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REVIEW

# What is the Role of the Neutrophil: Lymphocyte Ratio in Colorectal Cancer?

## Kolorektal Kanserde Nötrofil:Lenfosit Oranının Rolü Nedir?

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**ABSTRACT**

The composition and cell-to-cell interactions of the peripheral immune compartment are known to influence outcomes in multiple disease entities, both neoplastic and otherwise. There is an ongoing search for a reliable biomarker in the peripheral immune compartment that can predict outcomes in colorectal cancer, given its high mortality rates. The neutrophil:lymphocyte ratio (NLR) has been suggested as one such marker, given its accessibility. This review discusses the current evidence behind the use of the NLR in predicting different aspects of colorectal cancer (CRC) behaviour, from survival to recurrence, metastasis, tumour biology, response to therapy and CRC complications. We also discuss the debate in the literature surrounding the use of other peripheral immune compartment biomarkers compared with the NLR for this purpose and ideas for future research.
**Keywords:** Colorectal cancer, neutrophil: lymphocyte ratio, survival

**ÖZ**

Periferal immün kompartmanının kompozisyonunun ve hücreler arası etkileşimlerinin, hem neoplastik hem de neoplastik olmayan birçok hastalıkta sonlanımı etkilediği bilinmektedir. Periferik bağışıklık kompartmanında, yüksek mortalite oranı olan kolorektal kanserdeki sonlanımı tahmin edebilen güvenilir bir biyobelirteç için devam eden bir arayış vardır. Nötrofil:lenfosit oranının (NLO) kolay erişilebilirliği göz önüne alındığında, böyle bir belirteç olabileceği öne sürülmüştür. Bu derleme, sağkalım, nüks, metastaz, tümör biyolojisi, tedaviye yanıt ve komplikasyonlar gibi kolorektal kanser davranışının farklı yönlerini tahmin etmede NLO kullanımının arkasındaki mevcut kanıtları tartışmaktadır. Literatürdeki veriler ışığında, NLO'ya kıyasla diğer periferik immün kompartman biyobelirteçlerinin bu amaçla kullanımı tartışılacak ve gelecekteki araştırmalar için fikirler üzerinde durulacaktır.
**Anahtar Kelimeler:** Kolorektal kanser, nötrofil: lenfosit oranı, sağkalım

## Introduction

Colorectal cancer (CRC) is the world's third most common cancer and the fourth most common cause of cancer mortality. Blood-based biomarkers are attractive for the management of this disease, given their ease of access and amenability to repetitive sampling. Low-grade, chronic inflammation has long been associated with a range of diseases and poor outcomes. Many different markers of inflammation have been described over the years; however, apart from the erythrocyte sedimentation rate and plasma viscosity, these are not used in routine clinical assessment. One simple marker that has been widely described, the neutrophil:lymphocyte ratio (NLR), has been generally overlooked in clinical practice. The aim of this review is to discuss its role as a biomarker in CRC, compare its value against other biomarkers and encourage its wider adoption into mainstream clinical practice.

### What is the Neutrophil:Lymphocyte Ratio (NLR)?

The NLR is an inexpensive, readily available marker, which is proposed to provide additional risk stratification beyond other more traditional risk scores. Calculation of the NLR simply involves dividing the peripheral blood neutrophil count by the lymphocyte count on a full blood count. The NLR has been suggested as a good marker of systemic low-grade inflammation,[1] which is associated with a poorer outcome in many disease types.

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### The role of the NLR in Colorectal Cancer (CRC)

The concept of the influence of the NLR in CRC is not new. Back in 2005, a landmark study by Walsh et al.[2] identified that a NLR >5 (i.e. neutrophils present at 5 times the number of lymphocytes) was correlated with poor overall and cancer-specific survival in univariate analyses. Other studies have set a lower value of 2 or 3 to dichotomise populations, thus increasing the number of individuals in the poorer prognosis group.

This observation has since been replicated by subsequent studies (Table 1) and supported by pooled analysis of a meta-analysis.[3] With respect to single studies, there are many examples where this effect of NLR on CRC survival outcomes has been replicated. In patients undergoing elective resection of colorectal cancer, a lower postoperative NLR was found to correlate with longer cancer-specific and disease-free survival.[4] Similarly, another study[5] found that a high preoperative NLR (>3) in colon cancer patients was associated with worse disease-free survival and cancer-specific death [heart ratio (HR) 1,377 95% confidence interval (CI) 1,104-1,717, p=0.014]. It is of note that this difference was larger in colon cancer than in rectal cancer patients. Consistently, another study investigating patients with early-stage colorectal cancer[6] who were candidates for curative surgery found that there was a statistically significantly poorer outcome in 5-year disease-free survival and cancer-specific survival in those with a high NLR compared with those with a low NLR. Following a similar pattern of findings, a study looking at stage II colon cancer[7] found that an elevated NLR was an independent predictor of poorer overall survival but not disease-free survival when analysed using Cox regression analysis. A study conducted at our institute[8] found that the NLR predicted disease-free and overall survival in our patients with primary colorectal malignancy.

To summarise an overview of the literature, a systematic review[9] identified higher 3-year and 5-year survival rates in patients with a low NLR compared with those with a high NLR (77.8% vs 61.8%), and the range of cut-off values used to define the high- and low-NLR groups varied from 2 to 5.

### NLR in Metastatic Colorectal Cancer

Liver metastases develop in up to 40% of patients with a high recurrence rate, even after primary bowel resection. The NLR is suggested to be one such marker in multiple studies (Tables 2, 3).

A systematic review[9] identified multiple studies reporting survival results in patients with CRC and liver metastases. Similar to the pattern observed in non-metastatic disease, the low-NLR group had a better 3-year survival rate compared with the high NLR group (64.74% vs 45.1% respectively). This systematic review identified multiple studies showing a differential 5-year survival rate in this patient group, the 5-year survival being higher in patients with a low NLR than in those with a high NLR (47.6% vs 27%, respectively). A further meta-analysis, including 1,685 patients, found that an elevated pre-treatment NLR was associated with poor overall and recurrence-free survival in patients with colorectal liver metastasis.[10] A significant negative finding of the study was that there was no correlation between NLR and the timing and number of metastases at the time of diagnosis.

Using a cut-off value of 5, Halazun et al.[11] found that an increased NLR decreased the 5-year survival rate and risk of recurrence in patients who underwent resection for colorectal liver metastases. Neal et al.[12] found that in a multivariable analysis, a high NLR was independently associated with major infectious complications after hepatectomy, which may be an explanation for the worse survival rates in this patient group observed in previous studies.

A prospective, multicentre randomised Italian Trial in Advanced Colorectal Cancer[13] randomised patients to receive first-line chemotherapy with or without bevacizumab (an anti-angiogenic monoclonal antibody) and found that NLR was a marker of progression-free survival and overall survival in patients with metastatic colorectal cancer. Moreover, those with a high NLR treated with bevacizumab and chemotherapy had a worse overall survival than those treated with chemotherapy alone, although the pathophysiological explanation for this was unclear.

### NLR and the Tumour Recurrence Rate

CRC can recur locally at multiple sites, including intra-abdominal lymph nodes, the peritoneum and the retroperitoneum or anastomosis. Higher NLR values are associated with a higher tumour recurrence rate in patients with stage II and stage III disease.[9] A study based in Leeds[8] found that a NLR >/=5 was correlated with greater disease recurrence. The above finding was in agreement with a previously published paper[14], which found that a NLR >5 was a significant and independent factor predictive of recurrent colorectal cancer, when all stages of CRC were included. In a study population of patients with stage IIA colon cancer undergoing curative resection, an elevated NLR was found to be an independent predictor of worse recurrence-free survival[7], with a 5-year recurrence-free survival of 91.4% in those with a normal NLR and 63.8% for those with an elevated NLR.

### NLR and Tumour Biology

A systematic review identified multiple studies showing that poorly differentiated tumours were more likely to be correlated with higher NLR values[9] This same systematic review also identified multiple studies which showed a significant correlation between a high NLR and an advanced tumour stage.

**Table 1.** A summary of the literature discussing NLR and survival in patients with non-metastatic colorectal cancer

| Author | Title | Source | Sample size | NLR cut off | Findings |
|---|---|---|---|---|---|
| Li et al.[3] | Prognostic significance of elevated preoperative neutrophil-to-lymphocyte ratio for patients with colorectal cancer undergoing curative surgery: A meta-analysis | Medicine (Baltimore) | 5897 | 2.3-5 | An elevated NLR correlates with lower overall survival, disease-free survival, recurrence-free survival and disease-specific survival after treatment. |
| Kubo et al.[4] | Impact of the perioperative neutrophil-to-lymphocyte ratio on the long-term survival following an elective resection of colorectal carcinoma | International Journal of Colorectal Disease | 524 | NLR value was calculated prior to curative resection, on the first postoperative day and the third or fourth postoperative day: Patients with low median NLR value at all time points were given a score of 0, whereas those with a high median NLR at all time points were assigned a score of 3. Following the above scoring, those with a score of 0 or 1 were classed as the low perioperative NLR group, whereas the high perioperative NLR group had scores of 2 or 3.<br>The cut-off value for low and high NLR levels are as follows:<br>Median NLR pre-op 2.29<br>Median NLR postoperative day 1: 7.90<br>Median NLR: Postoperative day 3: 5.10_ | A high perioperative NLR is an independent risk factor for both cancer-specific and disease-free survival. |
| Chiang et al.[5] | Can neutrophil-to-lymphocyte ratio predict the survival of colorectal cancer patients who have received curative surgery electively? | International Journal of Colorectal Disease | 3857 | 3 | A NLR >3 was associated with worse 5 year disease-free survival, with a larger difference in colonic vs rectal cancer. An elevated NLR was also associated with clinicopathological factors related to advanced diseases. |
| Shin et al.[6] | Preoperative neutrophil-to-lymphocyte ratio predicts survival in patients with T1-2N0 colorectal cancer | Journal of Surgical Oncology | 269 | 3 | Preoperative NLR is a prognostic factor for disease-free survival and cancer-specific survival in stage I colorectal cancer patients. |
| Hung et al.[7] | Effect of preoperative neutrophil-lymphocyte ratio on the surgical outcomes of stage II colon cancer patients who do not receive adjuvant chemotherapy | International Journal of Colorectal Disease | 1040 | 5 | Cox regression analysis revealed that an elevated NLR is an independent predictor of overall survival but not disease-free survival. |
| Pine et al.[8] | Systemic neutrophil-to-lymphocyte ratio in colorectal cancer: the relationship to patient survival, tumour biology and local lymphocytic response to tumour | British Journal of Cancer | 358 | 5 | An elevated NLR predicts disease-free and overall survival and more advanced tumour biology. The NLR is not associated with tumour mutation status. |

NLR: Neutrophil:lymphocyte ratio

**Table 2.** A summary of the literature discussing NLR and prognosis in metastatic colorectal cancer patients

| Author | Title | Source | Sample size | NLR cut off | Findings |
|---|---|---|---|---|---|
| Haram et al.[9] | The prognostic value of neutrophil-to-lymphocyte ratio in colorectal cancer: A systematic review | Journal of Surgical Oncology | 10,259 | 5 | A NLR >5 is associated with worse 3- and 5-year survival in CRC patients with liver metastases. |
| Tang et al.[10] | Prognostic significance of neutrophil-to-lymphocyte ratio in colorectal liver | PLoS One | 1,685 | 2.5-5 | An elevated NLR is associated with poor overall survival and recurrence-free survival in colorectal patients with liver metastases. |
| Halazun et al.[11] | Elevated preoperative neutrophil-to-lymphocyte ratio predicts survival following hepatic resection for colorectal liver metastases | European Journal of Surgical Oncology | 440 | 5 | An elevated NLR is associated with a worse 5-year survival and tumour recurrence. |
| Neal et al.[12] | Preoperative systemic inflammation and infectious complications after resection of colorectal liver metastases | Archives of Surgery | 202 | 5 | A high NLR is associated with postoperative infectious morbidity and overall and disease-free survival on univariate analysis. |
| Passardi et al.[13] | Inflammatory indexes as predictors of prognosis and bevacizumab efficacy in patients with metastatic colorectal cancer | Oncotarget | 289 | 3 | The correlation between lower NLR levels and improved overall and progression- free survival was significantly associated with the addition of bevacizumab to first-line chemotherapy. |

NLR: Neutrophil:lymphocyte ratio, CRC: Colorectal cancer

**Table 3.** A summary of the literature discussing the NLR and the response to oncological treatment

| Author | Title | Source | Sample size | NLR cut off | Findings |
|---|---|---|---|---|---|
| Kaneko et al.[21] | Elevated Neutrophil-to-Lymphocyte Ratio Predicts Poor Prognosis in Advanced Colorectal Cancer Patients Receiving Oxaliplatin-Based Chemotherapy. | Oncology | 50 | 4.0 | An elevated NLR is associated with overall survival and the disease response rate in patients with advanced or recurrent CRC receiving oxaliplatin-based combination chemotherapy. |
| Dell'Aquila et al.[22] | Prognostic and predictive role of neutrophil/lymphocytes ratio in metastatic colorectal cancer: a retrospective analysis of the TRIBE study by GONO. | Annals of Oncology | 508 | 3 | The NLR had prognostic value in predicting overall survival, progression-free survival and the response rate in patients treated with FOLFIXIRI and bevacizumab. |
| Kishi et al.[23] | Blood neutrophil-to-lymphocyte ratio predicts survival in patients with colorectal liver metastases treated with systemic chemotherapy. | Annals of Surgical Oncology | 200 | 5 | In patients with colorectal liver metastases treated with chemotherapy and resection, a NLR >5 was an independent predictor of 5-year survival. In this patient group, preoperative chemotherapy normalised the NLR and improved survival.<br>In the non-resection group receiving chemotherapy only, an NLR >5 was an independent predictor of worse 3-year survival. |
| Botta et al.[24] | 1439 POSTER Treatment-related Changes in Systemic Inflammatory Status, Measured by Neutrophil-to-lymphocyte Ratio, is Predictive of Outcome in Metastatic Colorectal Cancer Patients. | European Journal of Cancer | 247 | 3 | NLR >3 was a significant prognostic factor for overall and progression-free survival in patients with metastatic colorectal cancer receiving first-line chemotherapy.<br>The reduction to a NLR <3 following treatment was associated with a longer time to event. |

**Table 3. continued**

| | | | | | |
|---|---|---|---|---|---|
| Chua et al.[25] | Neutrophil/lymphocyte ratio predicts chemotherapy outcomes in patients with advanced colorectal cancer. | British Journal of Cancer | 349 | 5 | In patients with unresectable metastatic colorectal cancer undergoing first- line palliative chemotherapy, the NLR was predictive of overall and progression-free survival. Normalisation of NLR following treatment could improve progression-free survival. |
| Turnbull et al.[26] | Chemotherapy to reverse diminished immune responses (IRs) associated with a raised neutrophil–lymphocyte ratio (NLR) in patients with advanced colorectal cancer (aCRC). | Journal of Clinical Oncology | 29 | 5 | A high NLR is associated with reduced overall survival and measured IRs in patients with advanced colorectal cancer. The NLR normalises after 6 weeks of first-line chemotherapy, and their depressed IRs can be reversed by chemotherapy. |
| Wood et al.[27] | Derived neutrophil-to-lymphocyte ratio as a prognostic factor in patients with advanced colorectal cancer according to RAS and BRAF status: a post-hoc analysis of the MRC COIN study. | Anticancer Drugs | 1603 | dNLR cut-off was 2.2 | In patients with metastatic colorectal cancer, a dNLR <2.2 was associated with better overall survival in patients in all mutation groups, but it did not predict the survival benefit from the addition of cetuximab to oxaliplatin. |
| Chen et al.[28] | Cytokine profile and prognostic significance of high neutrophil-lymphocyte ratio in colorectal cancer. | British Journal of Cancer | 1180 | 5 | The NLR is a prognostic factor across multiple settings of CRC, including surgically resected stage II/III CRC, metastatic colorectal cancer with liver metastases after hepatectomy and previously untreated and refractory metastatic CRC.<br><br>In a cohort of patients with colorectal cancer, patients with liver metastases who were refractory to standard treatments such 5 fluorouracil, NLR is not associated with tumour mutation status. |
| Grenader et al.[29] | Derived neutrophil-lymphocyte ratio is predictive of survival from intermittent therapy in advanced colorectal cancer: a post-hoc analysis of the MRC COIN study. | British Journal of Cancer | 1630 | dNLR >/=2.22 | The dNLR can predict survival in patients undergoing both continuous and intermittent chemotherapy in advanced colorectal cancer. However, the dNLR does not add to the platelet count in the selection of patients who would benefit from continuous rather than intermittent therapy. |
| Shen et al.[32] | Baseline neutrophil-lymphocyte ratio (≥2.8) as a prognostic factor for patients with locally advanced rectal cancer undergoing neoadjuvant chemoradiation. | Radiation Oncology | 224 | 2.8 | The baseline NLR can predict overall survival in patients with locally advanced rectal cancer undergoing neoadjuvant chemoradiation, but it did not predict the response to treatment. |
| Hodek et al.[33] | Neoadjuvant chemoradiotherapy of rectal carcinoma: Baseline haematologic parameters influencing outcomes. | Strahlentherapie und Onkologie | 173 | 2.8 | NLR was a prognostic factor for overall survival and primary tumour downstaging (treatment response) in patients with locally advanced rectal cancer treated with neoadjuvant chemoradiotherapy. |
| Carruther et al.[34] | Systemic inflammatory response is a predictor of outcome in patients undergoing preoperative chemoradiation for locally advanced rectal cancer. | Colorectal Disease | 115 | 5 | An NLR >/=5 was associated with decreased overall survival, time to local recurrence and worse disease-free survival in patients with locally advanced rectal cancer who had preoperative chemoradiation. |

NLR: Neutrophil:lymphocyte ratio

A study conducted on patients with stage I-III CRC undergoing curative cancer[5] found that an elevated NLR was associated with more aggressive clinicopathological factors such as increased size, tumour stage, elevated CEA, low albumin, the presence of disease complications and non-abdominal morbidity.

Pine et al.[8] found that an elevated NLR was associated with a higher stage, a greater incidence of extramural venous invasion as well as lymph node metastasis. In contrast, a lower NLR was associated with a less aggressive phenotype, for example, they had a pronounced lymphocytic reaction at the invasive margin, associated with a better prognosis.

### The NLR and Mismatch Repair Status

Microsatellites are short, repetitive stretches of DNA interspersed within the whole genome and are susceptible to high rates of mutation. A unique, hypermutable phenotype known as microsatellite instability (MSI-H) results from impaired DNA mismatch repair. Tumours displaying high levels of MSI-H have two molecular types: Lynch syndrome, which occurs from germline mutations of *MMR* genes, and sporadic colorectal cancers, which arise from epigenetic alterations of the hMLH1 promoter. Tumours displaying loss of MMR protein are known as MMR deficient (dMMR), whereas those with intact MMR protein expression are known as MMR proficient (pMMR), with dMMR tumours having a better prognosis. We know that dMMR tumours have a more favourable local immune response.[15] Several mechanisms have been suggested to link the systemic inflammatory response and MMR status. Llosa et al.[16] found that dMMR tumours have a high infiltration with CD8+ T lymphocytes and interferon gamma-producing Th1-cells, leading to an immunologically active anti-tumour micro-environment. Counterbalancing this, MSI tumours had differentially high expression of a number of immune checkpoint proteins e.g. PD1, PDL1, CTLA4, LAG3 and IDO, all of which act as a brake on the immune response to the tumour, making this patient group good candidates for immunotherapy. An alternative hypothesis[17] is that chronic inflammation can lead to dMMR colorectal cancers though IL6 production, which may change the localisation of human MutS homolog 3 and induce tumours with the dMMR phenotype. Pine et al.[8] failed to find a correlation between MMR status and NLR, whereas Park et al.[18] found that dMMR patients had higher neutrophil counts. This inconsistency led He et al.[19] to explore the relationship between NLR MMR status and survival. In agreement with Park et al.[18], they found that NLR and C-reactive protein (CRP) were more likely to be raised in dMMR patients with no distant metastases; however, this correlation was stage dependent. With respect to survival data, NLR was not found to be significantly correlated with disease- free and overall survival in dMMR patients, although it did predict survival in pMMR patients. A more recent study[20] found that among an array of markers of systemic inflammatory response, only a preoperative NLR >5 was associated with worse overall survival and greater recurrence in patients with dMMR CRC undergoing surgery. They also found an inversely proportional relationship between NLR and the local inflammatory response in this tumour group. Due to the above-described controversy in the literature on the prognostic effect of NLR in MSI tumours, this area should be a focus of future work.

### NLR and the Response to Oncological Treatment in Colorectal Cancer

A study of patients with advanced CRC receiving palliative oxaliplatin-based chemotherapy found that an elevated NLR was independently associated with poorer overall survival in a multivariate analysis.[21] A high NLR was also associated with a lower objective response and disease control rate compared with the low-NLR group. An analysis of NLR levels conducted in patients enrolled into a multicentre phase III TRIBE trial[22], which randomised unresectable metastatic CRC patients to receive the triplet FOLFOXIRI plus bevacizumab or doublet FOLFIRI plus bevacizumab, found that patients with an elevated NLR (>3) had significantly shorter progression-free survival (HR=1.27, 95% CI=1.05-1.55, p=0.017). They also reported a better objective response rate (65% vs 53% p=0.006), progression-free and overall survival in the triplet plus bevacizumab group. These data not only support the choice of FOLFOXIRI plus bevacizumab as a preferable first-line treatment for this patient group but also suggest that NLR measurement may be a useful tool for better patient selection for those who would derive more benefit from this more intense chemotherapy regimen.

Kishi et al.[23] demonstrated that the NLR can be normalised by chemotherapy in 17 out of 25 patients with metastatic colorectal cancer, which also has an impact on survival, suggesting that this biomarker may be useful for predicting the response to chemotherapy. Another retrospective multicentre study[24] was concordant with the above finding that chemotherapy can normalise the NLR in metastatic CRC patients and consequently achieve a longer time to event for these patients when compared with the patient group whose NLR did not normalise following treatment. In a study of 349 patients with advanced colorectal cancer, Chua et al.[25] found that normalisation of the NLR following a single cycle of chemotherapy resulted in improved progression-free survival, leading to the idea that manipulation of the systemic inflammatory response can be of clinical benefit. This observation was supported by Turnbull et al.[26], who

found that depressed immune responses in patients with a high baseline NLR could be reversed after 6 weeks of first-line chemotherapy in patients with advanced colorectal cancer, with increased expression of PD-1 on natural killer cells as well as B cells and monocytes, suggesting the identification of this patient group as candidates for immunotherapy.

If a lymphocyte count has not been undertaken, then the derived NLR can be calculated from the following equation:

dNLR = Absolute neutrophil count/(white blood cell count-absolute neutrophil count)

Wood et al.[27] found that a dNLR <2.2 was associated with better overall survival compared with a dNLR >/=2.2 in patients receiving oxaliplatin-based chemotherapy in patients with metastatic CRC with RAS and BRAF mutations. The wider literature suggests that the association of high NLR with worse survival is more pronounced in patients with metastatic disease, probably reflecting a greater tumour burden and a more significant chronic inflammatory process. In agreement with a previous study[28], the correlation between NLR and survival is independent of the mutation group (with the mutations studied being KRAS, NRAS, BRAF, PIK3CA, PTEN loss and CpG Island Methylator Phenotype testing).

Grenader et al.[29] examined whether the dNLR could predict the effect of intermittent vs continuous chemotherapy in patients with advanced colorectal cancer. They found a strong association between dNLR and overall survival but concluded that it does not add to the prognostic value of the platelet count in selecting patients that would benefit from continuous vs intermittent therapy and therefore cannot be used to select patients for chemotherapy-free breaks. These findings add to the conclusions of the COIN trial[30], which had previously reported that patients with normal baseline platelet counts would be candidates for intermittent chemotherapy without a survival cost, whereas those with thrombocytosis (platelet count >400,000) would have better outcomes without a treatment break. The above suggests that the platelet count is a better predictor than dNLR in this regard.

Extrapolating to other oncological treatments, this time with reference to radiotherapy, a raised pre-treatment NLR was associated with significantly worse overall survival in patients with solid tumours with a pooled hazard ratio of 1.90 (95% CI=1.66-2.17, p<0.001).[31] This suggests that this biomarker may be useful for risk stratification for patient selection for more aggressive radiotherapy.

With respect to patients with locally advanced rectal cancer, an elevated baseline NLR was noted to predict poorer overall survival but failed to predict the response to treatment following neoadjuvant chemoradiation.[32] Hodek et al.[33] evaluated a large group of patients with locally advanced rectal adenocarcinoma who were exposed to neoadjuvant chemoradiation. They found that a NLR range between 2.2 and 2.8 produced a significantly better overall survival and response to treatment; however, the NLR did not have a significant influence on pathologic complete remission. This pattern of observation was replicated by Carruther et al.[34], who observed that an elevated NLR was a useful prognostic marker in patients treated with chemoradiation. It had predictive power for overall survival, time to local recurrence and disease-free survival.

Placing the above findings into the clinical context, we know that a tumour-free circumferential resection margin (CRM) is a key determinant of cancer outcome following rectal cancer surgery[35] Preoperative MRI staging is used to select patients for neoadjuvant chemoradiotherapy once it is established that a clear CRM is unlikely to be achieved with initial surgery. The above findings suggest that apart from radiology, the NLR may be an inexpensive, easily accessible biomarker that may provide further prognostic information regarding outcomes of preoperative chemoradiotherapy.

### NLR and Postoperative Complications in Colorectal Cancer

Josse et al.[36] found that a NLR value of 2.3-5 was associated with the incidence of perioperative complications, of which wound infection was the most common (12%). The association between an elevated NLR and postoperative infectious complications was corroborated by Kubo et al.[4] Anastomotic dehiscence is a major postoperative complication of resectional surgery with high morbidity and mortality rates. A case control study[37] found that both CRP and NLR were significant predictors of anastomotic dehiscence. However, the granularity that this study provided was that NLR was not as effective as CRP in predicting anastomotic dehiscence, as it had a smaller area under the curve in receiver operating characteristic analysis.

Paliogiannis et al.[38] found that CRP had a high negative predictive value on postoperative day 4 in identifying patients who were unlikely to develop anastomotic leak and would be suitable for discharge. This study also found that the NLR value on postoperative day 4 was correlated with the incidence of anastomotic dehiscence as well as mortality and morbidity from this complication. However, in agreement with Walker et al.[37], this study also found that the accuracy of NLR based on receiver operating curve analyses had a poorer outcome, suggesting the inferiority of this biomarker in predicting anastomotic leakage compared with CRP.

### NLR as a Component of the Wider Systemic Inflammatory Response

The exact understanding of what drives a high NLR remains to be elucidated. However, Motomura et al.[39] have demonstrated a link between the presence of tumour-associated macrophages (derived from splenic monocytes) and IL17-producing T-cells (in both the peritumoral region and the peripheral blood) and a high NLR. The mechanistic explanation behind interleukin (IL)17 and a high NLR may be that IL17 plays a significant role in neutrophil chemotaxis through the release of CCL2 and CXC chemokines. The authors also suggest an interaction between IL17-producing T-cells and tumour-associated macrophages in the production of the same family of chemokines that attract neutrophils.

Considering how NLR affects tumour immunology, an unpublished study at our institution has found a differential cytokine profile in CRC patients with NLR <5 compared with those with a NLR >5. Seven cytokines were found to be preferentially upregulated in the low-NLR group. These are IL-1beta, IL2, IL7, IL13, bFGF, interferon gamma and MIP-1 alpha. The cocktail of cytokine production in the low-NLR group is thought to skew the immune response to an anti-tumour Th1 phenotype in contrast to the pro-tumour environment of the Th2 type immune response in the NLR >5 group. In a separate cohort of patients with metastatic colorectal cancer, Chen et al.[28] found that a high NLR was associated with increased expression of IL-6, IL-8, IL-2Rα, hepatocyte growth factor, granulocyte-macrophage colony-stimulating factor and vascular epidermal growth factor. These functional drivers of an active systemic inflammatory response are associated with angiogenesis, inflammation and tumour growth promotion and found to be specifically linked to the NLR.

### The NLR and the Microbiome

Apart from using the systemic inflammatory response in isolation to predict prognosis in colorectal cancer, there is the suggestion that NLR be used in conjunction with other prognostic parameters of CRC such as the gut bacterial landscape (the gut microbiome).

A previous study[40] observed that a more diverse gut microbial landscape, which is associated with a beneficial outcome in several conditions, is associated with a lower NLR, thus lending itself to the idea of manipulating the microbiome to alter the systemic immune response to cancer.

### Mechanistic Explanations for the Prognostic Value of NLR in Colorectal Cancer

Tumour-related angiogenesis through vascular endothelial growth factor (VEGF) production has been suggested to be a mechanism through which neutrophils have a pro-tumour effect. Neutrophils can activate cytokines such as IL16, and this is thought to promote cell adhesiveness, invasion and migration.[41] Lymphocytopenia may signify depression of innate cellular immunity with a decrease in T4 helper lymphocytes and increase in T8 suppressor lymphocytes. This overall balance is tipped towards a pro-neoplastic process when the NLR is raised.[2]

The link between NLR and the response to radiotherapy in solid cancers such as CRC may be hypoxia. With neoplastic progression, the supply of oxygen and nutrients does not match the demand, leading to necrosis and subsequent release of inflammatory mediators that recruit inflammatory cells such as neutrophils. This pro-tumour effect of hypoxia may explain the prognostic role of high NLR in predicting the response to radiotherapy.

## A Brief Summary of other Peripheral Serum Inflammatory Biomarkers in Colorectal Cancer[42]

### C-reactive Protein Level (CRP)

This is an acute-phase protein produced by the liver that plays a role in the systemic inflammatory response. Multiple studies[43,44,45] have found that elevated CRP is correlated with recurrence after surgery for colorectal cancer.

### The Glasgow Prognostic Score (GPS)

The GPS calculated from serum CRP and albumin is widely thought to reflect the systemic inflammatory response to cancer. In a cohort of 1,590 patients with primary colorectal adenocarcinoma[46], the authors found a predictive effect of GPS on long-term survival in multivariate analysis.

### Platelet-to-lymphocyte Ratio (PLR)

Platelet aggregation and the release of platelet-derived proangiogenic mediators into the vasculature of the tumour micro-environment through degranulation is suggested to influence tumour growth. The findings from a metanalysis[47] indicate that a high PLR can be used as a predictor of overall survival and clinicopathological parameters such as tumour differentiation and depth of infiltration in patients with CRC, but not disease-free survival.

### Carcinoembryonic Antigen (CEA)

This is an easily accessible peripheral blood marker whose postoperative level is routinely used as tumour marker for prognostication in colorectal cancer. In rectal cancer patients treated with neoadjuvant radiotherapy and chemotherapy, Toiyama et al.[45] found that elevated CEA was a predictor of poor overall survival. Another study[48] found that the blood CEA level was an independent predictive biomarker in patients with colorectal cancer.

### Comparing Biomarkers in Colorectal Cancer

When comparing the superiority of one biomarker over another, Kwon et al.[49] found that PLR was better than

NLR as a prognostic marker in CRC (HR=1.971, p=0.021). Survival curve analysis showed a consistent pattern of progressively poorer survival associated with a larger PLR. Moreover, the PLR was also significantly reported to be related to a positive lymph node ratio, which is known to have prognostic significance in colorectal cancer. Therefore, this study concluded that PLR is the most significant predictor of survival and is related to a more advanced tumour biology, although it is of note that serum CEA also retained significance in this study.

In concordance with the above, a study by Szkandera et al.[50] supported the role of PLR in predicting time to recurrence in CRC patients undergoing curative resection. Bong et al.[51] simultaneously examined the prognostic influence of PLR, NLR and CEA in predicting survival in patients with colorectal peritoneal carcinomatosis treated operatively and with chemotherapy. In a multivariate analysis, only PLR retained significance in predicting 5-year overall survival.

However, the above findings were contradicted by Choi et al.[52] Only a limited number of studies have evaluated both the NLR and PLR in the same population of patients in colorectal cancer. The study found that a high NLR was a negative independent prognostic factor in CRC and predicted a worse recurrence-free and overall survival. Interestingly, this study failed to find a significant association between PLR and survival, although it is of note that Kwon et al.[49] used a different threshold for high PLR than this study. The findings of Choi et al.[52] contradict those of a meta-analysis[53] which found that PLR was a negative predictor of cancer survival (HR=1.60, 95% CI=1.35-1.90), although it is of note that this study included a heterogenous patient population with cancers of different parts of the GI tract and who were exposed to a variety of oncological treatments. In agreement with Choi et al.[52], Zhan et al.[54] found no significant correlations between PLR and clinicopathological characteristics or survival outcomes.

The differential prognostic influence of PLR on CRC is suggested to be due to a variety of factors. Apart from a lack of consensus regarding the optimal cut-off value for PLR, the heterogeneity in tumour specificity and underlying genetic and biological differences between the variety of patient populations used are cited as root causes of these differences, making a fair comparison between studies difficult.

Another study[55] compared NLR and CEA as prognostic biomarkers in colorectal cancer. They found that an NLR <5 was correlated with a better 5-year overall and disease-free survival. A NLR >5 was also associated with more aggressive tumour biology (poorer tumour differentiation and larger tumour size). This study also found that there was a direct correlation between NLR and CEA levels. Pooled results of this meta-analysis found that a NLR >5 was correlated with a CEA >5. Subsequently, it was identified that a CEA <5 was correlated with a better complete pathological response (downstaging and complete regression) after receiving oncological therapy. Overall, this study concluded that NLR and CEA were both independent prognostic factors in CRC and directly correlated with each other. A retrospective study[56] found that in a population of patients with colorectal cancer, that there was no overall correlation between the CEA and NLR, although they retain individual prognostic significance. On the other hand, Kim et al.[57] argue for the combined use of both CEA and NLR as prognostic markers for outcomes in CRC patients with liver metastases. Zhan et al.[54] also advocate for the combined used of CEA and NLR for prognostic assessment of CRC patients as a superior biomarker to the independent use of these prognostic markers alone.

Maeda et al[42] investigated whether combining the GPS and NLR with clinicopathological factors such as performance status and the extent of distant metastasis was useful. They found that the median survival time was significantly shorter at only 5 months in the high-risk group (consisting of patients with three or four prognostic factors) vs 21.5 months in the intermediate risk group (consisting of patients with one or two prognostic factors) and 37 months in the low-risk group (consisting of patients without any prognostic factors). They suggest that this may be a simple risk classification tool for optimising treatments for patients with advanced colorectal cancer.

### The Role of NLR for All Cancers

A meta-analysis investigating the prognostic effect of NLR on a range of solid tumours found that it was consistently predictive of survival among a variety of cancers at various stages[58]. There was a differential role of NLR in survival in metastatic vs non-metastatic disease, which may also reflect differences in the underlying pathophysiology of the tumour burden or chronicity of the inflammatory process. There was a consistent effect of the NLR on cancer-specific survival, progression-free survival and disease-free survival across both the primary site of malignancy and the cancer stage.

### The Utility of the Neutrophil:Lymphocyte Ratio in Entities Outside of Cancer

Epidemiological studies have demonstrated that chronic low-grade inflammation, measured by the NLR, is linked to a broad range of risk factors for cardiovascular disease such as diabetes mellitus, hypertension, metabolic syndrome, obesity and hyperlipidaemia.[59] The NLR has also been noted to be of prognostic significance in respiratory conditions such as COPD (in acute exacerbations, as a marker of

functional status and mortality)[60], pulmonary embolism (in predicting short- and long-term mortality)[61] and COVID-19 (predicting the likelihood of acute respiratory distress syndrome and the requirement for ventilation).[60,61,62] The NLR also has a role to play in neurological conditions, particularly in acute cerebral haemorrhage.[63] The above evidence suggests that NLR may be a biomarker that can predict outcomes in both neoplastic and non-neoplastic conditions, where the systemic immune response plays a role in the pathophysiology of the disease.

### Conclusions, Controversies and Future Ideas

Studies have identified that NLR has a prognostic effect on multiple aspects of the disease course of those with colorectal cancer, both primary and metastatic. The time point of measurement of the NLR and the cut-off value of the NLR for classification of high and low groups was inconsistent between studies. Moreover, there is a differential effect of the NLR on colon vs rectal tumours. It has been suggested that the effect of NLR is more difficult to assess in rectal cancer patients due to the presence of confounding factors such as neoadjuvant or adjuvant radiotherapy, which makes survival analysis more complex. The pathophysiology of rectal cancers may also be different. For example, there is an anatomical difference in lymphatic drainage between colon and rectal cancer. More advanced lymphatic spread in rectal cancer may make curative surgery more challenging. These differences may explain the difference in the effect of elevated NLR in colon and rectal cancers.

It is of interest that tumour mutation status such as dMMR and pMMR may have a link with NLR, although its association with survival in this patient group is controversial.

Moreover, there is debate in the literature regarding the single best peripheral blood biomarker to use in colorectal cancer. There are studies arguing for the use of other biomarkers such as CRP over the NLR, particularly in cases of anastomotic leaks; however, there is a growing consensus for the use of combined use of biomarkers such as NLR, CEA, PLR and GPS.

The idea is that by predicting the poor outcome of patients with CRC, using the NLR, it may be possible to tailor their treatment to improve their outcomes. Some have suggested the use of COX 2 inhibitors, which have an inhibitory effect on VEGF.[23] Other suggestions include the use of preoperative granulocyte-macrophage colony-stimulating factor, which may increase the population of dendritic cells in the liver and support their interaction with CD8+ T-lymphocytes, thus having an anti-tumour effect. Another avenue to explore for CRC patients with liver metastases is the use of cancer vaccines to boost the lymphocytic response to tumours.

Future plans may involve harnessing the role of the systemic inflammatory response with other known prognostic factors of colorectal cancer, such as the gut microbiome. The clinical utility of the use of NLR would be to risk stratify patients who undergo curative surgery or oncological treatment such as chemo and radiotherapy. The normalisation of the NLR could be used as a predictive marker of the response to therapy. Moreover, if the consistency of the prognostic effect of NLR in CRC is established, this might lend itself to the idea of manipulating the NLR though the intravenous use of cytokines or interventions that change the gut microbial diversity and composition to alter the prognosis of CRC patients. We know that the gut microbiota can be influenced by oncological treatments such as radiotherapy, stem cell transplantation and chemotherapy. It would therefore be of interest to investigate the link between the microbiome, the NLR and the above oncological treatments in the context of CRC outcomes and response to treatment. This could yield insights into whether the iatrogenic modulation of these key prognostic factors of CRC could change outcomes.

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