

Diagnostic Performance of Systemic Inflammatory Indices in Testicular Germ Cell Tumors

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What's known on the subject? and What does the study add?

Systemic inflammation indices have demonstrated prognostic and diagnostic value in various solid tumors. However, in testicular germ cell tumors, existing studies have mostly focused on the prognostic significance of these markers, while their diagnostic roles have been investigated to a limited extent. This study suggests that the systemic immune inflammation index, systemic inflammation response index, and especially the pan-immune inflammation value may be useful in the diagnosis of testicular germ cell tumors. These markers may contribute to the diagnostic evaluation of testicular germ cell tumors and may warrant further investigation as adjunctive biomarkers in clinically challenging diagnostic settings.

Abstract

Objective: To evaluate the diagnostic performance of systemic inflammatory indices in patients with testicular germ cell tumors and to investigate their potential value as adjunctive diagnostic biomarkers.

Materials and Methods: In our study, 43 patients who underwent inguinal orchiectomy for testicular tumors between 2023 and 2025 were retrospectively reviewed. The control group consisted of 43 healthy individuals. Preoperative complete blood count parameters, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), systemic immune inflammation index (SII), systemic inflammation response index (SIRI), and pan-immune inflammation value (PIV), were calculated. The groups were compared using appropriate statistical tests. Diagnostic performance was evaluated using receiver operating characteristic (ROC) curve analysis.

Results: The groups were similar in age ($p=0.074$). In the testicular germ cell tumor group, the values of NLR ($p=0.011$), SII ($p=0.001$), SIRI ($p=0.005$), and PIV ($p=0.003$) were significantly higher, while the LMR was significantly lower ($p=0.002$). No significant difference was found between the groups in terms of PLR ($p=0.252$). In the ROC analysis, PIV had the highest discriminatory performance (area under the curve=0.800; 95% confidence interval: 0.710-0.891). The optimal threshold value for PIV was ≥ 402.13 , with a sensitivity of 55.8% and a specificity of 90.7%.

Conclusion: Systemic inflammatory indices may contribute to the diagnostic evaluation of testicular germ cell tumors. Among the evaluated biomarkers, PIV demonstrated the highest diagnostic performance. These findings should be confirmed in prospective studies evaluating clinically relevant diagnostic subgroups.

Keywords: Testicular cancer, systemic inflammation response index, systemic immune inflammation index, pan-immune inflammation value

Introduction

Testicular cancer is an uncommon malignancy; however, it predominantly affects young adult males and constitutes the most frequently diagnosed solid tumor within this population.

The global incidence of testicular cancer has been estimated at approximately 5.8 cases per 100,000 individuals, with epidemiological data demonstrating a progressive increase in incidence over recent decades, particularly in industrialized countries (1).

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Germ cell tumors (GCTs) comprise approximately 90% to 95% of all testicular malignancies. In routine clinical practice, the diagnosis of testicular cancer is primarily established through physical examination and supported by scrotal ultrasonography. Serum tumor markers, including alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (β -hCG), and lactate dehydrogenase (LDH), are widely used for diagnostic evaluation, staging, and treatment monitoring. Nevertheless, a considerable proportion of patients may present with normal serum tumor marker levels despite the presence of malignant disease. This limitation highlights the need for additional biomarkers that may complement existing clinical, laboratory, and radiological assessment tools. Furthermore, the growing adoption of risk-adapted treatment strategies underscores the importance of identifying novel biomarkers that may facilitate both diagnostic evaluation and therapeutic decision-making.

Accumulating evidence has established a close relationship between inflammation and carcinogenesis. Persistent inflammatory activity contributes to tumor initiation and progression through multiple biological mechanisms, including suppression of antitumor immune responses and promotion of tumor cell proliferation. In particular, neutrophil-mediated inflammatory responses may inhibit the cytotoxic activity of lymphocytes—including activated T lymphocytes—and natural killer cells, thereby impairing immune surveillance against malignant transformation. The resulting pro-inflammatory tumor microenvironment may promote angiogenesis, cellular proliferation, metastatic spread, and resistance to anticancer therapies. Consequently, inflammation is now recognized as a fundamental hallmark of cancer biology (2).

Several systemic inflammatory biomarkers derived from routinely available laboratory parameters have been investigated as potential indicators of cancer-related outcomes. Hematological variables, including leukocyte, monocyte, platelet, lymphocyte, hemoglobin, and C-reactive protein levels, have demonstrated prognostic relevance across a variety of malignancies (3-5). Moreover, inflammation-based indices calculated from circulating immune cell subsets, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR), have attracted increasing attention in recent years. These indices reflect the dynamic balance between tumor-promoting inflammatory processes and tumor-suppressive immune mechanisms and may serve as surrogate markers of the systemic inflammatory milieu associated with cancer progression. Previous studies have reported the potential clinical utility of these markers in several genitourinary malignancies, including urothelial carcinoma, renal cell carcinoma, and prostate cancer (6,7). However, evidence regarding their diagnostic significance in testicular cancer remains limited.

More recently, composite inflammatory indices, including the systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and pan-immune inflammation value (PIV), have emerged as promising biomarkers in oncological research. By integrating multiple circulating immune cell components into a single parameter, these indices may provide a more comprehensive assessment of systemic inflammatory status than conventional inflammatory ratios. Emerging data suggest that these markers possess prognostic significance in a variety of solid tumors, including GCTs (8,9). Beyond their prognostic implications, these indices may also improve the diagnostic evaluation of patients presenting with suspected testicular neoplasms.

The present study aimed to investigate the diagnostic performance of the NLR, PLR, LMR, SII, SIRI, and PIV in patients with testicular tumors. Additionally, we aimed to explore the potential role of these systemic inflammatory indices as adjunctive biomarkers in the diagnostic evaluation of patients with suspected testicular malignancy.

Materials and Methods

This retrospective study included 43 patients who underwent inguinal orchiectomy for testicular tumors between January 2023 and January 2025. The study protocol was reviewed and approved by the University of Health Sciences Türkiye, Kocaeli City Hospital Scientific Research Ethics Committee (approval no: 2026-39, date: 12.03.2026) and conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

Clinical, laboratory, and pathological data were retrospectively retrieved from the institutional electronic medical records system. The collected variables included patient age; preoperative serum tumor marker levels (AFP, β -hCG, and LDH); complete blood count parameters; and final histopathological diagnoses after orchiectomy. For comparative analysis, a control group of 43 healthy, age-matched men was included. Individuals with a history of malignancy, active infection, inflammatory disease, hematological disorder, or any known scrotal or testicular disease were excluded. The absence of scrotal and testicular pathology was confirmed by clinical evaluation, and none of the controls had evidence of a testicular mass or other scrotal abnormality.

Laboratory Measurements

Peripheral venous blood samples were collected within 24 hours prior to surgery. Hematological parameters reflecting systemic inflammatory status were obtained from routine preoperative complete blood count analyses. The recorded variables included absolute neutrophil, lymphocyte, monocyte, and platelet counts.

Based on these hematological parameters, several inflammation-based indices were calculated to evaluate systemic immune and inflammatory responses.

Calculation of Inflammatory Indices

The NLR, PLR, LMR, SII, SIRI, and PIV were calculated using the following formulas:

$NLR = \text{neutrophil } (10^9/L) / \text{lymphocytes } (10^9/L)$,

$PLR = \text{platelets } (10^9/L) / \text{lymphocytes } (10^9/L)$,

$LMR = \text{lymphocytes } (10^9/L) / \text{monocytes } (10^9/L)$,

$SII = \text{platelets } (10^9/L) \times \text{neutrophil } (10^9/L) / \text{lymphocytes } (10^9/L)$,

$SIRI = [(\text{neutrophil } (10^9/L) \times \text{monocytes } (10^9/L)) / \text{lymphocytes } (10^9/L)]$,

$PIV = [\text{neutrophil } (10^9/L) \times \text{platelets } (10^9/L) \times \text{monocytes } (10^9/L)] / \text{lymphocytes } (10^9/L)$.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed using appropriate normality tests and visual inspection methods. Variables demonstrating a normal distribution were expressed as mean $\pm$ standard deviation and compared using the independent samples t-test. Variables that did not conform to a normal distribution were presented as medians and interquartile ranges and were compared using the Mann-Whitney U test.

The diagnostic performance of systemic inflammation indices in differentiating malignant testicular tumors was evaluated using receiver operating characteristic (ROC) curve analysis. For each parameter, the area under the curve and the corresponding 95% confidence intervals (CIs) were calculated. Optimal threshold values were determined using the Youden index, and the corresponding sensitivity and specificity values were then obtained. All statistical tests were two-sided, and a p-value of less than 0.05 was considered statistically significant.

Results

A total of 86 participants were included in the study: 43 were patients with malignant testicular GCTs and 43 were healthy controls. The mean age was 34.12 ± 11.61 years in the malignant group and 30.35 ± 7.17 years in the healthy group, with no statistically significant difference between the groups ($p=0.074$).

Comparative analyses revealed significant differences in various systemic inflammation indices between testicular tumor patients and the healthy control group. The NLR was significantly higher in the malignant group compared to the healthy group (2.59 ± 1.11 vs. 2.02 ± 0.87 , $p=0.011$). Similarly, in patients with malignant tumors, the SII (728.06 ± 410.23 vs. 475.08 ± 189.91 , $p=0.001$), SIRI (2.12 ± 1.82 vs. 1.26 ± 0.75 , $p=0.005$), and PIV (592.70 ± 244.54 vs. 243.57 ± 126.88 , $p=0.003$) were found to be significantly higher compared to the control group (Table 1).

In contrast, the LMR was significantly lower in patients with malignant tumors compared to the control group (3.37 ± 1.23 vs. 4.27 ± 1.37 , $p=0.002$). No statistically significant difference was observed in PLR between the two groups (116.79 ± 32.48 vs. 108.24 ± 36.10 , $p=0.252$).

Next, ROC curve analyses were performed to evaluate the diagnostic performance of the inflammatory indices in differentiating patients with testicular tumors. Among all parameters examined, the PIV showed the highest discriminatory ability, with an area under the curve of 0.800 (95% CI: 0.710-0.891; $p<0.001$). The SII and the SIRI also showed good diagnostic performance; the area under the curve values were 0.729 (95% CI: 0.623-0.834; $p<0.001$) and 0.704 (95% CI: 0.595-0.814; $p=0.001$), respectively (Figure 1). The NLR showed moderate discriminatory capacity; the area under the curve was 0.662 (95% CI: 0.547-0.776; $p=0.010$) (Table 2).

The optimal threshold values, determined using the Youden index, were 2.44 for the NLR, 588.97 for the SII, 1.54 for the SIRI, and 402.13 for the PIV. The PIV showed the highest specificity (90.7%) and the highest Youden index (0.465), whereas its sensitivity was 55.8%. The SII showed 60.5% sensitivity and

Table 1. Comparison of demographic and systemic inflammatory parameters between the two groups

Variable	Tumor group (n=43)	Control group (n=43)	p-value
Age (year)	34.12 ± 11.61	30.35 ± 7.17	0.074
NLR	2.59 ± 1.11	2.02 ± 0.87	0.011
PLR	116.79 ± 32.48	108.24 ± 36.10	0.252
LMR	3.37 ± 1.23	4.27 ± 1.37	0.002
SII	728.06 ± 410.23	475.08 ± 189.91	0.001
SIRI	2.12 ± 1.82	1.26 ± 0.75	0.005
PIV	592.70 ± 244.54	243.57 ± 126.88	0.003

NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, LMR: Lymphocyte-to-monocyte ratio, SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index, PIV: Pan-immune inflammation value

79.1% specificity, while the SIRI showed 55.8% sensitivity and 81.4% specificity. The NLR showed 48.8% sensitivity and 79.1% specificity (Table 3).

Discussion

The relationship between inflammation and carcinogenesis has been extensively investigated in oncology. Persistent inflammatory activity contributes to tumor development

through several biological mechanisms, including the induction of genomic instability, promotion of angiogenesis, and enhancement of tumor cell survival. Simultaneously, chronic inflammation may impair effective antitumor immune responses. In their seminal work on cancer biology, Hanahan and Weinberg (2) identified inflammation as a fundamental hallmark of cancer, emphasizing its critical role in tumor initiation, progression, and resistance to therapy.

Cells of the immune system actively shape the tumor microenvironment and influence cancer behavior. Neutrophils and monocytes may facilitate tumor progression through the release of cytokines, proteolytic enzymes, and proangiogenic mediators. In contrast, lymphocytes, particularly cytotoxic T lymphocytes and natural killer cells, play a pivotal role in antitumor immune surveillance and contribute to the elimination of malignant cells. Consequently, alterations in the relative distribution of these immune cell populations may reflect the complex interplay between tumor biology and host immune responses (2).

In the present study, the SII, SIRI, PIV, and NLR differed significantly between patients with testicular tumors and healthy controls. These findings support the growing body of evidence indicating that systemic inflammatory alterations are detectable in patients with testicular malignancies.

Previous studies have highlighted the potential utility of inflammation-based biomarkers in testicular cancer. Wang et al. (10) demonstrated that inflammatory indices derived from routine blood tests, particularly the SII and NLR, exhibited significant diagnostic value in patients with testicular GCTs and were associated with tumor stage. These observations suggest that systemic inflammatory responses may reflect both tumor burden and the dynamic interactions between the tumor and the host immune system.

Similarly, Kayar et al. (11) evaluated the associations of hemoglobin, albumin, lymphocyte, and platelet score (HALP), NLR, and SII with testicular GCTs and reported that elevated HALP, SII, and NLR ratio values were significantly associated with advanced clinical stage, whereas the SIRI demonstrated limited predictive performance. Another study found a statistically significant association between higher PIV scores

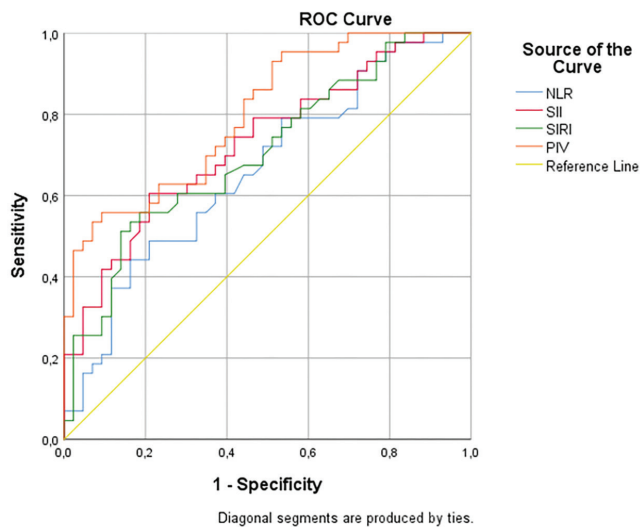


Figure 1. ROC curves showing the discriminatory performance of systemic inflammation indices in the diagnosis of testicular germ cell tumors

ROC: Receiver operating characteristic, NLR: Neutrophil-to-lymphocyte ratio, SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index, PIV: Pan-immune inflammation value

Table 2. Systemic inflammatory parameters (ROC) curves and AUC values

Variable	AUC (95% CI)	p-value
NLR	0.662 (0.547-0.776)	0.010
SII	0.729 (0.623-0.834)	<0.001
SIRI	0.704 (0.595-0.814)	0.001
PIV	0.800 (0.710-0.891)	<0.001

AUC: Area under the curve, CI: Confidence interval, ROC: Receiver operating characteristic, NLR: Neutrophil-to-lymphocyte ratio, SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index, PIV: Pan-immune inflammation value

Table 3. Optimal cut-off points for systemic inflammation indices, sensitivity, specificity, and Youden index values

Variable	Optimal cut-off	Sensitivity	Specificity	Youden index
NLR	≥2.44	48.8%	79.1%	0.279
SII	≥588.97	60.5%	79.1%	0.396
SIRI	≥1.54	55.8%	81.4%	0.372
PIV	≥402.13	55.8%	90.7%	0.465

NLR: Neutrophil-to-lymphocyte ratio, SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index, PIV: Pan-immune inflammation value

and advanced tumor stage, presence of metastasis, and lymph node involvement in patients with testicular cancer (12).

Although previous investigations have largely focused on the prognostic significance of inflammatory biomarkers, recent meta-analytic evidence has shown that elevated SII and SIRI values are significantly associated with adverse survival outcomes in patients with testicular cancer (13). While the present study was designed to evaluate diagnostic performance rather than long-term oncological outcomes, these findings further support the biological relevance of systemic inflammatory indices in testicular cancer.

In a recent study, Lesko and Mego (14) reported that systemic inflammatory indices measured after orchiectomy in patients with clinical stage I GCTs were associated with adverse pathological features and provided prognostic information beyond conventional clinicopathological factors used to estimate relapse risk. Collectively, these findings indicate that inflammation-based biomarkers may have clinical relevance throughout multiple stages of disease assessment.

Recently developed composite indices, including the SII, SIRI, and PIV, have attracted considerable attention because they integrate multiple immune and inflammatory cell populations into a single parameter. In the present study, all three indices were significantly elevated in patients with malignant tumors and demonstrated superior diagnostic performance compared with the NLR.

Among the evaluated markers, the PIV exhibited the highest discriminative ability, achieving an area under the curve value of 0.800 and a specificity of 90.7%. These findings suggest that an elevated PIV may be particularly useful for increasing the likelihood of malignancy in patients with suspected testicular tumors.

The superior performance of the PIV may be attributable to its incorporation of neutrophil, platelet, monocyte, and lymphocyte counts, thereby providing a more comprehensive representation of both systemic inflammation and host immune status. Likewise, SII and SIRI demonstrated good discriminatory performance, with areas under the curve of 0.729 and 0.704, respectively. These observations suggest that multidimensional inflammatory indices may better capture the complex interactions between tumor biology and systemic immune responses than conventional single-ratio markers.

Despite the growing evidence supporting the prognostic significance of inflammatory indices in testicular cancer, data regarding their diagnostic utility remain limited. The present findings extend the literature by demonstrating that readily available inflammation-based biomarkers may help differentiate patients with malignant testicular germ cell tumors from healthy

individuals. In particular, the PIV may represent a valuable adjunctive tool in patients with inconclusive radiological findings or normal conventional tumor marker levels.

The clinical implications of these findings warrant consideration. Complete blood count parameters are inexpensive, routinely obtained, and widely accessible in daily clinical practice. Incorporating systemic inflammatory indices into the preoperative assessment process may complement existing diagnostic evaluation and should be further investigated before routine clinical implementation.

The present study adds to the growing body of evidence supporting the role of systemic inflammatory responses in the pathobiology of testicular tumors. Large-scale prospective studies are warranted to validate these findings, establish clinically meaningful threshold values, and determine whether inflammation-based indices may complement existing diagnostic strategies or be integrated into multiparametric models for the evaluation of testicular cancer.

Study Limitations

This study has several limitations that should be acknowledged. First, its retrospective design and single-center setting may limit the generalizability of the findings. Second, the relatively small sample size limited statistical power for detailed subgroup analyses by histopathological subtype and tumor stage. Third, although the healthy control group was carefully selected to exclude individuals with known malignancies or with inflammatory, hematological, scrotal, or testicular diseases, the presence of undetected subclinical inflammatory conditions cannot be completely excluded. In addition, the use of healthy individuals, rather than patients with benign testicular masses, as the control group limits direct assessment of the discriminatory value of inflammatory indices for the differential diagnosis of testicular masses encountered in routine clinical practice. This study focused exclusively on the diagnostic performance of inflammatory indices and did not evaluate their association with long-term oncological outcomes, such as recurrence, disease progression, cancer-specific survival, or overall survival. Prospective, multicenter studies with larger patient cohorts, including patients with benign testicular lesions, are warranted to validate these findings and further define the clinical utility of these inflammatory biomarkers.

Conclusion

Systemic inflammatory indices derived from routine complete blood count parameters were significantly altered in patients with malignant testicular tumors compared with healthy controls. Among the evaluated biomarkers, the pan-immune-inflammation value demonstrated the highest diagnostic

performance, followed by the systemic immune-inflammation index and the systemic inflammatory response index. These inexpensive and widely available biomarkers may serve as useful adjunctive tools in the diagnostic evaluation of testicular GCTs. Their potential value in clinically challenging situations, such as those involving patients with normal serum tumor marker levels or inconclusive radiological findings, should be investigated in prospective studies.

Ethics

Ethics Committee Approval: The study protocol was reviewed and approved by the University of Health Sciences Türkiye, Kocaeli City Hospital Scientific Research Ethics Committee (approval no: 2026-39, date: 12.03.2026) and conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

Informed Consent: Because the study was designed retrospectively no written informed consent form was obtained from the patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ö.E., Ö.M., M.Ü., E.M.A., A.K.U., F.E.D., Concept: Ö.E., Ö.M., Design: Ö.E., Data Collection or Processing: Ö.E., Ö.M., M.Ü., F.E.D., Analysis or Interpretation: E.M.A., A.K.U., Literature Search: Ö.E., F.E.D., Writing: Ö.E.

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