Other studies have also noted the variables of age and nodal status to be significantly associated with worse outcomes.^{21,22} Importantly, there were no significant differences in age, nodal status and time from admission to surgery between the NLR groups, strengthening the evidence that NLR is an independent predictor of mortality. NLR may have not reached statistical significance at 30 days post-surgery due to the reduced number of post-surgical deaths at this point which, when coupled with the modest sample size, impaired statistical power. Analysis with a larger dataset will be required to clarify this.

It could be argued that as there were a greater number of patients with perforation in the higher NLR group, that this unstable group of patients were the only reason a high NLR was associated with higher mortality. However, the proportion of patients with perforation not surviving to 90 days was only marginally higher in the high NLR group (25.8% vs 23.1%) whereas the difference in mortality of all the patients irrespective of their presentation was markedly different (27.0% vs 14.9%).

It had previously been proposed that the relative lymphocytopenia, impairing immune response against cancerous cells, combined with the pro-angiogenic action of the associated neutrophilia, supporting tumour growth, explained the association between high NLR and poor long-term outcomes and disease recurrence.^{25,24} However, this study has demonstrated an association between NLR and short-term outcomes, which the traditional long-term hypothesis does not completely explain. It has more recently been suggested that severe cancer-induced inflammation causes a platelet aggravating factor associated neutrophilia, combined with leucocytosis due to a cortisol-related stress release.²⁵ The authors hypothesise that the severity of this inflammation, measured accurately by NLR, correlates with poor short-term surgical outcomes due to a combination of local factors (reduced blood flow to the operating site resulting in potential complications such as anastomotic leak) and increased severity of

Figure 3 Kaplan–Meier survival estimate graphical analysis showing the difference in cumulative survival between the high (≥ 5) and low (< 5) neutrophil–lymphocyte ratio (NLR) groups (log rank test *P* = 0.044)

Table 3 Univariate and multivariate analysis for the association between clinicopathological variables and neutrophil-lymphocyte ratio with mortality at 30 days post-surgery.

Variable	Univariate			Multivariate		
	HR	(95% CI)	P-value	HR	(95% CI)	P-value
Age (years)	1.067	1.024–1.112	0.002	1.065	1.020–1.112	0.004
Female sex	0.578	0.262–1.275	0.175	–	–	–
Perforation on admission	1.575	0.685–3.624	0.285	–	–	–
NLR high (≥ 5)	2.454	1.031–5.838	0.042	2.245	0.939–5.366	0.069
Time (admission–surgery, days)	1.073	1.030–1.118	0.001	1.060	1.019–1.103	0.004
Charlson Index	1.077	0.961–1.208	0.202	–	–	–
T stage	1.308	0.612–2.795	0.489	–	–	–
N stage	1.159	0.723–1.858	0.540	–	–	–
M stage	1.084	0.456–2.579	0.855	–	–	–
Dukes' score C/D	1.562	0.653–3.741	0.316	–	–	–
Tumour size (cm)	0.980	0.883–1.089	0.710	–	–	–
Open procedure	1.450	0.567–3.705	0.438	–	–	–

CI, confidence interval; HR, hazard ratio; NLR, neutrophil-lymphocyte ratio

medical complications, such as myocardial infarction and pulmonary embolism.^{26,27} All have been associated with early mortality post-colorectal cancer surgery.²⁸ This hypothesis would need to be thoroughly investigated in future work by including cause of death in the analysis.

Previous studies have been unable to agree on an ideal NLR cut-off for dichotomisation. This study identified an

NLR of 5 to be the ideal cut-off by which the marker could be a reliable predictor of overall survival postoperatively. This value concurs with other studies looking at patients with colorectal cancer who undergo elective surgery,^{13,14} but not with all.^{11,21} Further research will be needed to accurately identify the most suitable cut-off value. The modest sensitivity and specificity found in this study were

Table 4 Univariate and multivariate analysis for the association between clinicopathological variables and neutrophil-lymphocyte ratio with mortality at 90 days post-surgery.

Variable	Univariate			Multivariate		
	HR	(95% CI)	P-value	HR	(95% CI)	P-value
Age (years)	1.064	1.030–1.099	< 0.001	1.065	1.029–1.103	< 0.001
Female sex	0.689	0.368–1.290	0.244	–	–	–
Perforation on admission	1.347	0.673–2.697	0.400	–	–	–
NLR high (≥ 5)	1.947	1.004–3.773	0.049	2.236	1.195–4.965	0.014
Time (admission–surgery, days)	1.079	1.040–1.119	< 0.001	1.082	1.040–1.126	< 0.001
Charlson Index	1.216	1.110–1.331	< 0.001	1.080	0.970–1.203	0.161
T stage	1.280	0.699–2.343	0.423	–	–	–
N stage	1.681	1.133–2.494	0.010	2.020	1.336–3.056	0.001
M stage	2.153	1.137–4.077	0.019	0.971	0.329–2.872	0.958
Dukes' score C/D	2.350	1.077–5.127	0.032	0.851	0.248–2.915	0.797
Tumour size (cm)	0.969	0.883–1.065	0.517	–	–	–
Open procedure	1.030	0.513–2.071	0.933	–	–	–

CI, confidence interval; HR, hazard ratio; NLR, neutrophil-lymphocyte ratio

probably a reflection of analysis that focused on only those who underwent a surgical intervention; a future study involving patients who did not undergo intervention would likely reveal a more accurate representation of the sensitivity and specificity of NLR in the acute phase.

A strength of this study is its use of a homogenous sample, with patients undergoing procedures performed by a limited number of clinicians at a single institution, using similar decision-making criteria and surgical techniques. Conversely, the study does not reflect the breadth of variation in surgical management across the UK. Minimalistic exclusion criteria were used that did not exclude patients who had a previous diagnosis of colorectal cancer, since they also required an urgent decision regarding their management. Crucially, this is the first study exploring the relationship between NLR and outcome in acute patients and the results have the potential to be of clinical relevance and significance.

Limitations of the study include its retrospective nature and, as a result, some variables were uncontrolled and occasionally missing (e.g. time from decision to operate to surgery, time from admission blood tests to surgery). Crucially, it only includes those who underwent operative intervention. No comparison has been made with those who were deemed unsuitable for surgery, although it may be assumed that these patients were likely to have had either multiple comorbidities or such advanced disease that they were unsuitable for surgical intervention and are therefore likely to have had an extremely poor prognosis and outcome. A prospective follow-up study would address this weakness by providing baseline data for this group of patients, thereby allowing for comparison. While the sample is of comparable size to other studies investigating NLR, it is still a relatively small number of patients to allow for national extrapolation. Nevertheless, this is a new specific focus for the use of NLR and would benefit from hypothesis testing using nationwide surgical data. With 68% of the patients in this study receiving a laparotomy, the data collected from the National Emergency Laparotomy Audit (NELA) could be used to test our hypothesis.²⁹

The results of this study are certainly not sufficient to dictate the benefits of surgical intervention alone but NLR may have a role in assisting surgical decision making, including selection of appropriate patients to receive planned admissions to the intensive care unit postoperatively or using prophylactic stenting as a bridge to planned surgery. Higher NLR values may suggest to clinicians that curative resection would be more successful if delayed until acute inflammation secondary to bowel obstruction is reduced. With this study having initially tested the predictive value of NLR in the specific clinical context of an emergency colorectal cancer presentation, the next step would be to instigate a larger follow-up study combining NLR with other recognised significant variables to form a prognostic calculator specifically aimed at the emergency patient with colorectal cancer. NLR is a readily available biomarker that can be calculated easily in the ward environment, at no additional cost, without requiring any change in practice. Other prognostic scores do already

exist, such as the Portsmouth Physiologic and Operative Severity Score for the enUmeration of Mortality and morbidity score (P-POSSUM) and ColoRectal-POSSUM;³⁰ however, these are currently not validated solely for acute care and could not be assessed in this study due to retrospective data collection and absence of critical variables. As mentioned previously, future work including data from NELA would be able to incorporate P-POSSUM scoring. Further work in this area could focus on evaluating the use of NLR to guide surgical and postoperative intensive care decisions and should work to compare the predictive properties of NLR with known existing prognostic scores, with an intention of creating a new multivariate scoring system to guide acute surgical decision making.

Conclusions

This study suggests that a high preoperative NLR is significantly associated with worse outcomes in patients undergoing emergency surgery for colorectal cancer and suggests that NLR may be helpful in predicting a patient's prognosis following emergency surgery. NLR has the potential to contribute to the range of prognostic and outcome scoring systems already available (e.g. P-POSSUM, CR-POSSUM) and to aid clinicians in their decision-making process in this challenging group of patients.

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