RESEARCH ARTICLE

Pretreatment Neutrophil/Lymphocyte Ratio as a Prognostic Aid in Colorectal Cancer

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Abstract

Background: Colorectal cancers(CRC) are the third most common cancer in the western world, with surgery preferred for management of non-metastatic disease and post surgical treatment usually arranged according to the TNM staging system. However, there is still prognostic variation between patients who have the same stage. It is increasingly recognized that variations within disease course and clinical outcome in colorectal cancer patients are influenced by not only oncological characteristics of the tumor itself but also host response factors. Recent studies have shown correlation between the inflammatory response and clinical outcomes in various cancers. The neutrophil/lymphocyte ratio (NLR) has been described as a marker for immune response to various stimuli including cancer. Material-Methods: Two hundred eighty-one CRC patients were included in our retrospective analysis, separated into two groups according to a cut-off value for the NLR. Patient data including age, gender, vertical penetration, anatomic location, and differentiation of the tumor, TNM stage, survival rate, and disease-free survival were analyzed for correlations with the NLR. Results: Using ROC curve analysis, we determined a cut-off value of 2.2 for NLR to be best to discriminate between patient survival in the whole group. In univariate analysis, high pretreatment NLR (p=0.001, 95% CI 1.483-4.846), pathologic nodal stage (p<0.001, 95% CI 1.082-3.289) and advanced pathologic TNM stage (p<0.001, 95% CI 1.462-4.213) were predictive of shorter survival. In multivariate analysis, advanced pathologic TNM stage (p=0.001, 95% CI 1.303-26.542) and high pretreatment NLR (p=0.005, 95% CI 1.713-6.378) remained independently associated with poor survival. Conclusions: High pre-treatment NLR is a significant independent predictor of shorter survival in patients with colorectal cancer. This parameter is a simple, easily accessible laboratory value for identifying patients with poorer prognosis.

Keywords: Colorectal cancer - inflammatory response - neutrophil/lymphocyte ratio - prognosis

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Introduction

Colorectal cancer (CRC) is the 3rd most commonly diagnosed and leading cause of cancer death in both sexes in the USA (American Cancer Society, 2013). In Turkey, according to the Department of The Fight Against Cancer of Public Health Foundation, CRC is 3rd most common cancer in women, and 4th most common in men (Turkish Cancer Statistics, 2009). The preferred management of non-metastatic colon cancer is removal of the tumor with surrounding lymph nodes and post-surgical treatment regimen is closely related to the TNM (Tumor, Node and Metastasis) staging system (De Ridder et al., 2006; Suzuki et al., 2006). Even though TNM staging system has been regarded as a standard staging system for colorectal cancer, there are still variations between patients who have the same stage (Chiang et al., 2012). It is increasingly recognized that variations within disease course and clinical outcome in colorectal cancer patients are influenced by not only oncological characteristics of the tumor itself but also host response factors (Shin et al., 2012; Li et al., 2013). Many biomarkers have been studied as supplementary tools for further classification of the patients into the subgroups based on the current TNM staging system. Beside many other factors, the host immune system also plays an important role in cancer progression. Systemic inflammation, which was thought as secondary to tumor hypoxia or necrosis and related to anti-apoptosis also shows similar ability, although the exact reasons remains unclear (Hung et al., 2011; He et al., 2013). Many cancers arise from sites of infection, chronic irritation, and inflammation. It is now becoming clear that the tumor microenvironment, which is largely orchestrated by inflammatory cells, is an essential participant in the neoplastic process, promoting proliferation, survival, and migration. For this reason

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many studies have been focused on the evidence of the role of inflammation in carcinogenesis recently (Waldner et al., 2006, Roxburgh et al., 2010; Unal et al., 2013). Generally, studies described that lymphopenia means an impaired cell-mediated immunity, while neutrophilia is linked response to systemic inflammation (Zahorec et al., 2001). Therefore neutrophil lymphocyte ratio (NLR) has been used not only as a marker of inflammation but also as a prognostic index for several types of malignancies (Halazun et al., 2008; Cho et al., 2009; Cedres et al., 2012). Therefore, the aim of this study was to assess the prognostic value of pretreatment neutrophil-to-lymphocyte ratio (NLR) in predicting survival in patients with colorectal cancer.

Materials and Methods

A total of 496 colorectal cancer patients treated in our surgical clinic between January 1991 and December 2012 were enrolled. Data was obtained from a CRC database and medical records of the patients. Clinical information and follow-up were obtained from hospital charts and electronic records. Patients who received neo-adjuvant therapy or underwent palliative resection, pathological diagnosis other than adenocarcinoma, patients with inflammatory bowel disease and patients who had insufficient laboratory results were excluded. The remaining 281 patients were included in our retrospective analysis.

Adjuvant chemotherapy was given according to the lymph node involvement. Patients with node negative tumors did not receive chemotherapy. Patients showing poor prognostic indicators such as vascular invasion, perineural invasion and preoperative high levels of CEA were received 5- Fluorouracil based chemotherapy regardless of their nodal status.

Tumors located from the cecum to the splenic flexure were defined as right-sided cancers, and tumors located from the splenic flexure to the sigmoid colon were defined as left-sided cancers. Tumors originating from the recto sigmoid junction or rectum were defined as rectal cancers. Patients were staged using the 7th edition of the American Joint Committee on Cancer (AJCC) TNM staging system.

Patients' data including age, gender, vertical penetration, anatomic location, and differentiation of the tumor, TNM stage, survival rate, and disease-free survival were analyzed to find out if there is any correlation with the NLR.

NLR was calculated on the basis of preoperative blood sample analysis using the white blood cell (WBC) differentiated counts. NLR was defined as the absolute neutrophil count divided by absolute lymphocyte count. We used receiver-operating characteristic (ROC) curve for the determination of appropriate cut-off value of the NLR, which affects long-term survival in all stages.

Results

Among 281 patients, there were 167 (59.4%) men and 114 (40.6%) women. The mean age of the patients was 68±13.2 years. The tumors were located at the right colon in 72 patients (25.6%), at the left colon in 112 patients (39.9%) and at rectum in 97 patients (34.5%). With regard to differentiation most of tumors were moderately differentiated (74%). Median number of harvested lymph node was 11 (range 1 to 64) and total number of harvested lymph nodes was less than 12 in more than half of the patients (144 patients, 51.2%). Median follow up was 38.5 months (range 1 to 148 months) and 134 (47.7%) patients were died by their most recent follow up visit. Median NLR was 3.1 (range 0 to 33.9). The AJCC tumor stage was defined as stage I in 46 (16.4%) patients, stage II in 101 (35.9%) patients, stage III in 79 (28.1%) patients, and stage IV in 55 (19.6%) patients.

By using ROC curve analysis, we determined a cut-off value of 2.2 for NLR to be best to discriminate between patients' survival in the whole group. Clinical and pathological features according to NLR groups were summarized in Table 1.

Table 1. Clinical and Pathological Features According to Neutrophil Lymphocyte Ratio (NLR) Groups

		NLR ≤2.2 (n=84)	NLR ≤2.2 (n=197)	p value
Gender	Female	36	78	
	Male	48	119	0.35
Age (Mean±SEM)		68.8±1.3	67.7±1	0.426
Tumor Location	Right Colon	22	50	0.64
	Left Colon	30	82	
	Rectum	32	65	
pT Stage	1	5	8	
	2	19	20	0.022
	3	50	141	
	4	10	28	
pN Stage	0	48	118	
	1	26	52	0.802
	2	10	27	
TNM Stage	I	21	25	
	II	23	78	0.162
	III	28	51	
	IV	12	43	
Local Recurrence	Yes	9	24	
	No	59	119	0.328
Distant Metastasis	Yes	24	60	0.22
	No	47	89	
Follow-up (mean±SEM)		41.1±3.3	32.1±2.3	0.624

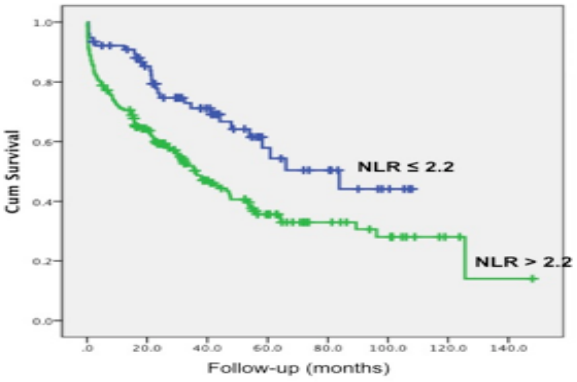

Figure 1. Kaplan-Meier Survival Curve for Overall Survival According to the Neutrophil Lymphocyte Ratio. A: Neutrophil/lymphocyte≤2.2; B: Neutrophil/lymphocyte>2.2

Table 2. Univariate and Multivariate Analysis of The Effects of Clinicopathological Factors on the Overall Survival of Patients with Colorectal Carcinoma

		Univariate Analysis HR (%95 CI)	p value	Multivariate Analysis HR (%95 CI)	p value
Gender	Female				
	Male	0.887 (0.528-1.489)	0.649	1.256 (0.695-2.271)	0.451
Age	≤60				
	>60	1.945 (0.824-3.311)	0.158	1.445 (0.89-2.971)	0.688
Tumor Location	Colon				
	Rectum	1.301 (0.761-2.225)	0.336	1.476 (0.770-2.831)	0.241
pT stage	T I-II				
	T III-IV	1.642 (0.959-4.337)	0.076	1.152 (0.710-3.397)	0.271
pN stage	N0				
	N1-2	2.086 (1.082-3.289)	p< 0.001	2.435 (0.525-11.291)	0.256
pTNM stage	Stage I-II				
	Stage III-IV	2.481 (1.462-4.213)	p< 0.001	5.880 (1.303-26.542)	p=0.001
NLR	≤2.2				
	>2.2	2.681 (1.483-4.846)	p=0.001	3.306 (1.713-6.378)	p=0.005

*NLR: Neutrophil lymphocyte ratio

Survival analyses

In univariate analysis, high pretreatment NLR (p=0.001, 95%CI 1.483-4.846), pathologic nodal stage (p<0.001, 95%CI 1.082-3.289) and advanced pathologic TNM stage (p<0.001, 95%CI 1.462-4.213) were predictive of shorter survival. In multivariate analysis, advanced pathologic TNM stage (p=0.001, 95%CI 1.303-26.542) and high pretreatment NLR (p=0.005, 95%CI 1.713-6.378) remained independently associated with poor survival (Table 2). Figure 1 shows the Kaplan Meier curves for overall survival regarding high (>2.2) versus low (≤2.2) derived neutrophil to lymphocyte ratio (p=0.001).

Discussion

The results of our study were similar to the existing literature and we also demonstrated that increasing pre-treatment NLR was associated with decreased overall survival after adjustment of known prognostic factors like nodal status or T stage. There are some limitations in our study. First of all, this is a retrospective study from one single institution, and total number of included patients is relatively small. Second, we did not have a chance to consider medical conditions that may affect the host's immune condition, because of insufficient data. And also it is possible that elevated NLR levels might have confounded by some unmeasured co-variates.

Pre-treatment elevated NLR was first described by Walsh et al. (2005) as a useful prognostic indicator in CRC. After that, emerging evidences from several studies have pointed out that NLR has a prognostic value in patients with pancreatic (Aliustaoglu et al., 2010), breast (Azab et al., 2012), lung (Kaya et al., 2013; Unal et al., 2013) and gastric (Jung et al., 2011) cancers. Recent literature has relatively fewer papers that focused on the significance of the pre-treatment NLR in CRC. But due to variance in the patient population, methodology and study design there is no homogenization on these studies. The cut-off value of our study was 2.2 while previous other studies have chosen 3 (Malietzis et al., 2013), 4 or 5 according to their methods. On the other hand some reports have studied different stages like we did, while others analyzed specific stage of patients in terms of survival analysis. Ding et al. (2010) studied only stage IIA patient; on the contrary Walsh et al. (2005) studied all Dukes stages patients. Additionally, Halazun et al. (2008) found that elevated NLR increases both risk of death and the risk of recurrence in patients who undergo surgery for CRC liver metastases. Furthermore Kishi et al. (2009) reported that NLR independently predicts survival in patients with liver metastasis of CRC treated with chemotherapy followed by resection or chemotherapy alone. Nonetheless, all of these studies emphasize that NLR has prognostic significance in cancer patients in terms of survival.

The prognosis of colorectal cancers is different even if they have the same stage of disease. Therefore, even after surgical resections and adjuvant chemotherapy for similar stages, some patients suffer from local recurrence and distant metastasis. That is why recent studies are focused on the other prognostic factors (including NLR), which may affect survival of CRC patients (Bolocan et al., 2012). The increase of knowledge in the field of inflammatory response, which generated by tumor cells, has led to the identification of some alternations in prognosis of CRC patients (Absenger et al., 2013).

The NLR, which is calculated by dividing absolute neutrophil count to absolute lymphocyte count, has been proposed as an easily reachable prognostic index of systemic inflammatory response in various diseases including colorectal cancer (Leitch et al., 2007). Neutrophils and lymphocytes play different role in cancer related inflammatory response. Neutrophils are described to be main source of circulating angiogenetic and growth factors, which helps the tumor progression whereas lymphocytes dominate host immune response via cytotoxic cell death and cytokines production that inhibit proliferation of tumor cells (Ownby et al., 1983; Strieter et al., 2006). Although these explanations, the meaning of elevated NLR remains unclear.

In conclusion, the present study identified that high pre-treatment NLR is a significant independent predictor

of shorter survival in patients with colorectal cancer. Pre-treatment NLR is a simple, easily accessible laboratory finding for identifying patients with poorer prognosis who treated both surgically and chemotherapeutically. Future clinical trials are needed to elucidate that potential mechanism of inflammatory response against tumor cells.

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