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Propensity score analysis of recurrence for neutrophil-to-lymphocyte ratio in colorectal cancer

Alpha I. Balde, MD, MS, FWAMS,[a] Suzhen Fang, PhD,[a] Linyun He, MD,[a] Zhai Cai, MD, PhD,[a] Shuai Han, MD, PhD,[a] Weiwei Wang, MD,[a] Zhou Li, MD, PhD,[a,] and Liang Kang, MD, PhD[b,**]*

[a] *Department of General Surgery, Zhujiang Hospital, Southern Medical University/The Second School of Clinical Medicine, Southern Medical University, Guangdong Province, China*

[b] *Department of Colorectal Surgery, The Sixth Affiliated Hospital of Sun Yatsen University, Guangzhou, China*

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ABSTRACT

Background: The perioperative serum neutrophil-to-lymphocyte ratio (NLR) has been proposed to predict adverse prognosis in colorectal cancer (CRC). However, its interpretation remains unclear. The present study aimed to clarify the prognostic value of NLR in predicting survival among CRC patients.

Materials and methods: A single-centre, retrospective, propensity score–matched study of adenocarcinoma patients who underwent D3 lymphadenectomy via laparoscopic or open surgery between 2010 and 2016 was conducted. A cutoff of 3.5 was used based on the receiver operating characteristic curve. To overcome selection biases, we performed a 1:1 match using six covariates.

Results: The high-preoperative NLR group had a higher recurrence rate than the low group ($P < 0.001$). Univariate analysis showed that increased NLR ($P < 0.001$), N1 ($P = 0.016$), and N2 ($P < 0.001$) were associated with worse recurrence-free survival (RFS). Multivariate analysis showed that N2 (hazard ratio [HR], 2.492; $P = 0.008$) was an adverse prognostic factor for RFS. Univariate analysis for overall survival (OS) revealed that high perioperative NLR ($P = 0.001$), N1 ($P = 0.01$), N2 ($P < 0.001$), and distant metastasis ($P < 0.001$) were adverse prognostic factors. Subsequent multivariate analysis showed that M1 (HR, 3.973; $P < 0.001$) and N2 (HR, 2.381; $P = 0.013$) were highly adverse factors for OS. Clinical assessments performed during a 21.14 (±16.20)-mo follow-up revealed that OS ($P = 0.001$) and RFS ($P < 0.001$) were worse in the high-perioperative group than in the low group between the matched groups.

Conclusions: An elevated preoperative NLR is a strong predictor of worse RFS and OS in CRC patients.

A.I.B. and S.F. contributed equally to this work, including the design of the study and the preparation of the manuscript, and should be considered co-first authors.

* *Corresponding author*. Department of General Surgery, Zhujiang Hospital, Southern Medical University, Guangzhou, Guangdong Province 510282, China. Tel./fax: +86 020 62782397.

** *Corresponding author*. Department of Colorectal Surgery, The Sixth Affiliated Hospital of Sun Yatsen University. Tel./fax: +86 020 62782397.

E-mail addresses: gzlizhou@smu.edu.cn (Z. Li), eonkang@163.com (L. Kang).

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Introduction

Colorectal cancer (CRC) remains the third most common cancer in North America and Europe.[1] The incidence of CRC in China has increased in the past 3 decades with the country's rapid economic development and improvements in living conditions.[2,3] Despite the development of surgical procedures and chemotherapy to improve the patients' quality of life, a considerable number of patients experience relapse after curative resection, which leads to a high mortality rate from CRC.

Because the first study on the association between inflammation and cancer was performed in the 19th century by Rudolf Virchow, increasing evidence has shown that the neutrophil-to-lymphocyte ratio (NLR) can be used as a prognostic factor in patients with several types of cancer.[1,4-15] The preoperative NLR has been proposed as a useful prognostic variable because of its easy accessibility, low cost, and the ability to collect data routinely during early clinical investigation and follow-up. These factors taken together with information from pathological reports may yield valuable information regarding prognosis and recurrence.

Previous studies have reported various statistically significant associations between preoperative NLR and overall survival (OS),[16-18] although one study failed to demonstrate such an association.[19] Associations between NLR and recurrence-free survival (RFS) have also been reported,[17,20-22] although two studies did not demonstrate cancer-specific survival. Another study identified a multivariate association between NLR and cancer-specific survival despite the lack of bivariate association.[16] Two others studies[20,23] identified the impact of NLR but focused on stage II CRC. Currently, most studies aiming to elucidate the relationship between NLR and postoperative outcomes are retrospective, and this type of study has the distinct limitation of nonmatched subjects, resulting in selection bias and confounding factors. The difficulty to control for an entire potential variable can result in selection bias that could influence the veracity and reliability of the conclusions.

To minimize the lack of evidence, some researchers have adopted a propensity score matching (PSM) approach, which has been utilized to overcome selection bias and increase the strength of the evidence in retrospective studies.[24] The best way to estimate the exposure effect without increasing bias is to include all variables that are related to outcomes regardless of the exposure. Therefore, we conducted the present study using PSM to determine the association between preoperative NLR and tumor recurrence and OS after CRC resection.

Materials and methods

A retrospective review in a maintained electronic database was performed to identify 280 adenocarcinoma patients who underwent D3 lymphadenectomy between 2010 and 2016 at our institution. However, only 200 patients met our criteria and were enrolled in this study. The inclusion criteria were classic colorectal adenocarcinoma diagnosed via colonoscopy and confirmed via pathology, D3 lymphadenectomy as the treatment method, and pathologically confirmed stage I to IV CRC based on the criteria set by the American Joint Committee on Cancer (AJCC). The exclusion criteria were as follows: preoperative chemotherapy ($n = 25$), bowel obstruction ($n = 10$) or bowel perforation (which can lead to emergency surgery) ($n = 5$), palliative surgery ($n = 20$), and failure to follow-up ($n = 20$).

The flow diagram for study subject screening and grouping is shown in Figure 1. Patients underwent detailed laboratory evaluations, including a blood count (1 wk before surgery and 3 and 6 mo after surgery), medical history review, and computed tomography of the abdomen. Standard demographic and clinicopathological data were collected, including gender, age, body mass index (BMI), symptoms, tumor location and size, and pathological results. Data from the last follow-up, including tumor recurrence and death, were collected and analyzed. We used the seventh pathological tumor node metastasis (TNM) staging system of the AJCC for tumor staging; nodal staging was performed according to the number and distribution of lymph node metastasis (LNM). Patients were grouped into N0 (no metastasis), N1 (one to three nodes with metastasis), and N2 groups (more than four nodes with metastasis). All patients were reviewed during multidisciplinary team conferences that included surgical oncologists, pathologists, and medical oncologists before surgery. This study was reviewed and approved by the Ethics Committee of Zhujiang Hospital.

Propensity score matching

To overcome selection biases, we performed a 1:1 match for each patient using six covariates—age, tumor size, BMI, Charlson Comorbidity Index (CCI), tumor location, and gender—to generate propensity scores. A total of 115 patients with an NLR <3.5 and 85 patients with an NLR ≥ 3.5 were balanced into 85 pairs. The OS and disease free survival rates were compared between the two matched groups. The best way of estimating the exposure effect without increasing the bias is to include all variables that are related to outcomes regardless of the exposure.

Statistical analyses

Continuous variables are presented as the mean $\pm$ standard deviation or median (interquartile range) depending on their normality, and categorical variables are presented as frequencies and percentages. The differences between clinicopathological characteristics grouped by NLR were compared using the Pearson χ^2 test or Fisher's exact test for categorical variables and Student's *t*-test or Wilcoxon rank sum test for continuous variables. Survival time curves and 5-y OS rates were determined by the Kaplan-Meier method with univariate analysis; differences were compared using the log-rank test. The Cox proportional hazard model of multivariate analysis permits calculation of independent prognostic factors. Variables with a univariate analysis $P < 0.1$ were included in the multivariate analysis. Each test was two tailed. Data management and statistical analyses were performed using the SPSS statistical program (SPSS 20.0, Chicago, Illinois). PSM was