Original Article

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May High Levels of Systemic Immune-inflammation Index Suggest a Further Stage in Seminomatous Testicular Germ Cell Tumors

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Abstract

Objective: This study aimed to investigate the relationship between preoperative systemic immune-inflammation index (SII) and postoperative tumor stage in patients with seminomatous testicular germ cell tumors.
Materials and Methods: A total of 33 patients who underwent radical orchiectomy and were histopathologically diagnosed with seminoma were included in the study. Patients with tumors localized to the testis were designated as group 1, while those with extratesticular spread (advanced-stage tumors) were classified as group 2. Each group was then compared based on preoperative SII levels.
Results: Group 1 consisted of 22 patients. The mean ages of groups 1 and 2 were 36.14 and 35.09 years, respectively, with no statistically significant difference between the groups ($p>0.05$). However, SII levels in group 2 were significantly higher than those in group 1, with a reported value of 924.70 ($p=0.002$). Moreover, a 10-unit increase in SII was found to increase the likelihood of advanced-stage tumors, with extratesticular spread, by approximately 6% (odds ratio =1.006).
Conclusion: This study demonstrated that high preoperative SII is significantly associated with advanced tumor stage in patients with seminoma.
Keywords: Seminom, systemic immune inflammation index, markers of inflammation, cancer, stage

Introduction

Testicular cancer accounts for 1% of all male neoplasms and 5% of all urological tumors (1). Over the past decade, the incidence of newly diagnosed testicular cancer cases has increased by an average of 0.8% per year. However, advancements in imaging techniques, the widespread adoption of cisplatin-based chemotherapy regimens, and multidisciplinary treatment approaches have significantly contributed to a decline in mortality rates (2). Radical inguinal orchiectomy and pathological assessment play a critical role in confirming the diagnosis of cancer in the evaluation of suspicious testicular masses (3). Germ cell tumors account for 90-95% of all testicular tumors (4,5). Seminomas, which account for more than half of testicular germ cell tumors, generally have a favorable prognosis (2). Although some cases exhibit elevated β-subunit of human chorionic gonadotropin (β-hCG) levels, no specific tumor marker for seminomas has been identified to date (6). In the 21st century, intensive research has continued to focus on tumor markers with different biological bases for the clinical follow-up of seminomas following radical orchiectomy.

Since Rudolf Virchow documented the presence of leukocytes in tumor tissues in the 19th century, numerous clinical and experimental studies have explored the relationship between cancer and inflammation. Today, chronic inflammation is widely recognized by oncologists as a key player in pro-tumorigenic processes, primarily by increasing the secretion of growth factors that promote rapid cell proliferation and cytokines that enhance cell motility (7,8). Consequently, the association between systemic inflammatory responses, cancer stage, and prognosis has been extensively investigated in clinical studies (1,9).

Systemic inflammatory markers can be readily assessed during the preoperative period through routine blood tests. In this context, several systemic inflammatory markers, incuding the neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR), have been described in previous studies (5). The systemic immune-inflammation index (SII) is another important inflammatory marker, calculated using platelet, neutrophil, and lymphocyte counts. Currently, SII is widely used in clinical studies investigating the relationship between cancer and

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inflammation, as it combines three independent prognostic factors into a single index, making it a popular biomarker. Elevated SII levels have been documented in various studies as being associated with aggressive biological behavior of tumor cells and decreased overall survival (1,5). However, there are a limited number of studies in the English literature analyzing the relationship between SII and testicular germ cell cancer. In this retrospective study, we aimed to evaluate the association between SII and seminomatous testicular germ cell tumors.

Materials and Methods

Patients

Our study was performed in accordance with the Declaration of Helsinki Principles and with the approval of Tokat Gaziosmanpaşa University Local Ethics Committee (decision no: 25-MOBAEK-040, date: 06.02.2025). Between 2010 and 2024, the data of patients who underwent radical orchiectomy due to a preliminary diagnosis of testicular cancer at our hospital were retrospectively analyzed. A total of 33 male patients diagnosed with seminomatous testicular germ cell tumors based on the histopathological evaluation of radical orchiectomy specimens were included in the study. For all patients, the following data were recorded: age, demographic characteristics, β-hCG, lactate dehydrogenase, alpha-fetoprotein levels, complete blood cell count, tumor stage, and histopathological findings, according to the 2009 tumor, node, metastasis classification. Routine blood samples were collected within 24 hours before surgery (5). Hematological parameters were analyzed using a biochemistry analyzer that underwent regular maintenance and quality control (Mindray BC6800, China).

To assess the statistical power of the study, a post-hoc power analysis was used. An effect size of 1.5, with an α error amount of 0.05 and a subject number of n=31, determined the power of the study using an independent two-sample test, determined the power of the study as 0.97. This value shows that the statistical power of the study is relatively high.

Classification of Groups

Patients without retroperitoneal or distant metastases on computed tomography and without elevated serum tumor markers after orchiectomy (stage 1B and 1A) were categorized as localized disease and designated group 1. Patients with retroperitoneal or distant metastases or with elevated serum tumor markers after orchiectomy (stage 1S, 2, and 3), were categorized as having non-localized disease, referred to as group 2 (10).

Measurement of SII

For each patient, SII values were determined. The SII value was calculated using the formula: neutrophil × platelet / lymphocyte count (1.5). The SII values between the groups were statistically compared, aiming to analyze their predictive power in identifying advanced-stage seminomatous germ cell tumors.

Exclusion Criteria

Patients with testicular stromal tumors, non-seminomatous germ cell tumors, testicular masses suspected to be metastases from other tumors, end-stage renal disease, diabetes mellitus, cardiovascular diseases, chronic inflammatory or rheumatic diseases, receiving immunosuppressive therapy, or with infectious pathologies were excluded from the study (3,5).

Statistical Analysis

Descriptive statistics were performed to provide information about the general characteristics of the study groups. Variables were expressed as the mean ± standard deviation and the median (min-max). Differences between groups were analyzed using an independent samples t-test. P-values less than 0.05 were considered statistically significant. Receiver operating characteristic (ROC) curve analysis determined the cut-off values of the variable, according to the diagnostic group, and the area under the ROC curve (AUC) was also calculated (IBM SPSS Statistics 22, SPSS inc., an IBM Co., Somers, NY).

Results

A total of 33 patient data points were analyzed. Patients with tumors localized to the testis were classified as group 1, which consisted of 22 patients. The mean ages of groups 1 and 2 were 36.14±10.40 years and 35.09±8.65 years, respectively. There was no statistically significant difference between the groups in terms of age distribution (p>0.05). The SII value in group 2 was 924.70±298.34, which was significantly higher than in group 1 (p=0.002). Similarly, NLR and PLR values were found to be high in group 2 (p=0.003 and p<0.001, respectively) (Table 1).

Table 1. The distribution of age, and inflammatory markers by groups

	Group				p-value
	Group 1 (n=22)		Group 2 (n=11)		
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	
Age	36.14±10.40	36 (22-54)	35.09±8.65	38 (22-46)	0.776
Neutrophil	4.85±1.73	4.48 (1.90-9.90)	4.79±.83	4.51 (3.73-6.40)	0.909
Platelet	249.64±55.49	237.00 (149.0-367.0)	257.27±50.01	255.0 (192.0-360.0)	0.703
Lymphocyte	2.32±.94	2.05 (1.60-5.80)	1.43±.51	1.30 (0.80-2.60)	0.006*
NLR	2.28±1.14	2.15 (1.00-5.82)	3.65±1.20	3.5 (2.17-5.63)	**0.003***
PLR	116.33±35.24	118.50 (37.93-175.56)	193.53±56.29	176.0 (126.54-286.2)	**<0.001***
SII	536.97±203.23	504.60 (211.0-972.0)	924.70±298.34	809.8 (550.6-1288.0)	0.002*

Group 1 = Stage 1A, stage 1B, Group 2 = Stage 1S, 2, 3, Test: Independent samples t-test, *: The p-value is significant at the 0.05 level
NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammation index, SD: Standard deviation

ROC analysis was performed to evaluate the predictive ability of SII scores in staging, and the following were calculated: AUC values, accuracy, sensitivity, specificity, positive and negative predictive values, and likelihood ratio (+) values, all with 95% confidence intervals, as shown in Table 2. The ROC curve is presented in Figure 1. As a result of the ROC analysis, the SII score was found to be statistically significant between groups 1 and 2 (AUC =0.855 (0.689-0.953), p<0.001), and the discriminatory power of SII was strong. The cut-off point for the SII score was determined as 525. For this cut-off point, classification success was determined as 100.0% sensitivity and 54.55% specificity (Table 2).

Moreover, a 10-unit increase in SII was associated with a 6% increase in the likelihood of advanced-stage tumors with extratesticular spread.

Table 2. The result of ROC analysis for tumor stage

	SII
AUC	0.855 (0.689-0.953)
Level of significance p-value (area=0.5)	<0.001*
Cut-off point	>525
Sensitivity (%95 CI)	100.0 (71.5-100.0)
Specificity (%95 CI)	54.55 (32.2-75.6)

*: The p-value is significant at the 0.05 level
ROC: Receiver operating characteristic, SII: Systemic immune-inflammation index, AUC: Area under the curve, CI: Confidence interval

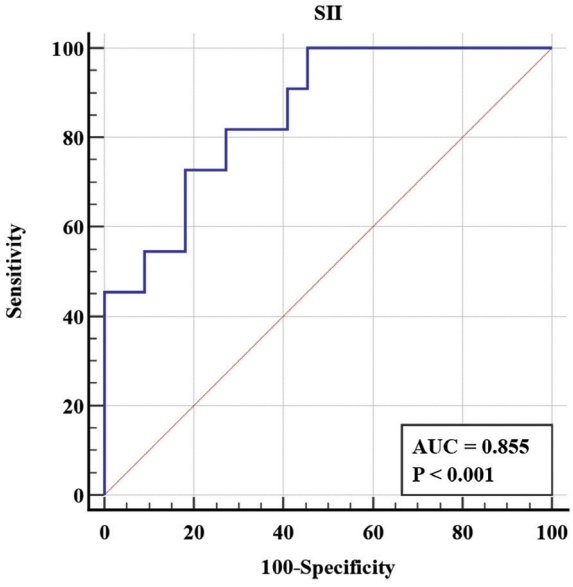

Figure 1. The result of ROC analysis for tumor stage

As a result of ROC analysis, performed according to the diagnosis group, the cut-off point for the predictor SII variable was calculated as >525. The area under the ROC curve (AUC) for this value was found to be 0.558. (0.689-0.953, 95% CI)

ROC: Receiver operating characteristic, SII: Systemic immune-inflammation index, AUC: Area under the curve, CI: Confidence interval

Discussion

In this study, we investigated the relationship between SII and tumor stage in patients with seminomatous testicular germ cell tumors. According to the data in our study, the SII value was found to be significantly higher in patients with advanced-stage tumors than in those with localized tumors. Moreover, a 10-unit increase in SII was found to increase the likelihood of advanced-stage tumors with extratesticular spread by approximately 6% (odds ratio =1.006).

Seminoma is the most common form of testicular cancer, accounting for 50% of all testicular malignancies (2). Approximately 80% of seminomas are diagnosed as stage 1 disease. These tumors are highly sensitive to both chemotherapy and radiotherapy. Unlike some specific malignancies, even in the metastatic stage, the likelihood of achieving a cure remains high. However, treatment-related morbidity should not be underestimated (6). Currently, physical examination, ultrasonography, and tumor markers are utilized by clinicians for preliminary diagnosis (4). Additionally, radiological imaging and tumor markers play a critical role in postoperative follow-up protocols (3,4). However, the sensitivity of these tumor markers is low, and they have high false-positive rates (3). Consequently, the search for an ideal biomarker for seminomas remains ongoing.

Inflammatory cells produce a vast array of cytokines that can induce tumor growth, invasion, angiogenesis, and metastasis. On the other hand, the hypothesis that the synthesis of inflammatory cytokines is triggered by the tumor microenvironment, and that this process is directly associated with changes in acute-phase reactants, has been widely accepted by many researchers (10). Neutrophils, which constitute the majority of inflammatory cells, promote tumor growth. Additionally, activated neutrophils suppress lymphocyte function and lead to a decrease in the antitumor immune response. Platelets, on the other hand, facilitate the epithelial-mesenchymal transition of tumor cells, thereby enhancing tumor invasion and metastasis. In this context, elevated SII reflects stronger pro-inflammatory activity and is thought to be associated with a greater number of circulating tumor cells and poorer tumor outcomes (4,5).

SII was first described approximately a decade ago and has been identified as a strong prognostic predictor in hepatocellular carcinoma (11). The popularity of SII has significantly increased in recent years, as it incorporates three independent inflammatory prognostic factors—platelet, neutrophil, and lymphocyte counts—which can be easily assessed using simple and routine blood tests (1,11). Additionally, SII is reported to provide a more comprehensive reflection of systemic inflammation and to have a higher predictive value compared to other inflammatory markers. In this context, SII has been extensively analyzed as a tumor marker in various types of cancer (11). A recent meta-analysis reported that SII could serve as a valuable prognostic indicator in urinary system cancers and contribute to the formulation of treatment strategies as an important inflammatory marker (12). In another meta-analysis, Li et al. (13) reported that elevated pre-treatment SII was associated with poor prognosis in urinary system cancers.

A review of previous literature indicates that studies investigating the relationship between SII and the progression of testicular cancer are limited. In their study on germ cell tumors, Chovanec et al. (14) reported that patients with low SII had significantly longer overall survival compared to those with high SII. Similarly, in the study conducted by Bumbasirevic et al. (15), it was observed that systemic inflammatory markers—including SII, NLR, PLR, LMR, and C-reactive protein—demonstrated strong performance in predicting metastatic disease in testicular germ cell tumors. In another study, Haberal et al. (16) evaluated the role of NLR, PLR, LMR, SII, and the De Ritis ratio in testicular tumors and documented that only SII was an independent prognostic factor for this malignancy. Wang et al. (4), in their study involving 112 cases (54 in the control group), reported that SII could be used as an effective tumor marker in predicting testicular germ cell tumors. Similarly, in the study conducted by Göger et al. (1), it was concluded that high SII values could serve as an important marker in the diagnosis and follow-up of testicular tumors. In the study by Imamoglu et al. (5), it was determined that SII values were significantly higher in advanced-stage seminomas compared to stage 1 seminomas. However, no significant association was observed in non-seminomas (5). In the existing literature, there are limited data on the relationship between SII and survival in testicular cancer. A recent systematic review by Salazar-Valdivia et al. (11) reported that high SII values were associated with poor overall and progression-free survival in testicular cancer (4). On the other hand, in the study by Şimsekoglu et al. (17), high SII levels were found to be associated with non-seminomatous testicular germ cell tumors; however, SII was not reported to be associated with survival outcomes. In our study, SII levels were found to be high in advanced-stage seminomatous testicular germ cell tumors. However, due to the limited study period, survival outcomes were not documented.

Study Limitations

The primary limitations of our study include its retrospective design, limited sample size, lack of survival data, and single-center nature.

Conclusion

Based on the findings of this retrospective study, elevated pre-orchiectomy SII levels were identified as a predictive marker of advanced-stage disease in seminomatous testicular germ cell tumors. In this context, it was calculated that a 10-unit increase in the SII level increased the likelihood of advanced tumors with extratesticular spread by approximately sixfold.

Ethics

Ethics Committee Approval: Our study was performed in accordance with the Declaration of Helsinki Principles and with the approval of Tokat Gaziosmanpaşa University Local Ethics Committee (decision no: 25-MOBAEK-040, date: 06.02.2025).

Informed Consent: Between 2010 and 2024, the data of patients who underwent radical orchiectomy due to a preliminary diagnosis of testicular cancer at our hospital were retrospectively analyzed.

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Contribution: There is not any contributors who may not be listed as authors.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.K., K.Y., Concept: E.K., K.Y., Design: E.K., K.Y., Data Collection or Processing: E.K., K.Y., Analysis or Interpretation: E.K., K.Y., Literature Search: E.K., K.Y., Writing: E.K., K.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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