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ORIGINAL PAPER

Increased neutrophil/lymphocyte ratio in testicular cancer

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Summary ***Objective: Testicular cancers, which are less common than other cancers, are important in terms of being seen in young people. Physical examination, imaging, laboratory and tumor markers are used for diagnosis. There are some studies of some blood parameters that can be involved in inflammation and tumorogenesis. We retrospectively compared hematological values measured in our patients who were diagnosed with testicular tumor in comparison with patients with similar age group who underwent varicocelectomy repair.***

Materials and methods: This cross-sectional retrospective study included 120 patients who underwent radical inguinal orchiectomy for testicular tumor between January 2010 and December 2018, and 171 patients who underwent varicocelectomy as a control group. Patients with an active infection and hematological disorders were excluded from the study. We evaulated hematological parameters including neutrophil (NEU), lymphocyte (LYM), platelet (PLT) count, and mean platelet volume. The study was conducted on 291 patients. divided in two groups: tumor (n = 120) and varicocele (n = 171).

Results: There was no statistically significant difference between the groups in terms of PLT / lymphocyte ratio and mean platelet volume (MPV) levels (p > 0.05). The neutrophil /lymphocyte ratio (NLR) of the tumor group was significantly higher than the varicocele group (p = 0.001; p < 0.05). There was a statistically significant difference between the tumor stages in terms of PLT / Lymphocyte ratios (p = 0.006; p < 0.05).

Conclusions: There was only a statistically significant increase in NLR values in the testicular tumor group compared to the varicocele group. Larger, randomized controlled studies are needed at this field.

KEY WORDS: *Testis; Cancer; Mean platelet volume (MPV); Neutrophil/lymphocyte ratio (NLR).*

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INTRODUCTION

Testicular cancers, which are less common than other cancers, are important because they are often seen in young people. It is the most common solid organ cancer in men between the ages of 15-35 while it contitutes 1-1.5% of all male cancers. In developed countries there is an increase incidence for testicular cancer (1). Both testes can be easily examined and results of early diagnosis of testicle tumours are very favorable enhancing the importance of early diagnosis and treatment of testicular tumors. Physical examination, imaging, laboratory and tumor markers are used for diagnosis. With early diagnosis more effective treatment schedules can be applied contributing to better survival. At this point, simple, inexpensive and easily applicable markers can be useful in the clinical approach. There are some studies that some blood parameters can be associated to inflammation and tumorogenesis. Studies have shown that inflammatory response is closely related to tumorigenesis and tumor invasion (2). Interactions occur between the tumor and inflammation according to complex and various mechanisms. At each stage of carcinogenesis; inflammation has an important role (3). Changes in systemic inflammatory response can be assessed by hematological parameters. For example, changes in *C-reactive protein* (CRP) and *neutrophil to lymphocyte ratio* (NLR) show signs of systemic inflammatory response in various malignancies (4). There are also reports that elevated NLR is associated with poor prognosis in some urothelial cancers (5). The vast majority of studies have reported that the increase in NLR is associated with poor prognosis in many malignant tumors. For this reason, NLR can be used not only as a marker of systemic inflammatory response, but also in various tumor types and inflammatory conditions (6). In order to predict cancer prognosis and inflammatory conditions, there is a growing interest in simple blood methods such as NLR. NLR, *lymphocyte-monocyte ratio* (LMR), *platelet-lymphocyte ratio* (PLR) and *mean platelet volume* (MPV) can be used as factors to determine the prognosis of patients in various clinical situations (7). Platelets are seedless cells derived from megakaryocytes in the bone marrow. Platelets, an element of the immune system, also play a role in cancer formation, progression and metastatization. It is known that activated platelets have critical roles in tumor proliferation, neoangiogenesis and release of mitogenic mediators in the microenvironment of cells that exhibit tumoral behavior, although their production, maturation and clearance from circulation are still not fully elucidated (8).

Yun ZY et al. Reported that decreased MPV may be a marker of poor prognosis in renal cell cancer (9). Because it is known that MPV is an index of bioactive platelets activated for any reason and incorporated into the inflammation process, rather than platelet count (10). These markers, which are easily applicable in practice, were retrospectively analyzed in our patients who were diagnosed with testicular tumor and compared with the values of patients with similar age group of patients who underwent varicocelectomy repair.

No conflict of interest declared.

Materials and methods

This cross-sectional retrospective study included 120 patients who underwent radical inguinal orchiectomy for testicular tumor between January 2010 and December 2018, and 171 patients who underwent varicocelectomy as a control group.

Patients with acute infections, chronic inflammatory disease, malignancies or hematological disorders, those using anticoagulant treatment, and subjects with a history of hormonal treatment in the last 12 months or blood product administration in the last month were excluded.

Hematological parameters were evaluated with peripheral blood samples taken preoperatively.

These hematological parameters include *neutrophil* (NEU), *lymphocyte* (LYM), platelet count, and *mean platelet volume* (MPV).

The staging of patients with testicular tumors was performed by examining the computed tomography and by measurement of beta human chorionic gonadotropin, alpha fetoprotein and *lactate dehydrogenase* (LDH) as tumor markers.

Statistical analysis

To evaluate the findings obtained in this study, IBM SPSS Statistics 22 for statistical analysis (*SPSS IBM, Turkey*) program was used. Conformity of the parameters to the normal distribution was evaluated by the Shapiro Wilks test. Descriptive statistical values were computed (mean, standard deviation, frequency) and the comparison of quantitative data were done by Kruskal Wallis test and the Mann Whitney U test was used for the determination of the group causing the difference. Mann-Whitney U test was used for the two-group comparisons of the parameters that did not show normal distribution, and Student's t test was used for the parameters with normal distribution. The cut-off point was chosen based on the ROC curve analysis.

A $p < 0.05$ was considered significant.

Results

The study was conducted on 291 patients with ages ranging from 1 to 85 years. The mean age was 34.25 ± 16.56 years. The cases were divided into two groups: tumor (n = 120) and varicocele (n = 171). There was no statistically significant difference between the groups in terms of PLT/lymphocyte ratio and MPV levels ($p > 0.05$). The neutrophil/lymphocyte ratio of the tumor group was significantly higher than the varicocele group ($p = 0.001$; $p < 0.05$) (Table 1, Figure 1).

There was a statistically significant difference between the tumor stages in terms of PLT/Lymphocyte ratios ($p = 0.006$; $p < 0.05$). Paired comparisons demonstrated that PLT/lymphocyte ratio of pT3 group was significantly higher than pT1 and pT2 ($p1 = 0.002$; $p2 = 0.003$; $p < 0.05$). There was no significant difference between pT1 and pT2 stages ($p > 0.05$).

There was no statistically significant difference in neutrophil/lymphocyte ratio and MPV levels between tumor stages ($p > 0.05$) (Table 2).

The ROC curve for *neutrophil/lymphocyte ratio* (NLR) was plotted in the diagnosis of testicular tumor. The area

Table 1.

Evaluation of groups in terms of PLT/Lymphocyte, Neutrophil/Lymphocyte ratio and MPV.

	Tumor Mean ± SD (median)	Varicocele Mean ± SD (median)	p
PLT/lymphocyte	128.91 ± 95.19 (110.4)	125.45 ± 63.3 (110.8)	0.907[1]
Neutrophil/lymphocyte	4.22 ± 3.54 (3.5)	3.49 ± 2.79 (2.7)	0.001*, [1]
MPV	8.05 ± 1.46	8.28 ± 1.56	0.214[2]

*[1] Mann Whitney U Test; [2] Student t test; * p < 0.05.*

Figure 1.

Stone expulsion duration in the groups.

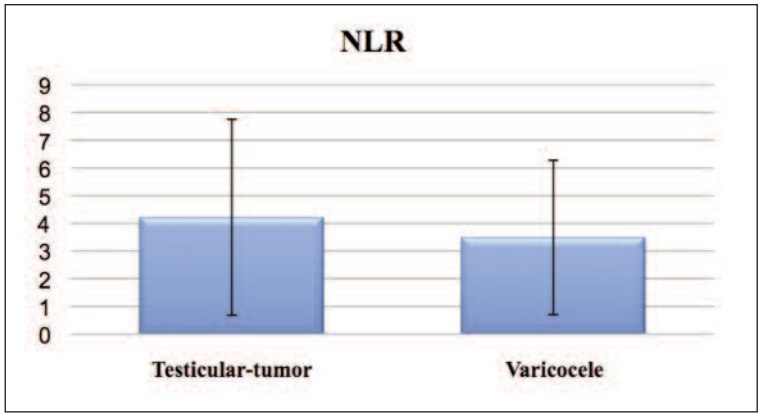


Table 2.

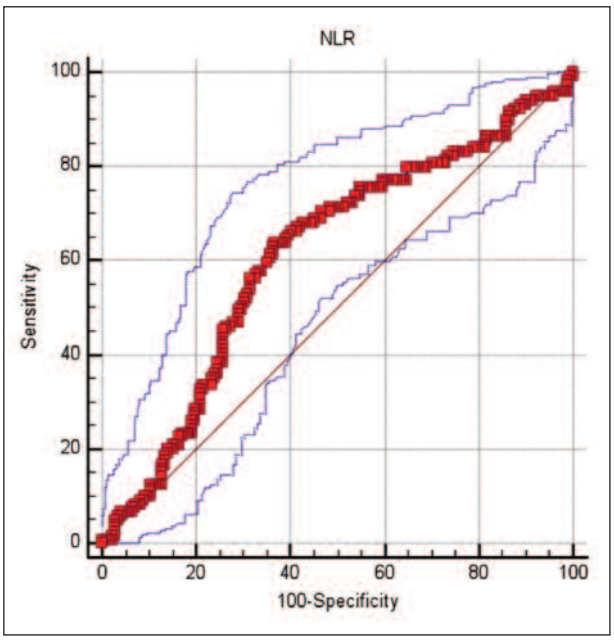
Evaluation of groups in terms of PLT/Lymphocyte, Neutrophil/Lymphocyte ratio and MPV.

	pT1 (n = 60) Mean ± SD (median)	pT2 (n = 43) Mean ± SD (median)	pT3 (n = 5) Mean ± SD (median)	p
PLT/Lymphocyte	115.57 ± 58.01 (108.1)	140 ± 135.35 (110.4)	231.27 ± 74.21 (212.5)	0006*
Neutrophil/lymphocyte	3.83 ± 2.58 (3.4)	4.62 ± 4.94 (3.5)	5.78 ± 1.87 (6.3)	0.108
MPV	8.26 ± 1.62 (7.9)	7.92 ± 1.19 (7.8)	7.24 ± 0.82 (7.2)	0.107

*Kruskal Wallis Test; * p < 0.05.*

NOTE: Since the number of patients with pT3 was 5, Kruskal Wallis test was used despite the normal distribution of MPV.

Figure 2.
ROC curve for NLR in the diagnosis of testicular tumor.



Cut off point determination for NLR in the diagnosis of testicular tumors.

under the curve is 0.612 and the standard deviation is 0.03. The area under the ROC curve was significantly higher than 0.5 ($p = 0.001$; $p < 0.05$). The cut-off point for NLR in the diagnosis of testicular tumor is > 3.16. The sensitivity of this value was 63.87% and the specificity was 63.16% (Figure 2).

Discussion

Inflammation plays an important role in tumor development and progression. The relationship between inflammation and cancer has long been known.

In 1863, *Virchow* put forward the hypothesis that cancer occurs in the areas of chronic inflammation, and that some irritants increase cell proliferation along with inflammation leading to tissue injury (11). Although the effect of this proliferation is clear, cells alone do not cause cancer.

Continuous cell proliferation, inflammatory cells, growth factors, activated stroma and DNA-damage enhancing agents increase or promote neoplastic risk. Neutrophils mediate inflammation through various biochemical mechanisms such as release of arachidonic acid metabolites and platelet aggravating factors (12). Neutrophilia could represent a consequence of ectopic production of myeloid growth factors as part of a paraneoplastic syndrome (13) or, more likely, a nonspecific response to cancer-related inflammation secondary to tissue destruction and cytokine releases. Lymphopenia is associated with cortisol induced stress response (12). High NLR occurring as a result of the added effect of increased NEU response to LYM suppression can support the development of cancer by inhibiting the antitumor immune response (14). Experimental data have shown that active neutrophils can stimulate tumor growth directly and indirectly (15).

NLR and *platelet/lymphocyte ratio* (PLR) have also been shown to be reliable markers of systemic inflammation by many studies (16). According to the type of malignancy, inflammatory and immune responses to systemic tumor cells and secreted peptides can vary. Today, systemic inflammatory response indicators such as cytokine, CRP, albumin, serum amyloid A and leukocytes have gained importance in the patients with malignancy and it has been thought that they can be independent prognostic factors (17). The immune system has a positive and negative effect on cancer development and progression. It can eliminate tumor cells or increase the metastatic ability and invasion capacities of active malignant cells, leading to tumor progression. The excess of circulating NEUs is thought to play an important role in tumor progression and angiogenesis.

Therefore, increased number of NEUs should be associated with poor prognosis (18). MPV represents the mean platelet size in the blood. It can be altered in various diseases such as cancer, thrombosis, sepsis, respiratory distress syndrome, and acute appendicitis (19). PLTs are frequently observed in the cancer microenvironment and are thought to stimulate proliferation and transformation of cancer cells by *platelet derived growth factor* (PDGF) release (20). In the study of *Russell et al.*, It was reported that increased PDGF alpha receptor expression was associated with bone metastasis in castration-resistant PCa (21). Even in the current literature, anti-platelet therapy has been reported to have a role in PCa adjuvant therapy (22). MPV measurement is a useful method in determining the presence of these activated PLTs (9). A high MPV means that your platelets are larger than average. This is sometimes a sign that you're producing too many platelets. Platelets are produced in the bone marrow and released into the bloodstream. Larger platelets are usually young and more recently released from the bone marrow. Smaller platelets are more likely to have been in circulation for a few days.

When someone has a low platelet count and a high MPV level, it suggests that the bone marrow is rapidly producing platelets. This may be because older platelets are being destroyed, so the bone marrow is trying to compensate. Increased MPV is associated with platelet activation, which can happen when platelets encounter tumor byproducts. Still, a high MPV doesn't mean you have cancer. The diagnostic role of *mean platelet volume* (MPV) is reported in various malignant tumors such as ovary (23), pancreas (24), and colon (25) cancers, the diagnostic and prognostic role of MPV cannot be precisely demonstrated for testicular tumors.

In a study conducted by *Gokcen K et al.*, 36 patients with testicular tumors were investigated. WBC, NEU, PLR, and NLR values were significantly higher in testicular tumors however MPV was significantly lower than the control group $p < 0.05$). Also differences between hematological parameters of patients with testicular cancer according to the stages were examined, and differences were observed between *mean corpuscular volume* (MCV), *mean corpuscular hemoglobin* (MCH) and *mean platlet volume* (MPV) ($p < 0.05$). MCV was significantly higher in Stage 1 compared

to Stage 2 or 3 tumour (p = 0.035 and p = 0.025, respectively). MCH was significantly higher in Stage 1 compared to Stage 3 (p = 0.022). MPV was significantly lower in Stage 1 compared to Stage 3 (p = 0.016) (26). In our study, the neutrophil/lymphocyte ratio of the tumor group was significantly higher than the varicocele group (p = 0.001; p < 0.05), but there was no statistically significant difference between the groups in terms of PLT/lymphocyte ratio and MPV levels (p > 0.05). On the other hand we found that there was no statistically significant difference between the tumor stages in terms of Neutrophil/lymphocyte ratio and MPV levels (p > 0.05). In contrast, there was a statistically significant difference in terms of PLT/lymphocyte ratios (p: 0.006; p < 0.05). As a result of paired comparisons PLT/lymphocyte ratio of pT3 group was significantly higher than pT1 and pT2 (p1: 0.002; p2: 0.003; p < 0.05). There was no significant difference between pT1 and pT2 stages (p > 0.05).

Limited numbers of reports are available on immune resistance in patients with testicular cancer.

Considerable evidence supports the view that the biological behavior of tumors and in particular, their capacity to metastasize are in part determined by immunological factors requiring participation of T lymphocytes, B lymphocytes, macrophages and natural killer cells. Immunological reactivity has been analyzed in a wide spectrum of solid tumors and a vast literature indicates a correlation between depressed cell-mediated immunity and the stage of the disease.

On the contrary, there is little evidence about the role of immunological factors in the development and spread of testicular tumors.

Conclusions

In this study, there was only statistically significant increase in NLR values in the testicular tumor group compared to the varicocele group. There was no statistically significant result for MPV and PLR. In the evaluation of patients with testicular tumors according to their stages, the PLT/lymphocyte ratio of the pT3 group was found to be significantly higher than the pT1 and pT2 stages. Although there are many studies on hematological parameters related to other cancers, there is limited data for testicular tumors in the literature.

The limitations of our study were that it was a retrospective one with limited study group and had not a prognostic predictive design. Larger, randomized controlled studies are needed at this field.

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