

Neutrophil-lymphocyte ratio as a predictive factor for tumor staging in colorectal cancer

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Received: 06.05.2013

Accepted: 06.08.2013

Published Online: 31.03.2014

Printed: 30.04.2014

Background/aim: In the preoperative period, simple methods to identify the tumor stage of colorectal cancer patients are needed. In recent years, the neutrophil-lymphocyte ratio (NLR) has been used as a predictive parameter for systemic inflammatory response in many different clinical entities. This study aims to determine if the NLR predicts the tumor stage in colorectal cancer patients in the preoperative period.

Materials and methods: A total of 206 patients diagnosed with colorectal cancer and admitted for surgical treatment over a 6-year period were identified from a retrospectively maintained database. NLR was calculated from preoperative full blood counts. NLRs were compared with the tumor stages as determined in histopathological reports and scanning tests to determine the extent of metastasis.

Results: We found NLRs to be statistically higher in patients with T3 and T4 tumors than in patients with T1 and T2 tumors (mean: 5.261 vs. 4.499, respectively, $P = 0.010$). Similarly, we found statistically higher NLR values in the N1 and N2 groups than in the N0 group (mean: 6.597 vs. 4.501, respectively, $P < 0.001$). Additionally, NLRs were statistically higher in M1 patients than in M0 patients (mean: 8.261 vs. 5.158, respectively, $P = 0.004$).

Conclusion: In the preoperative period, NLR was found to be a valuable predictive parameter for tumor staging in patients with colorectal cancer, thus informing us as to the kind of tumor we will meet when we open the abdomen.

Key words: Systemic inflammatory response syndrome, colorectal neoplasms, neoplasm staging

1. Introduction

The response of the body to a cancer has many parallels to inflammation. German pathologist Rudolf Virchow first found inflammatory cells in tumors 150 years ago (1). Lately the human inflammatory response to tumors has been more frequently investigated (2). Higher neutrophil-lymphocyte ratios (NLRs) have been accepted as a poor prognostic criterion in various cancer patients (3). In the present study we investigated the potential association between the preoperative NLR and the colorectal cancer (CRC) stage. In the preoperative preparation period, many laboratory and radiological test possibilities exist. First, any surgeon wants to know the invasion degree of the tumor before the operation without doubt. Thus, surgical planning would be more relevant. NLR is an inexpensive, simple, and noninvasive test, and it may be helpful for this purpose.

2. Materials and methods

After approval from the local ethics committee, we examined 288 patients who were diagnosed with CRC and

received for surgical treatment from January 2006 to January 2011. Peripheral white blood counts and percentages of neutrophils and lymphocytes before surgery were obtained from the database retrospectively, and the ratio of neutrophils to lymphocytes was directly calculated from the full blood count. Exclusion criteria included infectious signs determined at 1 week before admittance to the hospital, the presence of coronary artery or cerebrovascular disease, known additional malignancies, the presence of hematological problems or immunosuppressant conditions, a blood transfusion 1 month prior, and urgent conditions due to tumor occlusion. A total of 82 patients were excluded from the study. Hospital records of the remaining 206 patients were analyzed. Age, sex, family history, tumor localization, intraoperative findings and surgical procedure, preoperative NLR, and postoperative histopathology reports were assessed prior to enrollment.

2.1. Statistical analysis

Data analysis was performed using SPSS 17 for Windows. The Levene test was used for the evaluation of homogeneity

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of variances. Data were shown as mean ± standard deviation or median (min–max) where applicable. The differences between groups were compared by using the Student t-test or Mann–Whitney U test where appropriate. Categorical data were analyzed by the Pearson chi-square test where appropriate. A P-value of less than 0.05 was considered statistically significant.

The cutoff values of parameters for discrimination of the groups were determined using receiver operating characteristic (ROC) analysis. At each value, the sensitivity and specificity for each outcome under study were plotted, thus generating an ROC curve. The recommended cutoff value of the NLR for lower or higher stages of CRC was decided using ROC curve analyses. For T1–2/T3–4 analysis, the recommended cutoff value of the NLR was based on the most prominent point on the ROC curve for sensitivity (66.20%) and specificity (52.9%). Because these 2 parameters indicated a cutoff value of 2.38, the recommended NLR cutoff value was defined as 2.38. The area under the ROC curve was 0.275 (95% CI: 0.184–0.367, P < 0.001). For N0/N1–2 analysis, the recommended cutoff value of the NLR was based on the most prominent point on the ROC curve for sensitivity (66%) and specificity (66%). Because these 2 parameters indicated a cutoff value of 3.24, the recommended NLR cutoff value was defined as 3.24. The area under the ROC curve was 0.327 (95% CI: 0.252–0.402, P < 0.001).

3. Results

A total of 206 patients were included the study. The mean age was 60.9 years (range: 24–88), and there were 79 (38.3%) women and 127 men (61.7%). Family histories were positive in 11 (5.3%) of these patients. The most common localization site was the right colon (47 patients, 22.8%). There were synchronic localizations and multiple tumors in 7 (3.4%) patients (Table 1). Twenty patients died postoperatively within 6 months. TNM staging of the

Table 1. Tumor localizations of the patients with colorectal cancer.

Localization	n	%
Right colon	47	22.8
Transverse colon	5	2.4
Left colon-sigmoid colon	40	19.4
Rectum	104	50.5
Anal canal	3	1.5
Synchronic multiple	7	3.4
Total	206	100

patients according to the American Joint Committee of Cancer Staging System is given in Table 2.

In terms of tumor invasion depth, we found NLRs statistically higher in patients with T3 and T4 tumors than in patients with T1 and T2 tumors (mean: 5.261 vs. 4.499, respectively, P = 0.010). When we examined NLRs according to the lymph node involvement, we found statistically higher values in the N1 and N2 groups than in the N0 group (mean: 6.597 vs. 4.501, respectively, P < 0.001). However, there was no statistically important difference between the N1 and N2 groups. From the view of distant organ metastasis, NLRs were statistically higher in M1 patients than M0 patients (mean: 8.261 vs. 5.158, respectively, P = 0.004) (Table 3).

4. Discussion

Recently, the association of inflammation and cancer, and the effects of this association in prognosis, have been more thoroughly investigated. Balkwill and Mantovani (1) made an analogy of genetic damage and inflammation as the “match that lights the fire” and the “fuel that feeds the flames”. White blood cell counts and albumin and C-reactive protein levels are widely available information in many healthcare systems, but they display nonspecific changes following different clinic tables. Tilki et al. (4) investigated plasma-soluble thrombomodulin and soluble endothelial protein C receptor levels in patients with different CRC stages. They found no statistical differences between the patient groups, but they concluded that these proteins can play an important role in tumor development. In recent years the NLR has been found

Table 2. Cancer staging of the patients according to TNM system [American Joint Committee on Cancer (AJCC), 7th edition].

TNM staging (according to AJCC 7th edition)	Number of patients (n)	Percent in the study group (%)
Carcinoma in situ	1	0.5
I	34	16.5
IIA	61	29.6
IIB	4	1.9
IIIA	7	3.4
IIIB	41	19.9
IIIC	30	14.6
IV	28	13.6
Total	206	100

Table 3. Comparing the NLRs between patient groups with different cancer stages.

Colorectal cancer patients		NLR					P-value	Cutoff Value	Sens.	Spec.	PPV	NPV
		Mean	Std. dev.	Min.	Max.	Med.						
Tumor depth	T1-T2	4.499	5.562	0.66	37.5	2.86	0.010	2.38	66.2%	52.9%	72.9%	45.0%
	T3-T4	5.261	6.430	0.24	16.0	2.26						
Lymph node invasion	N0	4.501	5.534	0.24	37.5	2.57	<0.001	3.24	66.0%	66.0%	67.3%	64.7%
	N1-N2	6.597	7.672	0.33	48.2	4.05						
Distant organ metastasis	M0	5.158	6.09	0.24	43.0	3.14	0.004	3.48	64.3%	38.8%	14.2%	87.3%
	M1	8.261	9.891	0.33	48.2	4.30						

NLR: Neutrophil-lymphocyte ratio, Std. dev.: standard deviation, Min.: minimum, Max.: maximum, Sens.: sensitivity, Spec.: specificity, PPV: positive predictive value, NPV: negative predictive value.

as a simple index of inflammatory response. Sayan et al. (5) used NLR combined with interleukin and tumor makers and found these data valuable in the diagnosis of endometriosis. Tumor development and growth occur as a result of interactions among the tumor, host-derived stromal tissues including blood vessels, and host immune/inflammatory cells, with chronic inflammation having an important role in cancer development and progression (6). There are several possible explanations for the association between elevated NLR and poor oncologic outcome. As mentioned by Ding et al. (7), the host's immune response to a tumor is lymphocyte-dependent. First, elevated tumor-infiltrating lymphocytes in the primary tumor have been a well-recognized predictor of a good prognosis. Second, elevated neutrophils may result in an increase of potent proangiogenic factors that act directly on the nearby vasculature to promote development and progression of the neoplasm. Therefore, NLR can be considered as the balance between protumor inflammatory status and antitumor immune status.

CRC is the third leading cause of worldwide cancer mortality and is responsible for 1.1% of total deaths (6). We found a high mortality rate when the NLR was high in the postoperative 6-month period ($P = 0.047$). Walsh et al. (8) showed that a preoperative NLR of greater than 5 was linked to overall and cancer-specific survival in a 2-year prospective study of 200 patients. In different studies, preoperative NLR of greater than 4 or 5 was found to be a prognostic factor for recurrent CRC (7,9).

In the present study, we have investigated preoperative NLRs in patients with CRC and association with tumor stages according to the seventh edition of the American Joint Committee on Cancer TNM Staging System. We

obtained records retrospectively from the database. We found that when NLRs were elevated, there was increased tumor invasion depth (T), lymph node involvement (N), and distant organ metastasis (M). NLR values were statistically higher in CRC patients with T3-T4 invasion depth than patients with T1-T2 tumors. In patients with N1-N2 lymph node invasion, NLR values were higher than in the patients without lymph node invasion. Similar high values were found when we compared the patients with distant organ metastasis and patients without distant metastasis (Table 3). Patients with CRC in advanced stages were investigated for chemotherapy outcomes and survival. $NLR > 5$ values were found to be predictive (6,10). Cook et al. (11) found that postoperative NLR predicted complications following colorectal surgery. In that study, $NLR > 9.3$ on the first postoperative day correlated with an increased risk of complications. Despite the fact that in the study of Rashid et al. (12), it was not found to be a predictive survival parameter for esophageal cancer resection, NLR was a valuable predictive prognostic parameter in other cancer types (3,13,14).

In conclusion, t NLR is a valuable marker for systemic inflammatory response. In this study it was found to be a preoperative predictive parameter for the tumor stage in patients with CRC. Certainly, many opportunities are available to diagnose tumor stage in the preoperative period; however, the majority of them are very expensive. NLR calculation is an inexpensive and simple test that is always at hand. Thus, it may be useful to give an idea to the surgeon as to the kind of tumor he or she will confront when the abdomen is opened. Finding high NLR values provides estimation about the high invasion degree of a tumor or advanced N stage or metastasis.

References

1. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? *Lancet* 2001; 9255: 539–545.
2. Halazun KJ, Aldoori A, Malik HZ, Al-Mukhtar A, Prasad KR, Toogood GJ, Lodge JP. Elevated preoperative neutrophil to lymphocyte ratio predicts survival following hepatic resection for colorectal liver metastases. *Eur J Surg Oncol* 2008; 1: 55–60.
3. Proctor MJ, McMillan DC, Morrison DS, Fletcher CD, Horgan PG, Clarke SJ. A derived neutrophil to lymphocyte ratio predicts survival in patients with cancer. *Br J Cancer* 2012; 4: 695–699.
4. Tilki SÜ, Engin H, Gökmen A, Bilir C, Üstündağ Y. Plasma soluble thrombomodulin and soluble endothelial protein C receptor levels in colorectal cancer patients. *Turk J Med Sci* 2013; 43: 194–198.
5. Sayan CD, Özakşit MG, Sarıkaya E, Eryılmaz ÖG, Mollamahmutoğlu L, Deveer R. Serum interleukin-8, CA-125 levels, neutrophil-to-lymphocyte ratios, and combined markers in diagnosis of endometriosis. *Turk J Med Sci* 2013; 43: 417–423.
6. Chua W, Charles KA, Baracos VE, Clarke SJ. Neutrophil/lymphocyte ratio predicts chemotherapy outcomes in patients with advanced colorectal cancer. *Br J Cancer* 2011; 8: 1288–1295.
7. Ding PR, An X, Zhang RX, Fang YJ, Li LR, Chen G, Wu XJ, Lu ZH, Lin JZ, Kong LH et al. Elevated preoperative neutrophils to lymphocyte ratio predicts risk of recurrence following curative resection for stage IIA colon cancer. *Int J Colorectal Dis* 2010; 12: 1427–1433.
8. Walsh SR, Cook EJ, Goulder F, Justin TA, Keeling NJ. Neutrophil-lymphocyte ratio as a prognostic factor in colorectal cancer. *J Surg Oncol* 2005; 3: 181–184.
9. Mallappa S, Sinha A, Gupta S, Chadwick S. Preoperative neutrophil lymphocyte ratio greater than five is a prognostic factor for recurrent colorectal cancer. *Colorectal Dis* 2013; 3: 323–328.
10. Kishi Y, Kopetz S, Chun YS, Palavecino M, Abdalla EK, Vauthey JN. Blood neutrophil-to-lymphocyte ratio predicts survival in patients with colorectal liver metastases treated with systemic chemotherapy. *Ann Surg Oncol* 2009; 3: 614–622.
11. Cook EJ, Steward RW, Farooq N, Alberts JC, Justin TA, Keeling NJ. Post-operative neutrophil-lymphocyte ratio predicts complications following colorectal surgery. *Int J Surg* 2007; 1: 27–30.
12. Rashid F, Waraich N, Bhatti I, Saha S, Khan RN, Ahmed J, Leeder PC, Larvin M, Iftikhar SY. A pre-operative elevated neutrophil: lymphocyte ratio does not predict survival from oesophageal cancer resection. *World J Surg Oncol* 2010; 8: 1.
13. Kim YH, Choi WJ. The effectiveness of postoperative neutrophils to lymphocytes ratio in predicting long-term recurrence after stomach cancer surgery. *J Korean Surg Soc* 2012; 6: 352–359.
14. Azab B, Bhatt VR, Phookan J, Murukutla S, Kohn N, Terjanian T, Widmann WD. Usefulness of the neutrophil to lymphocyte ratio in predicting short- and long-term mortality in breast cancer patients. *Ann Surg Oncol* 2012; 1: 217–224.