

Can routine peripheral blood counts like neutrophil-to-lymphocyte ratio be beneficial in prediagnosis of testicular cancer and its stages?

Kaan Gokcen, Gokce Dundar¹, Halil Gulbahar, Gokhan Gokce, Emin Yener Gultekin

Department of Urology, Cumhuriyet University Faculty of Medicine, Sivas, ¹Urology Clinic, Cizre State Hospital, Sirnak, Turkey

Background: The purpose of this study was to assess the diagnostic role of preoperative hematological parameters, especially neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and mean platelet volume (MPV) in germ cell testicular malignancies and their prediagnostic role in staging of testicular cancer. **Materials and Methods:** In this cross-sectional retrospective study, we analyzed 39 patients who underwent radical orchiectomy due to a testicular cancer (Group 1) and 82 patients on whom varicocelectomy procedure was performed as control group (Group 2) between January 2006 and January 2016 in our clinic. Evaluation of the preoperative hematological parameters in both groups and also the subgroups in malignancy group according to histopathological stages was conducted in this study. **Results:** When the hematological parameters were compared, a statistically significant difference was found between the two groups in terms of neutrophil counts, NLR, PLR, and MPV. NLR and PLR were significantly higher and MPV was significantly lower in testicular cancer group compared to the control group. NLR was 3.1 ± 1.4 and 2.0 ± 1.5 , PLR was 141.3 ± 53.2 and 115.7 ± 44.8 , and MPV was 8.9 ± 1.0 and 9.3 ± 1.1 for testicular cancer and control groups, respectively ($P < 0.05$). Furthermore, differences were observed between only mean corpuscular volume, mean corpuscular hemoglobin, and MPV ($P < 0.05$) in different stages of malignancy. **Conclusion:** In accordance with these findings, NLR, PLR, and MPV may be helpful for prediagnosis of testicular malignancies. Hematological parameters will become important in the preoperative assessment for those patients.

Key words: Hematological parameters, neutrophil-to-lymphocyte ratio, testicular cancer

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INTRODUCTION

Studies have shown that inflammatory response is closely correlated with tumorigenesis and progression of the tumors.^[1] The interactions between the tumor and inflammation occur through complex and various mechanisms. Inflammation has a significant role in every stage of carcinogenesis including the onset of tumor, angiogenesis, apoptosis inhibition, and tumor metastasis.^[2]

Changes in the systemic inflammatory response can be reflected by measuring the hematological parameters. Blood-based indexes such as Modified Glasgow

Prognostic Score, neutrophil-to-lymphocyte ratio (NLR), and C-reactive protein (CRP) are examined for their capability of prognosis of various malignancies.^[3,4] It is shown that increased preoperative NLR is correlated with poor prognosis in patients with various malignancies including urothelial cancers.^[5] A great majority of the studies have reported that the increase in NLR is related to poor clinical results in many malignant tumors.^[6] It is shown that NLR can be used as an indicator of systemic inflammatory response in not only several tumor types but also other inflammatory situations and various diseases.^[6,7] It is reported that NLR, which is found at higher levels within the scope of preoperative assessments, can be an indicator related to poor prognosis factor and pathological staging in urologic

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Address for correspondence: Dr. Gokce Dundar, Urology Clinic, Cizre State Hospital, TR-73200, Sirnak, Turkey.

E-mail: dr@gokcedundar.com

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tumors,^[8,9] as well as gastric cancer,^[10] hepatocellular carcinoma,^[3] breast cancer,^[11] and pancreatic cancer.^[12]

In malignant tumors, platelets (PLTs) take place in the inflammatory process and may cause tumor progression and angiogenesis.^[13] A meta-analysis demonstrated that platelet-to-lymphocyte ratio (PLR) could act as a significant biomarker in the prognosis of various cancers.^[14] Even though the diagnostic role of mean platelet volume (MPV) is reported in various malignant tumors such as ovary,^[15] pancreas,^[16] and colon^[17] cancers, the diagnostic and prognostic role of MPV cannot be precisely revealed for testicular tumors.

Although testicular tumors constitute only approximately 1% of all the solid tumors in men, it is the most common solid malignancy affecting men between the ages of 15 and 35.^[18] Testicular tumors are gathered in two main categories as germ cell tumors with a prevalence of 95% and sex cord-stromal tumors with a prevalence of 5%.

The purpose of this study was to assess whether preoperative hematological parameters have a predictive role in the diagnosis of testicular cancer and the determination of its stages.

MATERIALS AND METHODS

This cross-sectional retrospective study included 39 patients who underwent radical orchiectomy due to testicular cancer and 82 patients as the control group who underwent varicocelectomy between January 2006 and January 2016 in a urology service in a tertiary care center. Inclusion criteria were the determination of germ cell testicular malignancies in the pathology results for the patient group and the presence of varicocelectomy operation for control group. Exclusion criteria were the presence of nongerm cell testicular malignancies in testicular cancer group and the presence of an active infection process in both groups. Hematological parameters were evaluated by peripheral blood samples taken during preoperative period. These hematological parameters were as follows: white blood cell (WBC), neutrophil (NEU), lymphocyte (LYM), monocyte, eosinophil, red blood cell, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), MCH concentration, red cell distribution width, PLT, platelet hematocrit, and MPV.

Staging of the patients with testicular tumor was performed by examining the computed tomography and beta-human chorionic gonadotropin, alpha-fetoprotein, and lactate dehydrogenase (LDH) parameters as tumor markers. For this study, the approval of the University Ethics Committee for Non-invasive Clinical Trials was obtained

(No: 2016-02/04). All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional and/or National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Analysis of variance was used on variables that fit parametric distribution for the comparison of variables having more than two categories, and similarly, Student's *t*-test was used on variables that fit parametric distribution for the comparison of variables with only two categories. Least square difference method was used as a *post hoc* test when a significant result was obtained from the analysis of variance. Confidence level of the tests was set as 95%.

RESULTS

Mean age of patients in cancer group and control group was 30.1 ± 7.0 and 28.5 ± 5.5 (mean \pm standard deviation) years, respectively. There was no significant difference between their ages ($P = 0.224$). Among the testicular cancer patients, 25 were in Stage 1, 4 were in Stage 2, and 10 were in Stage 3. The mean ages and standard deviations according to stages were as follows: 32.0 ± 7.2 , 26.8 ± 2.5 , and 26.4 ± 5.9 in Stages 1, 2, and 3, respectively ($P = 0.055$; >0.05). WBC, NEU, PLR, and NLR values were significantly higher in patients with testicular cancer; however, MPV was significantly lower ($P < 0.05$). WBC was 8.4 ± 2.2 and 7.1 ± 1.5 , NEU was 5.7 ± 2.1 and 4.1 ± 1.3 , NLR was 3.1 ± 1.4 and 2.0 ± 1.5 , PLR was 141.3 ± 53.2 and 115.7 ± 44.8 , and MPV was 8.9 ± 1.0 and 9.3 ± 1.1 for testicular cancer and control groups, respectively ($P = <0.001$, <0.001 , <0.001 , <0.013 , and <0.047 , respectively, <0.05). There was no significant difference between the groups in terms of other hematological parameters. Hematological parameters of the groups were shown in Table 1.

Cutoff values and receiver operating characteristic analysis of NEU, NLR, PLR, and MPV according to cancer group and control group are shown in Table 2 and Figure 1.

Differences between hematological parameters of patients with testicular cancer according to the stages were examined, and differences were observed between MCV, MCH, and MPV ($P < 0.05$). MCV was significantly higher in Stage 1 compared to Stage 2 or 3 ($P = 0.035$ and $P = 0.025$, respectively). MCH was significantly higher in Stage 1 compared to Stage 3 ($P = 0.022$). MPV was significant lower in Stage 1 compared to Stage 3 ($P = 0.016$). Hematological parameters of patients with testicular cancer according to the stages were displayed in Table 3.

Even though NLR and PLR were significantly higher in patients with testicular cancer; when this discrepancy was

Table 1: Hematological parameters of groups and Student's t-test results

Parameter (unit)	Testicular cancer (n=39)	Control (n=81)	Reference value	P
WBC ($10^3/\mu\text{L}$)	8.4±2.2	7.1±1.5	4-11	<0.001*
NEU ($10^3/\mu\text{L}$)	5.7±2.1	4.1±1.3	2-7.5	<0.001*
LYM ($10^3/\mu\text{L}$)	2.0±0.6	4.6±1.4	1-3.47	0.271
MON ($10^3/\mu\text{L}$)	0.5±0.2	0.5±0.2	0.3-0.8	0.095
EOS ($10^3/\mu\text{L}$)	0.1±0.1	0.2±0.1	0-0.40	0.128
RBC ($10^6/\mu\text{L}$)	5.4±0.4	5.5±0.4	4.6-6.2	0.096
HB (g/dL)	16.1±1.3	16.2±0.9	14-18	0.841
HCT (%)	46.5±5.7	47.4±2.9	42-52	0.241
MCV (fL)	87.6±4.7	86.1±4.9	80-94	0.100
MCH (pg)	29.8±1.7	29.3±1.8	27-34	0.173
MCHC (g/dL)	34.1±0.9	34.1±0.9	30-35	0.916
RDW (%)	13.2±1.0	13.2±0.8	11.7-14.3	0.983
PLT ($10^3/\mu\text{L}$)	263.3±66.7	243.2±51.6	150-400	0.103
MPV (fL)	8.9±1.0	9.3±1.1	6.1-11	0.047*
PCT (%)	0.2±0.1	0.2±0.1	0.12-0.36	0.369
LMR (%)	4.3±1.6	13.1±54.0	Unknown	0.143
PLR (%)	141.3±53.2	115.7±44.8	Unknown	0.013*
NLR (%)	3.1±1.4	2.0±1.5	Unknown	<0.001*

*P<0.05. Data were presented as mean±SD. WBC=White blood cell; NEU=Neutrophil; LYM=Lymphocyte; MON=Monocyte; EOS=Eosinophil; RBC=Red blood cell; HB=Hemoglobin; HCT=Hematocrit; MCV=Mean corpuscular volume; MCH=Mean corpuscular hemoglobin; MCHC=Mean corpuscular hemoglobin concentration; RDW=Red cell distribution width; PLT=Platelet; MPV=Mean platelet volume; PCT=Platelet hematocrit; LMR=Lymphocyte-to-monocyte ratio; PLR=Platelet-to-lymphocyte ratio; NLR=Neutrophil-to-lymphocyte ratio; SD=Standard deviation

Table 2: Cutoff values of neutrophil, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and mean platelet volume

Parameter	Cutoff value	Sensitivity (%)	Specificity (%)	PPV	NPV
NEU	4.36	0.769	0.610	0.847	0.484
NLR	2.25	0.667	0.744	0.824	0.553
PLR	124.69	0.564	0.744	0.782	0.512
MPV	7.35	0.974	0.061	0.833	0.330

PPV=Positive predictive value; NPV=Negative predictive value; NLR=Neutrophil-to-lymphocyte ratio; NEU=Neutrophil; PLR=Platelet-to-lymphocyte ratio; MPV=Mean platelet volume

examined, no significant differences were found between those patients according to the stages ($P = 0.247$, $P = 0.791$, respectively).

DISCUSSION

Inflammation has a critical role in tumor development, progression, clinical presentation, and prognosis. According to the type and prevalence of malignancy, systemic inflammatory and immune responses to the tumor cells and the peptides secreted by them vary. Tumor and the interaction of its host have important effects on tumor development. Today, in patients with malignancies, systemic inflammatory response indicators such as cytokines, CRP, albumin, serum amyloid A, and leukocytes

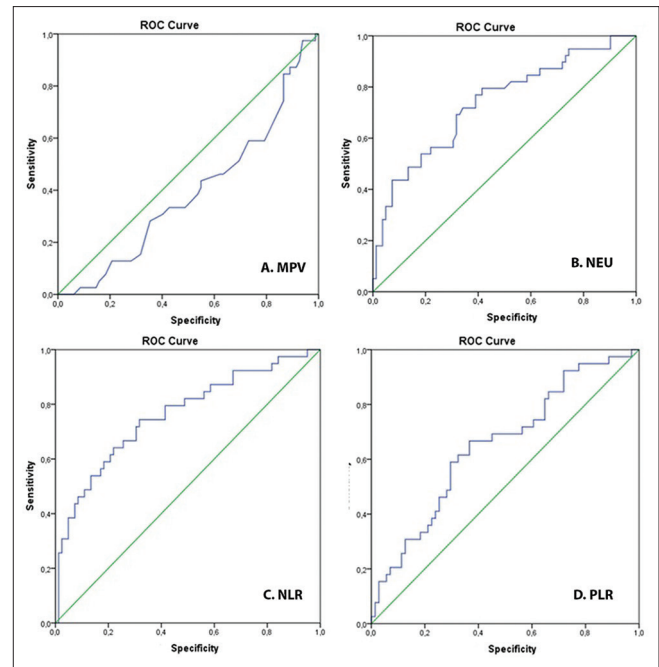


Figure 1: Receiver operating characteristic analysis of neutrophil, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and mean platelet volume

have gained importance, and it is thought that they can be independent prognostic factors.^[9]

Immune system has a binary function on the development and progression of cancer. It may eliminate the tumor cells or may cause the progression of the tumor by increasing the invasive capacities and metastatic skills of the active malignant cells. It is thought that excess number of circulating NEUs has an important role in the progression and angiogenesis of the tumor. Thus, the increased NEU count should be related to poor prognosis.^[19]

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.^[20,21] Neutrophilia can be a result of ectopic production of myeloid growth factors as a part of paraneoplastic syndrome or may form an inflammation response related to cancer together with the cytokines appearing as a result of tissue destruction.^[22] Experimental studies have shown that activated NEUs can directly and indirectly activate tumor growth.^[23] Molecular pathways used by inflammatory mediators can support the angiogenesis and metastasis of cancer cells and thus affect the tumor response of the treatments.^[24]

Peripheral blood tests before treatment or during diagnosis may reflect the inflammatory situations in the tumor. Through complete blood count, which is a cheap

Table 3: Hematological parameters of patients with testicular cancer according to the stages and F-test results

Parameter (unit)	Stage 1	Stage 2	Stage 3	Reference value	P
WBC ($10^3/\mu\text{L}$)	8.5±2.3	7.1±1.4	8.7±2.2	4-11	0.434
NEU ($10^3/\mu\text{L}$)	5.8±2.1	4.3±1.3	6.1±2.1	2-7.5	0.322
LYM ($10^3/\mu\text{L}$)	2.0±0.6	2.1±0.4	1.9±0.5	1-3.47	0.812
MON ($10^3/\mu\text{L}$)	0.5±0.2	0.4±0.2	0.5±0.1	0.27-0.80	0.436
EOS ($10^3/\mu\text{L}$)	0.1±0.1	0.2±0.2	0.1±0.1	0-0.40	0.428
RBC ($10^6/\mu\text{L}$)	5.4±0.4	5.4±0.1	5.4±0.4	4.6-6.2	0.980
HB (g/dL)	16.4±1.2	15.6±1.2	15.6±1.3	14-18	0.140
HCT (%)	46.9±6.8	45.7±3.3	45.9±3.0	42-52	0.856
MCV (fL)	89.1±4.4	84.0±5.0	85.3±3.7	80-94	0.021 ^{a,b}
MCH (pg)	30.3±1.4	28.7±2.0	28.9±1.8	27-34	0.029 ^b
MCHC (g/dL)	34.1±0.8	34.2±0.9	33.9±1.1	30-35	0.792
RDW (%)	13.0±0.8	13.6±2.0	13.4±0.9	11.70-14.30	0.399
PLT ($10^3/\mu\text{L}$)	257±61	293±49	267±86	150-400	0.612
MPV (fL)	8.7±0.9	8.63±1.3	9.6±0.8	6.05-11	0.043 ^b
PCT (%)	0.2±0.1	0.25±0.03	0.3±0.1	0.12-0.36	0.217
LMR (%)	4.1±1.6	5.44±1.5	4.2±1.6	Unknown	0.294
PLR (%)	137.6±51.0	138.7±20.3	151.4±68.6	Unknown	0.791
NLR (%)	3.1±1.3	2.1±0.7	3.4±1.6	Unknown	0.247

^aDifference is between stages 1 and 2 ($P<0.05$); ^bDifference is between stages 1 and 3 ($P<0.05$). Data were presented as mean±SD. WBC=White blood cell; NEU=Neutrophil; LYM=Lymphocyte; MON=Monocyte; EOS=Eosinophil; RBC=Red blood cell; HB=Hemoglobin; HCT=Hematocrit; MCV=Mean corpuscular volume; MCH=Mean corpuscular hemoglobin; MCHC=Mean corpuscular hemoglobin concentration; RDW=Red cell distribution width; PLT=Platelet; MPV=Mean platelet volume; PCT=Platelet hematocrit; LMR=Lymphocyte-to-monocyte ratio; PLR=Platelet-to-lymphocyte ratio; NLR=Neutrophil-to-lymphocyte ratio; SD=Standard deviation

and straightforward test, NLR, PLR, MPV, and other hematological parameters can be calculated and provide prognostic information for the patients in the treatment of diseases.^[25]

In previous studies, correlation was determined between high NLR and tumor grade and stage, detected in 122 patients who underwent transurethral resection-bladder due to bladder tumor and were newly diagnosed with muscle noninvasive bladder tumor.^[26] In most of the studies assessing the correlation between radical cystectomy results and NLR, high NLR results and worse ratios are found in disease-specific and general survival.^[8,27]

Wei *et al.* published a meta-analysis from 17 published studies including 3159 cases to assess the prognostic value of NLR in the patients with urinary system cancer. In this meta-analysis, high NLR in the subgroup analyses performed according to cancer type is correlated with poor general survival in renal cell carcinoma, bladder cancer, and urothelial carcinomas.^[28]

NLR threshold value is accepted as 2.5 in addition to determination of age, female gender, NLR, and PLT counts as an invasiveness indicator in urothelial carcinoma.^[25] In a study conducted on RCC cases, it was shown that an NLR of 2.78 and above and a PLR of 185 and above were associated with decreased general survival.^[29] In the present study, it was found that NLR was 3.07 ± 1.38 in the group of patients with testicular cancer and 2.01 ± 1.49 in the control

group of patients undergoing varicocelectomy. We found that an NLR threshold value of 2.25 can be acceptable in testicular tumors.

In a study conducted on 36 patients with testicular tumor to examine NLR in patients with testicular tumor, a significant difference was found compared to the control group similar to the results obtained in this study.^[29] In addition, in the present study, it was determined that NLR showed no statistically significant difference in various stages of the tumor. In the present study, a statistically significant difference was found between the groups in terms of PLR, like NLR ($P < 0.05$).

In the study of Song *et al.*, conducted on patients with upper urinary system urothelial carcinoma undergoing nephroureterectomy, it was found that NLR and PLR were significantly higher in the patients having advanced-stage tumors, similar to the results obtained in the present study. In this study, it was found that lymphocyte/monocyte ratio (LMR) significantly decreased in advanced-stage tumors, and NLR was a superior predictive factor than LMR.^[30] In the present study, even though LMR was lower in the patients with testicular tumor, the difference was not statistically significant.

CONCLUSIONS

In the present study, it was found that particularly NLR, PLR, and MPV were significantly higher in testicular tumor

compared to the control group as similar to other cancers. While there are numerous studies on other cancers related to hematological parameters, there is a limited amount of data for testicular tumor in the literature. These practical and simple hematological parameters may be associated with the diagnosis of testicular cancer and its stage. Especially, NLR, PLR, and MPV may be helpful in diagnosis of germ cell testicular malignancies in addition to other accepted serum tumor markers. However, these parameters were insufficient in predicting the stage of the tumor as indicated by the results of this study, which was a limitation of our study due to the low number of the patients in each stage subgroup.

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Conflicts of interest

There are no conflicts of interest.

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