The Hemoglobin-Red Cell Distribution Width and Neutrophil -Lymphocyte Ratio in Predicting Lamina Propria Invasion in Bladder Tumors?

Mesane Tümörlerinde Hemoglobin-Redcell Distrubition Width Oranı (Hb/RDW) ve Neutrophil-Lymphocyte Oranı (NLR) Lamina Propria İnvazyonunu Tahmin Etmede Kullanılabilir mi?

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Özet

Amaç: Non-musculer invazive bladder cancer (NMIBC) hastalarında Hemoglobin-Red cell Distrubition Width oranı (Hb/RDW) ve Nötrofil/Lenfosit oranının (NLR) mesanenin transüretral rezeksiyonu öncesi lamina propria invazyonunu öngörmede önemini araştırmak.

Gereç ve Yöntemler: Ocak 2010- Haziran 2016 yılları arası mesanenin transüretral rezeksiyonu sonrası patolojisi NMIBC olan hastaların verileri retrospektif değerlendirildi. Hastalar Grup 1: Ta (mukoza tutulumu), Grup 2: T1 (submukoza tutulumu) olarak 2 gruba ayrıldılar. Hastaların yaşları, cinsiyetleri, tümör boyutu ve tümör sayıları belirlendi. Preoperatif tam kan değerlerinden lökosit (WBC), hemoglobin (Hb), nötrofil (N), lenfosit (L), monosit (M), platelet (PLT), mean platelet volümü (MPV), Red cell Distrubition Width (RDW) değerleri belirlendikten sonra NLR, PLR, LMR değerleri hesaplandı. Hb/RDW oranı belirlendi.

Bulgular: Patolojik evresi NMIBC olan 369 hasta değerlendirildi. Gruplar arasında yaş farkı yoktu. Grup 1 (Ta); 219 hasta, 66.3±10.7 yıl olup grup 2 (T1); 150 hasta, 66.9±10.4 yıl oldu (p=0.638). NLR grup 2'de grup 1'den yüksek olup (sırasıyla 2.4 (1.5), 2.2 (1.5) ve p=0.042) istatistiksel olarak bu yükseklik anlamlıdır. Gruplar arasında Hb ve RDW oranları bakımından farklılık izlenmemesine rağmen Hb/RDW oranı grup 2'de grup 1'den düşüktür (sırasıyla 0.89±21, 0.94±19 ve p=0.019) ve istatistiksel olarak bu azalma anlamlıdır.

Abstract

Objective: To investigate the importance of the Hemoglobin/Red cell distribution width ratio (Hb/RDW) and Neutrophil/Lymphocyte ratio (NLR) in predicting bladder lamina propria invasion before transurethral resection in non-muscular invasive bladder cancer (NMIBC) patients

Meterial and Methods: The data of the patients whose pathology after transurethral resection of the bladder was NMIBC between January 2010 and June 2016 were evaluated retrospectively. Group 1 had Ta (mucosa involvement) and Group 2 had T1 (submucosa involvement) lesions. The age, gender, tumor size and number of tumors of the patients were identified. The preoperative blood leucocyte (WBC), hemoglobin (Hb), neutrophil (N), lymphocyte (L), monocyte (M), platelet (PLT), mean platelet volume (MPV), and red cell distribution width (RDW) values were identified and the NLR, PLR, LMR values calculated. The Hb/RDW ratio was determined.

Results: A total of 369 patients were evaluated. The mean age was similar between groups. Group 1 (Ta) consisted of 219 patients (66.3±10.7 years) and Group 2 (T1) 150 patients (66.9±10.4 years) (p=0.638). NLR was higher in Group 2 than Group 1 (2.4 (1.5) and 2.2 (1.5), respectively, p=0.042) and this difference was statistically significant. The Hb/RDW ratio in Group 2 was lower than in Group 1 (0.89±21 and 0.94±19, respectively, p=0.019) and this difference was statistically significant.

Sonuç: Preoperatif dönemde periferik kandan kolay yolla elde edilebilen Hb/RDW oranında azalma ve NLR yükselmenin lamina propria invazyonu (T1) ile ilişkili olabileceğini düşünmekteyiz. Bu çalışmaların prospektif geniş serili çalışmalarla desteklenmesi gerekir.

Anahtar Kelimeler: Kas dışı invaziv mesane kanseri, Hemoglobin-kırmızı hücre dağılım genişliği oranı, Nötrofil-lenfosit oranı, Lamina propria invazyonu.

Conclusion: We believe that a decrease in the Hb/RDW ratio and increase in NLR, which can be easily determined from the peripheral blood in the preoperative period, can be associated with lamina propria invasion (T1). These studies should be supported with prospective large series.

Keywords: Non-muscular invasive bladder cancer, Hemoglobin-red cell distribution width ratio, Neutrophil-lymphocyte ratio, Lamina propria invasion.

INTRODUCTION

Bladder cancer (BC) is a very common genitourinary tract cancer and is the 7th most common cancer type among men worldwide (1). Approximately 75-85% of newly diagnosed BC cases are limited to the mucosa (stage Ta and carcinoma in situ (CIS)) or submucosa (stage T1) (2). BC has a recurrence rate of 30-80% and progression rate of 1-45% within 5 years (3). Since the aim in BC patients is to functionally and anatomically protect the bladder, the treatment is quite difficult. Despite intensive treatment performed while protecting the bladder, the disease shows a 20-30% rate of progression to the muscle invasion stage (T2). Bladder cancer patients are classified into low, intermediate and high risk groups by the European Organization for Research and Treatment of Cancer (EORTC) to help the treatment (4). Patients are primarily divided into risk groups to predict 1- and 5-year recurrence and progression based on the recurrence rate, number of tumors, tumor size, T stage, grade, and simultaneous CIS presence in this classification (4).

Cancer has been shown to trigger the systemic inflammatory response (SIR) and cause changes in the circulating inflammatory cells in recent studies (5). Well-known risk factors such as smoking, chronic infections and long-term exposure to industrial chemicals support the importance of chronic inflammation in the pathogenesis of bladder cancer (6). SIR may accelerate tumor development and distant metastasis through various mechanisms such as the secretion of inflammatory mediators and cytokines, apoptosis inhibition, and DNA damage in tumor cells (5). Since biomarkers related to systemic inflammation can be easily measured in routine whole blood counts, these markers have been extensively investigated in recent years.

New parameters such as the neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and lymphocyte/monocyte ratio (LMR) representing SIR have been proven to be useful as prognostic factors in cancer monitoring and treatment in the literature (7,8). Preoperative increased NLR levels have been reported to be associated with a poor prognosis and pathological stage in some types of cancer including BC (9).

The red cell distribution width (RDW) is a measure of the heterogeneity of erythrocytes in the circulation and is routinely studied during a complete blood count (CBC). RDW has been shown to reflect the inflammatory state of the body (10). Studies regarding the use of RDW in the diagnosis of malignant tumors have recently attracted attention (11,12). RDW was reported to be an important indicator of progression in patients with cancer (13). The Hb/RDW has been shown to be a new prognostic parameter in cancer patients in a recent study (14). Its possible use in evaluating the patient's general health status, inflammation and immune function has been reported (15).

Platelets also have important and versatile roles in cancer progression. The pathophysiology of cancer and inflammation has been shown to be related to the platelet count and mean platelet volume (MPV), which are markers of platelet function and activation (15).

We aimed to investigate the importance of NLR, PLR, LMR, and MPV, which can also be used as systemic inflammation markers, and the noval prognostic biomarker Hb/RDW; for predicting preoperative lamina propria invasion (T1 Stage), before the first transurethral resection of the bladder (TUR-M) in BC patients in this study.

Table 1: The characteristics of the patients.

		Group 1 (Ta) N=219	Group 2 (T1) N=150	
Age		66.3±10.7	66.9±10.4	0.638*
Gender	Male	182	130	0.382**
	Female	37	20	
Follow-up duration		50 (33)	50 (33)	0.875***
Grade	PUNLMP	15(6.8%)	-	<0.01**
	Low	163 (74.4%)	46 (30.7%)	
	High	41 (18.7%)	104 (69.3%)	
Tumor size	<3 cm	135 (61.6%)	63 (42%)	<0.01**
	>3 cm	84 (38.4%)	87 (58%)	
Tumor number	Single	136 (62.1%)	84 (56%)	<0.01**
	Multiple	83 (37.9%)	66 (44%)	
Recurrence		92 (42%)	80 (53.3%)	0.01**
Progression		50 (22.8%)	40 (26.7%)	0.459

Table 2: Comparison of the preoperative blood results.

	Group 1 (Ta)	**Group 2 (T1)**	**p**
WBC (10^9/l)	8.2 (2.9)	8.3 (3.0)	0.443
Neutrophil (10^9/l)**	4.7 (2.2)	5.0 (1.9)	0.098
Lymphocyte (10^9/l)**	2.1 (1.1)	1.9 (1.0)	0.536
Monocyte (10^9/l)**	0.5 (0.2)	0.5 (0.2)	0.867
NLR**	2.2 (1.5)	2.4 (1.5)	**0.042**[+]
PLR**	112 (66)	120 (68)	0.062
LMR**	3.9 (2.2)	3.6 (2.0)	0.400
Erythrocyte	4,6± 0.52	4,5±0.55	0.253
Hb	13.6±1.7	13.2±1.7	0.094
RDW**	14.1 (2.1)	14.7 (2.3)	0.296
Hb/RDW	0.94±19	0.89±21	**0.019**[++]
PLT	244±70	255±70	0.069
MPV	8.7 (1.6)	8.7 (1.4)	0.282
PCT	0.21 (0.08)	0.22 (0.08)	0.174
PDW	16.6 (1.5)	16.5 (1.5)	0.371

NLR: neutrophil/lymphocyte, PLR: platelet/lymphocyte, RDW: Red Cell Distribution Width

* Results are mean±SD, [++]Student's t-test

** Results are median (Interquartile range) [+]Mann-Whitney U

MATERIAL AND METHODS

Local Ethics Committee approval was obtained for the study. The data of the patients who had undergone TUR-M surgery due to a bladder tumor between January 2010 and June 2016 at our clinic with a pathologic diagnosis of NMIBC were evaluated and who complied with the inclusion criteria were included in the study. Those with preoperative infections, hematological malignancy, active hemorrhage, patients receiving anticoagulant treatment or who had received a blood transfusion in the last 2 months, and patients with unexplained leukocytosis or a connective tissue disease were excluded.

The patients were divided into two groups as Ta and T1 according to the pathological stage in the bladder tumor TNM classification as specified in the 2016

Table 3: Evaluation of the parameters tested for their ability to predict T1 using univariate logistic regression analysis

Variable	Univariate analysis	
	OR (95% CI)	P value
Hb/RDW	0.293 (0.103-0.832)	0.021*
Hb	1.636 (0.976-2.0745)	0.062
RDW	1.020 (0.920-1.131)	0.711
WBC	1.052 (0.960-1.153)	0.280
Neutrophil	1.098 (0.984-1.225)	0.094
Lymphocyte	0.929 (0.732-1.178)	0.929
NLR	1.106 (0.988-1.238)	0.081
PLR	1.002 (0.998-1.006)	0.303
PLT	1.003 (1.000-1.006)	0.070
MPV	0.926 (0.788-1.089)	0.354
LMR	1.009 (0.900-1.009)	0.882

Hb: Hemoglobin, RDW: Red cell distribution width, WBC: White blood cell, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet /Lymphocyte ratio, MPV: Mean platelet volume, P<0.05

Table 4: Correlation of various parameters with NLR and Hb/RDW in Group 2 (T1) patients (n=150).

	NLR		Hb/RDW	
Parameters	r	p	r	p
Age	0.080	0.330	-0.116	0.156
WBC	0.178*	0.030	-0.066	0.421
PLT	-0.078	0.340	-0.017	0.833
N	0.506*	<0.001	-0.170*	0.037
L	-0.724*	<0.001	0.152	0.064
RDW	0.059	0.475	-0.736*	<0.001
PLR	0.598*	<0.001	-0.158	0.053
MPV	0.067	0.419	0.139	0.090
NLR			-0.219*	0.007

* Correlation is significant at the .05 level (2-tailed).

MPV: Mean platelet volume, RDW: Red cell distribution width, Hb: Hemoglobin, WBC: White blood cell, L: Lymphocyte

European Association of Urology (EAU) . Age, gender, and radiological images were recorded from the patients' files, surgery notes and the hospital data system. Preoperative CBC, leucocyte (WBC), hemoglobin (Hb), neutrophil (N), lymphocyte (L), monocyte (M), platelet (P), MPV, RDW, NLR (calculated by dividing N by L), PLR (calculated by dividing P by L), and LMR (calculated by dividing L by M) values were also identified. The Hb/RDW ratio was obtained by dividing the Hb value (g/dL) by the RDW (%) value.

Routine CBC was performed with LH780 Analyzers (Beckman Coulter Inc., Fullerton, CA) from anti-

coagulant tubes with ethylene diamine tetraacetic acid as part of the preoperative protocol. The results of a whole blood count analysis within the 30 days before surgery from the patient files were accepted as suitable for the study. Patients who had undergone TUR-M surgery until 2016 June were included in the study and were followed-up for at least 12 months. The patients are still being followed-up and we included those followed-up on June 2017 at the latest in this study.

Statistical Analysis

Statistical analysis was performed using SPSS version 22 (IBM SPSS, Istanbul, Turkey). Parameters with
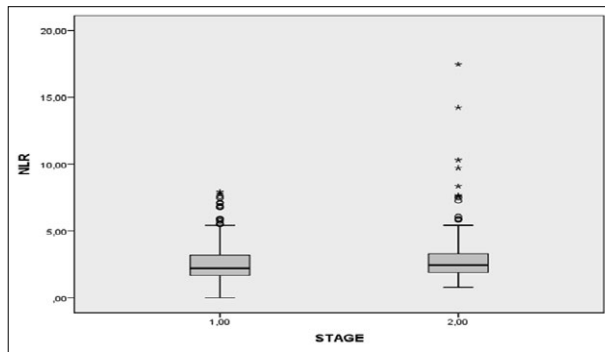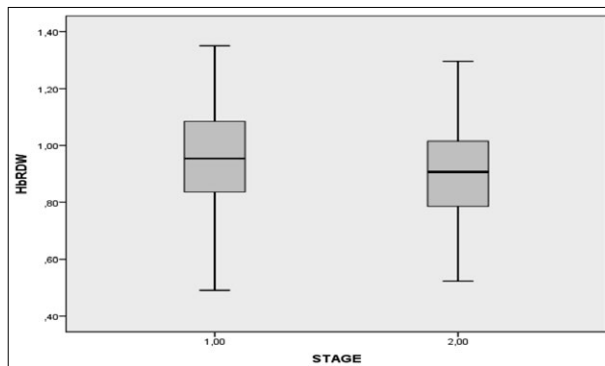
Figure 1: The distribution of NLR by group.

Figure 2: The distribution of Hb/RDW ratios by group.

a normal distribution were evaluated using the KolmogorovSmirnov test. Comparison of quantitative data and intergroup comparisons of parameters were performed using Student's t-test or the Mann-Whitney U test. The chi square test was used for the comparison of qualitative data. ROC curves were created to identify the cut-off points for all CBC variables. Logistic regression analysis was also used to determine predictors of T1 stage tumors. The Spearman test was used for correlation. $P < 0.05$ was considered to indicate a statistically significant difference between the values.

RESULTS

Of the 399 patients that underwent TUR-M surgery with a diagnosis of bladder tumor, 30 patients were excluded and the data of 369 patients were evaluated. We excluded 30 patients who were treated with anticoagulants, received transfusions or were infected from the study. The patients were divided into 2 groups and the characteristics of the groups are shown in Table 1. No statistically significant age difference was present between the two groups. Group 1 (Ta) included 219

patients with a mean age of 66.3±10.7 years and Group 2 (T1) 150 patients with a mean age of 66.9±10.4 years (p=0.638). Both groups were followed-up for 50 (33) months. The percentage of high grade tumors was statistically significantly higher in Group 2 than Group 1 (30.7% vs. 18.7%, p<0.0001).

Comparison of the groups based on the data obtained from the preoperative CBC results is presented in Table 2. The N and L count differences between the two groups were statistically insignificant (4.7 (2.2) vs. 5.0 (1.9), p=0.098; 2.1 (1.1) vs. 1.9 (1.0) p=0.536; respectively). NLR was found to be higher in Group 2 than in Group 1 (2.4 (1.5) vs 2.2 (1.5), p=0.042 (Table 2) (Figure 1).

The Hb/RDW ratio was statistically significantly lower in Group 2 than in Group 1 (0.89±21 vs. 0.94±19, p=0.019) (Figure 2). The optimum cut-off value for NLR for predicting preoperative lamina propria invasion in patients with BC was >2.1 (area under the curve [AUC 0.551 (95%Cl 0.501- 0.619) p=0.049 (Figure 3). We found a sensitivity of 63.3% and specificity of 50% for NLR> 2.1 in predicting preoperative lamina propria invasion for T1.

We found the optimal cut-off for Hb/RDW (area under the curve [AUC 0.564 (95% Cl 0.504- 0.623) for lamina propria invasion (T1 stage) to be >0.9 with a sensitivity of 62.0% and specificity of 50% (p=0.038) (Figure 4).

Binomial logistic regression analysis was performed to identify T1 stage-related CBC parameters. Univariate analysis indicated that Hb/RDW (0.293 (0.103-0.832), P = 0.021) values showed significant differences according to T1 existence. We found the Hb/RDW ratio to show a significant difference according to T1 presence in univariate analysis (0.293 (0.103-0.832), P = 0.021) (Table 3). A weak negative correlation was found between Hb/RDW and Neutrophil (r=-0.170, p=0.037) and also NLR (r=-0.219, p=0.007) with Spearman correlation analysis in the T1 group (Table 4).

DISCUSSION

We found a decrease in Hb/RDW and an increase in NLR among the preoperative blood parameters in patients with lamina propria invasion (T1) in this

study. There was no significant difference between the Ta and T1 groups for any of the other CBC parameters. As far as we know, this study is the first to investigate whether the Hb/RDW ratio could be used for predicting lamina propria invasion in BC.

RDW can increase in cancer-related nutritional deficiencies (iron, vitamin B12 or folic acid), bone marrow depression and chronic inflammation. Possible RDW use as a biomarker is also reported in patients with cancer while high RDW has been associated with a poor prognosis (16). RDW elevation has been investigated very rarely as a potential biomarker of cancer activity in urological cancers (13). Hb has been reported to be useful in making clinical decisions in BC patients (17). Pre-cystectomy Hb levels have been shown to be associated with the histopathologic features and to provide additional prognostic information, especially for patients with localized bladder cancer (17). The Hb/RDW ratio was first investigated by Sun et al. in patients with squamous cell carcinoma of the esophagus in the literature. A low Hb/RDW ratio (<0.989) was reported to increase the mortality risk of these patients 1.416 times. We found the cutoff point to be 0.9, similar as Sun et al. The Hb and RDW findings were not found to be valuable by themselves in their study, similar to ours (14). The Hb/RDW ratio showed poor correlation with the neutrophil and NLR values in our study (Table 4).

BC is often associated with chronic or recurrent inflammation, and high rates of inflammatory cells in the tumor region play a critical role in carcinogenesis (18). SIR results in a change of circulating WBC levels. High NLR reflects a decrease in the lymphocyte-mediated response to malignancy with an increase in the neutrophil-associated inflammatory response (16). NLR elevation has been reported to be associated with muscle invasive disease, extravesical spread, and poor prognosis and survival (20-23). We et al. reported the prognostic significance of NLR elevation in cancer in their meta-analysis (24). The sensitivity and specificity of NLR and Hb/RDW in predicting preoperative lamina propria invasion were found to be low.
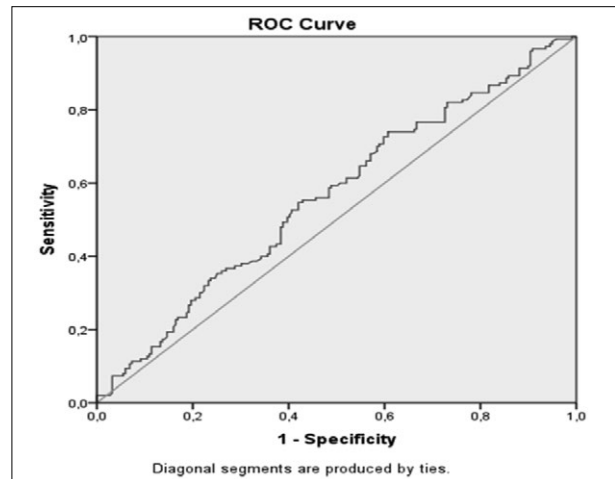

Figure 3: The ROC curve for NLR in predicting preoperative lamina propria invasion.
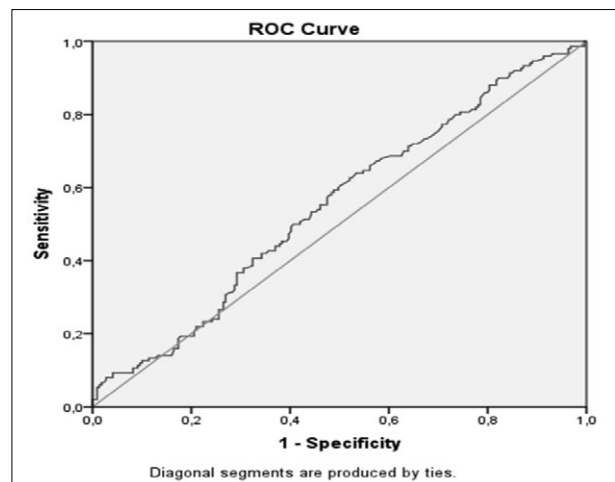

Figure 4: ROC curve for Hb/RDW in predicting preoperative lamina propria invasion.

The optimum cut-off value of NLR for predicting preoperative lamina propria invasion in patients with BC was found to be > 2.1 in this study. There is no established value for the NLR cut-off value for bladder cancer in previous studies in the literature. A preoperative NLR value > 1.84 was shown to be useful in predicting lamina propria invasion in patients with NIMBC and the value to be higher in T1 than in Ta in a recent study (25).

Some reports suggest that platelets protect tumor cells by hiding them from the host cell (26). Tumors cells have also been shown to facilitate vascular endothelial adhesion. P selectin in active platelets plays a

role in tumor growth and metastasis (27). Can et al. have reported MPV and PLT to be important parameters in predicting invasion in bladder cancers (22). However, we found the platelet count and MPV to be useless in differentiating Ta from T1. The reason for the lack of a difference in MPV could be that the duration between the time of obtaining the blood and that of the device result output was unknown as the study was retrospective (28). The time between obtaining the blood and the whole blood count is known to significantly affect the MPV value (29,30).

CONCLUSION

Bladder tumor treatment is quite complicated and difficult since the aim is to protect the bladder. The treatment of lamina propria invasive bladder tumors is also an important issue. This study has shown that a low Hb/RDW ratio and high NLR, systemic inflammation markers that can be easily determined from the peripheral blood, may be associated with lamina propria invasion. From this point of view, we believe that our study will make a significant contribution to the literature. On the other hand, this study needs to be supported by large-scale prospective studies.

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