# A derived neutrophil to lymphocyte ratio predicts clinical outcome in stage II and III colon cancer patients

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# A derived neutrophil to lymphocyte ratio predicts clinical outcome in stage II and III colon cancer patients

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**Background:** Inflammation has a critical role in the pathogenesis and progression of cancer. Recently, the derived neutrophil to lymphocyte ratio (absolute count of neutrophils divided by the absolute white cell count minus the absolute count of neutrophils; dNLR) has been shown to influence clinical outcome in various cancer entities. In this study, we analysed the dNLR with clinical outcome in stage II and III colon cancer patients.

**Methods:** Three-hundred and seventy-two patients with stage II and III colon cancer were included in this retrospective study. Kaplan–Meier curves and multivariate Cox proportion analyses were calculated for time to recurrence (TTR) and overall survival (OS).

**Results:** In univariate analysis, the elevated preoperative dNLR was significantly associated with decreased TTR (hazard ratio (HR) 2.38, 95% confidence interval (CI) 1.57–3.6, $P<0.001$) and remained significant in multivariate analysis. Patients with dNLR $>3$ had a median TTR of 83 months, and patients with dNLR $\leqslant 3$ showed a median TTR of 132 months. In OS analysis, a dNLR $>2.2$ was significantly associated with decreased OS in univariate (HR 1.85, 95% CI 1.11–3.08, $P=0.018$) and multivariate analysis. Patients with dNLR $>2.2$ showed a median OS of 121 months, and patients with dNLR $\leqslant 2.2$ had a median OS of 147 months.

**Conclusion:** The dNLR may be an independent prognostic marker for TTR and OS in patients with stage II and III colon cancer. Independent validation of our findings is warranted.

Colon cancer is the third cause of cancer overall and the second leading cause of cancer-related death in Europe and the United States. Approximately 50% of colorectal cancer patients develop metastases; prognosis for these patients is poor, with 5-year survival rates of $<10\%$ (Boyle and Ferlay, 2005; Jemal *et al*, 2008). Adjuvant 5-fluorouracil-based chemotherapy is the standard treatment for patients with stage III and high-risk stage II colon cancer after curative surgery (Schmoll *et al*, 2012). However, a large number of colon cancer patients does not benefit from adjuvant treatment, either because these patients are cured by surgery alone or because they develop tumour recurrence or distant metastases despite adjuvant treatment. There is intense interest in the elucidation of prognostic and predictive biomarkers that will improve clinical outcome through patient classification in stage II and III colon cancer. High tumour stage and histological grade, the number of resected lymph nodes, venous, lymphatic or perineural invasion, emergency surgery (due to obstruction or perforation) and a high preoperative carcinoembryonic antigen (CEA) level have been identified as unfavourable clinicopathological prognostic factors in previous studies (Le Voyer *et al*, 2003; Gill *et al*, 2004;

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O'Connell *et al*, 2004; Morris *et al*, 2006; Quah *et al*, 2008). In addition, a large number of translational research studies evaluated the association of various molecular biomarkers with clinical outcome in colon cancer, but high costs, lack of standardisation and regional availability limit the application in routine clinical practice (Roth *et al*, 2010; Salazar *et al*, 2011).

It is widely accepted that inflammation has a critical role in the pathogenesis and progression of cancer. Genetic alterations, which activate oncogenes or result in the inactivation of tumour-suppressor genes, induce the transcription of inflammatory mediators. This generates a tumour-related inflammatory micro-environment and could explain the presence of inflammatory cells in tumours without epidemiological evidence for inflammation (Mantovani *et al*, 2008). On the other hand, systemic inflammatory response to tumours causes changes in the haematological components like white blood cells, specifically the neutrophils, lymphocytes and monocytes. The relative value of a combined index of neutrophil and lymphocyte counts (neutrophil to lymphocyte ratio, NLR) has been shown to influence the clinical outcome in various cancer entities, including cervical carcinoma (Lee *et al*, 2012), kidney cancer (Pichler *et al*, 2013), gastro-intestinal cancers (Walsh *et al*, 2005; Kishi *et al*, 2009; Ding *et al*, 2010) and lung cancer (Sarraf *et al*, 2009). Recently, a derived score composed of white cell and neutrophil counts (absolute count of neutrophils divided by the absolute white cell count minus the absolute count of neutrophils; dNLR) has been evaluated in a large number of cancer patients, showing similar prognostic value to the NLR (Proctor *et al*, 2012). Because there is a wealth of clinical trial data, where only white cell and neutrophil counts have been recorded in computer databases, which could be used to examine, in detail, the clinical value of the haematopoietic tissue-derived systemic inflammatory response, the present study specifically evaluated the effect of the preoperative dNLR on time to recurrence (TTR) and overall survival (OS) in patients with stage II and III colon cancer (Proctor *et al*, 2012).

## MATERIALS AND METHODS

**Subjects.** A total of 372 patients with histologically confirmed stage II and III colon cancer were included in this retrospective study. All patients were treated and/or included in the colon cancer surveillance program between 1996 and 2011 at the Division of Clinical Oncology, Department of Medicine, Medical University of Graz, Austria. Follow-up care was performed in regular intervals (3-month interval in years 1–3, 6-month interval in years 4–5 and 12-month interval in years 6–10 after diagnosis). Follow-up investigations included clinical examination, laboratory including CEA and carbohydrate antigen 19-9, radiological assessment (liver scan or ultrasound and chest X-ray every 6 months within the first 3 years) and colonoscopy every 2 years. Clinical and histopathological features were retrospectively obtained from the patient's history. Follow-up data of all patients were available. The preoperative white blood cell count was obtained within 3 days before surgery. The dNLR was calculated as the absolute count of neutrophils divided by the absolute white cell count of leukocytes minus the absolute count of neutrophils. This study has been approved by the Institutional Review Board of the Medical University of Graz. All participants were Caucasians.

**Statistical analyses.** The primary endpoint of the study was TTR; the secondary endpoint was OS. Time to recurrence was calculated from the date of diagnosis of colon cancer to the date of tumour recurrence and was censored at the time of death or at the last follow-up if the patients remained tumour-free at that time. Overall survival was calculated from the time of diagnoses to the date of death of any cause. The optimal cut-off levels for the dNLR were determined by applying receiver operating curve (ROC) analysis. The dNLR was correlated with the clinicopathological features by $\chi^2$-test. The association between the clinicopathological features and the dNLR with TTR and OS was analysed using Kaplan–Meier curves and compared by the log-rank test. In the multivariate Cox-regression analysis, the model was adjusted for prognostic clinicopathological factors significantly associated with TTR and OS in univariate analysis. Hazard ratios (HRs) estimated from the Cox analysis were reported as relative risks with corresponding 95% confidence intervals (CIs). All statistical analyses were performed using the Statistical Package for Social Sciences version 20.0 (SPSS Inc., Chicago, IL, USA). A two-sided $P<0.05$ was considered statistically significant.

## RESULTS

Baseline patient characteristics and tumour biological factors are shown in Table 1. The median age at time of diagnosis was 64 years (range 27–95 years). The median follow-up time was 68 months (range 1–190 months). Applying ROC analysis, the optimal cut-off levels for the dNLR was 3 for TTR and 2.2 for OS, respectively. For the NLR, ROC analysis provided an optimal cut-off level of 3.7 for TTR and 4 for OS. The ROC curves are shown in Supplementary Figures 1 and 2. The ROC curves for dNLR and NLR were 0.619 ($P=0.0005$) and 0.639 ($P<0.0001$) for TTR, respectively. The ROC curves for dNLR and NLR were 0.599 ($P=0.008$) and 0.625 ($P=0.0004$) for OS, respectively. The Spearman's rank correlation between the dNLR and NLR was 0.938 ($P<0.001$). The dNLR and NLR were available in 354 (95.2%) out of 372 patients.

In our study cohort, we found a significant association between tumour-invasion depth, lymph node involvement and clinical stage with TTR and OS (Table 1). Because clinical stage derives from tumour-invasion depth and lymph node involvements, only clinical stage was included in further multivariate models.

None of the clinicopathological features were associated with the dNLR (Supplementary Table 1).

Of the 372 colon cancer patients, 94 (25.3%) developed tumour recurrence and 72 (19.4%) died within the follow-up period. The tumour recurred in 50 (20.1%) out of 249 patients with a dNLR $\leqslant 3$ and in 41 (39%) out of 105 patients with a dNLR $>3$ ($P<0.001$). Death occurred in 23 (14.1%) out of 140 patients with a dNLR $\leqslant 2.2$ and in 46 (31.7%) out of 145 patients with a dNLR $>2.2$ ($P=0.018$), respectively.

Three-year, 5-year and 10-year recurrence-free survival was 83.9%, 80.7% and 79.9% in patients with dNLR $\leqslant 3$ and 61.9%, 61% and 61% in patients with dNLR $>3$ ($P<0.001$, for all time intervals), respectively. Three-year, 5-year and 10-year overall survival rate was 92.6%, 89.6% and 86.5% in patients with dNLR $\leqslant 2.2$ and 81.7% ($P=0.002$), 77% ($P=0.002$) and 75.9% ($P=0.012$) in patients with dNLR $>2.2$, respectively.

In univariate analysis, the elevated preoperative dNLR was significantly associated with decreased TTR (HR 2.38, 95% CI 1.57–3.6, $P<0.001$; Figure 1) and remained significant in the multivariate analysis including clinical stage (HR 2.25, 95% CI 1.48–3.4, $P<0.001$; clinical stage: HR 2.27, 95% CI 1.4–3.67, $P<0.001$). Patients with a dNLR $>3$ had a median TTR of 83 months, whereas patients with a dNLR $\leqslant 3$ showed a median TTR of 132 months. In OS analysis, the elevated preoperative dNLR was significantly associated with decreased OS in univariate analysis (HR 1.85, 95% CI 1.11–3.08, $P=0.018$; Figure 2) and multivariate analysis including clinical stage (HR 1.78, 95% CI 1.07–2.97, $P=0.026$; clinical stage: HR 1.95, 95% CI 1.14–3.35, $P=0.016$). Patients with a dNLR $>2.2$ showed a median OS of 121 months, whereas patients with a dNLR $\leqslant 2.2$ had a median OS of 147 months.

Table 1. Baseline patient characteristics and their association with TTR and OS in univariate analysis

| | | | TTR | | OS | |
|---|---|---|---|---|---|---|
| **Parameter** | ***n*** | **%** | **HR (95% CI)** | ***P*-value** | **HR (95% CI)** | ***P*-value** |
| **Gender** | | | | | | |
| Male | 217 | 58.3 | 1 (reference) | 0.417 | 1 (reference) | 0.801 |
| Female | 155 | 41.7 | 1.19 (0.80–1.79) | | 1.06 (0.66–1.70) | |
| **Tumour location** | | | | | | |
| Left | 130 | 34.9 | 1 (reference) | 0.781 | 1 (reference) | 0.273 |
| Right | 242 | 65.1 | 1.06 (0.69–1.63) | | 0.77 (0.48–1.23) | |
| **Tumour-invasion depth** | | | | | | |
| T1 | 7 | 1.9 | 1 (reference) | 0.010 | na, because of the low number of events for T1 and T2 (T1–3 *vs* T4: 2.487 (1.53–4.04)) | <0.001 |
| T2 | 18 | 4.8 | 0.65 (0.06–7.17) | | | |
| T3 | 260 | 69.9 | 1.43 (0.20–10.34) | | | |
| T4 | 87 | 23.4 | 2.78 (0.38–20.36) | | | |
| **Lymph node involvement** | | | | | | |
| N0 | 156 | 41.9 | 1 (reference) | <0.001 | 1 (reference) | <0.001 |
| N1 | 142 | 38.2 | 1.47 (0.87–2.48) | | 1.25 (0.69–2.26) | |
| N2 | 73 | 19.6 | 4.02 (2.42–6.69) | | 3.28 (1.85–5.83) | |
| Unknown | 1 | 0.3 | | | | |
| **Tumour grade** | | | | | | |
| G1 | 23 | 6.2 | 1 (reference) | 0.776 | 1 (reference) | 0.092 |
| G2 | 240 | 64.5 | 1.39 (0.51–3.83) | | 0.78 (0.28–2.20) | |
| G3 | 107 | 28.8 | 1.46 (0.51–4.16) | | 1.34 (0.47–3.83) | |
| Unknown | 2 | 0.5 | | | | |
| **Tumour stage** | | | | | | |
| II | 154 | 41.4 | 1 (reference) | <0.001 | 1 (reference) | 0.017 |
| III | 217 | 58.3 | 2.36 (1.48–3.75) | | 1.86 (1.12–3.11) | |
| Unknown | 1 | 0.3 | | | | |
| **Adjuvant chemotherapy** | | | | | | |
| No | 141 | 37.9 | 1 (reference) | 0.605 | 1 (reference) | 0.181 |
| Yes | 230 | 61.8 | 1.12 (0.73–1.72) | | 0.73 (0.73–1.72) | |
| Unknown | 1 | 0.3 | | | | |

Abbreviations: CI = confidence interval; HR = hazard ratio; na = not applicable; OS = overall survival; TTR = time to recurrence.

In interaction analysis for TTR, there was a significant association between dNLR and adjuvant chemotherapy ($P = 0.015$). Including only patients who underwent curative surgery alone, we found a significant association between dNLR $>3$ and TTR in uni- and multivariate analysis (HR 3.44, 95% CI 1.70–6.99, $P = 0.001$ and HR 3.03, 95% CI 1.47–6.14, $P = 0.03$, respectively; Figure 3; clinical stage in multivariate analysis: HR 3.17, 95% CI 1.53–6.59, $P = 0.002$). In patients who underwent adjuvant chemotherapy, the association was also significant, however, with a lower HR (univariate: HR 1.91, 95% CI 1.14–3.21, $P = 0.014$; multivariate: HR 1.84, 95% CI 1.1–3.1, $P = 0.021$; Figure 4; clinical stage in multivariate analysis: HR 2.47, 95% CI 1.12–65.43, $P = 0.025$).

To analyse how our ROC analysis-based threshold level compares with the dNLR threshold level for OS in the subgroup of colorectal cancer patients provided by Proctor *et al* (2012), we validated the cut-off level of 2 in our study cohort (Guthrie *et al*, 2013). In univariate analysis, the dNLR $\geqslant 2$ was significantly associated with decreased OS (HR 1.72, 95% CI 1.01–2.92, $P < 0.046$) but lost its significance in the multivariate analysis including clinical stage (HR 1.65, 95% CI 0.97–2.8, $P < 0.066$; clinical stage: HR 1.96, 95% CI 1.14–3.37, $P = 0.015$). Patients with a dNLR $\geqslant 2$ had a median OS of 123 months, whereas patients with a dNLR $<2$ showed a median OS of 147 months.

In a second step, we analysed the association between NLR based on ROC analysis-derived cut-off levels and TTR and OS. In univariate analysis, the elevated preoperative NLR was significantly associated with decreased TTR (HR 2.46, 95% CI 1.6–3.78, $P < 0.001$) and remained significant in the multivariate analysis including clinical stage (HR 2.36, 95% CI 1.53–3.4, $P < 0.001$; clinical stage: HR 2.27, 95% CI 1.4–3.37, $P = 0.001$). Patients with a NLR $>3.7$ had a median TTR of 104 months whereas patients with a NLR $\leqslant 3.7$ showed a median TTR of 138 months. In OS analysis, the elevated preoperative NLR was significantly associated with decreased OS in univariate analysis (HR 2.34, 95% CI 1.43–3.81, $P = 0.001$) and multivariate analysis (HR 2.22, 95% CI 1.36–3.62, $P = 0.002$; clinical stage: HR 1.85, 95% CI 1.01–3.19, $P = 0.026$). Patients with a NLR $>4$ showed a median OS of 113 months, whereas patients with a NLR $\leqslant 4$ had a median OS of 150 months.

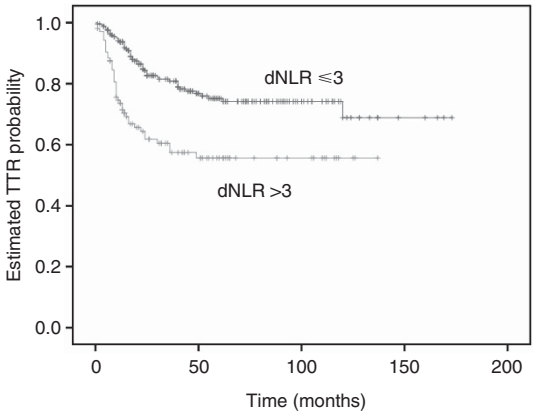


Figure 1. Preoperative dNLR and TTR in all colon cancer patients.

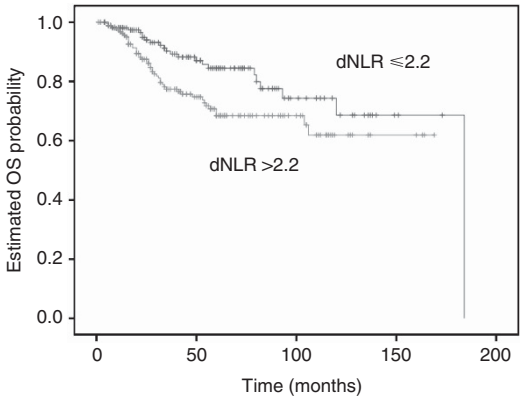


Figure 2. Preoperative dNLR and OS in all colon cancer patients.

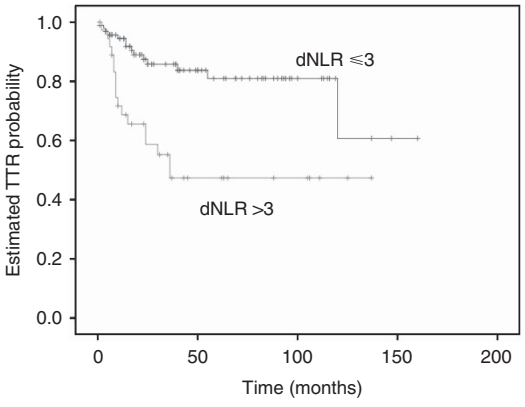


Figure 3. Preoperative dNLR and TTR in colon cancer patients who underwent surgery alone.

We then analysed the NLR with a predefined cut-off level of 5 based on previous studies evaluating early-stage colon cancer patients (Guthrie *et al*, 2013). In univariate analysis, the elevated preoperative NLR was significantly associated with decreased TTR (HR 1.91, 95% CI 1.26–2.9, $P=0.002$) and remained significant in the multivariate analysis including clinical stage (HR 1.81, 95% CI 1.19–2.75, $P=0.006$; clinical stage: HR 2.31, 95% CI 1.43–3.73, $P=0.001$). Patients with a NLR $\geqslant 5$ had a median TTR of 88 months, whereas patients with a NLR $<5$ showed a median TTR of 129 months. In OS analysis, the elevated preoperative NLR was

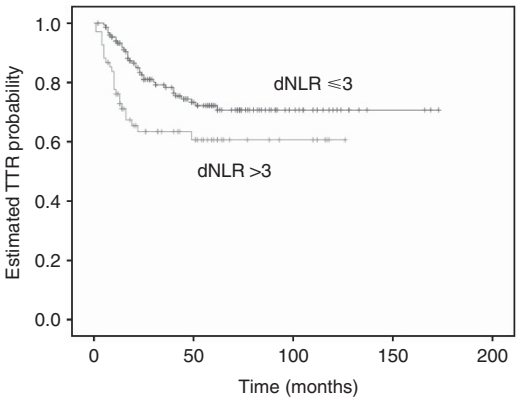


Figure 4. Preoperative dNLR and TTR in colon cancer patients who underwent adjuvant chemotherapy.

significantly associated with decreased OS in univariate analysis (HR 1.82, 95% CI 1.12–2.94, $P=0.016$) and multivariate analysis (HR 1.68, 95% CI 1.03–2.73, $P=0.037$; clinical stage: HR 1.91, 95% CI 1.11–3.29, $P=0.019$). Patients with a NLR $\geqslant 5$ showed a median OS of 113 months, whereas patients with a NLR $<5$ had a median OS of 143 months.

## DISCUSSION

The results of our study show that the dNLR is an independent prognostic marker in our study cohort including patients with stage II and III colon cancer. The derived ratio of neutrophils to leukocytes minus neutrophils may reflect the systemic response of the host to the tumour. Several translational research studies already demonstrated an effect of changes in white blood cells counts on clinical outcome in various cancer entities (Ege *et al*, 2008; Halazun *et al*, 2009; Kishi *et al*, 2009; Ding *et al*, 2010; Chua *et al*, 2011; Chiang *et al*, 2012; Pichler *et al*, 2013).

Leukocytes are mainly composed of neutrophils and lymphocytes. Lymphocytes are involved in cytotoxic cell death and cytokine production, which inhibits proliferation and metastatic capacity of tumour cells by immune response against the tumour (Ownby *et al*, 1983). In recent studies, normalisation of an initial lymphocytopenia in breast cancer patients treated with chemotherapy leads to an increased clinical outcome (Nieto *et al*, 2004), and an elevated lymphocyte count was significantly associated with prolonged OS in patients with multiple myeloma (Ege *et al*, 2008). In colorectal cancer patients, tumour-infiltrating lymphocytes have been shown to be independent prognostic factors of survival in all clinical stages (Ropponen *et al*, 1997). Furthermore, lymphocytosis was found to be significantly associated with increased OS in metastatic colorectal cancer patients (Leitch *et al*, 2007). Elevated neutrophil counts, however, may reflect tumour progression by providing an adequate environment for its growth. The presence of intratumoural neutrophils was significantly associated with larger tumour size and decreased survival in a study including patients with renal cell carcinoma (Jensen *et al*, 2009). Elevated blood neutrophil counts lead to poor progression-free survival (PFS) and OS in a study cohort including 1410 patients with nasopharyngeal cancer (He *et al*, 2012).

A combined index using neutrophil and lymphocyte counts has already been shown to predict colorectal cancer survival. Chua *et al* (2011) found that a NLR $>5$ is associated with worse OS in patients with metastatic colorectal cancer, while normalisation of the NLR after one cycle of chemotherapy resulted in improvement of PFS. Walsh *et al* (2005) showed an association between NLR $>5$

and decreased OS in colorectal cancer patients of all clinical stages, whereas Ding *et al* (2010) found an association between a preoperative NLR >4 and decreased recurrence-free survival in colon cancer patients who underwent surgery alone.

The first study evaluating the dNLR included 12 118 patients with various cancer entities and found a similar prognostic effect for dNLR and NLR (Proctor *et al*, 2012). However, they found a small but persistent superiority of the prognostic value of the NLR over the dNLR. The authors hypothesised that the dNLR is broadly mixing two cell types, lymphocytes and monocytes, with possible opposing effects in terms of predictive value. In the normal range, the relative proportion of lymphocytes to monocytes is approximately 6:1. Even though there may be a fall in the absolute proportion of lymphocytes and an increase in the absolute proportion of monocytes in cancer patients, the white blood count minus monocytes is dominated by lymphocytes. Therefore, the dNLR is likely to be a reasonable approximation of the NLR, and the potential error introduced by the presence of monocytes in the fraction is therefore likely to be small (Proctor *et al*, 2012). The optimal threshold in their study for dNLR was 2 : 1 for OS and cancer-specific survival, which is similar to the cut-off level found in our study. A subset analysis considering only colorectal cancer patients with Duke stage C and D found a significant decreased OS and cancer-specific survival for the elevated dNLR independent of sex and age. Of note, blood samples were taken within 2 years of cancer diagnosis in their study, not taking into account infections causing alterations in the haematological variables of the patients included (Proctor *et al*, 2012).

When we applied the dNLR cut-off level provided by Proctor *et al* for OS to our study cohort, we found a significant association with OS in univariate but not in multivariate analysis. In NLR analyses, we found for both the ROC-optimised and the predefined literature-based cut-off levels a significant association between NLR and TTR and OS. However, there was a small but persistent superiority in predicting TTR and OS of the ROC based over the literature-based cut-off levels. This difference is likely to be due to the optimised ROC-analysis approach matching our study cohort. When we compared the prognostic value of ROC-based dNLR and NLR, we found a similar prognostic effect. However, similar to the study by Proctor *et al*, we found a small but persistent superiority of the prognostic value of the NLR over the dNLR.

When we compared the effect of the dNLR in patients who underwent surgery alone with that in patients who underwent surgery and adjuvant chemotherapy, we found in both groups a significant association between high dNLR and decreased TTR. However, the effect was superior in the group of patients who underwent curative surgery alone compared with patients who underwent adjuvant chemotherapy (HR of 3.44 *vs* 1.91, respectively). This may support the conclusion that a high dNLR is a negative prognostic marker, and that such high-risk patients may benefit from adjuvant chemotherapy. The exact mechanism, however, how chemotherapy effects on dNLR and vice versa remains to be determined.

The strengths of our study are the well-defined study cohort and the narrow time frame for blood collection within 3 days before surgery, excluding possible clinical significant infections. However, because of the retrospective design of our study, a selection bias cannot be fully excluded. Furthermore, because of the exploratory nature of this study, we calculated optimised dNLR cut-off levels for TTR and OS using ROC analysis. If different cut-off levels for different endpoints are valuable or if one threshold level can reliably predict different endpoints needs to be determined in validation studies.

In summary, the results of the present study show that the dNLR may be an independent prognostic marker for TTR and OS in patients with stage II and III colon cancer. Independent validation of our findings is warranted.

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