



The hematological parameters in testicular cancer

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ABSTRACT

Although testicular cancer (TCa) is rare neoplasm that occurs in young men aged between 18 and 35 years. The risk factors are cryptorchidism, family history, and infertility. The aim of this study was to investigate the diagnostic efficacy of neutrophil to lymphocyte ratio for the diagnosis of TCa. The patients who underwent orchiectomy in our unit reviewed retrospectively. Age of the patients, the laboratory results and pathological reports were recorded. The neutrophil to lymphocyte ratio (NLR) was calculated as the neutrophil counts divided to the lymphocyte counts. The patients were divided into two groups according to the pathology record. The testicular malign neoplasms are included in group 1 and group 2 includes the patients who had cryptorchidism and atrophic testes without any malignancy and inflammation. For statistical analysis, student *t* test was used for comparing the data between groups and the area under curves were used for NLR, neutrophil and lymphocyte counts in the diagnosis of testicular malign neoplasms. There were 285 patients in the present study. The patients' age was between 10 and 90 with a mean age of 36.87 ± 11.83 and 37.24 ± 20.31 years in groups respectively. The neutrophil, white blood cell counts and NLR were significantly higher in group 1 and lymphocyte count was lower in patients with testicular cancer with statistical significance. The area under curve was 0.645, 0.626, 0.578 for NLR, neutrophil and lymphocyte counts for the diagnosis of TCa. Mixed germ cell tumor was the most common histologic subtype with an incidence of 51.58% (n:65 patients) and seminomas were reported 37.30% (n:47 patients) of the patients. Testicular cancer has low incidence when compared the other urologic malignancies. There are only three tumor markers that include alpha-fetoprotein, human chorionic gonadotropin and lactate dehydrogenase for testicular cancer diagnosis. The current study showed Neutrophil to lymphocyte ratio (NLR) may be used as a biomarker for TCa. Further studies are needed to define the association between NLR and testicular cancer.

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1. Introduction

Testicular cancer (TCa) is relatively rare neoplasm that accounts one percent of all neoplasms.¹ The TCa incidence is 5.6 per 100000 men in the world.² Although its low incidence, TCa is the most common tumor among young adult men and the patients are usually diagnosed in the age of 15–35 years.³ The classification of testicular tumors includes three groups; germ cell tumors, sex-cord stromal tumors and miscellaneous tumors. Germ cell tumors are divided into two groups; seminoma and nonseminomatous germ cell tumors. Seminomas and lymphomas are the most common testicular tumor in young adult men and older than 60 years of men

respectively.

Alpha-fetoprotein (AFP) and human chorionic gonadotropin (hCG) are tumor markers for testicular cancer diagnosis, staging and prognosis.⁴ Inflammation has an important role in the development and progression of some cancers by promoting cancer cell proliferation, angiogenesis, metastasis and tumor response to the systemic therapies.⁵ Neutrophils, lymphocytes and platelets play a critical role in the tumor inflammation and immunology. The neutrophil to lymphocyte ratio (NLR) that is calculated as the absolute neutrophil counts divided to the absolute lymphocyte is widely used as an inflammatory marker and can be easily acquired from complete blood counts.⁶ In systemic inflammation; neutrophilia, lymphopenia and thrombocytosis usually develop in the peripheral blood.⁷ Elevated NLR is associated with systemic and local inflammation not only provides favorable microenvironment for tumor invasion and metastasis but also suppresses the host immune system.⁶

Cancer and inflammation are linked and cancer patients have

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local and systemic changes in inflammatory parameters such as NLR, erythrocyte sedimentation rate, alterations of inflammatory cytokines and acute phase proteins (fibrinogen, ferritin, albumin, c-reactive protein and transferrin).⁸ Increased NLR have been showed in some cancers such as colon, esophageal, gastric, breast and ovarian cancers.⁵ Yüksel et al.¹ investigated the NLR in testicular cancer diagnosis in small number of patients. The aim of this study is to investigate the NLR, neutrophil and lymphocyte counts in the testicular cancer patients.

2. Material and methods

Data of the patients who underwent orchiectomy between January 2006 and January 2016 were reviewed retrospectively. Patients with orchitis, benign tumors, torsion and concomitant of prostate cancer were excluded from the study. Age, complete blood analysis before the operation at least 24 h and pathological reports of the patients were recorded. The neutrophil to lymphocyte ratio (NLR) was calculated as the neutrophil counts divided to the lymphocyte counts. A total of 285 patients were included in the study. The patients were divided into two groups; group 1 with testicular malign neoplasms and group 2 includes the patients who underwent orchiectomy for cryptorchidism and atrophic testes without any malignancy and inflammation. The neutrophil, lymphocyte levels and neutrophil to lymphocyte ratio were compared between groups.

For statistical analysis, MedCalc Statistical Software demo version 16.2.0 (MedCalc Software bvba, Ostend, Belgium; <https://www.medcalc.org>; 2016) was used. Student *t*-test was used for comparing each parameter between groups. Data was expressed as mean \pm standard deviation and median value; $p < 0.05$ was considered as statistical significance. The area under the receiver operating characteristic (ROC) curves were measured for NLR, neutrophil and lymphocyte counts in the diagnosis of testicular malign neoplasms.

3. Results

The current study includes 285 patients; 126 and 159 patients were in group 1 and 2. The patients' age was between 10 and 90 with a mean age was 36.87 ± 11.83 and 37.24 ± 20.31 years in groups respectively. The patients characteristics are shown in Table 1. The neutrophil, white blood cell counts and NLR were significantly higher in group 1 than group 2. Lymphocyte count was lower in patients with testicular cancer with statistical significance.

The area under curve was calculated with ROC analysis. Fig. 1 shows the NLR, neutrophil and lymphocyte counts for the diagnosis of testicular cancer. Area under curve was 0.645, 0.626, 0.578 for NLR, neutrophil and lymphocyte counts (Table 2). There was significant difference between NLR and lymphocyte ($p = 0.03$). The cutoff value for NLR was >1.64 with sensitivity of 98.41% and specificity of 28.30%. When we use >2.52 and >4 the specificity was increased 43.40% and 74.21% and the sensitivity was decreased to 75.40% and 38.10 respectively. The cutoff value of lymphocyte and

Table 1
The haematological parameters of the patient.

	Group 1(n:126)	Group 2(n:164)	p value
Age, years	36.87 ± 11.83 (34.5)	37.24 ± 20.31 (32)	0.857
Neutrophil ($10^6/l$)	7857 ± 3261 (7525)	6597 ± 3731 (5690)	0.003*
Lymphocyte($10^6/l$)	2026 ± 656 (2055)	2374 ± 1085 (2250)	0.001*
NLR	4.54 ± 3.89 (3.50)	3.44 ± 2.89 (2.80)	0.006

The data were expressed as mean \pm standard deviation (median), p value for mean \pm standard deviation comparison.

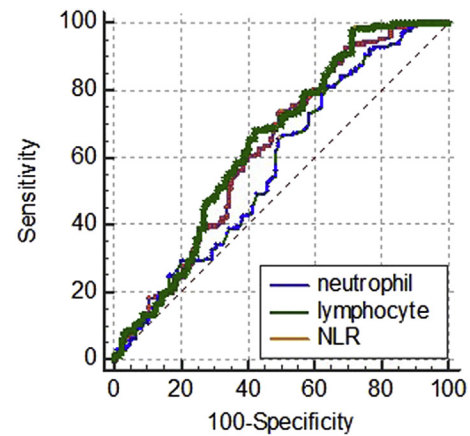


Fig. 1. The area under ROC curves for NLR, neutrophil and lymphocyte.

Table 2
The area under curve of the parameters.

Variable	AUC	SE	95% CI	p value
Neutrophil	0,626	0032	0,567 to 0,683	0,311 ^a
Lymphocyte	0,578	0033	0,519 to 0,636	0,033 ^c
NLR	0,645	0032	0,587 to 0,701	0,406 ^b

AUC: Area under curve SE: Standard error CI:Confidence Interval.

^a Comparison of neutrophil and lymphocyte.

^b Comparison of neutrophil and NLR.

^c Comparison of NLR and lymphocyte.

neutrophil was ≤ 2240 and > 5690 . The sensitivity and specificity of 65.87%–50.94% and 73.81%–50.31% for lymphocyte and neutrophil respectively.

In group 1, mixed germ cell tumor was the most common histologic subtype with an incidence of 51.58%(n:65 patients) and seminomas were reported 37.30% (n:47 patients) of the patients. In group 2, 74 patients were underwent orchiectomy for cryptorchidism and 85 patients had atrophic testes.

4. Discussion

Testicular tumors are usually classified as; germ cell tumors, sex cord-stromal tumors and miscellaneous tumors.³ Testicular germ cell tumor (TGCT) is the most common form that accounts more than 95% of all testicular malignancies.⁹ Treatment option is based on histopathology; although seminomas are sensitive to both radiotherapy and chemotherapy, nonseminomatous TGCT respond to chemotherapy only. In contrast, sex cord-stromal tumors are resistant to both radiotherapy and chemotherapy and are generally treated with orchiectomy and retroperitoneal lymphadenectomy. The authors reported that TGCT consists 95.2% and non-seminomatous tumors were the most common form with 64.7% of the patients.² Bhatti et al.,⁴ investigated the patients with testicular tumor and found that mixed germ cell was the most common type of tumor(48%). The current study showed that non seminomatous TGCT was detected in 59.52% of the patients and mixed germ cell tumor was the most common type with an incidence 51.58% of all patients.

It is now widely established that outcomes in patients with cancer are not associated by tumor characteristics alone, patient-related factors have important role for the clinical outcome.¹⁰ Cancer-associated inflammation is a key determinant of disease progression and survival. The host immun response in the form of systemic inflammation has been shown to independently predict the outcome in most of the cancers. There are some alterations in

circulating white blood cells such as neutrophilia with a relative lymphocytopenia in the systemic inflammatory response. Elevated NLR is a valuable predictive marker for various cancer types such as lung cancer, invasive bladder and testicular cancers.^{1,5,11} In addition, NLR has a prognostic value not only for these cancer diseases but also for sarcoidosis and depression diseases.^{12,13}

Elevated NLR means systemic and local inflammation that is associated with high infiltration of tumor-associated macrophages that provides tumor growth, invasion and evasion.⁶ In addition; macrophages and neutrophils produce tumor growth factors including epidermal growth factor, vascular endothelial growth factor, interleukin-6 and 8. These factors have a critical role for tumor microenvironment. Proangiogenic and proinvasive matrix-degrading enzymes including matrix metalloproteinase, elastases, cysteine cathepsin proteases and heparanase that promote tumor metastasis are produced by these cells. Relative lymphocytopenia means a lower level of CD4⁺ T helper lymphocytes that results suboptimal lymphocyte-mediated immune response to malignancy.¹⁴ Elevated NLR shows both increased neutrophil-dependent inflammatory reaction and decreased lymphocyte-mediated antitumor immune response. Thus elevated NLR may reflect the combined prognostic information both neutrophil-dependent inflammatory reaction and lymphocyte-mediated immune response, is a stronger predictor of the outcome than either of them considered alone.

The neutrophil to lymphocyte ratio is also widely used inflammatory marker that can be acquired from complete blood cell counts, it is cheap and easily calculated from blood cell count compared with other inflammatory markers. Although it has low cost and effective marker for malignancy, the cut-off NLR varies in the literature. The level was reported between 2 and 5 in a meta-analysis of Luo et al.⁶ Çetin et al.⁸ reported the cut-off level was 3.04 for the survival of the patients with metastatic renal cell carcinoma. Lee et al.¹¹ found the NLR cut-off >3.89 to predict the invasive bladder carcinoma preoperatively. The authors investigated the patients with localized testicular cancer and reported the NLR threshold value was 2.06.¹ The current study showed that NLR was higher in patients with testicular cancer ($p = 0.006$) and the cut-off >1.64 had a sensitivity of 98.41%.

Most of the articles for NLR were kidney, bladder and upper urinary tract neoplasms in the literature. To date there is only one study for testicular tumors in database of Pubmed. Yüksel et al.¹ investigated small group of patients (n:36 patients) with localized testicular cancers. They found the NLR value was 3.18 which was statistically higher than the control group. Our study revealed that NLR value was 4.57 and 3.44 in the patients with and without testicular cancer.

There are some limitations in the present study. Firstly, this study is retrospective design with including relatively small number of patients. Secondly, concurrent inflammatory conditions such

as infection or haematological disorder were not evaluated and the final stage of the patients were not analysed. Finally, there was missing data for disease specific and overall survival of the patients. To date, all of these limitations; this study includes the largest number of patients for investigating the association between NLR and testicular cancer.

In conclusion, there was statistically significant difference for NLR between the patients with and without testicular cancer. The NLR can be diagnostic biomarker for the patients with testicular cancer. Further well designed prospective multicenter studies are needed to define the diagnostic importance of NLR in testicular cancer.

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