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# The predictive role of preoperative full blood count markers and the De-Ritis ratio in the diagnosis of testicular tumor

## *Preoperatif tam kan sayımı belirteçleri ve De-Ritis oranının testis tümörünün tanısındaki prediktif yeri*

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**ABSTRACT**

**Aim:** To determine the value of neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), systemic immune-inflammation (SII) index and De-Ritis ratio, which are among preoperative whole blood and biochemical parameters, in the diagnosis of testicular tumor.

**Materials and Methods:** The data of patients who underwent inguinal orchiectomy for testicular tumor in our clinic between October 2010 and December 2019 and patients who underwent varicocelectomy, as a control group, were retrospectively analyzed. Patients with missing data, under 18 years of age or with additional morbidity were excluded from the present study. Prediction values for NLR, PLR, LMR, SII index and De-Ritis ratio were determined and the value of these parameters in the diagnosis of testicular tumor was examined.

**Results:** Thirty-four (14.1%) patients underwent inguinal orchiectomy while 207 (85.9%) patients underwent varicocelectomy in the present study. The median age of the patients during surgery was 27 (23-32) years. The number of patients with seminoma, mixt germ cell tumor, yolk sac tumor and embryonal carcinoma was 18 (52.9%), 12 (35.3%), 3 (8.8%) and 1 (2.9%), respectively. It was determined that 61.8% of the patients with testicular tumors were in the T2 stage and 35.3% had metastasis. The cut-off values for NLR, PLR, LMR and SII index were determined as 1.76, 133.43, 7.81 and 571.63, respectively. There was no statistically significant cut-off value for De-Ritis ratio ($p = 0.183$). The only significant factor for predicting testicular tumor was SII index in multivariate analysis ($p < 0.001$).

**Conclusion:** SII index is a predictive factor that can be used in the diagnosis of testicular tumor.

**Keywords:** Inflammation, cancer, lymphocyte count, neutrophil count, testicular tumor.

***ÖZ***

***Amaç:*** *Preoperatif tam kan ve biyokimyasal parametrelerden nötrofil-lenfosit oranı (NLO), trombosit-lenfosit oranı (TLO), lenfosit-monosit oranı (LMO), sistemik immün-inflamasyon (SII) indeksi ve De-Ritis oranının testis tümörü tanısındaki yerinin belirlenmesi.*

***Gereç ve Yöntem:*** *Ekim 2010 ile Aralık 2019 tarihleri arasında kliniğimizde testis tümörü nedeniyle inguinal orşiektomi yapılan hastaların ve kontrol grubu olarak varikoselektomi yapılan hastaların verileri retrospektif olarak incelendi. Verileri eksik olan, 18 yaşın altında olan veya ek morbiditesi olan hastalar çalışma dışında bırakıldı. NLO, TLO, LMO, SII indeksi ve De-Ritis oranı için kestirim değerleri belirlendi ve bu parametrelerin testis tümörü tanısındaki yeri incelendi.*

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***Bulgular:*** *Çalışmaya dahil edilen hastaların 34'ünü (%14,1) testis tümörlü hastalar, 207'sini (%85,9) varikoselektomi yapılan hastalar oluşturmaktaydı. Hastaların ameliyat esnasındaki ortanca yaşlarının 27 (23-32) yıl olduğu görüldü. Testis tümörlü hastaların 18'inde (%52,9) seminom, 12'sinde (%35,3) mikst germ hücreli tümör, 3'ünde (%8,8) yolk sac tümörü ve 1'inde (%2.9) embriyonel karsinom izlendi. Testis tümörlü hastaların %61,8'inin T2 evresinde ve %35,3'ünde metastaz olduğu belirlendi. NLO, TLO, LMO ve SII indeksi için sırasıyla kestirim değerleri 1,76, 133,43, 7,81 ve 571,63 olarak belirlendi. De-Ritis oranı için istatistiksel olarak anlamlı bir kestirim değeri bulunamadı (p=0.183). Çok değişkenli analiz yapıldığında, sadece SII indeksinin testis tümörünün öngörülmesinde anlamlı olduğu görüldü (p<0.001).*

***Sonuç:*** *SII indeksi testis tümörü tanısında kullanılabilecek prediktif bir faktördür.*

***Anahtar Sözcükler:*** *Inflamasyon, kanser, lenfosit sayısı, nötrofil sayısı, testis tümörü.*

## INTRODUCTION

Testicular tumor is the most common malignancy in the male population aged 15-40 years, with an increasing incidence over the last 30 to 40 years (1). Testicular germ cell tumors account for approximately 90-95% of all testicular tumors. Conventionally used tumor markers for the diagnosis of germ cell testicular tumors include alpha fetoprotein (AFP), beta human chorionic gonadotropin (bHCG), and lactate dehydrogenase (LDH). However, currently, studies are ongoing to reveal different markers other than these (2).

It is believed that inflammatory conditions may have a role in the development of malignancy (3). Therefore, hematological and biochemical parameters have been used for diagnostic and prognostic purposes in various cancers. For this purpose, various parameters have been created from complete blood and biochemical data. These parameters primarily consist of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) (4, 5). In 2014, Hu et al. defined the systemic immune-inflammation (SII) index by evaluating complete blood parameters together (6). The De-Ritis ratio was first described in 1957 and has been shown to be useful in the diagnosis of viral hepatitis (7). Studies in the literature have shown that the De-Ritis ratio can also be used for diagnostic and prognostic purposes in different malignancies (8, 9).

In the literature, there is no sufficient data regarding studies diagnostically evaluating hematological and biochemical parameters together in testicular tumors (10-12). Therefore, this study we aimed to evaluate preoperative hematological and biochemical parameters together to determine their role in the diagnosis of testicular tumor.

## MATERIALS and METHODS

The data of patients who underwent inguinal orchiectomy for a testicular tumor in Kecioren Training and Research Hospital between October 2010 and December 2019 were retrospectively analyzed. Patients who underwent inguinal varicocelectomy in the same period were included in the study as the control group. Patients with missing data, under 18 years of age, using immunosuppressive drugs, having liver-related diseases or liver metastases were excluded from the study. This study was approved by ethics committee (Kecioren Research and Training Hospital, Clinical Research Ethics Committee, 2012-KAEK-15/2239, 23.02.2021).

At the time of diagnosis, patients with testicular tumors were evaluated using thoraco-abdominopelvic computed tomography for the presence of metastasis. Patients' age, tumor size, and preoperative AFP, bHCG, and LDH values were recorded. The complete blood parameters of neutrophil count and percentage, lymphocyte count and percentage, monocyte count, and platelet count were obtained from the preoperative examinations of the patients performed in the past preoperative 2 weeks. These data were used to calculate NLR, PLR, LMR, SII index, and De-Ritis ratio. The SII index was calculated using the following formula: platelet count x NLR (SII=PxNLR) (6). The De-Ritis ratio was calculated using the following formula: aspartate aminotransferase (AST)/alanine aminotransferase (ALT) (7).

Patients with a testicular tumor and patients who underwent varicocelectomy were compared in terms of blood parameters. Subgroup analysis was performed in patients with testicular tumors; and metastatic and non-metastatic patients were compared in terms of blood parameters. Statistical Package for the Social Sciences

(SPSS) version 24.0 (IBM Corp.) software was used for statistical analysis of the data. The distribution of data was evaluated by the Kolmogorov-Smirnov test. The Mann-Whitney U test was used for analysis of the quantitative data, and the median and interquartile range were used to present the data. The predictive values of blood parameters were calculated using receiver operating characteristics (ROC) curves. Parameters that were found to be significant in univariate analysis were analyzed by multivariate analysis. Binary logistic regression analysis backward stepwise technique was used for multivariate analysis. The level of statistical significance was set at $p<0.05$.

## RESULTS

Of the patients included in the study, 34 (14.1%) had a testicular tumor and 207 (85.9%) had undergone varicocelectomy. The median age of the patients during surgery was 27 (23-32) years. The median testicular tumor size was 45 (range, 30-70) mm. Demographics and preoperative clinical data of patients were given in Table-1. Considering the pathologies of the patients operated for a testicular tumor, 18 patients (52.9%) had seminoma, 12 patients (35.3%) had a mixed germ cell tumor, 3 patients (8.8%) had a yolk sac tumor, and 1 patient (2.9%) had embryonal carcinoma. Of the patients with a testicular tumor, 61.8% (n=21) had T2 stage disease and 35.3% (n=12) had metastasis.

The testicular tumor group had significantly higher median NLR, median SII index, and median PLR than the varicocelectomy group ($p<0.001$, $p<0.001$, $p=0.014$, respectively). The varicocelectomy group had a significantly higher median LMR ($p<0.001$). The testicular tumor group had a numerically higher median De-Ritis ratio, but the difference was not statistically significant ($p=0.183$).

The threshold values of NLR, PLR, LMR, and SII index were 1.76, 133.43, 7.81, and 571.63, respectively. The De-Ritis ratio did not have a statistically significant threshold value ($p=0.183$) (Table-2) (Figure-1). The multivariate analysis revealed that only the SII index was significant in predicting testicular tumor ($p<0.001$) (Table-3).

Patients with metastasis at the time of diagnosis and non-metastatic patients were compared in terms of blood parameters. There is no statistically significant difference between the groups in terms of NLR, PLR, LMR, De-Ritis ratio and SII index ($p=0.631$, $p=0.826$, $p=0.466$, $p=0.296$, $p=0.423$, respectively).

**Table-1.** Demographics and preoperative clinical data of patients.

| | | |
|---|---|---|
| **Surgery Type (N, %)** | Varicocelectomy | 207 (85.9) |
| | Inguinal Orchiectomy | 34 (14.1) |
| **Age, years, median (IQR)** | | 27 (9) |
| **Neutrophil count, ($10^3$/uL), median (IQR)** | | 4.2 (1.8) |
| **Lymphocyte count, ($10^3$/uL), median (IQR)** | | 2.3 (0.7) |
| **Platelet count, ($10^3$/uL), median (IQR)** | | 229 (77) |
| **Monocyte count, ($10^3$/uL), median (IQR)** | | 0.5 (0.2) |
| **ALT, U/L, median (IQR)** | | 20 (13) |
| **AST, U/L, median (IQR)** | | 21 (7) |

**Table-2.** Sensitivity, specificity and threshold values of NLR, PLR, LMR, SII Index and De-Ritis Ratio.

| | Threshold Value | Sensitivity (%) | Specificity (%) | 95% CI | p |
|---|---|---|---|---|---|
| **NLR** | 1.76 | 88.2 | 49.8 | 0.734 (0.642-0.826) | <0.001 |
| **PLR** | 133.43 | 44.1 | 86.5 | 0.631 (0.518-0.745) | 0.014 |
| **LMR** | 7.81 | 5.9 | 98.6 | 0.311 (0.210-0.413) | <0.001 |
| **SII Index** | 571.63 | 73.5 | 79.7 | 0.759 (0.663-0.856) | <0.001 |
| **De-Ritis Ratio** | 0.893 | 79.4 | 38.2 | 0.571 (0.469-0.673) | 0.183 |

NLR: neutrophil–lymphocyte ratio, PLR: platelet–lymphocyte ratio, LMR: lymphocyte–monocyte ratio, SII: systemic immune-inflammation.

**Table-3.** Multivariate analysis for factors predicting testicular tumor.

| | Testicular Tumor Risk | |
|---|---|---|
| | **OR (95%CI)** | **p** |
| **NLR** | 2.111 (0.543-8.203) | 0.281 |
| **PLR** | 1.598 (0.635-4.024) | 0.320 |
| **LMR** | 4.469 (0.519-38.505) | 0.173 |
| **SII Index** | 10.913 (4.740-25.122) | <0.001 |

OR: Odds ratio, NLR: neutrophil–lymphocyte ratio, PLR: platelet–lymphocyte ratio, LMR: lymphocyte–monocyte ratio, SII: systemic immune-inflammation.

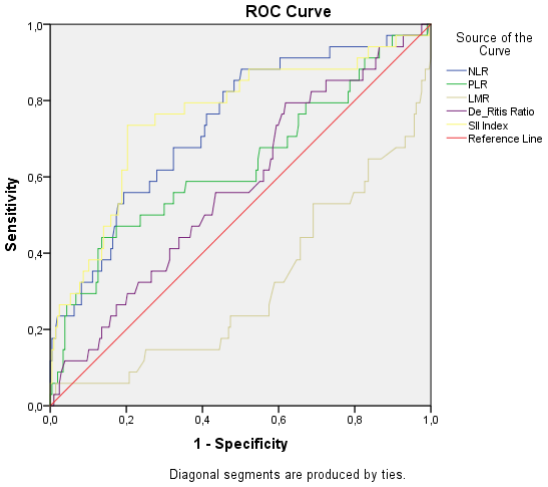


**Figure-1.** Receiver operating characteristic (ROC) curves for the neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), systemic immune-inflammation (SII) index and De-Ritis ratio against testicular tumor risk.

## DISCUSSION

In this cross-sectional study, the univariate analysis revealed that NLR, PLR, LMR, and SII index were correlated with testicular tumor development. In multivariate analysis, only the SII index was an independent prognostic factor. However, we could not find any correlation between the De-Ritis ratio and testicular tumor. Subgroup analysis was performed in patients with testicular tumors, but it was observed that the presence of metastases did not make any difference in terms of parameters.

Today, local and systemic inflammation is known to be one of the important parameters in cancer development (3, 13). The process of tumoral inflammation is also critical for angiogenesis and invasion. While low lymphocyte count is associated with cellular immunity disorder, elevated levels of neutrophil are correlated with growth factors and chemokines associated with angiogenesis (14, 15). For these reasons, various inflammatory markers have been found to be associated with progression in different cancers. These markers are primarily composed of NLR, LMR, PLR, albumin-to-globulin ratio, and AST-to-platelet ratio (4, 5, 16, 17). Various studies have shown that these markers may have prognostic significance in testicular tumors (10, 11, 18). In line with the current literature, the univariate analysis in our study revealed that high NLR and PLR, and low LMR were significant in predicting testicular tumors, and threshold values were obtained for these parameters. The multivariate analysis showed that these factors did not retain a level of significance. The reason for this was thought to be due to the fact that the SII index, which includes all these factors in a holistic way, was significant in the multivariate analysis.

The SII index was developed by Hu et al. in 2014 (6). Their study showed that the SII index was prognostic for recurrence and survival in patients with hepatocellular carcinoma. When the literature is reviewed, the SII index has been evaluated in different cancers and has been shown to be prognostic for treatment response and survival (19, 20). In testicular tumors, a high SII index has been shown to be associated with a poor prognosis (11, 21, 22). In parallel with this, the SII index was also found to be higher in testicular tumor patients in our study. We are of the opinion that the SII index including the combination NLR and PLR, which are other important complete blood parameters, makes this marker a significant prognostic marker. A comprehensive interpretation by looking at a single marker makes it more valuable. The limited number of testicular tumor patients prevented us from carrying out prognostic evaluations in terms of stages. Therefore, the significance of the SII index on the basis of stage

could not be evaluated in the present study. A comparison was made only in terms of the presence of metastases, and it was determined that there was no difference between the groups.

The De-Ritis ratio was first defined in 1957 and was initially used for viral hepatitis (7). However, it has been reported in the literature that it is a prognostic factor in solid organ tumors such as nasopharyngeal, liver, bladder, and renal cell carcinoma (23-25). Considering the relationship between testicular tumor and the De-Ritis ratio, there are conflicting results in the literature. In their studies, Guner et al. and Gorgel et al. showed that a high De Ritis ratio was associated with a poor prognosis, on the contrary, the study of Olcucu et al. found no significant correlation between the De-Ritis ratio and testicular tumor stage (12, 26, 27). Our study also showed no significant correlation between the De Ritis ratio and testicular tumor development. The smaller number of our testicular tumor patients than the above mentioned studies may have been effective in this result. Studies including a higher number of patients are needed to elucidate the relationship between the De-Ritis ratio and testicular tumor.

The major limitations of our study are its single-center and retrospective design. Secondly, the relatively small number of patients in the testicular tumor group is another limitation of our study. Although the complete blood and biochemical data of the patients were obtained from the preoperative data, non-inclusion of other acute phase reactants in the study can be considered another limitation. The small number of high stage patients prevented us from making a stage-based evaluation in patients with testicular tumors. Despite the current limitations, we believe that the evaluation of different markers together increased the value of our study, contributed to the existing literature, and gave an idea for future studies.

## CONCLUSION

The SII index, one of the hematological parameters, is an independent predictive factor that can be used for the diagnosis of testicular tumors. The fact that it is an inexpensive examination and is routinely evaluated before surgery is considered its important advantage. Prospective studies with larger patient populations will contribute to our knowledge on this subject.

**Conflict of interest:** Authors declared no conflict of interest.

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