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Peripheral Blood Neutrophil to Lymphocyte Ratio is Positively Correlated with Tumour Aggressiveness in Testicular Cancer

Mustafa Ozan Horsanali, Kutan Ozer and Emin Ozbek*

Department of Urology, Izmir Katip Çelebi University Ataturk Training and Research Hospital, Turkey

Abstract

Introduction: Testicular cancer represents between 1% to 1.5% of all male neoplasms and 5% of urological tumours in general. The Neutrophil to Lymphocyte Ratio (NLR), which can easily be calculated from routine Complete Blood Counts (CBCs) with differentials, is a marker of host inflammation and has been shown to be an independent prognosticator for a variety of solid malignancies.

Materials and Methods: We have retrospectively analyzed 128 patients who diagnosed testicular cancer between January 2006 and July 2012. Patient demographics, preoperative full blood count and standard histologic tumour characteristics were recorded. Factors analyzed included patient age, tumour size, histological subtype, Pathological Tumour (pT) stage, N stage, neutrophil count, lymphocyte count, preoperative and postoperative NLR, alfa fetoprotein, B-HCG and LDH levels. Routine full blood count results were collected as part of the pre-treatment protocols.

Results: Totaly 128 patients were analyzed retrospectively. The mean lymphocyte counts of all patients were 4.74 ±2.88 (range 0.32-5.72) and neutrophil counts were 5.93 ± 2.88 (range 1.87-17). The mean NLR was 3.70 ± 2.87 (range 1.04-21.94). The cut-off rate for NLR was calculated as 3,72. 87 patients were <3,72 NLR and 41 patients were ≥3,72 NLR. The mean age for the group <3,72 NLR were 41 (10,6%) and for group ≥3,72 NLR were 34,9 (8,5%) months. There were statistically significant association between age and NLR ratio (p: 0,002).

Discussion: NLR is one of the widely used markers for systemic inflammatory reactions. Although increased pretreatment NLR is associated with a poor outcome for various types of cancers, we found a positive association between preoperative NLR and age, tumour histopathology, preoperative serum markers and rete testes invasion. In the group of NLR < 3,72 , tumour serum markers were lower than NLR>3,72 group. In the seminoma histopathology NLR value was < 3,72 and that was statistically significant.

Conclusion: NLR is a simple, rapid and reliable method of how to evaluate the extent of stress or systemic inflammation. Our prognostic model based on the NLR and pathologic factors could be helpful in clinical practice. Also, clinicians should remember that baseline NLR differs among individuals.

Keywords: Neutrophil; Lymphocyte; Neutrophil to lymphocyte ratio, Testis cancer; Stage

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Correspondence:
Mustafa Ozan Horsanali, Department of Urology, Izmir Katip Çelebi University Ataturk Training and Research Hospital, Turkey,
E-mail: drozanhorsanali@yahoo.com

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Introduction

Testicular cancer represents between 1% to 1.5% of all male neoplasms and 5% of urological tumours in general, with 3-10 new cases occurring per 100,000 males/per year in Western societies. Only 1-2% of cases are bilateral at diagnosis. The histological type varies, although there is a clear predominance (90-95%) of germ cell tumours. Peak incidence is in the third decade of life for nonseminoma, and in the fourth decade for pure seminoma [1]. Inflammation has an important role in the development and progression of many malignancies. Putative mechanisms include the increased supply of factors that promote carcinogenesis and tumour progression by cells of the innate immune systems and decreased antitumoral response by immune cells of the adaptive system [2]. The Neutrophil to Lymphocyte Ratio (NLR), which can easily be calculated from routine Complete Blood Counts (CBCs) with differentials, is an emerging marker of host inflammation and has been shown to be an independent prognosticator for a variety of solid malignancies [3].

Table 1: Mean of blood parameters.

	Mean
	1.91±0.70
Neutrophil	5.93±2.88
NLR	3.70±2.87

Neutrophil–Lymphocyte Ratio (NLR) is also used as a parameter of systemic inflammation in intensive care patients [4]. Cancerous tissue, besides leading to systemic inflammatory response, may also lead to a localized, more generalized, and nonspecific inflammatory response due to destruction and disruption caused by the physical effects of the tumor. Therefore, NLR is a rapid and simple index of systemic inflammatory response [5].

An increased pretreatment NLR is associated with poor prognosis in colorectal, gastric, and ovarian cancer; malignant mesothelioma; and renal cell carcinoma (RCC) [4,6-8]. According to our knowledge, relation between NLR and testicular cancer has not been reported previously. The objective of our investigation was to evaluate the association between NLR and oncological parameters in patients undergoing radical orchiectomy for testicular cancer Table 1.

Materials and Methods

We have retrospectively analyzed 128 patients who diagnosed testicular cancer between January 2006 and July 2012 in Izmir Katip Celebi University Atatürk Training and Research Hospital. Patient demographics, preoperative full blood count and standard histologic tumour characteristics were recorded. It was compiled from individual patient's medical records, laboratory results, and pathology reports. Factors analyzed included patient age, tumour size, histological subtype, Pathological Tumour (pT) stage, N stage, neutrophil count, lymphocyte count, preoperative and postoperative NLR, alfa fetoprotein, B-HCG and LDH levels. Routine full blood count results were collected as part of the pre-treatment protocols. Demographics and serum values for the NLR were measured on the day before the operation to ascertain the baseline values for neutrophil and lymphocyte counts Table 2. The NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count. Exclusion criteria for the present study were presence of hematologic disorders or malignensies, active infection at the time of surgical intervention, prior blood transfusion and the presence of other cancer types.

Table 2: Tumour characteristics for NLR groups.

	NLR< 3.72 (n=87)		NLR≥ 3.72 (n=41)		p value
AGE (Mean)	41,0		34,9		0.002
Pre-op AFP	**n**	**%**	**n**	**%**	
<1000	82	94,3	31	75,6	0.006
>=1000	5	5,7	10	24,4	
Pre-op B-HCG					
<5000	85	94,3	29	70,7	<0.001
>=5000	2	5,7	12	29,3	
Pre-op LDH					
<225	52	59,8	11	26,8	0.001
>=225	35	40,2	30	73,2	
Lymphocyte (mean)	2,2		1,4		<0.001
Neutrophil (mean)	4,6		8,7		
Histology	**n**	**%**	**n**	**%**	
MIXGERM CELL	26	29,9	22	53,7	0,017
SEMINOMA	39	44,8	9	22	
OTHER	22	25,3	10	24,4	
Tumour size(mean)	4,5		5,3		0.190
Lymphovasculer invasion	**n**	**%**	**n**	**%**	
No	58	66,7	24	58,5	0.371
Yes	29	33,3	17	41,5	
Rete testes invasion	**n**	**%**	**n**	**%**	
No	83	95,4	32	78	0.004
Yes	4	4,6	9	22	
Spermatic cord invasion	**n**	**%**	**n**	**%**	
No	82	94,3	34	82,9	0.053
Yes	5	5,7	7	17,1	
Epididimal invasion	**n**	**%**	**n**	**%**	
No	82	94,3	36	87,8	0.289
Yes	5	5,7	5	12,2	

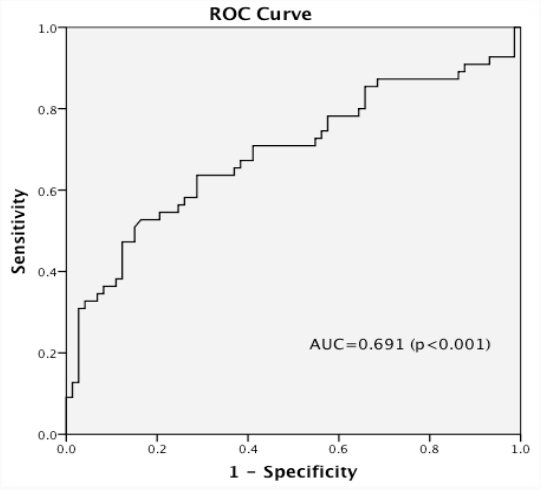

Figure 1: ROC curve for NLR.

Istatistical Analysis

SPSS 15 statistical package program was used to evaluate the statistical analysis. Descriptive statististics were presented as mean, standard devation, median and min-max values for continuous variables, frequencies and percentages for categorical variables. Student t test was used while analyzing the mean differences of continuous variables between two NLR groups also chi square test was used to conceive the relationship between NLR and other categorical variables. You den Index and ROC Curve analysis were used to define a cut-off value for NLR. We run Kaplan Meier analysis to understand the difference in OAS between two NLR groups. Differences with a P value of <0.05 were considered statistically significant.

Results

Totally 128 patients were analyzed retrospectively. The mean age of the patients were 39.01 ±10.33 ranging from 19-71 and median age was 38,5. The mean tumour size of the patients was 4.74 ± 2.88 cm ranging from 0 to 17. 48 (37,5 %) patients have mixed germ cell histopathology, 48 (37,5%) patients have seminoma histopathology and 32 (25%) patients have other type of testicular cancer. The mean lymphocyte counts of all patients were 4.74 ± 2.88 (range 0.32-5.72) and neutrophil counts were 5.93 ± 2.88 (range 1.87-17). The mean NLR was 3.70 ± 2.87 (range 1.04-21.94) (Table 1). 82 (64,1 %) of the patients were pT1 stage, 34 (26,6%) were pT2 stage and 12 (9,4%) patients were pT3 stage. 79 (61,7%) patients were N0, 12 (9,4%) were N1 and 12 (9,4%) patients N3 and 25 (19,5%) patients were N3 stage. The mean overall survival of the all patients were 42.37 ±32.04 (range 1-124) month. At the follow up 116 (90,6%) patients were alive and 12 (9,4%) patients were died because of the metastatic disease. The cut-off rate for NLR was calculated as 3,72 by ROC test (Figure 1). 87 patients were <3,72 NLR and 41 patients were ≥3,72 NLR. The mean age for the group <3,72 NLR were 41 (10,6%) and for group ≥3,72 NLR were 34,9 (8,5%) months. There were statistically significant association between age and NLR ratio (p: 0,002). There were statistically significance between NLR and tumor histopathology, preoperative AFP, B-HCG, LDH, rete-testes invasion and N stage. In the patients who have <3,72 NLR, 26 of 87 patients were mixed germ cell carcinoma and 39 patients were seminoma histopathology (p:0,017). In these group the mean tumor size was 4,5 cm (p:0.190) (Table 2). 59 of 87 patients were pT1 stage, 23 of pT2 stage and 5 of pT3 (p: 0,110). 65 of 87 patients were N0, 7 of N1, 5 of N2 and 10 of N3 (p <0,001) (Table 3). 58 patients have lymphovascular invasion (p: 0,371), 83 patients have rete-testes invasion (p: 0,004), 82 patients had epididymal invasion (p: 0,289) and only one patient has positive surgical margin. For this group, 82 patients have <1000 preoperative AFP level and 5 patients have ≥1000 AFP levels (p: 0,006). 85 patients have <1000 B-HCG level and 2 patients have ≥1000 B-HCG levels (p <0,001). 52 patients have <225 LDH level and 35 patients have ≥225 LDH levels (p: 0,001) (Table 4).

Table 3: TNM characteristics for NLR groups.

	NLR< 3.72 (n=87)		NLR≥ 3.72 (n=41)		p value
T stage	**n**	**%**	**n**	**%**	
T1	59	67,8	23	56,1	0,110
T2	23	26,4	11	26,8	
T3	5	5,7	7	17,1	
N stage					
N0	65	74,7	14	34,1	<0.001
N1	7	8	5	12,2	
N2	5	5,7	7	17,1	
N3	10	11,5	15	36,6	
M stage					
M0	81	93,1	27	65,9	<0.001
M1	6	6,9	14	34,1	

Table 4: Preoperative tumor marker's characteristic.

	N	%
PRE-OP AFP		
<1000	113	88,3
1000-10000	11	8,6
>10000	4	3,1
PRE-OP BHCG		
<5000	114	89,1
5000-50000	6	4,7
>50000	8	6,3
PRE-OP LDH		
<225	63	49,2
225-1500	60	46,9
>1500	5	3,9

Discussion

NLR is one of the widely used markers for systemic inflammatory reactions. Increasing evidence supports the association between cancer progression and inflammation [9]. Although increased pretreatment NLR is associated with a poor outcome for various types of cancers [4,6,7,10], no study of association between NLR and testicular cancer has been done to date. To our knowledge we are the first to investigate the clinical value of NLR for patients with testicular cancer.

Our study's goal was to determine whether preoperative NLR can be incorporated in age, tumor histopathology, tumour serum markers and TNM stage. There was statistically significance between preoperative NLR values between age, tumor histopathology, rete testes invasion and preoperative tumour markers. There is

heterogeneity in reported thresholds used to define an elevated NLR in the literature (range 2-7.7). This may reflect variations in the host response for different disease sites and stages, or may reflect the different approaches used when determining cutoff values. Not all studies used an accepted method for cutoff point determination, and in some instances the rationale for the cutoff point decision was not described [11]. In our study we used Youden test to calculate cut off value of NLR and 3,7 value was calculated as cutoff value for NLR [12]. Showed a correlation between the NLR ratio of the patients with early gastric cancer and the prognosis of the patients [13]. Showed that NLR independently predicts survival in patients with colorectal liver metastases treated with chemotherapy followed by resection or chemotherapy only. When chemotherapy normalizes the high NLR, improved survival is expected. Also, in one study, elevated preoperative NLR was identified as an adverse predictor of outcome in patients undergoing potentially curative resection for hepatocellular carcinoma, and, therefore, patients with high preoperative NLR should be considered candidates for additional therapies after resection [14]. Reported that increased preoperative NLR was strongly associated with a poor prognosis in patients with Upper Urinary Tract Urothelial Carcinoma (UUTUC) by multivariate analysis [15]. In contrast, an increased NLR was strongly associated with pathologic T stage, tumor grade, and LVI. Twenty-two (26.5%) of the 83 patients with an NLR <2.5 had stage pT3 disease or higher compared with 36 (66.7%) of the 54 patients with an NLR >=2.5. Twenty- three (27.7%) of the 83 patients with NLR <2.5 had grade 3 disease compared with 36 (66.7%) of the 54 patients with an NLR >= 2.5. Thirty-three (39.8%) of the 83 patients with an NLR <2.5 were LVI positive compared with 39 (72.2%) of the 54 patients with an NLR >= 2.5. These pathologic factors are important for predicting the prognosis of UUTUC. In our study we found a positive association between preoperative NLR and age, tumour histopathology, preoperative serum markers and rete testes invasion. In the group of NLR <3,72, tumour serum markers were lower than NLR >3,72 group and first group was older than second group. For seminoma histopathology NLR value was <3,72 and these was statistically significant. In the NLR<3,72 group lymph node invasion was higher than other group. NLR can easily evaluated with preoperative peripheral blood count. We consider that results of our study can help phycision to predict prognosis and survival of the patients. Because we found that the patients with NLR <3,72 have lymph node metastasis and rete testes invasion as a poor prognostic factors. So these patients OAS are worst than the patients with NLR >3,72. In addition, NLR can be predictive factor for other therapies such as chemotherapy or radiotherapy after surgery. And also NLR is the easy preoperative test for physician to evaluate patients with testicular cancer.

Conclusion

Neutrophilia and lymphocytopenia are typical phenomena of the innate immune response to various stressful insults. Relation of neutrophils and lymphocytes during the development of systemic inflammatory response expressed as NLR is a simple, rapid and reliable method of how to evaluate the extent of stress or systemic inflammation. NLR can be used routinely in daily clinical practice of intensive medicine. Our prognostic model based on the NLR and pathologic factors could be helpful in clinical practice. Further multicenteral studies with more patients are needed to confirm our suggestions. Also, clinicians should remember that baseline NLR differs among individuals.

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