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ORIGINAL ARTICLE

Preoperative neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio as new prognostic factors for patients with colorectal cancer

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Summary

Purpose: *The objective of this study was to preoperatively evaluate blood platelet to lymphocyte ratio (PLR) and neutrophil to lymphocyte ratio (NLR) for their prognostic value in patients with colorectal cancer (CRC).*

Methods: *We retrospectively reviewed 347 patients who underwent colorectal surgery for CRC in the Istanbul Education and Research Hospital and the Antalya Education and Research Hospital. The prognostic value of preoperative PLR, NLR, and other clinical and laboratory parameters was assessed with univariate and multivariate analysis.*

Results: *Median overall survival (OS) was 61.8 months [95% CI for hazard ratio (HR) 46.24–77.14]. Significant parameters in univariate analysis, which were the preoperative levels of carcinoembryonic antigen (CEA) (p=0.055), albumin (p=0.003), hemoglobin (p=0.012), PLR (p=0.004), and NLR (p=0.054) were assessed by multivariate analysis which showed that only albumin retained its significance (p=0.008). Median OS was 70.1 vs 44.8 months with PLR ≤ 180 vs PLR > 180 (log rank; p=0.005). Median OS was "Not reached" (NR) vs 43.5 months with NLR ≤ 3 vs NLR > 3 (log rank; p=0.012).*

Conclusions: *This study showed that preoperative levels of CEA, albumin, PLR, and NLR have significant prognostic value for patients with CRC.*

Key words: *colorectal cancer, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, prognostic*

Introduction

CRC is the third most commonly diagnosed cancer in males and the second in females [1]. Sixty-one percent of all patients treated for CRC (all stages and sites combined) survive 5 years [2]. However, mortality rates for this form of cancer continue to increase in many countries [3].

Inflammation is important for tumor progression. Many cancers arise from sites of infection, chronic irritation, and inflammation [4]. The prognostic value of peripheral blood markers has also been demonstrated in many cancers. The presence of systemic inflammation has been significantly associated with poor prognosis for many kinds of cancers, including CRC [6-9]. The relationship between poor prognosis and elevated white blood cells, platelets, or their ratios may be explained through an inflammatory process evoked by cancer cells [4]. Accordingly, anti-inflammatory agents have been associated with a reduced risk of developing CRC and improved CRC-specific sur-

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vival [10,11].

At present, there is little information on the influence of these prognostic markers on OS in patients with CRC undergoing elective, potentially curative surgical resection. The aim of the present study was to examine the prognostic role of preoperative PLR and NLR for OS following elective potentially curative resection for CRC.

Methods

Studied were patients who underwent surgical resection of CRC at Istanbul Education and Research Hospital and Antalya Education and Research Hospital between March 2008 and May 2015. Patient files were retrospectively screened to obtain information about patient age and gender and stage of the tumor, development of metastases, and survival rates. Staging was based on the criteria set forth by American Joint Committee on Cancer (AJCC) Staging Manual (7th Edn, 2010).

Exclusion criteria

Exclusion criteria for this study were the following: patients who had received blood transfusions or heparin treatment within the last 2 months, cases with active bleeding, bleeding diathesis, hyper- or hypothyroidism, infection, disseminated intravascular coagulation, and connective tissue disorders. A total of 347 patients with CRC were reviewed.

Table 1. Patient baseline characteristics

Characteristics	*Patients*	
	N	%
Gender		
Female	136	39.2
Male	211	60.8
Age, years		
Median	65	
Range	31-90	
Stage		
I	43	12.4
II	103	29.6
III	181	52.2
IV	20	5.8
Baseline hemoglobin (g/dl)		
Median	12.1	
Range	4-16.8	
Baseline albumin (g/dl)		
Median	3.8	
Range	2-5.3	
Baseline CEA		
Median	3	
Range	0-586	
Baseline PLR		
≤ 180	163	50.6
>180	159	56.5
Baseline NLR		
≤ 3	154	44.4
>3	193	55.6

For abbreviations see text

Platelet to lymphocyte ratio

Before operation, PLR was calculated as the platelet count divided by the lymphocyte count. Using a number of different cut-off points, a PLR of 180 was found to represent the optimum stratification point at which the survival difference between the two groups was maximized.

Neutrophil to lymphocyte ratio

Before operation, NLR was calculated as the neutrophil count divided by the lymphocyte count. Using a number of different cut-off points, a NLR of 3 was found to represent the optimum stratification point at which the survival difference between the two groups was maximized.

Statistics

Statistical analyses were performed using SPSS software version 20.0. OS was defined as the duration between the date of onset of a treatment and the date of death. Survival was analysed by Kaplan-Meier method and univariate Cox regression analysis. The variables were investigated using visual (histograms, probability plots) and analytical (Kolmogorov-Smirnov/Shapiro-Wilk's test) methods to determine whether they were normally distributed. Descriptive analysis was carried out using means and standard deviations for normally distributed variables (PLR and NLR measurements). Variables with a p value <0.10 in univariate analysis were also evaluated by multivariate analysis. A p value <0.05 was considered statistically significant.

The effect of PLR, NLR, and albumin level on survival of CRC patients was investigated using the log rank test. A 5% type I error level was used to infer statistical significance.

Results

Patient, disease, and treatment characteristics

In this study, we evaluated the data from 347 patients with operated CRC. The mean follow-up period was 29.8±2.3 months. The median patient age was 65 years (range 25-90). Of the patients, 60.8% were male and 39.2% female.

NLR ≤3 was found in 154 (44.4%) patients, whereas 193 (55.6%) patients showed a NLR >3. Likewise, PLR ≤180 was noted in 184 (53%) patients, whereas 163 (47%) patients showed a PLR>180.

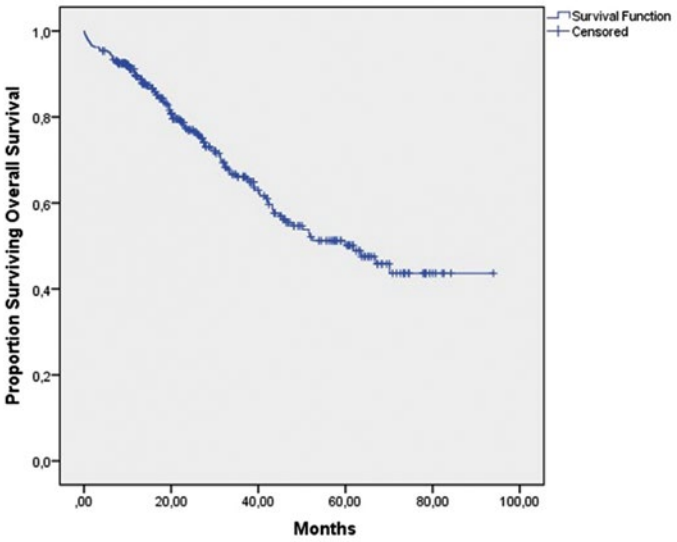

Figure 1. Overall survival in patients with colorectal cancer.

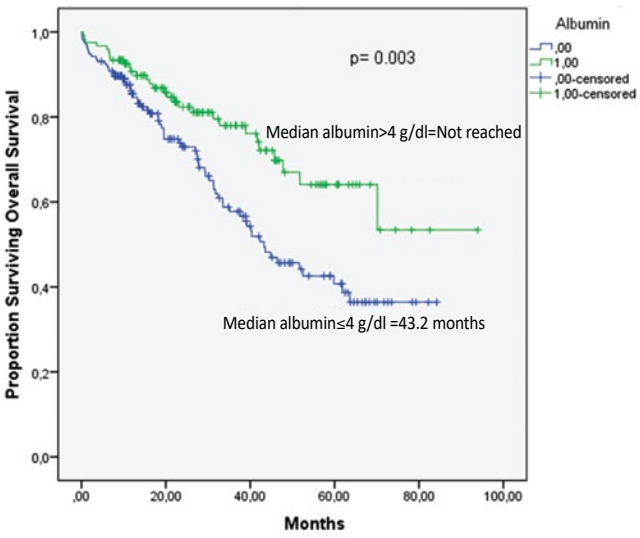

Figure 2. Overall survival in patients with albumin ≤ 4g/dl vs > 4 g/dl.

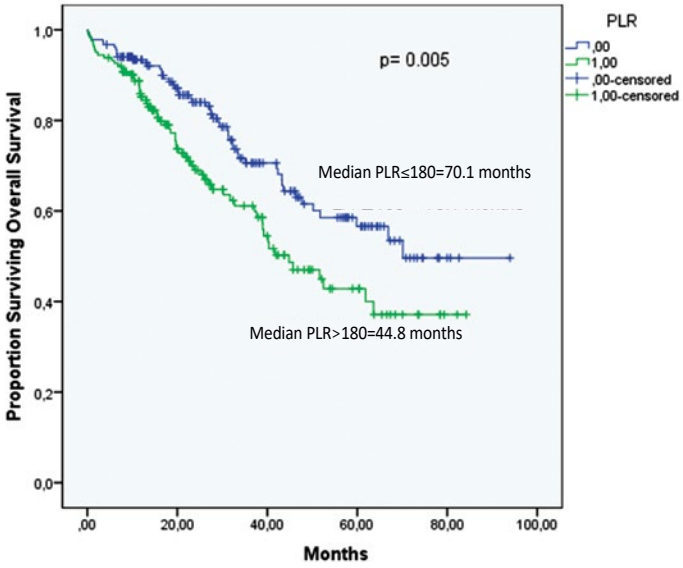

Figure 3. Overall survival in patients with PLR ≤ 180 vs > 180.

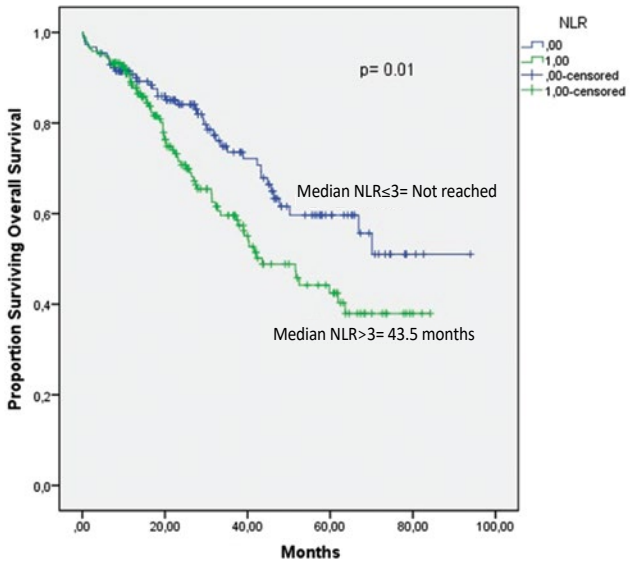

Figure 4. Overall survival in patients with NLR ≤ 3 vs NLR > 3.

Fifteen patients (5.8%) had metastases at the time of operation (Table 1).

Survival analysis

Patient median OS was 61.8 months (95% CI for HR 46.24–77.14) (Figure 1). No significant relationships were found between OS and age, sex, or LDH level. Univariate analysis revealed that OS was marginally affected by CEA (p=0.055, 95% CI for HR 1.000-1.005), and significantly affected by albumin level (p=0.003; 95% CI for HR 0.49–0.86), hemoglobin (p=0.012; 95% CI for HR 0.79–0.97), PLR (p=0.004; 95% CI for HR 1.00-1.003), and NLR (p=0.054; 95% CI for HR 0.99-1.083). However, albumin level (p=0.008; 95% CI for HR 0.47-0.89) retained significance in multivariate analysis.

Median OS was 43.2 months vs NR in patients with albumin ≤ 4 g/dl vs > 4 (log rank; p=0.003) (Figure 2). Median OS was 70.1 vs 44.8 months with PLR ≤ 180 vs PLR > 180 (log rank; p=0.005) (Figure 3). Median OS was NR vs 43.5 months with NLR ≤ 3 vs NLR > 3 (log rank; p=0.012) (Figure 4).

Discussion

The results of this study showed the prognostic value of preoperative CEA, albumin, PLR, and NLR for patients with CRC.

Recently, inflammatory markers have been

considered for investigation of tumor progression and risk of recurrence in solid tumors. Platelets and neutrophils can release certain growth factors such as platelet-derived growth factor (PDGF), platelet factor, transforming growth factor beta (TGFb), chemokines (interleukin-8), and vascular endothelial growth factor (VEGF). These growth factors can stimulate tumor growth and angiogenesis. The relationship between poor prognosis and elevated white blood cells, platelets, or their ratio may be explained by this hypothesis [4,12]. Blood NLR and PLR are simple, rapidly available laboratory markers. The prognostic significance of PLR has been demonstrated in patients with various cardiovascular diseases such as hypertension and coronary artery disease [13]. A large study that included over 8,700 patients showed the importance of inflammatory markers such as PLR in predicting the outcome of various cancers [14]. Raungkaewmanee et al. reported that PLR and NLR predict outcomes in patients with epithelial ovarian cancer. They showed that patients with higher pretreatment PLR had significantly shorter PFS and OS [15]. Similarly, Feng et al. found that PLR and NLR were associated with tumor progression and could be considered as independent markers of poor prognosis in patients who underwent esophagectomy for esophageal squamous cell carcinoma without neoadjuvant or adjuvant treatment [16]. Another trial showed that the preoperative PLR represents a significant independent prognostic index in patients with resected pancreatic adenocarcinoma. The median OS in patients with a PLR of 150 or less was 19.7 months, 13.7 months in those with a PLR of 151 to 300, and 5.8 months in patients with a value greater than 300 [17]. In our study, we found that univariate analysis revealed that OS was significantly affected by NLR, PLR, CEA, and albumin level. A median OS of 61.8 months was found in the whole group with CRC. Median OS in patients with a PLR of 180 or less was 70.1 months, and 44.8 months in patients with a value greater than 180 (p=0.005).

For patients who were undergoing curative operation for CRC, NLR is strongly associated with the recurrence rate in early-stage colon cancers [18]. Recently, meta-analysis of 13 articles involving 4,056 CRC patients showed that high preoperative NLR values were associated with worse prognosis on OS and DFS [19]. Our study showed that median OS in patients with a NLR was NR vs 43.5 months in patients with a value greater than 3 (p=0.012).

Currently, albumin level not only reflects the nutritional status alone but is also affected by systemic inflammation [20]. Albumin level has been shown to be independently associated with poor outcomes in patients with CRC. Chiang et al. reported that pre-operative serum albumin level substantially predicts postoperative morbidity and mortality among patients with CRC who undergo elective colectomy [21]. Likewise, the outcome of our patients showed that OS was significantly affected by albumin level (p=0.008). Median OS was 43.2 months vs NR in patients with albumin ≤ 4 g/dl vs > 4 g/dl (p=0.003).

We should mention some limitations of the present study. Some of the patients included in this study were metastatic at the time of operation. This caused a relative heterogeneity of the patient cohort. Some of the patient information about time to relapse was missing. Therefore, we did not evaluate the relationship between DFS and NLR and PLR values.

In conclusion, preoperative PLR and NLR are cheap, rapidly available, obtainable worldwide, non-invasive, and safe for patients. These metrics can be used effectively for patients with CRC. NLR and PLR may be used to identify patients at risk for poor OS and to assist in the clinical decision-making process for administering adjuvant chemotherapy in high NLR or PLR CRC patients undergoing potentially curative surgery.

Conflict of interest

The authors declare that they have no conflict of interest.

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