Original Article

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# Predictive Value of Preoperative De-Ritis Ratio at Tumor Staging in Testicular Germ Cell Tumors

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## Abstract

**Aim:** The de-ritis ratio (DRR), which refers to the ratio of aspartate transaminase (AST) to alanine transaminase (ALT), is used in the assessment of several malignancies. Preoperative prediction of tumor anvasiveness remains an important issue. The aim of this study was to investigate the possible association between tumor progression and the DRR (AST/ALT).

**Methods:** The medical records of 103 patients who underwent radical orchiectomy because of testicular cancer between January 2010 and January 2020 in a single tertiary center were retrospectively assessed in this cross-sectional study. Parameters including age, blood parameters including AST, ALT, beta-human chorionic gonadotropin (B-hCG), alpha-fetoprotein, lactate dehydrogenase (LDH), complete blood count, pathology results, treatment schemes, imaging results, preoperative and postoperative DRR (AST/ALT), and tumor stage were noted.

**Results:** The mean age of the 103 patients was 34.9±10.45. The pathological T-stage was T1 for 26 (25.2%), T2 for 65 (63.1%), and T3 for 12 (11.6%). The mean follow-up of the patients was 31.44±10.32 (13-53) months. The risk of retroperitoneal lymph node involvement and metastasis at a DRR was calculated as 1.37 (area under the curve, 0.853 with a sensitivity of 90% and specificity of 89%; 95% confidence interval, 0.689-0.897). Preoperative B-hCG level and LDH were statistically significantly higher in the AST/ALT>1.37 group (p=0.002 and p=0.012). Thirty-five (30.4%) of patients with NSGHT had an AST/ALT>1.37. Seminoma was observed in 25.6% (n=21) of patients with AST/ALT>1.37 (p=0.107). The higher stage was significantly associated with an elevated DRR (p=0.019).

**Conclusion:** The DRR appears to be a useful and cost-effective preoperative marker for predicting localized and non-localized disease in Tca at the time of diagnosis.

**Keywords:** Testicular cancer, De-ritis ratio, Germ cell tumor, Aspartate transaminase, Alanine transaminase

## Introduction

Testicular neoplasms account for approximately one percent of all malignancies in men (1). These malignancies are the most common solid tumors in men in the second to fourth decade of life (2). Germ cell tumors are seen in approximately 90-95% of all testicular tumors and are divided into two groups: seminomatous and non-seminomatous. The mortality rate of these tumors is low, but the economic, psychological, and physical problems caused by these tumors in young men are extremely important. Advancements in treatment modalities have improved the cure rate of testicular cancers regardless of the tumor's spread; therefore, the preoperative prediction of testicular cancer has recently become increasingly important. Currently, the five-year survival rates are around 97% (3,4).

In the clinical routine, serum tumor markers such as alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), and lactate dehydrogenase (LDH) have an extremely important role in definitive diagnosis, treatment, and follow-up. These markers have also been used for the risk stratification of patients with testicular cancer.

However, these markers have low specificity and sensitivity; therefore, several investigations have been conducted to establish more reliable markers (5). In addition to these markers, alternative tumor markers have also been investigated for predicting the prognosis of testicular tumors. Recent studies have reported that the neutrophil-to-lymphocyte ratio (NLR) and aspartate aminotransaminase (AST)-to-alanine aminotransaminase (ALT) ratio, also called the de-ritis ratio (DRR), could be used as predictive values for solid tumors (6,7).

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The AST/ALT ratio was first described in 1957 by Fernando De Ritis and was used in liver diseases, especially in viral hepatitis (8,9). In the past few years, this ratio has become more important for non-hepatic diseases such as peripheral arterial occlusive disease, acute ischemic stroke, and type 2 diabetes mellitus (7). Later, Wu et al. (7) found that the ratio is not only associated with hepatocellular damage and systemic diseases but also plays an important prognostic role for several cancer types, such as breast cancer, esophageal cancer, and pancreatic cancer. Recently, two studies have investigated the relationship between the prognosis of testicular germ cell tumors and the DRR (10,11). However, we believe that there is still a lack of literature investigating the role of the DRRand the association of tumor metastasis with testicular cancer.

In our study, we aimed to determine the prognostic role of the DRR for determining metastasis and lymph node involvement. Furthermore, we investigated the association between the DRR and progression-free survival (PFS).

## Methods

### Compliance with Ethical Standards

Informed consent was obtained from all patients, and ethical approval was obtained from the Clinical Research Ethics Committee of University of Health Sciences Turkey, Istanbul Dr. Lutfi Kirdar City Hospital (approval no: 2020/514/184/3, dated: 26.08.2020).

### Subjects and Study Design

The data of 133 patients who underwent radical orchiectomy because of testicular cancer between January 2010 and January 2020 in a single tertiary center was retrospectively retrieved from our medical records. Sixteen patients with non-germ cell tumors and 7 patients whose histopathological results were missing were excluded. Seven patients with a history of hematologic disease, secondary malignancy, hepatic disease, diabetes mellitus, liver-eliminated drugs, or liver hepatitis were excluded from the study (Figure 1). Follow-up with all patients was routinely performed according to the European Association of Urology Guidelines.

Patients' age and blood parameters, including pre-operative and postoperative AST, ALT, beta-hCG (B-hCG), AFP, LDH, and pre-operative and postoperative DRR, were noted. AST (U/L) and ALT were routinely analyzed on the pre-operative day and postoperative week 1. Complete blood count, AFP, LDH, and B-hCG were analyzed on the pre-operative day and the third postoperative week. All serum parameters were analyzed in the same laboratory. Tumor characteristics (tumor size, tumor type, surgical margin, rete testis invasion, spermatic cord invasion, and tumor stage) were evaluated according to the 2016 TNM classification. Patients were scanned using thoracoabdominal computed tomography for lymph nodes and distant organ metastases. Progression-free survival was calculated from the date of surgery to the date of progression.

Patients were divided into two groups according to TNM. Patients with pathological stage pT1 (stage 1) were classified as stage 1; pT2-T4 and 1S, including any regional lymph node positivity without distal organ metastasis, were defined as stage ≥2.

Patients are also divided into seminomatous and non-seminomatous germinatous testicular cancers. The association between the DRR and pathological outcomes was analyzed in detail and subjected to statistical analysis.

### Statistical Analysis

Descriptive values for continuous variables are presented as mean ± standard deviation. Categorical variables are presented as numbers and percentages. The Shapiro-Wilk test was used to define the distribution of the variables. Categorical variables were analyzed using the chi-square test and the Fisher's exact test. Continuous variables were compared using the Mann-Whitney U test. The receiver operating characteristic (ROC) curve method was used to assess the diagnostic significance of AST/ALT for metastasis and lymph node involvement. A threshold with the highest sensitivity and specificity was determined using the ROC curve. Overall survival was estimated using the Kaplan-Meier method, with differences evaluated by the log-rank test. A 2-sided p-value <0.05 was considered statistically significant. IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA) was used for statistical analyses.

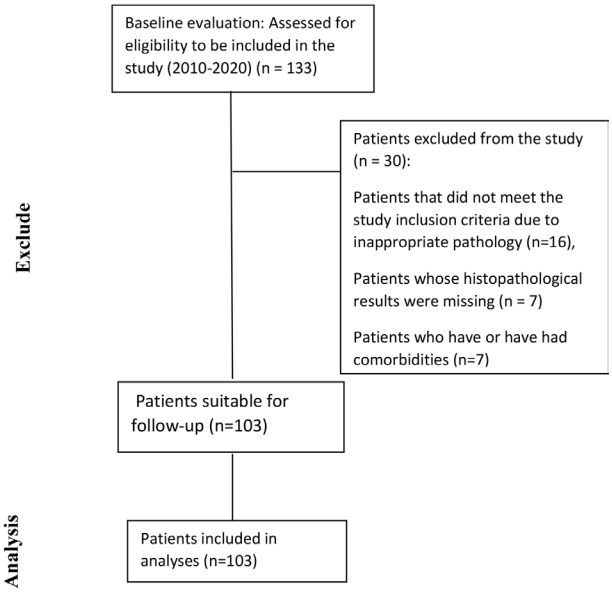


**Figure 1.** Flowchart of the study

## Results

The mean age of the 103 patients was 34.9±10.45. The preoperative mean AST and ALT levels were 22.8 (14-81) U/L and 23.3 (8-145) U/L, respectively. Median preoperative serum beta-hCG, AFP, and LDH levels were 16.2 (0-245497) mIU/mL, 6.41 (1-21000) ng/mL, and 313.1 (23-2581) U/L, respectively. Further demographic and clinical data are summarized in Table 1.

The mean tumor size was 50.99±22.98 (6-130) mm. The pathological diagnosis was seminoma in 47 patients and non-seminomatous germ cell tumor in 56 patients. The pathological T stage was T1 for 26 (25.2%), T2 for 65 (63.1%), and T3 for 12 (11.6%) patients. The mean follow-up of the patients was 31.44±10.32 (13-53) months.

The risk of retroperitoneal lymph node involvement and metastasis at a DRR was calculated as 1.37 [area under the curve (AUC), 0.853 with a sensitivity of 90% and specificity of 89%; 95% confidence interval, 0.689-0.897] (Figure 2). Overall, forty-seven patients had an AST/ALT rate <1.37 and 56 patients had an AST/ALT rate >1.37. No statistical difference was determined between AST/ALT rate <1.37 and AST/ALT rate >1.37 in terms of age, tumor type, tumor size, and preoperative AFP (p=0.164, p=0.107, p=0.456, p=0.523, respectively).

Preoperative B-hCG level and LDH were statistically significantly higher in the AST/ALT>1.37 group (p=0.002 and p=0.012). 30.4% (n=35) of patients with NSGHT had an AST/ALT >1.37. Seminoma was observed in 25.6% (n=21) of patients with AST/ALT >1.37 (p=0.107) (Table 2).

A higher stage was statistically significantly associated with an elevated DRR (p=0.019). Overall, thirteen (13.9%) patients showed progression after a mean follow-up of 25.9±5.7 (15-36) months. Lower PFS was associated with a >1.37 DRR, as shown in Kaplan-Meier analysis (Figure 3).

**Table 1. Demographic and clinical data of patients with testicular cancer (n=103)**

| Variable | Value |
|---|---|
| Age, mean ± SD (range) | 34.9±10.45 (18-58) |
| Preoperative AST (U/L) | 22.8 (14-81) |
| Preoperative ALT (U/L), median (range) | 23.3 (8-145) |
| Preoperative de-Ritis ratio | 1.23±0.47 |
| Preoperative AFP (ng/mL) | 6.41 (1-21000) |
| Preoperative hCG (mU/mL) | 16.2 (0-245497) |
| Preoperative LDH (U/L) | 313.1 (23-2581) |
| Pathological T stage, n (%)<br>T0<br>T1<br>T2<br>T3<br>T4 | <br>0<br>26 (25.2)<br>65 (63.1)<br>12 (11.6)<br>0 |
| Stage<br>Stage 1<br>Stage ≥2 | <br>63 (61.3)<br>40 (38.7) |
| Tumor size, mm, mean ± SD (range) | 50.99±22.98 (6-130) |
| Tumor type, n (%)<br>Seminoma<br>NSGHT | <br>47 (45.6)<br>56 (55.4) |

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, AFP: Alpha-fetoprotein, hCG: Human chorionic gonadotropin, LDH: Lactate dehydrogenase, SD: Standard deviation, NSGHT: Non-seminomatous germ cell tumor

**Table 2. Comparison of De-Ritis <1.37 and >1.37**

| Variable | AST/ALT <1.37 | AST/ALT >1.37 | p-value |
|---|---|---|---|
| Age, mean ± SD (range)* | 35.94±9.95 | 33.92±9.1 | 0.164 |
| Tumor type, n (%)<br>Seminoma<br>NSGHT^^ | <br>26 (21.4)<br>21 (25.6) | <br>21 (25.6)<br>35 (30.4) | 0.107 |
| Preoperative AFP (ng/mL), median (range)* | 4.35(1-3000) | 9.2 (1-21000) | 0.523 |
| Preoperative HCG, (mU/mL)* | 5.67 (1-7696) | 32.78 (1-24547) | 0.002 |
| Preoperative LDH, (U/L), median (range)* | 269.8 (23-1446) | 469 (63-2581) | 0.012 |
| Stage^^<br>Stage 1<br>Stage ≥2 | <br>35 (75.6)<br>12 (24.4) | <br>28(50)<br>28 (50) | 0.019* |
| Tumor size, mm, mean ± SD (range)* | 49.53±25.81 | 52.01±22.02 | 0.456 |

^^Chi-square test, *Mann-Whitney U test, SD: Standard deviation, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, AFP: Alpha-fetoprotein, hCG: Human chorionic gonadotropin, LDH: Lactate dehydrogenase, NSGHT: Non-seminomatous germ cell tumor

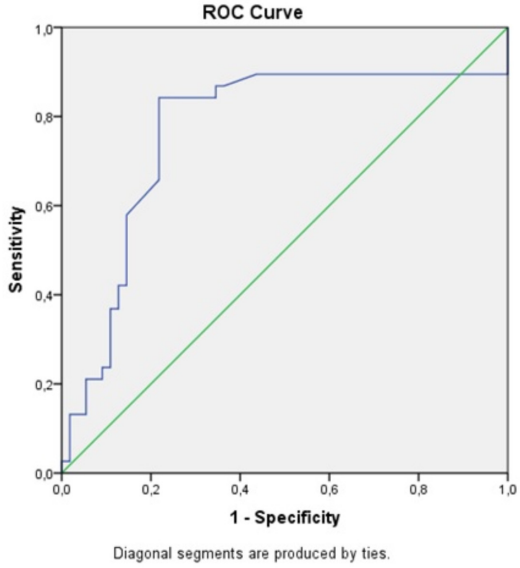


**Figure 2.** The risk of retroperitoneal lymph node involvement and metastasis in testicular cancer patients at a De-Ritis ratio level of 1.37 (area under the curve, 0.853; 95% confidence interval, 0.689-0.897)
*ROC: Receiver operating characteristic curve*

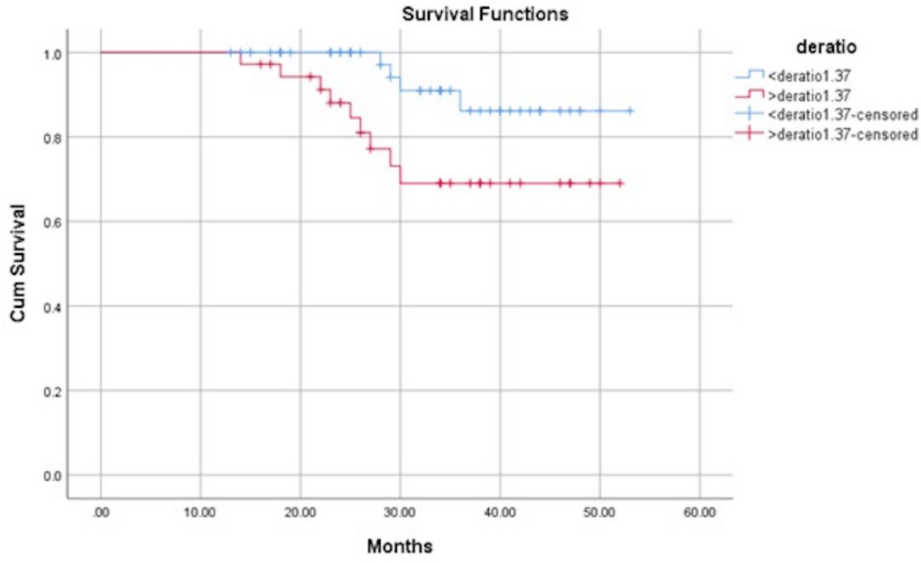


**Figure 3.** Kaplan Meier's analysis demonstrates the risk for progression free survival between the two groups

## Discussion

Searching for preoperative predictive markers for cancer has been increasing recently and remains important. Cost-effectiveness plays an important role in the diagnosis and follow-up of oncological cases, and research on simple parameters is ongoing. AFP, B-hCG, and LDH are widely used for the diagnosis and prognosis of testicular cancer. These markers are cost-effective and easy to apply; however, they have low specificity and sensitivity. Furthermore, normalization of marker levels after orchiectomy does not rule out the presence of metastatic disease, whereas persistence of marker levels after orchiectomy may be associated with metastatic disease (12,13). In addition to these available biomarkers, the utility of microRNA in predicting testicular cancer prognosis has been investigated. MicroRNA has been reported to be a useful biomolecule for the diagnosis, prognosis, and treatment of testicular cancer (10). However, this biomolecule seems not to be useful for daily practice.

Aspartate aminotransaminase and alanine aminotransaminase are enzymes that mainly originate from liver cells and are released into the blood circulation. They are used in daily practice and are usually measured when planning anesthesia for surgery. Different tissues produce AST; however, ALT is liver-specific (14). Crucial metabolic interactions between protein and carbohydrate metabolism are the primary functions of both enzymes. These enzymes are crucial for cells with high metabolic activity, and aerobic glycolysis is dependent on AST (8). The role of AST in the glycolysis mechanism is to contribute to NADH/NAD+ conversion in the malate-aspartate pathway (15). Hsu and Sabatini (16) determined that aerobic glycolysis in malignant cells is higher than that in non-malignant cells. As a result, AST is hypothesized to increase abnormally in cancer cells because of the Warburg effect. Therefore, the AST/ALT ratio has been associated with tumor metabolism in many glucose-using malignancies (Botros). DRR has been reported as a biomarker in some studies previously (7).

Articles have been published on the relationship between the AST/ALT ratio and malignancy (7,15,17-20). Wu et al. (7) published a pooled analysis of 9400 patients for the prognostic value of the AST/ALT ratio in solid tumors in 2019. They included 18 major reviews on renal cell carcinoma, hepatocellular carcinoma, pancreatic cancer, bladder cancer, liver cancer, and urinary tract urothelial carcinoma in the meta-analysis. In the results, they found that the AST/ALT ratio is predictive of decreased overall survival and cancer-specific survival. Only in a subgroup that looked for races, there was no significant result for Caucasians (7).

To the best of our knowledge, only four studies have investigated the association between testicular cancer and the DRR until now (10-12,21). In a study by Gorgel et al. (11), the preoperative elevated DRR was defined as an independent prognostic factor for testicular tumors. Increased AST and ALT levels were strongly predictive of retroperitoneal lymph node involvement. The optimal threshold of the AST/ALT ratio for lymph node involvement and/or metastases was 1.30 in this study (0.674; 95% confidence interval, 0.563-0.786) (11). These authors reported that without the presence of retroperitoneal lymph node involvement or metastasis on radiological

examination, markers cannot reveal information for lymph node metastases and stated the evidence of the opposite for the DRR. We did not find any investigation in their study supporting this statement. Furthermore, these authors reported that increased preoperative hCG levels were predictive of retroperitoneal lymph node involvement and metastasis, as expected. Bozkurt et al. (12) found that DRR was an independent prognostic factor for lung metastasis. The optimal DRR threshold was 1.21 for lung metastasis [AUC: 0.724 with a sensitivity of 81% and specificity of 74%] (12). This study demonstrated that DRR is an inexpensive parameter that can be used not only for predicting testicular tumor stage but also for predicting lung metastasis (12). Guner et al. (10) suggested that the optimal threshold of DRR is 1.35 (AUC: 0.791 with a sensitivity of 80% and a specificity of 73%). The investigators concluded that the DRR was related to a higher stage and worse overall survival (10). Olcucu et al. (21) evaluated the relationship between testicular tumors and four preoperative inflammation markers, namely neutrophil-lymphocyte ratio, lymphocyte-monocyte ratio, platelet-lymphocyte ratio, neutrophil-monocyte ratio, and DRR. In this study, four preoperative inflammation markers were defined as predictive factors for metastasis, but no significant statistical difference was detected for DRR (21).

Although there is no established threshold for the DRR for testicular tumors, the optimal cut-off value for low and high DRRs was found to be 1.37. This threshold was similar to that in previous studies. Concordant with the aforementioned studies, a high DRR was associated with the occurrence of metastasis and retroperitoneal lymph node involvement. Moreover, we determined an association between DRR and PFS in the Kaplan-Meier analysis. Previously, Guner et al. (10) found that elevated DRR was associated with early-term mortality in a Kaplan-Meier analysis. Furthermore, the authors stated that a high DRR was associated with a higher stage. This result supports our findings. Individual pathological variables were not investigated in our study, as these variables were found not to be associated with DRR in previous studies (10).

In addition to the DRR, the association between the NLR and testicular germ cell tumors was investigated in previous studies. Similar to the DRR, NLR is an easily acquired, inflammatory, and inexpensive marker. The authors concluded that the use of NLR might be predictive of the distinction between localized and non-localized TGCT in the early postoperative period. A persistent value in NLR after orchiectomy indicated non-localized disease in their study (21,22).

### Study Limitations

Despite our study providing important information about the association of progression and metastasis with the DDR, there are some limitations in the study that should be mentioned. The study was retrospectively designed and included a relatively small population of patients with testicular cancer. Second, we did not measure this ratio in the early postoperative period; therefore, we could not find the half-life or DRR. AST and ALT levels can be affected by many factors, such as undetected liver diseases, alcohol consumption, dietary habits, and drug interactions. Because of the low sample size and short follow-up period, the association of DRR with cancer-specific survival and overall survival could not be investigated.

## Conclusion

The DRR appears to be a useful and cost-effective preoperative marker for predicting localized and non-localized disease in Tca at the time of diagnosis. Clinicians should be aware of metastasis and retroperitoneal node involvement in patients with elevated DRR before surgery. Furthermore, DRR may serve as a biomarker for predicting PFS. Prospective studies with large sample sizes are essential to reaching certain conclusions.

### Ethics

**Ethics Committee Approval:** Ethical permission for the study was obtained from the Clinical Research Ethics Committee of University of Health Sciences Turkey, Istanbul Dr. Lutfi Kirdar City Hospital (approval no: 2020/514/184/3, dated: 26.08.2020).

**Informed Consent:** Informed consent was obtained from all patients.

**Peer-review:** Internally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: C.C., E.D., O.O., Concept: C.C., O.O., Design: C.C., E.D., O.O., Data Collection or Processing: C.C., E.D., Analysis or Interpretation: C.C., Literature Search: C.C., E.D., Writing: E.D., O.O.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

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