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ORIGINAL RESEARCH

# Preoperative and Postoperative Neutrophil-Lymphocyte Ratio and Platelet-Lymphocyte Ratio Measured From the Peripheral Blood of Patients with Colorectal Cancer

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**Background:** The neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) have been confirmed to be related to the clinicopathological features and prognosis of colorectal cancer (CRC) patients. However, the results have been inconsistent, and few studies have focused on a specific point in time during surgery and dynamic changes prior to and after surgery.

**Methods:** We conducted a retrospective analysis of 349 CRC patients and explored the value of NLR, PLR and their dynamic changes in predicting clinicopathological variables and prognosis in CRC.

**Results:** Preoperative NLR (Pre-NLR) was correlated with CEA, CA199 levels, tumor location and tumor stage ($P$=0.041, $P$=0.002, $P$=0.001 and $P$=0.012, respectively), whereas postoperative NLR (post-NLR) was relevant to age, sex, CA125 levels and T stage significantly ($P$=0.032, $P$=0.002, P=0.026, P=0.019, respectively). When comparing post- and pre-NLR values, there was a positive connection between increases in NLR and BMI, tumor location, T stage, and tumor stage ($P$=0.034, $P$=0.005, $P$=0.023, $P$=0.023, respectively). In addition, Preoperative PLR (pre-PLR) was correlated with sex, smoke and drink history, CEA and CA199 levels, tumor location, T stage and tumor stage ($P$=0.006, $P$=0.037, $P$=0.040, $P$=0.006, $P$=0.005, $P$<0.001, $P$=0.007, $P$=0.003 respectively), while postoperativePLR (post-PLR) was only associated with tumor location ($P$=0.010). Increases in PLR were significantly related to sex, smoking history, tumor location and differentiation ($P$=0.001, $P$=0.002, $P$<0.001, $P$=0.034, respectively). Patients with CRC who had a high post-PLR experienced significantly shorter relapse-free survival (RFS) compared to other patients (HR 0.607 (0.381–-0.968), $P$=0.036). Furthermore, this high post-PLR has tendency association with shorter overall survival (OS) (HR 0.596 (0.338–-1.050), $P$=0.076).

**Conclusion:** These findings suggest that levels and changes in NLR/PLR are associated with several unfavorable clinicopathological features in CRC patients. Furthermore, patients with high levels of post-PLR exhibit a worse prognosis.

**Keywords:** colorectal cancer, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, prognosis, peripheral blood

## Introduction

According to GLOBOCAN 2020 data, colorectal cancer (CRC) ranks as the third most prevalent cancer globally.[1] Nearly half of CRC patients present with metastasis at the time of primary diagnosis, and colon cancer patients represent two-thirds of all CRC patients.[2] Currently, in the eighth edition of the American Joint Committee on Cancer (AJCC) TNM staging system, tumour histopathology and location are used to predict CRC prognosis.[3] However, clinical outcomes may differ even among patients with the same tumour stage and differentiation. Thus, new reliable prognostic markers are required to predict prognosis and guide appropriate treatment regimens.

In recent years, a number of scholarly investigations have documented that cancer-related inflammation (CRI) can initiate and promote tumour growth and metastasis in the peripheral blood and tumour microenvironment.[4–6] Peripheral

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blood markers such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been significantly associated with poor prognosis for breast,[7] hepatocellular,[8] gastric,[9] renal[10] and lung cancer.[11] Similarly, NLR and PLR have been associated with the prognosis of CRC patients in some studies.[12–14] A meta-analysis was conducted to confirm the prognostic prediction ability of NLR and PLR in CRC and showed that elevated NLR and PLR had a significant relationship with poor overall survival (OS).[15] Additionally, it has been shown that combining NLR and PLR may augment their roles in the prediction in cancer prognosis.[16,17] However, the results have reached inverse conclusions. Kang et al found that the diagnostic superiority of monocyte-to-lymphocyte ratio (MLR) over NLR and PLR has been established, while NLR has shown potential as a prognostic marker for CRC.[18] Ying et al has demonstrated that an elevated NLR before surgery, rather than PLR, can serve as an independent prognostic biomarker for CRC.[19] Moreover, the cut-off values of NLR and PLR vary among different studies. There are few relevant reports in the literature with regard to whether the patient's prognosis is influenced by the postoperative (post-) NLR/PLR levels and the alterations observed in relation to the preoperative (pre-) values.[20] Hence, it is imperative to conduct additional research to explore the worth and prognostic implications of pre-NLR/PLR, post-NLR/PLR, and related alterations in colorectal cancer, given their substantial clinical importance.

# Materials and Methods

## Patients and Samples

We conducted a retrospective analysis of 349 CRC patients who underwent surgery in the Department of Anal and Intestinal Surgery, Affiliated Dongyang People's Hospital of Wenzhou Medical University, Dongyang, between January 2008 and December 2011. All patients were confirmed to have CRC based on histopathological evidence. The inclusion criteria for this study consisted of patients who had undergone radical colorectal cancer resection and received a pathological diagnosis of colorectal cancer. These patients did not receive any chemotherapy or other antineoplastic treatment prior to the surgery. Additionally, their peripheral blood test results were available both 7 days before and 7–14 days after the operation. They did not have any autoimmune diseases, hematologic diseases, or acute or chronic infections prior to the surgery. Furthermore, these patients had complete clinical, pathological, and follow-up data. On the other hand, the exclusion criteria included patients who did not undergo surgical treatment, those with incomplete case information or follow-up data, and those who received neoadjuvant therapy and had autoimmune diseases, hematologic diseases, acute or chronic infection.

## Clinicopathological and Laboratory Data

For each patient, we analysed the blood routine data obtained 7 days preoperatively and 7–14 days postoperatively but before any chemotherapy, chemoradiation or immunotherapy, and their laboratory data and clinicopathological data from the electronic medical records system. Routine blood examinations were performed using the Sysmex XE-2100 apparatus (Sysmex Corporation). The NLR was operationally defined as the ratio of neutrophil count to lymphocyte count, while PLR was operationally defined as the ratio of the platelet count to lymphocyte count. Median values were used as the cut-off values for pre-NLR/post-NLR, and pre-PLR/post-PLR, and variations in NLR and PLR were categorized as increases or decreases.

## Follow-up Data

The enrolled patients were followed up for at least 5 years. Postoperatively, follow-up will be conducted through outpatient visits and review of patient readmission records. The follow-up interval will be every 6 months, unless the patient deceases, in which case the follow-up will be discontinued. Local recurrence or metastasis will be diagnosed based on clinical imaging examination results or pathological histology results. The primary endpoints were overall survival (OS) and relapse-free survival (RFS). Relapse-free survival (RFS)was defined as the interval between postoperative day l and the occurrence of tumour relapse/metastasis. Overall survival (OS) was defined as the duration from postoperative day l to the patient's demise (excluding deaths due to nontumor factors).

## Statistical Analysis

SPSS 23.0 statistical software (SPSS Inc., Chicago, IL, USA) and GraphPad Prism 8 (GraphPad Software Inc., San Diego, CA, USA) were used to analyse the data. The relationships between clinicopathological data and NLR/PLR were examined by the chi-square test. Survival analysis was performed by GraphPad Prism 8 and KaplanMeier survival analysis. The Cox proportional hazard model was utilized in conducting multivariate survival analysis to ascertain the independent risk factors that impact the prognosis of patients with CRC. Relative risk was assessed through the utilization of hazard risk (HR) and 95% confidence interval (95% *CI*). Statistical significance was determined by a $p$ value<0.05.

# Results

## Characteristics and Distribution of the Study Population

Of all 349 CRC patients, 204 patients were male, and 145 patients were female. The majority of patients were older than 60 years (245/349, 70.2%) and without smoke (234/344, 68.0%) or drink (224/341, 65.7%). Most tumour markers were normal (CEA 62.6%; CA125 95.6%; CA199 81.0%; CA724 79.5%). A total of 160 patients were confirmed to have colon cancer, including 84 with left colon cancer and 76 with right colon cancer. A total of 189 patients had rectal cancer. According to the 8th AJCC TNM staging system, 49 patients had clinical stage I, 139 had clinical stage II, 134 had clinical stage III and 27hadclinical stage IV CRC. The degree of differentiation included 35 patients with highly differentiated (G1) carcinomas, 274 patients with moderate differentiation (G2) and 40 patients with poorly differentiation (G3). At the conclusion of the follow-up period, 246 patients had follow-up information, 53 (21.5%) patients had dead, and 77 (31.3%) had developed local recurrence or distal metastasis.

Some clinicopathological features of CRC patients have missing data, including: 5 cases of smoking, 8 cases of alcohol consumption, 33 cases of BMI, 63 cases of CEA, 142 cases of CA125, 65 cases of CA199, 271 cases of CA724, 51 cases of post-NLR/PLR data. The baseline clinicopathological characteristics stratified by pre-NLR/post-NLR, pre-PLR/post-PLR, and variations in NLR and PLR are described in Tables 1 and 2. Among 349CRC patients, a total of 51 cases were found to have missing postoperative NLR data as a result of peripheral blood test loss. The optimal median cut off value was 2.61 for pre-NLR, 2.98 for post-NLR, 145.38 for pre-PLR, and 215.86 for post-PLR. NLR and PLR variations were grouped as up and down. A total of 174 patients (174/349, 49.9%) had a high pre-NLR (≥2.61), 149 patients(149/298, 50.0%) had a high post-NLR (≥2.98), and 166 patients (166/298, 55.7%) had increases in NLR. Similarly, the pre-PLR value was high in 174 patients (174/349, 49.9%), the 149 patients had high post-PLR values (149/298, 50%), and 229 patients (229/298, 76.8%) had increases in PLR.

## Correlations of NLR and PLR with Clinicopathological Variables

In CRC patients with CEA≥5, CA199≥37, colon tumor, and higher tumor stage, the prevalence of high pre-NLR was significantly greater in comparison to those with CEA<5, CA199<37, rectal tumors, and low-stage groups ($P$=0.041, $P$=0.002, $P$=0.001, and $P$=0.012, respectively). Additionally, the levels of pre-NLR were higher in CA724≥6.9 and T3-4 groups compared to CA724<6.9 and T1-2 groups, however, there was no statistically significant discrepancy observed ($P$=0.057 and $P$=0.062, respectively). Post-NLR was higher in patients with age≥60, male sex, CA125<35 and T1-2 groups significantly ($P$=0.032, $P$=0.002, P=0.026, P=0.019, respectively). The postoperative rate of NLR increase was significantly higher in patients with BMI≥23.9, rectal cancer, T1-2 stages, and low-stage groups ($P$=0.034, $P$=0.005, $P$=0.023, $P$=0.023, respectively).

In addition, pre-PLR was significantly higher in CRC patients with female sex, without smoke and drink history, CEA≥5, CA199≥37, colon cancer, T3-4 stage and high-stage groups ($P$=0.006, $P$=0.037, $P$=0.040, $P$=0.006, $P$=0.005, $P$<0.001, $P$=0.007, $P$=0.003 respectively), comparing to those with CEA<5, CA199<37, rectal tumors, T1-2 stage and low-stage groups. Post-PLR was exhibited a significant higher level in patients with colon cancer compared to those with rectal cancer ($P$=0.010). Additionally, the level of post-PLR was higher in CA199≥37 compared to CA199≤37 group, but the result did not yield any statistically significant difference ($P$=0.065). Furthermore, the postoperative rate of PLR

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**Table 1** Clinical Characteristics of the Patients With Different Pre-NLR, Post-NLR and NLR Variation

| Group | No. of patients (N=349) | Preoprerative NLR | | *P* value | No. of patients (N=298) | Postoperative NLR | | *P* value | No. of patients (N=298) | NLR variation | | *P* value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | <2.61 | ≥2.61 | | | <2.98 | ≥2.98 | | | Down | Up | |
| Age | | | | | | | | | | | | |
| <60y | 104 | 57(54.8%) | 47(45.2%) | 0.256 | 91 | 54(59.3%) | 37(40.7%) | **0.032*** | 91 | 45(49.5%) | 46(50.5%) | 0.235 |
| ≥60y | 245 | 118(48.2%) | 127(51.8%) | | 207 | 95(45.9%) | 112(54.1%) | | 207 | 87(42.0%) | 120(58.0%) | |
| Gender | | | | | | | | | | | | |
| Male | 204 | 106(52.0%) | 98(48.0%) | 0.421 | 174 | 74(42.5%) | 100(57.5%) | **0.002*** | 174 | 71(40.8%) | 103(59.2%) | 0.151 |
| Female | 145 | 69(47.6%) | 76(52.4%) | | 124 | 75(60.5%) | 49(39.5%) | | 124 | 61(49.2%) | 63(50.8%) | |
| Smoke | | | | | | | | | | | | |
| No | 234 | 109(46.6%) | 125(53.4%) | 0.064 | 196 | 104(53.1%) | 92(46.9%) | 0.138 | 196 | 93(47.4%) | 103(52.6%) | 0.158 |
| Yes | 110 | 63(57.3%) | 47(42.7%) | | 98 | 43(43.9%) | 55(56.1%) | | 98 | 38(38.8%) | 60(61.2%) | |
| Drink | | | | | | | | | | | | |
| No | 224 | 106(47.3%) | 118(52.7%) | 0.253 | 193 | 99(51.3%) | 94(48.7%) | 0.537 | 193 | 89(46.1%) | 104(53.9%) | 0.444 |
| Yes | 117 | 63(53.8%) | 54(46.2%) | | 99 | 47(47.5%) | 52(52.5%) | | 99 | 41(41.4%) | 58(58.6%) | |
| BMI | | | | | | | | | | | | |
| <23.9 | 254 | 133(52.4%) | 121(47.6%) | 0.300 | 216 | 110(50.9%) | 106(49.1%) | 0.998 | 216 | 101(46.8%) | 115(53.2%) | **0.034*** |
| ≥23.9 | 62 | 37(59.7%) | 25(40.3%) | | 55 | 28(50.9%) | 27(49.1%) | | 55 | 17(30.9%) | 38(69.1%) | |
| CEA | | | | | | | | | | | | |
| <5 | 179 | 96(53.6%) | 83(46.4%) | **0.041*** | 162 | 79(48.8%) | 83(51.2%) | 0.594 | 162 | 65(40.1%) | 97(59.9%) | 0.095 |
| ≥5 | 107 | 44(41.1%) | 63(58.9%) | | 86 | 45(52.3%) | 41(47.7%) | | 86 | 44(51.2%) | 42(48.8%) | |
| CA125 | | | | | | | | | | | | |
| <35 | 198 | 99(50.0%) | 99(50.0%) | 0.744 | 169 | 80(47.3%) | 89(52.7%) | **0.026*** | 169 | 77(45.6%) | 92(54.4%) | 0.654 |
| ≥35 | 9 | 4(44.4%) | 5(55.6%) | | 8 | 7(87.5%) | 1(12.5%) | | 8 | 3(37.5%) | 5(62.5%) | |
| CA199 | | | | | | | | | | | | |
| <37 | 230 | 123(53.5%) | 107(46.5%) | **0.002*** | 203 | 106(52.2%) | 97(47.8%) | 0.131 | 203 | 90(44.3%) | 113(55.7%) | 0.766 |
| ≥37 | 54 | 16(29.6%) | 38(70.4%) | | 43 | 17(39.5%) | 26(60.5%) | | 43 | 18(41.9%) | 25(58.1%) | |
| CA724 | | | | | | | | | | | | |
| <6.9 | 62 | 32(51.6%) | 30(48.4%) | 0.057 | 56 | 30(53.6%) | 26(46.4%) | 0.473 | 56 | 23(41.1%) | 33(58.9%) | 0.903 |
| ≥6.9 | 16 | 4(25.0%) | 12(75.0%) | | 14 | 6(42.9%) | 8(57.1%) | | 14 | 6(42.9%) | 8(57.1%) | |
| Location | | | | | | | | | | | | |
| Left colon | 84 | 31(36.9%) | 53(63.1%) | **0.001*** | 77 | 39(50.6%) | 38(49.4%) | 0.646 | 77 | 43(55.8%) | 34(44.2%) | **0.005*** |
| Right colon | 76 | 32(42.1%) | 44(57.9%) | | 66 | 36(54.5%) | 30(45.5%) | | 66 | 34(51.5%) | 32(48.5%) | |
| Rectum | 189 | 112(59.3%) | 77(40.7%) | | 155 | 74(47.7%) | 81(52.3%) | | 155 | 55(35.5%) | 100(64.5%) | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Differentiation | | | | | | | | | | | | |
| Well | 35 | 15(42.9%) | 20(57.1%) | 0.220 | 31 | 12(38.7%) | 19(61.3%) | 0.390 | 31 | 15(48.4%) | 16(51.6%) | 0.423 |
| Moderately | 274 | 144(52.6%) | 130(47.4%) | | 232 | 120(51.7%) | 112(48.3%) | | 232 | 105(45.3%) | 127(54.7%) | |
| Poorly | 40 | 16(40.0%) | 24(60.0%) | | 35 | 17(48.6%) | 18(51.4%) | | 35 | 12(34.3%) | 23(65.7%) | |
| Node status | | | | | | | | | | | | |
| Negative | 194 | 97(50.0%) | 97(50.0%) | 0.952 | 164 | 83(50.6%) | 81(49.4%) | 0.816 | 164 | 77(47.5%) | 87(53.7%) | 0.307 |
| Positive | 155 | 78(50.3%) | 77(49.7%) | | 134 | 66(49.3%) | 68(50.7%) | | 134 | 55(41.0%) | 79(59.0%) | |
| T stage | | | | | | | | | | | | |
| T1+T2 | 68 | 41(60.3%) | 27(39.7%) | 0.062 | 58 | 21(36.2%) | 37(63.8%) | **0.019*** | 58 | 18(31.0%) | 40(69.0%) | **0.023*** |
| T3+T4 | 281 | 134(47.7%) | 147(52.3%) | | 240 | 128(53.3%) | 112(46.7%) | | 240 | 114(47.5%) | 126(52.5%) | |
| Stage | | | | | | | | | | | | |
| I | 49 | 31(63.3%) | 18(36.7%) | **0.012*** | 42 | 15(35.7%) | 27(64.3%) | 0.180 | 42 | 15(35.7%) | 27(64.3%) | **0.023*** |
| II | 139 | 65(46.8%) | 74(53.2%) | | 117 | 64(54.7%) | 53(45.3%) | | 117 | 59(50.4%) | 58(49.6%) | |
| III | 134 | 72 (53.7%) | 62 (46.3%) | | 116 | 57 (49.1%) | 59 (50.9%) | | 116 | 43(37.1%) | 73(62.9%) | |
| IV | 27 | 7 (25.9%) | 20 (74.1%) | | 23 | 13 (56.5%) | 10 (43.5%) | | 23 | 15(65.2%) | 8(34.8%) | |

**Note**: Bold values mean P value has statistically significant difference: *p<0.05.

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**Table 2** Clinical Characteristics of the Patients With Different Pre-PLR, Post-PLR and PLR Variation

| Group | No. of Patients (N=349) | Preoperative PLR | | *P* value | No. of Patients (N=298) | Postoperative PLR | | *P* value | No. of Patients (N=298) | PLR Variation | | *P* value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | <145.38 | ≥145.38 | | | <215.86 | ≥215.86 | | | DOWN | UP | |
| Age | | | | | | | | | | | | |
| <60y | 104 | 55(52.9%) | 49(47.1%) | 0.505 | 91 | 44(48.4%) | 47(51.6%) | 0.706 | 91 | 19(20.9%) | 72(79.1%) | 0.537 |
| ≥60y | 245 | 120(49.0%) | 125(51.0%) | | 207 | 105(50.7%) | 102(49.3%) | | 207 | 50(24.2%) | 157(75.8%) | |
| Gender | | | | | | | | | | | | |
| Male | 204 | 115(56.4%) | 89(43.6%) | **0.006*** | 174 | 90(51.7%) | 84(48.3%) | 0.481 | 174 | 28(16.1%) | 146(83.9%) | **0.001*** |
| Female | 145 | 60(41.4%) | 85(58.6%) | | 124 | 59(47.6%) | 65(52.4%) | | 124 | 41(33.1%) | 83(66.9%) | |
| Smoke | | | | | | | | | | | | |
| No | 234 | 108(46.2%) | 126(53.8%) | **0.037*** | 196 | 101(51.5%) | 95(48.5%) | 0.458 | 196 | 56(28.6%) | 140(71.4%) | **0.002*** |
| Yes | 110 | 64(58.2%) | 46(41.8%) | | 98 | 46(46.9%) | 52(53.1%) | | 98 | 12(12.2%) | 86(87.8%) | |
| Drink | | | | | | | | | | | | |
| No | 224 | 102(45.5%) | 122(54.5%) | **0.040*** | 193 | 94(48.7%) | 99(51.3%) | 0.649 | 193 | 50(25.9%) | 143(74.1%) | 0.139 |
| Yes | 117 | 67(57.3%) | 50(42.7%) | | 99 | 51(51.5%) | 48(48.5%) | | 99 | 18(18.2%) | 81(81.8%) | |
| BMI | | | | | | | | | | | | |
| <23.9 | 254 | 132(52.0%) | 122(48.0%) | 0.685 | 216 | 110(50.9%) | 106(49.1%) | 0.998 | 216 | 49(22.7%) | 167(77.3%) | 0.186 |
| ≥23.9 | 62 | 34(54.8%) | 28(45.2%) | | 55 | 28(50.9%) | 27(49.1%) | | 55 | 8(14.5%) | 47(85.5%) | |
| CEA | | | | | | | | | | | | |
| <5 | 179 | 95(53.1%) | 84(46.9%) | **0.006*** | 162 | 83(51.2%) | 79(48.8%) | 0.594 | 162 | 35(21.6%) | 127(78.4%) | 0.929 |
| ≥5 | 107 | 39(36.4%) | 68(63.6%) | | 86 | 41(47.7%) | 45(52.3%) | | 86 | 19(22.1%) | 67(77.9%) | |
| CA125 | | | | | | | | | | | | |
| <35 | 198 | 100(50.5%) | 98(49.5%) | 0.097 | 169 | 85(50.3%) | 84(49.7%) | 0.500 | 169 | 31(18.3%) | 138(81.7) | 0.179 |
| ≥35 | 9 | 2(22.2%) | 7(77.8%) | | 8 | 5(62.5%) | 3(37.5%) | | 8 | 3(37.5%) | 5(62.5%) | |
| CA199 | | | | | | | | | | | | |
| <37 | 230 | 117(50.9%) | 113(49.1%) | **0.005*** | 203 | 107(51.7%) | 96(46.4%) | 0.065 | 203 | 43(21.2%) | 160(78.8%) | 0.527 |
| ≥37 | 54 | 16(29.6%) | 38(70.4%) | | 43 | 16(37.2%) | 27(62.8%) | | 43 | 11(25.6%) | 32(74.4%) | |
| CA724 | | | | | | | | | | | | |
| <6.9 | 62 | 26(41.9%) | 36(59.1%) | 0.436 | 56 | 26(46.4%) | 30(53.6%) | 0.811 | 56 | 15(26.8%) | 41(73.2%) | 0.508 |
| ≥6.9 | 16 | 5(31.3%) | 11(68.7%) | | 14 | 7(50.0%) | 7(50.0%) | | 14 | 5(35.7%) | 9(64.3%) | |
| Location | | | | | | | | | | | | |
| Left colon | 84 | 24(28.6%) | 60(71.4%) | **<0.001***** | 77 | 31(40.3%) | 46(59.7%) | **0.010*** | 77 | 30(39.0%) | 47(61.0%) | **<0.001***** |
| Right colon | 76 | 44(57.9%) | 32(42.1%) | | 66 | 43(65.2%) | 23(34.8%) | | 66 | 19(28.8%) | 47(71.2%) | |
| Rectum | 189 | 107(56.6%) | 82(43.4%) | | 155 | 75(48.4%) | 80(51.6%) | | 155 | 20(12.9%) | 135(87.1%) | |
| Differentiation | | | | | | | | | | | | |
| Well | 35 | 16(45.7%) | 19(54.3%) | 0.091 | 31 | 16(51.6%) | 15(48.4%) | 0.970 | 31 | 10(32.3%) | 21(67.7%) | **0.034*** |
| Moderately | 274 | 145(52.9%) | 129(47.1%) | | 232 | 116(50.0%) | 116(50.0%) | | 232 | 46(19.8%) | 186(80.2%) | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Poorly | 40 | 14(35.0%) | 26(65.0%) | | 35 | 17(48.6%) | 18(51.4%) | | 35 | 13(37.1%) | 22(62.9%) | |
| Node status | | | | | | | | | | | | |
| Negative | 194 | 97(50.0%) | 97(50.0%) | 0.952 | 164 | 85(51.8%) | 79(48.2%) | 0.485 | 164 | 41(25.0%) | 123(75.0%) | 0.403 |
| Positive | 155 | 78(50.3%) | 77(49.7%) | | 134 | 64(47.8%) | 70(52.2%) | | 134 | 28(20.9%) | 106(79.1%) | |
| T stage | | | | | | | | | | | | |
| T1-T2 | 68 | 44(64.7%) | 24(35.3%) | **0.007*** | 58 | 27(46.6%) | 31(53.4%) | 0.558 | 58 | 9(15.5%) | 49(84.5%) | 0.124 |
| T3-T4 | 281 | 131(46.6%) | 150(53.4%) | | 240 | 122(50.8%) | 118(49.2%) | | 240 | 60(25.0%) | 180(75.0%) | |
| Stage | | | | | | | | | | | | |
| I | 49 | 33(67.3%) | 16(32.7%) | **0.003*** | 42 | 21(50.0%) | 21(50.0%) | 0.904 | 42 | 7(16.7%) | 35(83.3%) | 0.241 |
| II | 139 | 63(45.3%) | 76(54.7%) | | 117 | 61(52.1%) | 56(47.9%) | | 117 | 31(26.5%) | 86(73.5%) | |
| III | 134 | 72(53.7%) | 62(46.3%) | | 116 | 55(47.4%) | 61(52.6%) | | 116 | 23(19.8%) | 93(80.2%) | |
| IV | 27 | 7(25.9%) | 20(74.1%) | | 23 | 12(52.2%) | 11(47.8%) | | 23 | 8(34.8%) | 15(65.2%) | |

**Note**: Bold values mean P value has statistically significant difference: *p<0.05, ***p<0.001.

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increase was significantly higher in patients with male sex, smoke history, rectal cancer and moderately differentiation ($P$=0.001, $P$=0.002, $P$<0.001, $P$=0.034, respectively).

## Prognostic Values of NLR and PLR

Out of the 246 patients with CRC for whom follow-up information was available, recurrence or metastasis was detected in 78 patients. Among them, 53 had died by the final follow-up. For all individuals, the 5-year OS and RFSwere78.5% and 68.3%, respectively. The associations of pre-NLR/post-NLR, pre-PLR/post-PLR, and variations in NLR and PLR with OS and RFS in patients with CRC were examined by KaplanMeier survival analysis and their charts were made by GraphPad Prism 8.

There was no significant difference in OS among the groups with pre-NLR, post-NLR, NLR variation (P=0.521, P=0.574 and P=0.255, respectively; Figure 1A, C, E). Similarly, the differences in RFS were insignificant among the groups with pre-NLR, post-NLR, NLR variation (P=0.393, P=0.931, P=0.705, respectively; Figure 1B, D, F). Additionally, no significant differences were observed in OS (P=0.501 and P=0.323, Figure 2A and E) and RFS (P=0.396 and P=0.774, Figure 2B and F), among the groups with pre-PLR and PLR variation. Importantly, high post-PLR has tendency association with shorter OS (HR 0.596 (0.338–1.050), P=0.076, Figure 2C). Furthermore, the results revealed that high post-PLR showed significant association with shorter RFS (HR 0.607 (0.381–0.968), P=0.036, Figure 2D).

In the univariate analysis, T stage (T1-2 vs T3-4, HR=0.216, 95% CI=0.113−0.415, $P$=0.005) and node status (negative vs positive, HR=0.387, 95% CI=0.215−0.649, $P$<0.001) were significantly related to OS (Table 3). These parameters were further included in the multivariate Cox proportional hazards analysis, along with other clinical parameters and pre-NLR/post-NLR, pre-PLR/post-PLR, and NLR and PLR variations. Multivariate analyses revealed that node status (HR=0.382, 95% CI=0.184−0.751, $P$=0.006) was an independent prognostic indicator for OS in CRC patients. Additionally, T stage (T1-2 vs T3-4, HR=0.235, 95% CI=0.138−0.401, $P$<0.001), node status (negative vs positive, HR=0.466, 95% CI=0.282−0.707, $P$<0.001) and post-PLR (<215.86 vs ≥215.86, HR=0.607, 95% CI=0.381−0.968, $P$=0.036) were associated with RFS significantly (Table 4). Further multivariate analyses also revealed that node status (negative vs positive, HR=0.469, 95% CI=0.271−0.811, $P$=0.007) and post-PLR (<215.86 vs ≥215.86, HR=0.539, 95% CI=0.312−0.934, $P$=0.027) was independent prognostic indicator for RFS in CRC patients, and T stage (T1-2 vs T3-4, HR=0.397, 95% CI=0.157−1.002, $P$=0.050) has tendency independent prognostic significance for RFS. These results indicated no correlations of pre/post NLR, pre-PLR and their variations with CRC survival.

# Discussion

Currently, treatment strategies for CRC patients have made slow progress. Researchers are trying to identify potential molecular factors to predict prognosis, but this is an expensive process that requires sophisticated laboratory equipment. Accordingly, highly specific low-cost, easy-to-obtain factors are constantly sought to monitor treatment efficacy and detect early cancer recurrence.

Recent researches have revealed that the inflammation plays a pivotal role in the progression of cancer. Cancer often appears in areas of chronic irritation, inflammation, and infection, which is why inflammatory cells are deemed significant in cancer progression. As part of this process, neutrophils have different functions in different cancers,[21] which can promote hepatic metastasis of CRC.[22] Lymphocytes are thought to be antitumorigenic factors, which can eliminate tumor cells through cytotoxic effects,[23,24] and platelets are correlated with neoangiogenesis,[25] contributing to tumour progression. As a result, NLR and PLR, which reflect systematic inflammatory responses, are potential prognostic factors.

Prior studies have demonstrated that NLR and PLR are closely related to the outcome of CRC patients. Meta-analysis showed that a high NLR was related to OS and RFS,[15,26] and an increased PLR was related to worse survival.[27] In CRC patients, the sensitivity and specificity of NLR in ROC curve analysis were 66.9% and 77.6%, respectively. For adenomatous polyps, the sensitivity and specificity were 36.7% and 80.9%, respectively,[28] which showed that NLR may provide information in distinguish CRC and adenomatous polyps. Furthermore, NLR differs between tumour patients and healthy volunteers.[29] In addition, Chen et al found that a high NLR was associated with old age, larger

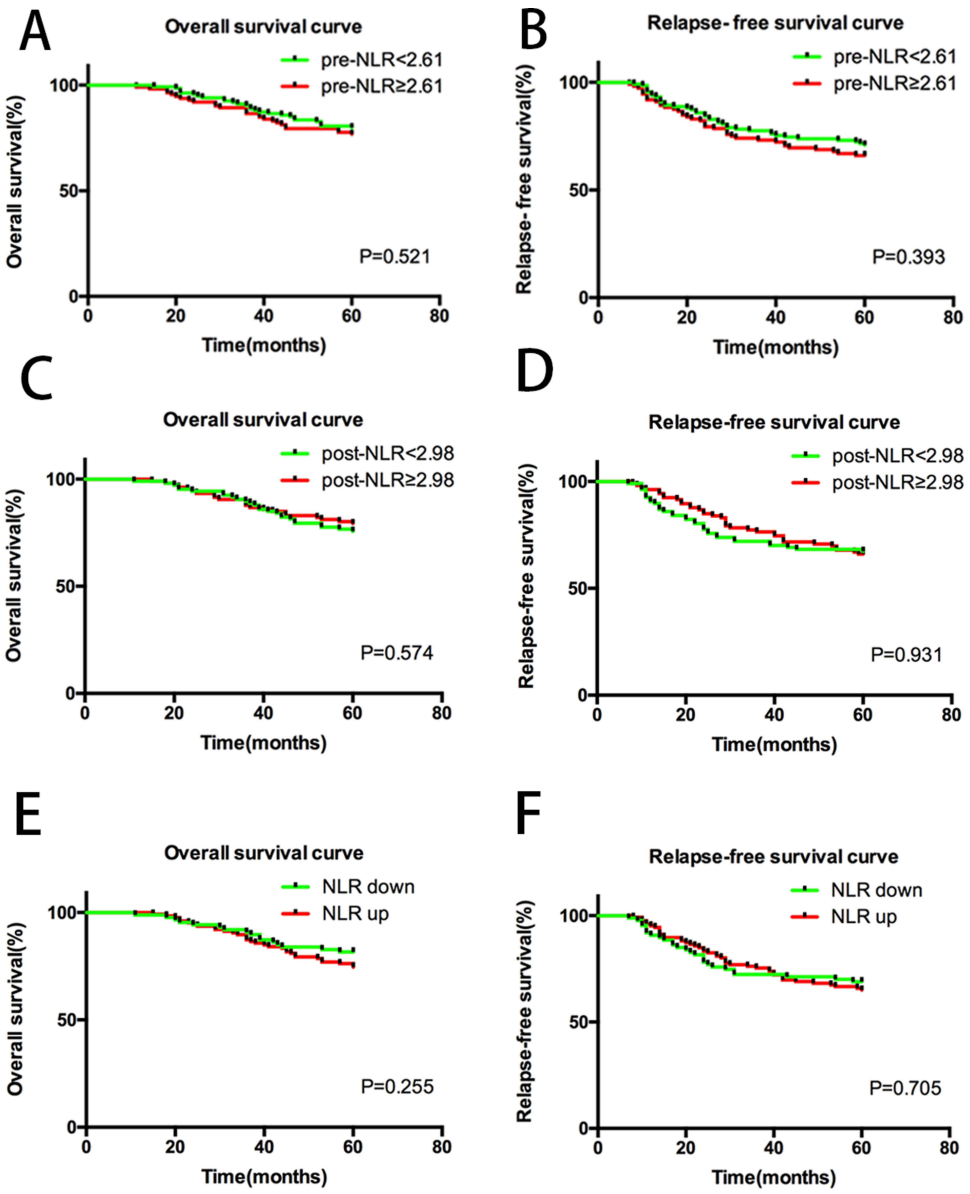


**Figure 1** Relationship between neutrophil-lymphocyte ratio (NLR) levels and prognosis of patients with colorectal cancer (CRC). (**A**) Associations of preoperative NLR levels with overall survival(OS). (**B**) Associations of preoperative NLR levels with relapse-free survival (RFS). (**C**) Associations of postoperative NLR levels with OS. (**D**) Associations of postoperative NLR levels with RFS. (**E**) Associations of NLR changes preoperatively and postoperatively with OS. (**F**) Associations of NLR changes preoperatively and postoperatively with RFS. *P*-values were calculated using the Mantel–Cox Log rank test.

tumour size, advanced pT stage, and positive lymphatic and distant metastasis.[30] A high pre-NLR was also considered a negative independent prognostic factor in rectal cancer,[31] but not in CRC.[32] Furthermore, a high pre-PLR was correlated with the survival of rectal cancer patients undergoing neoadjuvant chemoradiotherapy.[13] Jakubowska et al found that the post-NLR was associated with lymphatic metastasis and the quantity of metastatic lymph nodes, but was not considered a prognostic factor.[32] Ying et al found that preoperatively elevated NLR, but not PLR, could be an independent prognostic biomarker for CRC.[19] Meanwhile, NLR can be used to predict synchronous or metachronous colorectal cancer liver metastasis and OS in CRC patients.[33] Kocak et al explored the dynamic changes of NLR and PLR during chemotherapy in metastatic colorectal cancers, unfortunately, the results were negative.[34] In conclusion, the research emphasis and results of the NLR and PLR in CRC patients were inconsistent. Until now, no study has shown the predictive role of dynamic changes during operation in NLR and PLR in CRC patients, which worth to further explore.

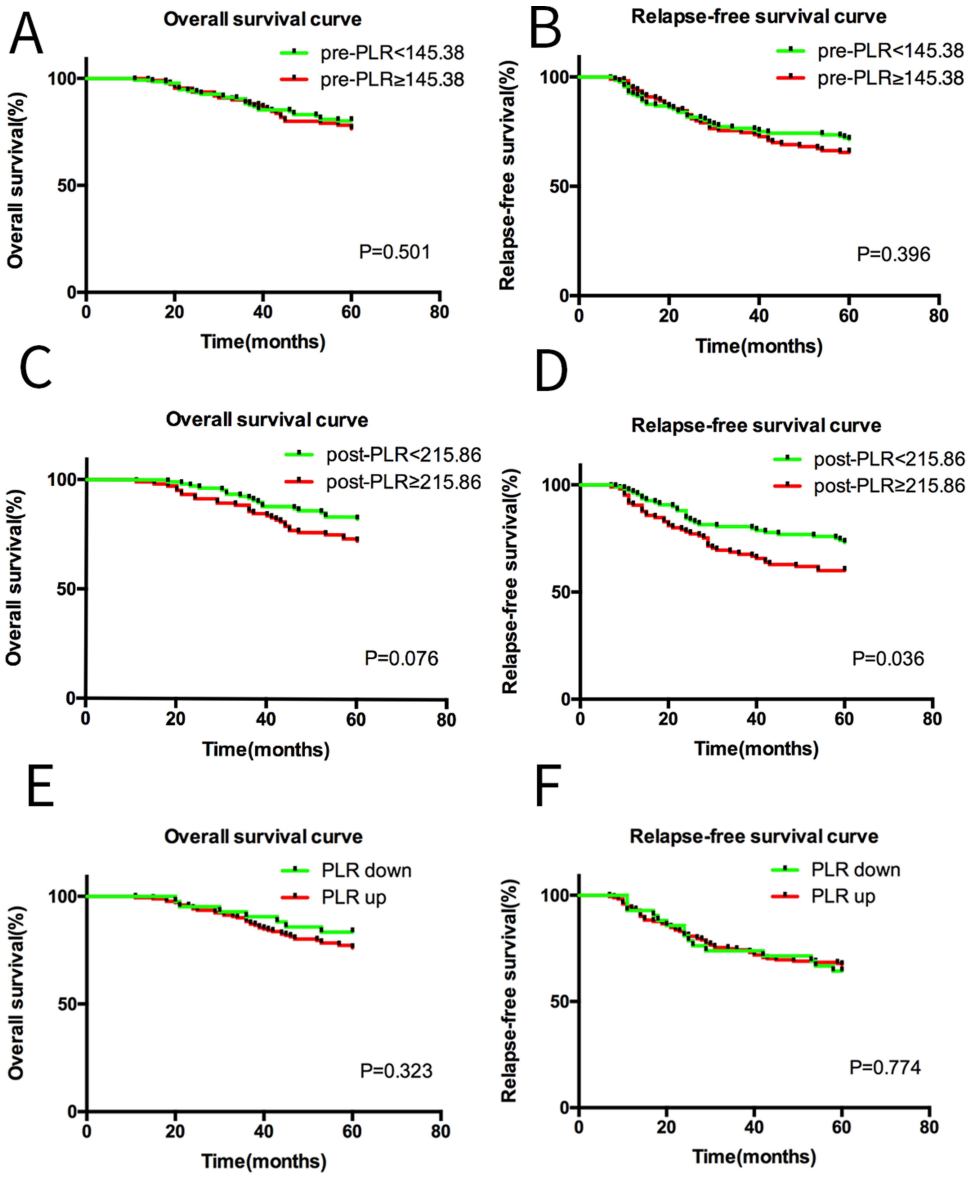


**Figure 2** Relationship between platelet-lymphocyte ratio (PLR) levels and prognosis of patients with colorectal cancer (CRC). (**A**) Associations of preoperative PLR levels with overall survival(OS). (**B**) Associations of preoperative PLR levels with relapse-free survival (RFS). (**C**) Associations of postoperative PLR levels with OS. (**D**) Associations of postoperative PLR levels with RFS. (**E**) Associations of PLR changes preoperatively and postoperatively with OS. (**F**) Associations of PLR changes preoperatively and postoperatively with RFS. *P*-values were calculated using the Mantel–Cox Log rank test.

In designing our study, we chose the blood result obtained after surgery (7–14 days) for each patient, as this could reduce the influence of surgery on inflammation markers. CEA and CA199 can be considered to point advanced stage in gastrointestinal cancer,[35] which related to poor survival. We found that the pre-NLR/PLR was related to the CEA and CA199 level, but undiscovered its correlation with CRC survival independent of stage. Moreover, our study found that NLR, PLR and their variation were related to age, sex, BMI, smoke and drink history, T stage and tumor stage, which could influence the prognosis of CRC. Nevertheless, Fu et al found that pre-NLR was significantly associated with CRC survival in stageI-II, and CEA level has poorer OS in stage III-□ CRC.[36] It may be owing to the different sample size of stage in different studies, which need further exploration.

In terms of the tumor location, we found that high pre/post NLR and pre-PLR were significantly correlated with left colon cancer, and their variations were significantly correlated with rectal cancer. The values of NLR and PLR were high in colon cancer than rectal cancers. It has been shown that tumours arise from the right colon, left colon, and rectum, and

**Table 3** Univariate and Multivariate Cox Regression Analysis for Overall Survival According to Clinicopathological Information and NLR, PLR

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | **HR (95% CI)** | ***P* value** | **HR (95% CI)** | ***P* value** |
| Age (<60 vs ≥60) | 0.847 (0.479–1.496) | 0.577 | | |
| Gender (male vs female) | 1.122 (0.648–1.942) | 0.683 | | |
| History of smoke (no vs yes) | 0.772 (0.402–1.483) | 0.437 | | |
| History of alcohol (no vs yes) | 1.069 (0.604–1.891) | 0.820 | | |
| BMI (<23.9 vs ≥23.9) | 0.777 (0.365–1.656) | 0.489 | | |
| CEA (<5 vs ≥5) | 0.817 (0.419–1.568) | 0.534 | | |
| CA199 (<37 vs ≥37) | 0.509 (0.191–1.356) | 0.081 | | |
| T stage (T1-2 vs T3-4) | 0.216 (0.113–0.415) | **0.005*** | | |
| Node status (negative vs positive) | 0.387 (0.215–0.649) | **<0.001***** | 0.382(0.184–0.751) | **0.006*** |
| Pre-NLR (<2.61 vs ≥2.61) | 0.839 (0.488–1.441) | 0.521 | | |
| Post-NLR (<2.98 vs ≥2.98) | 1.176(0.668–2.071) | 0.574 | | |
| NLR variation (down vs up) | 0.708(0.399–1.257) | 0.255 | | |
| Pre-PLR (<145.38 vs ≥145.38) | 0.832(0.484–1.430) | 0.501 | | |
| Post-PLR (<215.86 vs ≥215.86) | 0.596(0.338–1.050) | 0.076 | | |
| PLR variation (down vs up) | 0.670(0.332–1.354) | 0.323 | | |

**Notes**: Statistically significant difference: *p<0.05, ***p<0.001.

**Table 4** Univariate and Multivariate Cox Regression Analysis for Relapse-Free Survival According to Clinicopathological Information and NLR, PLR

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | **HR (95% CI)** | ***P* value** | **HR (95% CI)** | ***P* value** |
| Age (<60 vs ≥60) | 1.038 (0.646–1.670) | 0.875 | | |
| Gender (male vs female) | 1.224 (0.777–1.926) | 0.391 | | |
| History of smoke (no vs yes) | 0.843 (0.515–1.380) | 0.480 | | |
| History of alcohol (no vs yes) | 0.967 (0.598–1.563) | 0.890 | | |
| BMI (<23.9 vs ≥23.9) | 0.998 (0.553–1.799) | 0.994 | | |
| CEA (<5 vs ≥5) | 0.657(0.374–1.084) | 0.098 | | |
| CA199 (<37 vs ≥37) | 0.629 (0.629–1.356) | 0.158 | | |
| T stage (T1-2 vs T3-4) | 0.235 (0.138–0.401) | **<0.001***** | 0.397 (0.157–1.002) | **0.050*** |
| Node status (negative vs positive) | 0.466 (0.282–0.707) | **<0.001***** | 0.469 (0.271–0.811) | **0.007*** |
| Pre-NLR (<2.61 vs ≥2.61) | 0.824 (0.526–1.292) | 0.393 | | |
| Post-NLR (<2.98 vs ≥2.98) | 1.021(0.641–1.625) | 0.931 | | |
| NLR variation (down vs up) | 0.912(0.568–1.465) | 0.705 | | |
| Pre-PLR (<145.38 vs ≥145.38) | 0.825(0.527–1.293) | 0.396 | | |
| Post-PLR (<215.86 vs ≥215.86) | 0.607(0.381–0.968) | **0.036*** | 0.539 (0.312–0.934) | **0.027*** |
| PLR variation (down vs up) | 1.086(0.606–1.948) | 0.082 | | |

**Note**: Statistically significant difference: *p<0.05, ***p<0.001.

each has distinct biological and molecular characteristics.[37,38] Recent studies show that right colon cancer seem to have a worse survival comparing with left colon cancer,[39] which owing to the more complex lymphatic system causing a cancer-related inflammatory response.[40] Furthermore, the potential for bias exists in the majority of studies that encompassed colon and rectal cancer according to the different treatment and prognosis.[41] This interesting fact can explain our results, we believe that the application of pre/post NLR, PLR and their variation could be useful in different location cancers.

We further explored the impact of clinicopathologic parameters, NLR, PLR and their variation for CRC survival. The results showed that high post-PLR showed significant association with shorter RFS and OS in univariate analysis.

Furthermore, post-PLR is an independent risk factor affecting the patients' RFS. However, we did not detect that pre-NLR/post-NLR, pre-PLR and their variations had a significant relationship with the prognosis of CRC patients. Xie et al found that the higher variation of NLR and PLR stratified by four groups tended to have worse RFS and OS.[20] In our study, we divided the variation into up and down groups, which may explain the difference. Moreover, pre-NLR, pre-PLR and NLR variation were significantly correlated with T stage and tumor stage, which are factors that result in worse prognosis. Our study also proved T stage and tumor stage were significantly related to OS and RFS of CRC. All of the above indicated that post-PLR may be a good prognostic factor for CRC patients.

In this study, we used the median value as the cut-off point for NLR and PLR levels. This decision was made for two reasons. Firstly, we found that there is no unified method in the literature to determine the cut-off values, with various studies reporting mean, median, or ROC curve-based values. Secondly, after attempts to use ROC curves to determine the cut-off values, we found it to be unsuccessful, leading us to ultimately choose the median value. However, About NLR and PLR, a predetermined threshold has not been proposed and will necessitate additional multicentre, international, large-scale investigations.

In summary, elevated post-PLR demonstrates certain prognostic significance in individuals diagnosed with CRC, and the utilization of peripheral blood as a supplementary indicator for tumor prognosis is advantageous due to the test's convenience and reproducibility. Nevertheless, the outcomes of this study conducted at a single center necessitate additional corroborative evidence from future multicenter, large-scale investigations. In addition, this study focused on determining the causes of death related to specific diseases to more accurately assess the direct effects of treatment. However, it did not comprehensively consider all-cause mortality. Furthermore, the data analyzed was limited to the period from 2008 to 2011. Future endeavors will include expanding the database, including the most recent data, and further exploring all-cause mortality to improve clinical recommendations.

## Data Sharing Statement

All data produced or examined in this study have been incorporated into the published article. The primary data were acquired from the corresponding authors upon request.

## Ethics Statement

Ethical approval to report this case was obtained from the Medical Ethics Committee of Dongyang Hospital, Wenzhou Medical University (Approval No.: Dongrenyi 2022-YX-309). This study is in line with the Helsinki Declaration of the World Medical Association. The study only collected routine blood test results from patients, and personal information of patients was kept confidential. According to local legislation and institutional requirements, written informed consent for participation was not required from the participants or their legal guardians/next of kin.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare no conflicts of interest.

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