Neutrophil/lymphocyte ratio predicts chemotherapy outcomes in patients with advanced colorectal cancer

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METHODS: Clinical information and baseline laboratory parameters were available for 349 patients, from two independent cohorts, with unresectable mCRC receiving first-line palliative chemotherapy. Associations between baseline prognostic variables, including inflammatory markers such as the NLR and tumour response, progression and survival were investigated.

RESULTS: In the training cohort, combination-agent chemotherapy ($P = 0.001$) and NLR $\leq 5$ ($P = 0.003$) were associated with improved clinical benefit. The ECOG performance status $\geq 1$ ($P = 0.002$), NLR $> 5$ ($P = 0.01$), hypoalbuminaemia ($P = 0.03$) and single-agent chemotherapy ($P < 0.0001$) were associated with increased risk of progression. The ECOG performance status $\geq 1$ ($P = 0.004$) and NLR $> 5$ ($P = 0.002$) predicted worse overall survival (OS). The NLR was confirmed to independently predict OS in the validation cohort ($P < 0.0001$). Normalisation of the NLR after one cycle of chemotherapy in a subset of patients resulted in improved progression-free survival ($P = 0.012$).

CONCLUSION: These results have highlighted NLR as a potentially useful clinical biomarker of systemic inflammatory response in predicting clinically meaningful outcomes in two independent cohorts. Results of this study have also confirmed the importance of a chronic systemic inflammatory response influencing clinical outcomes in patients with mCRC.

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Colorectal cancer (CRC) is the third leading cause of worldwide cancer mortality after lung and stomach cancer and is responsible for 639,000 deaths or 1.1% of total deaths (World Health Organisation, 2004). There have been major advances in the treatment of metastatic CRC (mCRC) in the last 10–15 years, involving the introduction of new cytotoxic and molecular targeted therapies. However, use of these newer treatments result in increased toxicities and are prohibitively expensive. Hence, there is a need for accurate predictors of outcomes from treatment, in particular, in identifying those patients who are more likely to benefit by being assisted in rationalising increasingly expensive treatments, especially in under-resourced communities.

Tumour development and growth occurs as a result of interactions among the tumour, host-derived stromal tissues including blood vessels and host immune/inflammatory cells (see Figure 1), with chronic inflammation having an important role in cancer development and progression (Balkwill and Mantovani, 2010; Coussens and Werb, 2002). Lymphocytic infiltration in primary colorectal tumour tissue with different lymphocyte subpopulations has been investigated as potential prognostic factors (Pages et al, 2005; Galon et al, 2006). This chronic inflammatory state also has effects on normal tissues, including the liver, resulting in an ongoing release of ‘acute-phase proteins’ that may be used to monitor this process. Current prognostication in advanced CRC, as in other malignancies, involves a poorly defined combination of clinical experience with the use of relatively crude and subjective covariates, such as performance status, with few markers in clinical practice apart from the use of k-ras mutation status and treatment with epidermal growth-factor receptor inhibitors (Bokemeyer et al, 2009; Koopman et al, 2009; Van Cutsem et al, 2009; Chua et al, 2010).

Over the last 10 years, laboratory markers of a systemic inflammatory response, including plasma C-reactive protein concentration (CRP), hypoalbuminaemia and Glasgow Prognostic Score (GPS, which combines CRP and albumin), and absolute white cell or its components (neutrophils, neutrophil/lymphocyte ratios (NLRs) and platelet/lymphocyte ratios (PLRs)) have been investigated as prognostic and predictive markers in different cancer populations, with the best evidence for their use demonstrated in surgical patients with CRC (Roxburgh and McMillan, 2010). Emerging evidence suggests that elevated baseline levels of...
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In total, there were 349 patients with available clinical information and baseline laboratory parameters. The training set consisted of 171 patients enrolled in first-line chemotherapy trials at the Sydney Cancer Centre for advanced CRC between 1999 and 2007. The independent validation set included 178 patients from a community-based clinical database in the province of Alberta and included patients referred to medical oncology units at the Cross Cancer Institute who received first-line chemotherapy for advanced CRC between 2004 and 2007 (Prado et al., 2008). Table 1 lists the comparative baseline clinical information and laboratory parameters for both cohorts before chemotherapy commencement.

Methods

Baseline clinical information and biochemical evaluation, including full blood count (neutrophils, lymphocytes, haemoglobin and platelets) and albumin before chemotherapy commencement, were collected in a database for patients in both the training and validation sets. Alkaline phosphatase was also collected in the training set. Prognostic variables with >10% missing data were not included in the analysis. Differential white-cell counts (neutrophils and lymphocytes) were also collected for patients before cycle 2 of chemotherapy. Response rates, dates of progression and survival were available for patients in the training set; however, only survival data were available for patients in the validation cohort. Dates of death were followed up by the investigators through hospital records, local Cancer Registries or phone contact through patient relatives, local medical practitioners and palliative-care services. Patients were consented to undergo analyses before commencing chemotherapy, and the study was approved by institutional research ethics committees in both Sydney and Edmonton.

Statistical analysis

Statistical analyses were performed using SPSS Graduate Version 17.0 (IBM Corporation 2010, Somers, NY, USA). Response rates were determined according to criteria determined by individual clinical trials, RECIST criteria. Clinical response was defined as either complete or partial response and non-response as either stable or progressive disease. Clinical benefit was defined as complete response, partial response and stable disease and no benefit as progressive disease alone. Progression-free survival proportion was estimated using the Kaplan-Meier method. Univariable Cox proportional hazards regression models were used to assess the unadjusted association between clinical markers and survival, defined as the time to chemotherapy discontinuation due to toxicity, disease progression or death. Multivariable Cox models with backwards, stepwise selection were used to define the final, best-fit model based on the likelihood ratio test.

 patrons and methods

Study population

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Table 1 Baseline patient characteristics in the training and validation sets before commencement of chemotherapy

| Training set (n = 171) | Validation set (n = 178) | P-value |
|-----------------------|--------------------------|---------|
| Age, median (range)   | 61 (33 – 84)             | 63 (32 – 85) | 0.40 |
| Gender (M/F)          | 110/61 (64/36)           | 100/73 (56/44) | 0.22 |
| Primary cancer site   |                          |         |
| Colon                 | 103 (64)                 | 116 (65) |         |
| Rectum                | 52 (32)                  | 23 (13)  |         |
| Synchronous           | 4 (3)                    | 39 (22)  |         |
| Synchronous           | 2 (1)                    | 0        | <0.0001 |
| ECOG performance status |                      |         |
| 0                     | 85 (50)                  | 30 (17)  |         |
| 1                     | 81 (47)                  | 96 (54)  |         |
| ≥2                    | 5 (3)                    | 52 (29)  | <0.0001 |
| Chemotherapy regimen  |                          |         |
| Single agent only     | 43 (25)                  | 34 (19)  |         |
| Combination           | 128 (75)                 | 92 (52)  |         |
| chemotherapy ± biologicals |                  |         |
| Unknown               | 0                        | 52 (29)  | <0.0001 |
| Number of sites       |                          |         |
| ≤1                    | 91 (53)                  | NA       |         |
| >1                    | 80 (47)                  | NA       |         |
| Baseline levels of prognostic factors |       |
| Albumin, median (range), g/l⁻¹ | 40 (27 – 48) | 39 (20 – 47) |       |
| Carcinoembryonic antigen, median (range) | 38.6 (0.7 – 945) | NA |       |
| Haemoglobin, median (range) | 127 (82 – 162) | 122 (78 – 170) |       |
| Neutrophils, median (range) | 5.5 (1.5 – 14.8) | 5.1 (1.9 – 21.4) |       |
| Lymphocytes, median (range) | 1.4 (0.4 – 4.9) | 1.5 (0.2 – 3.3) |       |
| Neutrophil – lymphocyte ratio, median (range) | 3.7 (1.0 – 30.8) | 3.5 (0.9 – 74.5) |       |
| ≤5                    | 120 (71)                 | 123 (69) |       |
| >5                    | 49 (29)                  | 55 (31)  |       |

Abbreviations: ECOG = Eastern Cooperative Oncology Group; F = female; M = male; NA = not available. *Missing data for 10 patients (training set).

RESULTS

Patient characteristics

Baseline clinical demographics and laboratory values for both training and validation sets are presented in Table 1. There were no differences in age and gender between the two cohorts. However, a significantly higher proportion of patients in the validation cohort had rectal cancer as the primary tumour site and had ECOG PS ≥ 1. The majority of patients in both cohorts received combination chemotherapy ± a biological agent.

Prognostic variables in training set

Table 2 shows the univariate analyses between prognostic variables of interest and clinical benefit, PFS and OS in the training set. At the time of analysis, all patients had progressed on chemotherapy and 169 patients were deceased. The overall clinical response (complete response and partial response) was 55% (93 out of 168 evaluable patients) and clinical benefit (complete response, partial response and stable disease) was 75% (128 out of 168 evaluable patients). The median PFS was 6.7 months (95% CI 5.6 – 7.8 months) and OS was 15.3 months (95% CI 12.4 – 18.2).

Clinical benefit and response

Younger age (<65 years old), ECOG performance status 0, absence of hypoalbuminaemia, normal alkaline phosphatase, low or normal neutrophil counts and NLR ≤ 5 were associated with improved clinical benefit (Table 2). Similarly, younger age (<65 years old), ECOG performance status 0 and NLR ≤ 5 were associated with improved clinical response. In addition, combination-agent chemotherapy was also associated with improved clinical response.

PFS and OS

Variables predicting improved PFS included younger age, ECOG performance status 0, combination-agent chemotherapy, single site of metastasis, absence of neutrophilia or hypoalbuminaemia and NLR ≤ 5 (Table 2 and Figure 2A). The following variables were associated with improved OS: younger age, ECOG PS 0, combination-agent chemotherapy, absence of neutrophilia or anaemia. Hypoalbuminaemia, elevated alkaline phosphatase and NLR > 5 were also significantly associated with worse OS (Table 2 and Figure 2B).

Multivariate analysis

In multivariate analysis performed in the training set (Table 3), combination-agent chemotherapy and NLR ≤ 5 were associated with improved clinical benefit. The ECOG performance status ≥ 1, NLR > 5, hypoalbuminaemia and single-agent chemotherapy were associated with increased risk of progression. The ECOG performance status ≥ 1 and NLR > 5 predicted worse OS.

Prognostic variables according to NLR

Table 4 summarises analysis of baseline characteristics and prognostic variables according to NLR groups. Patients with NLR > 5 were more likely to suffer from hypoalbuminaemia (P-level < 0.0001) and elevated alkaline phosphatase (P-level 0.008). The association between NLR and gender (P-level 0.06) and number of metastatic sites (P-level 0.05) approached statistical significance.

NLR in validation cohort

At the time of analysis, 82% (146 out of 178) of patients were deceased. The median OS in this cohort was 16.8 months (95% CI 13.1 – 20.4 months). Independent predictors of survival from the training cohort (ECOG performance status and NLR) were tested in the validation cohort. The NLR was statistically significantly associated with OS (P-level < 0.0001). Patients with NLR ≤ 5 had median OS of 19.1 months (95% CI 15.3 – 22.8) compared with patients with NLR > 5 (median OS 11.3 months; 95% CI 8.3 – 14.3; Figure 2C). The ECOG performance status was not predictive of survival in this cohort (median OS for ECOG 0 was 21.5 months (95% CI 4.1 – 38.9) and PS ≥ 1 15.7 months (95% CI 13.1 – 18.3; P-level 0.15)).

Normalisation of NLR pre-cycle 2 and correlation with PFS and OS (training cohort)

Patients were categorised into the following categories: (1) patients with NLR ≤ 5 at baseline (n = 120; cohort 1), (2) NLR > 5 at baseline and before cycle 2 of chemotherapy (n = 21; cohort 2) and...
(3) NLR > 5 at baseline with normalisation of NLR ≤ 5 before cycle 2 of chemotherapy (n = 21; cohort 3). Patients with normalisation of NLR before cycle 2 of chemotherapy (cohort 3) had an improved PFS of 5.8 months (95% CI 4.1 – 7.5) compared with patients without normalisation of NLR pre-cycle 2 (cohort 2; median PFS 3.7 months; 95% CI 0.6 – 6.8 months; P-level 0.012; Figure 3A). Normalisation of NLR before cycle 2 of chemotherapy was not performed in the validation cohort, as there was > 10% of missing data for this patient group.

## DISCUSSION

This is the first study, to our knowledge, to describe the use of NLR in a non-selected unresectable mCRC setting for patients receiving first-line palliative chemotherapy to provide useful information regarding prognostication, and the data have been validated in an independent community-based cohort. These results support the use of NLR as a marker of systemic inflammatory response and as an independent predictor of clinical benefit, progression and survival in patients receiving chemotherapy for mCRC. An NLR cutoff > 5 was able to identify a subset of patients least likely to respond to chemotherapy (40% vs 16%) and those at higher risk of progression and death (HR 1.6 and 1.7, respectively). A cutoff

### Table 2

| Variable                 | Total no. (%) | Clinical benefit (%) | P-value | Survival (months) | Median (95% CI) | P-value | Survival (months) | Median (95% CI) | P-value |
|--------------------------|---------------|----------------------|---------|------------------|-----------------|---------|------------------|-----------------|---------|
| **Age, years**           |               |                      |         |                  |                 |         |                  |                 |         |
| ≤ 65                     | 113 (66)      | 90 (81)              | 0.04    | 7.4 (5.8 – 9.0)  | 17.5 (14.5 – 20.8) | 0.03    |                   |                 |         |
| > 65                     | 58 (34)       | 38 (67)              |         | 5.5 (4.3 – 6.7)  | 12.1 (10.9 – 13.3) |         |                   |                 |         |
| **Gender**               |               |                      |         |                  |                 |         |                  |                 |         |
| Male                     | 110 (64)      | 81 (74)              | 0.44    | 6.1 (4.7 – 7.6)  | 15.8 (12.6 – 19.0) | 0.85    |                   |                 |         |
| Female                   | 61 (36)       | 47 (80)              |         | 7.3 (5.1 – 9.5)  | 14.6 (10.0 – 19.2) |         |                   |                 |         |
| **ECOG PS**              |               |                      |         |                  |                 |         |                  |                 |         |
| 0                        | 85 (50)       | 69 (84)              | 0.02    | 9.0 (8.2 – 9.7)  | 18.5 (16.1 – 21.0) | 0.003   |                   |                 |         |
| ≥ 1                      | 86 (50)       | 59 (69)              |         | 4.9 (4.0 – 5.7)  | 11.5 (9.3 – 13.7) |         |                   |                 |         |
| **Primary site**         |               |                      |         |                  |                 |         |                  |                 |         |
| Colon                    | 103 (64)      | 76 (75)              |         | 6.3 (5.1 – 7.5)  | 12.9 (10.8 – 15.1) |         |                   |                 |         |
| Rectosigmoid junction    | 52 (32)       | 40 (77)              |         | 8.5 (6.9 – 10.1) | 18.3 (16.9 – 19.8) |         |                   |                 |         |
| Rectum                   | 4 (3)         | 3 (75)               |         | 5.0 (0 – 12.6)   | 4.3 (9.0 – 25.6)   |         |                   |                 |         |
| Synchronous              | 2 (1)         | 1 (50)               | 0.86    | 3.9 (—)          | 11.4 (—)          | 0.51    |                   |                 |         |
| **Chemotherapy**         |               |                      |         |                  |                 |         |                  |                 |         |
| Single                   | 43 (25)       | 23 (54)              | 0.07    | 3.9 (2.3 – 5.5)  | 11.0 (8.2 – 13.9) | 0.01    |                   |                 |         |
| Combination              | 128 (75)      | 105 (84)             |         | 8.0 (6.9 – 9.1)  | 17.5 (14.5 – 20.6) |         |                   |                 |         |
| **Number of sites**      |               |                      |         |                  |                 |         |                  |                 |         |
| 1                        | 91 (53)       | 72 (82)              | 0.07    | 8.4 (7.2 – 9.6)  | 17.5 (14.3 – 20.6) | 0.18    |                   |                 |         |
| > 1                      | 80 (47)       | 56 (70)              |         | 5.0 (4.0 – 6.0)  | 12.3 (7.4 – 17.3) |         |                   |                 |         |
| **Neutrophil count**     |               |                      |         |                  |                 |         |                  |                 |         |
| < ULN                    | 133 (78)      | 105 (80)             | 0.02    | 7.8 (6.7 – 9.0)  | 17.4 (15.5 – 19.4) | 0.004   |                   |                 |         |
| ≥ ULN                    | 38 (22)       | 23 (62)              |         | 4.8 (3.4 – 6.2)  | 9.4 (6.6 – 12.1)  |         |                   |                 |         |
| **Haemoglobin**          |               |                      |         |                  |                 |         |                  |                 |         |
| ≥ LLN                    | 79 (46)       | 61 (77)              | 0.77    | 7.7 (5.9 – 9.4)  | 17.5 (15.5 – 19.6) | 0.03    |                   |                 |         |
| < LLN                    | 92 (54)       | 67 (78)              |         | 6.0 (4.8 – 7.2)  | 12.7 (10.1 – 15.4) |         |                   |                 |         |
| **Albumin**              |               |                      |         |                  |                 |         |                  |                 |         |
| > LLN                    | 117 (69)      | 32 (63)              | 0.005   | 4.9 (3.9 – 5.9)  | 18.3 (16.5 – 20.1) | 0.002   |                   |                 |         |
| ≤ LLN                    | 53 (31)       | 96 (83)              |         | 8.0 (6.9 – 9.0)  | 10.4 (7.7 – 13.2) |         |                   |                 |         |
| **Alkaline phosphatase** |               |                      |         |                  |                 |         |                  |                 |         |
| < ULN                    | 96 (56)       | 77 (82)              | 0.04    | 8.0 (6.9 – 9.1)  | 18.3 (15.6 – 21.1) | 0.007   |                   |                 |         |
| ≥ ULN                    | 74 (44)       | 50 (69)              |         | 5.5 (4.3 – 6.7)  | 11.5 (9.5 – 13.5) |         |                   |                 |         |
| **NLR**                  |               |                      |         |                  |                 |         |                  |                 |         |
| ≤ 5                      | 120 (71)      | 99 (84)              | 0.001   | 8.0 (6.9 – 9.0)  | 18.3 (16.2 – 20.4) | 0.009   |                   |                 |         |
| > 5                      | 49 (29)       | 29 (60)              |         | 4.7 (4.1 – 5.3)  | 10.0 (8.6 – 11.5) |         |                   |                 |         |

Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; OS = overall survival; LLN = lower limits of normal; NLR = neutrophil/lymphocyte ratio; PFS = progression-free survival; PS = performance status; ULN = upper limits of normal. *Missing data (< 10%) for some prognostic variables.
of evaluable patients, which resulted in a 2-month PFS normalisation after one cycle of chemotherapy in 50% (21 out of 42) of patients. The use of NLR and normalisation of NLR after cycle 1 are confirmed, this would provide additional prognostic information to clinicians at an earlier time point before conventional staging with computed tomography scans and potentially identify a proportion of patients in whom further treatment may be futile. For example, in the training cohort, there was NLR normalisation after one cycle of chemotherapy in 50% (21 out of 42) of evaluable patients, which resulted in a 2-month PFS improvement (5.8 vs 3.7 months) compared with patients without NLR normalisation. These data will permit not only retrospective evaluations of established large cohorts with known outcome data to corroborate these findings but also to undertake correlation with molecular characteristics, such as microsatellite instability and B-raf mutations, which are associated with worse cancer outcomes.

The strengths in our training cohort were that patient data were retrospectively analysed from robust prospectively collected data through entry into clinical trials. As the patients were eligible for enrolment in a clinical trial, it is highly unlikely that the elevated NLR was due to other active inflammatory diseases or infection or were requiring high doses of steroids; however, these issues should be specifically assessed in future studies. Other independent predictive variables identified from the training cohort, such as performance status, use of combination chemotherapy and hypoalbuminaemia, have also been reported from previous studies and strengthens the case for this cohort being representative of a palliative mCRC population. The median OS in both cohorts (15.3 and 16.8 months in training and validation cohorts, respectively) are shorter than those reported using modern combination chemotherapy regimens, which have median OS upwards of 24 months. However, a significant proportion of the patients in both cohorts received single-agent chemotherapy, with patients enrolled in chemotherapy trials from as early as 1999. There were also significant baseline differences in the types of chemotherapy regimens between the Australian and Canadian cohorts. In the Canadian cohort, up to 29% of patients did not have the type of chemotherapy specified, which may account for some of the survival difference between the two cohorts. The validation cohort in this study failed to identify performance status as an
The NLR is a simple, readily available and robust laboratory variable. Other authors have advocated the use of GPS or a modified GPS, based on albumin and CRP levels, and validated its use as a prognostic variable particularly in the pre-operative setting. Two studies have reported the use of GPS in patients receiving chemotherapy for mCRC and gastro-oesophageal malignancies (Crumley et al., 2008; Ishizuka et al., 2009). However, this assessment is complicated by the requirement for an additional blood test to measure CRP levels, which may not be readily available as was in the case of both our training and validation sets. The NLR, as a continuous variable, may also be a more accurate and dynamic variable reflecting acute changes in the inflammatory state of a patient rather than GPS, which is applied as a static, categorical variable. The NLR and GPS have not been compared in the same population in CRC patients, and this comparison should be undertaken to discern whether these two indices are overlapping or additive as indicators of cancer-associated inflammation. In CRC, the use of NLR has previously been confirmed as an independent prognostic factor in a cohort of patients with liver-only colorectal metastases, the majority of whom proceeded to hepatic resection post chemotherapy (Kishi et al., 2009). Although this is an important subset of patients with mCRC, these patients would have been highly selected for surgical intervention and not representative of the majority of patients with mCRC. The findings in our study are not only consistent with this earlier report but also supports the use of NLR in a more generalised patient population and would have been highly selected for surgical intervention and not representative of the majority of patients with mCRC. The findings in our study are not only consistent with this earlier report but also supports the use of NLR in a more generalised patient population. The NLR is probably more reflective of day-to-day clinical practice.

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### Table 4 Baseline characteristics according to NLR

| Variable                        | NLR ≤ 5 | NLR > 5 | P-level |
|---------------------------------|---------|---------|---------|
| Age (median)                    | 61      | 61      | 0.32    |
| Gender                          |         |         |         |
| Male                            | 72 (60%)| 37 (76%)|         |
| Female                          | 48 (40%)| 12 (24%)| 0.06    |
| ECOG performance status         |         |         |         |
| 0                               | 69 (58%)| 24 (49%)|         |
| 1 and 2                         | 60 (50%)| 25 (51%)| 0.90    |
| Number of metastatic sites      |         |         |         |
| 1                               | 69 (58%)| 20 (41%)|         |
| > 1                             | 51 (42%)| 29 (59%)| 0.05    |
| Primary site                    |         |         |         |
| Colon                           | 70 (62%)| 31 (67%)|         |
| Rectum and rectosigmoid junction| 42 (37%)| 14 (30%)|         |
| Synchronous                     | 1 (1%)  | 1 (1%)  | 0.61    |
| Site of metastases              |         |         |         |
| Liver                           | 96 (80%)| 44 (90%)| 0.13    |
| Lung                            | 37 (31%)| 17 (35%)| 0.63    |
| Other                           | 43 (36%)| 21 (43%)| 0.39    |
| Anaemia                         |         |         |         |
| Present                         | 64 (53%)| 28 (57%)|         |
| Absent                          | 56 (47%)| 21 (43%)| 0.65    |
| Hypoalbuminaemia                |         |         |         |
| Present                         | 26 (22%)| 26 (53%)|         |
| Absent                          | 93 (78%)| 23 (47%)| <0.0001 |
| Alkaline phosphatase levels     |         |         |         |
| < ULN                           | 75 (63%)| 20 (41%)|         |
| ≥ ULN                           | 44 (37%)| 29 (59%)| 0.008   |

Abbreviations: ECOG = Eastern Cooperative Oncology Group; NLR = neutrophil/lymphocyte ratio; ULN = upper limits of normal.
as post-ST-segment elevation myocardial infarction (Núñez et al., 2008) and percutaneous coronary intervention (Duffy et al., 2006) in which the systemic inflammation response has been implicated as a major contributing factor. This adds credibility for the use of NLR as a potential biomarker of the systemic inflammatory response.

In recent years, there have been significant developments and discoveries in cancer genomics. The development of gene-expression-based arrays or examining germline single-nucleotide polymorphisms for defining prognosis or predicting response to therapy has limited clinical application even in the two most common malignancies, lung and breast cancers (Hartman et al., 2010; Subramanian and Simon, 2010). For example, Wacholder et al. (2010) discovered that the inclusion of 10 common breast cancer genetic variants only modestly improved the performance of existing risk-assessment models in >11,000 patients, with little change in the predicted breast-cancer risk among most women, using currently available genetic information. These tests are also expensive and confined to use in developed countries, with limited application in under-resourced communities. A useful biomarker needs to be not only accurate and reproducible but also easily accessible. The prognostic importance of the systemic reaction to tumours has been relatively ignored in the quest for tumour-based molecular assessments of outcome. These data will encourage a re-evaluation of that approach.

These results have highlighted the use of a potential clinical biomarker of systemic inflammatory response in predicting clinically meaningful outcomes in two independent cohorts. In addition, results of the study have also confirmed the importance of a chronic systemic inflammatory response influencing clinical outcomes in patients with mCRC. Validation of these results in larger patient populations will allow many potential applications in the treatment of mCRC, a major cause of morbidity worldwide. Clinical applications include (1) prognostication and in-patient stratification in clinical trials, (2) as a marker of response to chemotherapy treatment and, more excitingly, (3) in identifying patients for possible interventions with anti-inflammatory media-tors. The results of this study, we believe, strongly support the use of NLR in these settings, and more importantly, as a dynamic marker of interactions among tumour, host and the systemic inflammatory response.

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Conflict of interest

The authors declare no conflict of interest.

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