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Retrospective Study

Preoperative neutrophil-to-lymphocyte ratio as a predictor of postoperative symptomatic anastomotic leakage in elderly patients with colon cancer: A multicenter propensity score-matched analysis

Wang CY *et al*. A multicenter study of AL

Abstract

BACKGROUND

The neutrophil-to-lymphocyte ratio (NLR), a composite inflammatory biomarker, was associated with the prognosis in patients with colorectal tumors. However, whether the NLR can be used as a predictor of symptomatic postoperative anastomotic leakage (AL) in elderly patients with colon cancer is unclear.

AIM

To assess the role of the NLR in predicting the occurrence of symptomatic AL after surgery in elderly patients with colon cancer.

METHODS

Data from elderly colon cancer patients who underwent elective radical colectomy anastomosis at three centers between 2018 and 2022 were retrospectively analyzed. Receiver operating characteristic curve analysis was performed to determine the best predictive cutoff value for the NLR. Twenty-two covariates were matched using a 1:1 propensity score matching method, and univariate and multivariate logistic regression analyses were used to determine risk factors for the development of postoperative AL.

RESULTS

Of the 577 patients, 36 (6.2%) had symptomatic ALs. The optimal cutoff value of the NLR for predicting AL was 2.66. After propensity score matching, the incidence of AL was significantly greater in the ≥ 2.66 NLR subgroup than in the < 2.66 NLR subgroup (11.5% *vs* 2.5%; $P = 0.012$). Univariate logistic regression analysis revealed statistically significant differences between intraoperative and intra 2 d postoperative blood transfusion, preoperative albumin concentration, preoperative prognostic nutritional index, and preoperative NLR and AL occurrence ($P < 0.05$); multivariate logistic regression analysis revealed that an NLR ≥ 2.66 [odds ratio (OR) = 5.51; 95% confidence interval (CI): 1.50-20.26; $P = 0.010$] and intraoperative and intra 2 d postoperative blood transfusion (OR = 2.52; 95%CI: 0.88-7.25; P = 0.049) were identified as risk factors for the occurrence of symptomatic AL.

CONCLUSION

A preoperative NLR ≥ 2.66 and intraoperative and intra 2-d postoperative blood transfusions were associated with a higher incidence of postoperative symptomatic AL in elderly patients with colon cancer. The preoperative NLR has predictive value for postoperative symptomatic AL after elective surgery in elderly patients with colon cancer.

Key Words: Age; Colon cancer; Anastomotic leak; Neutrophil-to-lymphocyte ratio; Propensity score-matched

Wang CY, Li XL, Ma XL, Yang XF, Liu YY, Yu YJ. Preoperative neutrophil-to-lymphocyte ratio as a predictor of postoperative symptomatic anastomotic leakage in elderly patients with colon cancer: A multicenter propensity score-matched analysis. *World J Gastrointest Surg* 2024; In press

Core Tip: The relationship between the preoperative neutrophil-to-lymphocyte ratio (NLR) and postoperative symptomatic anastomotic leakage (AL) in elderly patients with colon cancer was investigated in this study primarily. The findings showed that a higher preoperative NLR corresponded to a greater incidence of postoperative symptomatic AL. Moreover, in elderly patients with colon cancer after elective surgery, the preoperative NLR may serve as a predictor of postoperative symptomatic AL.

INTRODUCTION

Older patients with colon cancer are becoming more common as the global elderly population continues to grow[1]. Increasing age also increases the risk of complications during and after colorectal surgery. Anastomotic leakage (AL) is a serious complication after colorectal surgery and may increase the risk of postoperative death in elderly patients[2] and severely affect the prognosis. Therefore, early prediction of the probability of AL occurrence and timely preventive measures are important for ensuring surgical safety and patient prognosis.

In recent years, various inflammatory response markers, such as the C-reactive protein-to-albumin (ALB) ratio, platelet-to-lymphocyte ratio, and neutrophil-to-lymphocyte ratio (NLR), have been shown to be highly useful for predicting postoperative complications and prognosis in patients with colorectal cancer[3-5]. The effect of elevated peripheral blood NLRs on postoperative complications, cancer prognosis and patient survival related to colorectal cancer has been confirmed by previous studies[6-9]. However, there are few data related to the role of the NLR in predicting the postoperative occurrence of AL in elderly patients with colon cancer. Therefore, in this study, we evaluated the role of the preoperative NLR as a predictive marker for symptomatic AL after radical resection in elderly patients with colon cancer.

MATERIALS AND METHODS

Patients and data collection

Clinical data from elderly patients (≥ 65 years old) with primary colon cancer who underwent radical colon cancer surgery at the First Hospital of Lanzhou University, the Second Hospital of Lanzhou University or Gansu Provincial People's Hospital from January 2018 to December 2022 were retrospectively collected. The clinicopathologic characteristics of these patients included the following: Basic information including sex, age, body mass index (BMI), smoking status, history of abdominal surgery, nonsteroidal drug use, hypertension, diabetes mellitus, pulmonary disease and neoadjuvant chemotherapy; surgical information including the American Society of Anesthesiologists (ASA) score, surgical approach (open/laparoscopic/robotic), anastomotic approach (end-to-end/end-to-lateral/lateral-to-lateral), and intraoperative and 2-d postoperative blood transfusion; and tumor pathological characteristics, including tumor location, T-stage, N-stage, tumor diameter, and serological examination, including preoperative neutrophil count, preoperative lymphocyte count, preoperative hemoglobin, preoperative serum ALB concentration and carcinoembryonic antigen (CEA). The relevant preoperative serological indices were collected within 1 wk before surgery. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Medical Ethics Committee of the First Hospital of Lanzhou University (leading center of the study, approval No. LDYYLL-2023-363). The requirement for informed consent was waived by the Medical Ethics Committee of the First Hospital of Lanzhou University due to the retrospective nature of the study and the absence of any risk.

Definition

The diagnosis of AL includes three main aspects: Clinical symptoms, drainage fluid characteristics, and abdominal computed tomography (CT) scans. Patients with clinical symptoms (such as fever) and signs of peritonitis underwent CT for further diagnosis. AL is classified as asymptomatic (grade A) or symptomatic (grades B and C) based on severity and clinical signs. Symptomatic AL requires aggressive therapeutic intervention (such as drainage and irrigation, antibiotics, endoscopic surgery, *etc.*) or secondary surgical treatment and is diagnosed if one of the following manifestations is present: (1) Abnormal fluid such as pus and intestinal contents draining from the postoperative abdominal drainage tube; or (2) Fluid or gas collection around the anastomosis seen on abdominal CT or contrast enema. The follow-up for AL was within 15 d postoperatively. NLR = neutrophil count (10^9/L)/lymphocyte count (10^9/L), prognostic nutritional index (PNI) = serum ALB (g/L) + 5 × lymphocyte count (10^9/L).

Inclusion and exclusion criteria

The inclusion criteria were as follows: ≥ 65 years of age, pathologically confirmed primary colon cancer, elective radical resection of colon cancer with one-stage anastomosis, and complete clinical and pathological data. The exclusion criteria were as follows: Patients with grade A AL without specific clinical management, patients with intraoperative prophylactic stoma, patients with postoperative pathologic results showing M1 staging, and patients with incomplete postoperative data.

Propensity score matching and statistical analysis

A database was created in Excel, a propensity score-matched (PSM) analysis was performed in RStudio (2023.03.1+446), and the data analysis was performed in SPSS 26.0 software, with the significance set at $P < 0.05$. In all cohorts, the normality of the continuous variables was assessed with the Shapiro-Wilcoxon test, and continuous variables with a normal distribution are presented as the mean ± SD. Continuous data not conforming to a normal distribution are presented as the median (interquartile spacing) and were further analyzed by the independent Student's t test or Mann-Whitney U test. Categorical variables are expressed as the frequency (percentage), and comparisons were made using the χ^2 test, Fisher's exact test, or rank sum test. Receiver operating characteristic (ROC) curve analysis was used to identify the best critical value for the NLR prediction of AL.

A 1:1 PSM analysis was performed using the nearest neighbor method. The caliper value was set to 0.2 times the standard deviation of the propensity score. To reduce selection bias and confounding factors, logistic regression analysis was used to calculate propensity scores for age, sex, BMI, smoking history, abdominal surgery history, nonsteroidal drug use, hypertension, diabetes mellitus, lung disease, neoadjuvant chemotherapy, tumor location, ASA classification, surgical approach, anastomosis, intraoperative and intra 2-d postoperative blood transfusion, T stage, N stage, tumor diameter, CEA, preoperative hemoglobin, preoperative ALB, and preoperative PNI. The standardized mean difference (SMD) was measured to determine the balance between the two groups before and after propensity score matching. An SMD of < 0.2 indicated that an adequate balance was achieved between the two groups. After matching, covariates with $P < 0.05$ in the univariate logistic regression analysis were entered into the multivariate logistic regression analysis to determine the risk factors for the occurrence of postoperative symptomatic ALs.

RESULTS

Study population and clinical characteristics

The study population enrollment process is shown in Figure 1. A total of 577 patients were ultimately included in the present study, 36 of whom (6.2%) developed symptomatic AL. The basic, preoperative, intraoperative and postoperative data of the patients are shown in Table 1. Sex, intraoperative and intra 2-d postoperative blood transfusion, N stage, preoperative ALB level, preoperative NLR and preoperative PNI were significantly different between the AL group and the group without AL ($P < 0.05$).

NLR

The continuous variable NLR was used as the test variable, and the dichotomous variable AL was used as the outcome variable. ROC curve analysis revealed that the area under the curve for the preoperative NLR was 0.683 [95% confidence interval (CI): 0.612-0.755]. For all patients, the sensitivity (0.861), specificity (0.543) and Youden index (0.405) of the NLR in predicting the occurrence of postoperative symptomatic AL in elderly patients undergoing radical resection for colon cancer were highest when the NLR was 2.66 (Figure 2).

PSM based on the optimal cutoff value for the NLR

Of the 577 patients, 295 (51.1%) had an NLR < 2.66, and 282 (48.9%) had an NLR ≥ 2.66 (Table 2). After 1:1 PSM, 122 matched pairs were generated, and patients were divided into NLR < 2.66 (n = 122) and NLR ≥ 2.66 (n = 122) groups (Table 2). All covariates were well balanced with an SMD less than 0.2, and the difference between the NLR < 2.66 and NLR ≥ 2.66 groups was not statistically significant (Table 2). Before (1.4% *vs* 11.3%, $P < 0.001$) (Figure 3A) and after (2.5% *vs* 11.5%, $P = 0.012$) (Figure 3B) PSM, the incidence of symptomatic AL was significantly lower in the NLR < 2.66 subgroup than in the NLR ≥ 2.66 subgroup.

Analysis of risk factors associated with AL after PSM

According to the univariate logistic regression analysis, intraoperative and intra 2 d postoperative blood transfusion, preoperative ALB concentration, preoperative PNI and preoperative NLR were associated with the occurrence of postoperative AL (Table 3). Multivariate logistic regression analysis revealed that intraoperative blood transfusion and postoperative blood transfusion with 2 d [odds ratio (OR) = 2.52; 95%CI: 0.88-7.25; P = 0.049] and a high NLR (≥ 2.66) (OR = 5.51; 95%CI: 1.50-20.26; P = 0.010) were significantly associated with the occurrence of symptomatic AL after radical resection for colon cancer in elderly individuals.

DISCUSSION

The main finding of this study was that the incidence of postoperative symptomatic AL in 577 elderly patients who underwent radical colon cancer resection was 6.2%. The optimal cutoff value of the preoperative NLR for predicting symptomatic AL after radical colon cancer resection was determined by the ROC curve to be 2.66. After PSM, the incidence of AL was significantly greater in the ≥ 2.66 NLR subgroup than in the < 2.66 NLR subgroup, and a preoperative NLR ≥ 2.66 was significantly associated with the occurrence of AL after radical colon cancer resection. In addition, the incidence of postoperative symptomatic AL was greater in elderly colon cancer patients who were transfused intraoperatively and within 2 d postoperatively than in those in the nontransfused group.

When inflammation and infection occur, neutrophils rapidly migrate to the site of inflammation, responding first to tissue damage and playing a key role in the host's resistance to infection[10]. Elevated peripheral blood neutrophil levels are characteristic of pathogenesis and are a hallmark of the inflammatory response. However, persistent neutrophilic infiltration is a hallmark of chronic inflammation and leads to tissue damage[11]. Furthermore, in one study, the number of lymphocytes involved in the immune state decreased with the progression of inflammatory disease, and this increase in lymphocyte count was a cause of decreased cellular immune function[12]. That is, cellmediated immune responses are strongly dependent on lymphocytes. The NLR is an easily accessible marker identified as a good indicator of systemic inflammatory status in the general population[13]. The NLR has a better ability to predict systemic inflammation and prognosis than does the leukocyte, neutrophil or lymphocyte count alone[14,15].

Previous studies have suggested that the post-colorectal AL may be associated with the NLR. First, Josse *et al*[16] reported that a preoperative NLR ≥ 2.3 was significantly associated with postoperative complication rates and that the incidence of AL increased non significantly. Subsequently, Miyakita *et al*[17] showed that a preoperative NLR ≥ 2.21 was significantly associated with postoperative AL in patients with rectal cancer (OR = 4.51; P = 0.0329). In addition, Paliogiannis *et al*[9] showed that a higher NLR was associated with the occurrence of postoperative AL in patients undergoing elective colorectal surgery. According to our findings, high preoperative NLRs are a risk factor for the development of symptomatic ALs after radical resection in elderly patients with colon cancer. The OR for the occurrence of symptomatic AL in the high NLR subgroup (≥ 2.66) was 5.51, indicating that the preoperative NLR may help to predict the risk of postoperative symptomatic AL in elderly patients with colon cancer before surgery, which could allow patients to take effective preventive measures. However, the predictive role of inflammatory indicators should be validated in larger clinical studies. In particular, for more effective prevention of AL occurrence, prevention methods should be explored through interventional prospective studies with risk stratification based on preoperative NLR values.

This study revealed that intraoperative and postoperative blood transfusions within 2 d were associated with the occurrence of postoperative symptomatic AL, which is consistent with previous findings[18,19]. Most of the transfusions were due to excessive surgical blood loss or severe anemia. Hemoglobin is associated with blood flow and oxygenation at the anastomotic margin and is an important factor in anastomotic healing. However, blood transfusion may lead to impaired blood rheology[20], which adversely affects microcirculation; transfusion may also induce immunosuppression[21], which increases the risk of infectious diseases around the anastomosis. Therefore, careful blood transfusion intraoperatively and within 2 d postoperatively may be an intervention to reduce the occurrence of postoperative AL in elderly patients undergoing radical colon cancer resection.

This study has several limitations. First, because this study was retrospective, we could not assess all the covariates that might have influenced the analysis. Therefore, our study may be affected to some extent by unavoidable selection bias. However, we performed a PSM analysis to minimize bias. Second, preoperative NLR values may be influenced by patients' infectious comorbidities, and there is no standard optimal cutoff value for the NLR. Therefore, these findings should be extended with caution. Third, further studies are needed to validate the relationship between the preoperative NLR and other postsurgical symptomatic ALs, as these parameters have not been specifically evaluated.

CONCLUSION

Symptomatic AL was associated with a high preoperative NLR and intraoperative and intra 2-d postoperative blood transfusions. In elderly patients who underwent radical colon cancer resection, a preoperative NLR ≥ 2.66 was significantly associated with the likelihood of postoperative symptomatic AL occurrence. We recommend the preoperative use of the NLR as a predictive marker for the risk of AL for better preoperative evaluation and selection of the best surgical and care plan for elderly patients undergoing elective radical colon cancer resection.

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