Comparison of inflammation-based biomarkers in metastatic testicular cancer at initial diagnosis

Ibrahim Hacibey, Eymen Ozer, Berke Demiriz, Onuralp Nisli, Batu Akalin, Harun Ozdemir, Halil Lutfu Canat
Department of Urology, Basaksehir Çam and Sakura City Hospital, Istanbul, Turkey

Cite as: Hacibey I, Ozer E, Demiriz B, et al. Comparison of inflammation-based biomarkers in metastatic testicular cancer at initial diagnosis. *Can Urol Assoc J* 2026 May 4; Epub ahead of print. http://dx.doi.org/10.5489/cuaj.9538

Published online May 4, 2026

Corresponding author: Dr. Hacibey Ibrahim, Basaksehir Çam and Sakura City Hospital, Department of Urology, Istanbul, Turkey; drihacibey@gmail.com

***

ABSTRACT

Introduction: This study evaluated the diagnostic accuracy of six systemic inflammatory indices, including the 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 aggregate index of systemic inflammation (AISI), for identifying metastatic disease at the initial diagnosis of testicular germ cell tumors (TGCTs).
Methods: A total of 194 patients with histologically confirmed TGCTs treated between 2020 and 2025 were retrospectively analyzed. Pre-treatment complete blood counts were used to calculate inflammatory indices. Metastatic status was defined based on cross-sectional imaging, including contrast-enhanced chest, abdominal, and pelvic computed tomography. Associations with metastasis were assessed using Mann-Whitney U tests, univariate logistic regression, and receiver operating characteristic (ROC) analyses. Optimal cutoff values were determined by Youden's index.
Results: At initial diagnosis, a total of 194 patients were included, of whom 28 (14.4%) had imaging-confirmed metastatic disease. Patients with metastases exhibited significantly higher SII, SIRI, AISI, NLR, and PLR values and significantly lower LMR values compared with non-metastatic patients (all $p<0.001$). In pre-adjusted analyses, NLR (area under the curve [AUC] 0.781) and SIRI (AUC 0.755) demonstrated the strongest discriminatory performance for metastatic disease. ROC-derived cutoff values were 3.14 for NLR, 152.3 for PLR, 2.68 for LMR, 682.1 for SII, 2.84 for SIRI, and 1222.7 for AISI.
Conclusions: Systemic inflammatory indices derived from routine blood counts are significantly associated with metastatic TGCTs at initial presentation. This study provides initial evidence supporting the potential clinical relevance of SIRI and AISI, alongside

established markers such as NLR and SII, as complementary tools for early risk stratification. Prospective, multicenter studies are warranted to validate these findings.

INTRODUCTION

Testicular cancer is the most common malignancy affecting young adult males, with testicular germ cell tumors (TGCTs) accounting for more than 90% of cases, including both seminomatous and non-seminomatous subtypes (1). While the prognosis is generally excellent, especially for localized disease, a notable proportion of patients present with metastatic spread at the time of initial diagnosis, necessitating prompt systemic evaluation and treatment (2). Early identification of such cases is essential for guiding appropriate oncological management and improving long-term outcomes (1,2).

Systemic inflammation plays a central role in cancer development and progression by promoting tumor growth, angiogenesis, immune evasion, and metastatic spread (3,4). Consequently, several hematologic indices derived from routine complete blood count parameters, such as the 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 aggregate index of systemic inflammation (AISI), have been investigated across a wide range of solid tumors as potential biomarkers for diagnosis, prognosis, and treatment stratification (5–8). These indices are inexpensive, reproducible, and easily accessible in daily clinical practice.Their potential utility in reflecting tumor-related systemic inflammation makes them attractive tools for assessing disease severity, including the presence of metastatic involvement (6,8).

In testicular cancer, previous studies have primarily focused on the prognostic value of inflammatory markers such as NLR and SII, particularly in relation to survival outcomes and advanced pathological stage (7-10). Although systemic inflammatory markers have been investigated in testicular cancer, mainly in relation to prognosis and treatment outcomes in metastatic disease, including studies such as that by Fankhauser et al. data specifically addressing optimal cut-off values for identifying metastatic disease at initial presentation remain limited (11). In addition, evidence regarding composite inflammatory markers, particularly SIRI and AISI, remains scarce in TGCTs, despite growing data supporting their relevance in other urologic and non-urologic malignancies. (5,8).

This study aims to evaluate the ability of pre-treatment inflammatory indices—including NLR, PLR, LMR, SII, SIRI, AISI—to distinguish between metastatic and non-metastatic testicular cancer at initial diagnosis. By analyzing a contemporary cohort treated at a tertiary center, we seek to clarify whether these biomarkers may serve as complementary tools alongside established imaging and serum tumor markers in early disease stratification.

METHODS

Study design and patient selection

This retrospective, observational study included patients diagnosed with testicular cancer at a tertiary academic center between April 2020 and May 2025. The study was approved by the institutional ethics committee (Approval No:2025.10.362) and conducted in accordance with the principles of the Declaration of Helsinki**.** Patients were identified from institutional electronic medical records. Inclusion criteria were: (1) histopathologically confirmed testicular germ cell tumor (seminomatous or non-seminomatous), (2) availability of complete preoperative blood count data within 72 hours prior to radical orchiectomy and before initiation of any systemic or local oncologic treatment, and (3) recorded staging at diagnosis based on contrast-enhanced thoracoabdominopelvic computed tomography performed as part of the same pre-treatment diagnostic evaluation period. Patients with active infections, chronic inflammatory diseases, autoimmune conditions, hematologic malignancies, missing clinical data, or those who had received treatments such as corticosteroids or emergency antibiotics prior to complete blood count sampling were excluded to minimize confounding. The presence of metastasis was defined according to the 8th edition of the American Joint Committee on Cancer (AJCC) TNM staging system, including evidence of retroperitoneal or distant lymphadenopathy, visceral metastases, or elevated tumor markers consistent with systemic disease. All patients classified as metastatic had radiologically documented metastatic disease on contrast-enhanced imaging; no patients were considered metastatic based solely on serum tumor marker elevation.

Demographic data, tumor histology (seminoma, non-seminoma, mixed), and preoperative serum tumor markers (AFP, β-HCG, LDH) were recorded. Hematological parameters were obtained from routine preoperative complete blood count (CBC) tests, conducted within 0 to 3 days prior to surgery. All CBCs were analyzed using the same automated hematology analyzer to minimize inter-assay variability.

Calculation of inflammatory indices

For each patient, systemic inflammatory indices were calculated using absolute peripheral blood cell counts obtained from the preoperative CBC. The formulas were as follows: neutrophil-to-lymphocyte ratio (NLR) = neutrophil count / lymphocyte count; platelet-to-lymphocyte ratio (PLR) = platelet count / lymphocyte count; lymphocyte-to-monocyte ratio (LMR) = lymphocyte count / monocyte count; systemic immune-inflammation index (SII) = (platelet count × neutrophil count) / lymphocyte count; systemic inflammation response index (SIRI) = (neutrophil count × monocyte count) / lymphocyte count; and aggregate index of systemic inflammation (AISI) = (platelet count × neutrophil count × monocyte count) / lymphocyte count. All values were automatically calculated from the raw CBC parameters and cross-checked by two independent investigators.

Statistical analysis

Statistical analyses were performed using the Python 3.13 programming language. The pandas, numpy, statsmodels, scikit-learn, and imbalanced-learn libraries were utilized for data processing and analysis. For continuous variables, mean ± standard deviation and median [interquartile range, IQR] values were calculated. The distributional characteristics of the variables were assessed using the Shapiro–Wilk test, which demonstrated that none of the variables (SII, SIRI, AISI, NLR, LMR, PLR) followed a normal distribution. To evaluate the relationship between metastasis status and these variables, the Mann–Whitney U test was applied. Results were presented as median [IQR], and a p-value <0.05 was considered statistically significant.

Associations between inflammatory indices and metastatic status were initially evaluated using univariate logistic regression models, with results expressed as odds ratios (ORs) and 95% confidence intervals (CIs).

Subsequently, multivariable logistic regression analyses were performed to assess whether inflammatory indices were independently associated with metastatic disease after adjustment for relevant clinical covariates. Variables entered into multivariable models included age, tumor histology (seminoma vs non-seminoma), primary tumor T stage, and serum tumor markers (AFP, β-hCG, and LDH). To avoid multicollinearity, inflammatory indices were entered into the multivariable models individually rather than simultaneously. The predictive performance of each hematologic index for metastasis was evaluated using Receiver Operating Characteristic (ROC) curve analysis. The Area Under the Curve (AUC) was calculated and interpreted (0.5: random prediction, 1.0: perfect discrimination). The optimal cut-off value for each variable was determined using Youden's Index (J = Sensitivity + Specificity – 1).

Given the imbalance between metastatic and non-metastatic cases, the synthetic minority oversampling technique (SMOTE) was applied as a secondary sensitivity analysis to explore the robustness of findings under balanced class conditions. SMOTE-adjusted analyses were not intended to reflect real-world diagnostic accuracy but to assess the stability of observed associations. Results derived from the original, unmodified dataset were considered primary. No imputation was performed for missing data, and analyses were conducted using a complete-case approach. Outliers were not excluded a priori, as inflammatory indices may exhibit wide biological variability in oncologic populations. It is acknowledged that synthetic oversampling may inflate measures of association and statistical significance, potentially limiting external validity; therefore, SMOTE-based results were interpreted cautiously. A two-sided p-value <0.05 was considered statistically significant.

RESULTS

A total of 202 patients who underwent radical orchiectomy during the study period were initially screened. After exclusions due to missing CBC data or concomitant conditions, 194 patients were included in the final analysis. Based on initial imaging and clinical staging, patients were classified into two groups: metastatic (n = 28, 14.4%) and non-metastatic (n = 166, 85.6%) at the time of diagnosis. The mean age of the study population was 32.9 ± 11.2 years, with a median tumor size of 20 mm (range: 68.4 ± 249.6 mm). The descriptive statistics of hematologic, biochemical and pathological parameters are presented in Table 1. A comparison of baseline demographic, tumor-related, and inflammatory characteristics between metastatic and non-metastatic groups is presented in Supplementary Table S1.

Patients with metastatic disease had significantly higher levels of SII (1288.1 vs. 565.3, $p<0.001$), SIRI (3.61 vs. 1.56, $p<0.001$), AISI (1037.6 vs. 389.5, $p<0.001$), NLR (4.12 vs. 2.28, $p<0.001$), and PLR (173.0 vs. 112.1, $p<0.001$), whereas LMR values were significantly lower in the metastatic group (2.10 vs. 3.57, $p<0.001$). Detailed comparisons are provided in Table 2.

Receiver operating characteristic (ROC) curve analyses demonstrated that all six inflammatory indices had acceptable diagnostic accuracy for identifying metastatic disease. In the primary analysis based on the original, unmodified dataset (pre-SMOTE), SII, SIRI, AISI, NLR, and PLR demonstrated statistically significant associations with metastasis (all $p < 0.001$), whereas LMR did not reach significance (OR = 0.730, 95% CI: 0.524–1.017, p = 0.063). Although LMR demonstrated moderate discriminatory ability on ROC analysis (AUC 0.780), its association with metastatic disease did not reach statistical significance in univariate logistic regression before SMOTE. Among these indices, SIRI (OR = 1.43; 95% CI: 1.17–1.74 ; AUC = 0.75) and NLR (OR = 1.47; 95% CI: 1.23–1.76 ; AUC = 0.78) showed the strongest predictive values for metastasis (Table 3). After adjustment for age, stage, and lymphovascular invasion, NLR and SIRI remained independently associated with metastatic disease at initial diagnosis. SII, AISI, and PLR also demonstrated significant adjusted associations, with odds ratios close to unity due to their larger numerical scale, whereas LMR did not retain a statistically significant association in the multivariate model.Multivariable regression results are presented in Table 3.

In SMOTE-adjusted sensitivity analyses, all six indices were statistically significant predictors of metastatic disease. SIRI (OR = 1.54 ; 95% CI: 1.34–1.78 ; AUC = 0.78) and NLR (OR = 1.64 ; 95% CI: 1.40–1.92 ; AUC = 0.82) remained robust indicators of metastasis. SII (OR = 1.00 ; 95% CI: 1.00–1.00 ; AUC = 0.82) and AISI (OR = 1.00 ; 95% CI ; 1.00 – 1.00 ; AUC = 0.78) also demonstrated significant predictive capacity; the smaller odds ratios reflect the larger numerical scale of these indices rather than a weaker association with metastatic disease (Supplementary Table S2). Importantly, LMR, which was not significant prior to SMOTE, emerged as a protective factor against metastasis (OR = 0.82 ; 95% CI: 0.72–0.95 ; AUC = 0.82 ; p = 0.008). PLR also exhibited predictive ability with an AUC increase from 0.73 to 0.85 after SMOTE. Collectively, these findings indicate that systemic inflammatory indices, particularly SIRI, NLR, and PLR, possess strong discriminative ability for metastasis, as evidenced by both significant ORs and favorable AUC values (Supplementary Table S2). The corresponding ROC curves are illustrated in Figure 1.

Optimal thresholds derived from Youden's J index were as follows: SII 682.1, SIRI 2.84, AISI 1222.7, NLR 3.14, LMR 2.68, and PLR 152.3. As shown in Table 4, these cut-off values yielded sensitivities ranging from 46% to 82% and specificities ranging from 63% to 94%. Post-SMOTE analysis yielded slightly lower cut-offs for most indices, including SII 669.1, SIRI 2.67, AISI 1143.9, NLR 2.97, LMR 2.64, and PLR 146.2. These values, along with corresponding sensitivity, specificity, PPV, and NPV, are displayed in Table 4.

DISCUSSION

In this study, six systemic inflammatory indices, including NLR, PLR, LMR, SII, SIRI, and AISI, were systematically evaluated for their ability to discriminate metastatic from non-metastatic testicular cancer at initial diagnosis.. Our results demonstrated that patients with metastatic disease had significantly higher NLR, PLR, SII, SIRI, and AISI values, whereas LMR values were significantly lower compared with non-metastatic patients. ROC curve analysis confirmed the discriminative capacity of all indices, with clinically relevant cut-off thresholds (NLR: 3.14; PLR: 152.3; LMR: 2.68; SII: 682.1; SIRI: 2.84; AISI: 1222.7) providing acceptable sensitivity and specificity.

Our findings are largely in line with prior reports on classical indices such as NLR, PLR, LMR, and SII. For instance, Wang et al. retrospectively analyzed patients with testicular germ cell tumors and proposed an NLR cut-off of 3.38 (AUC 0.704; sensitivity 51.4%, specificity 88.6%) and an SII cut-off of 881.24 (AUC 0.725; sensitivity 45.7%, specificity 91.4%) to distinguish tumor presence, both significantly elevated in TGCT patients compared to controls (5). Similarly, in a separate case-control study, NLR values above 2.06 were associated with testicular cancer, with ROC analysis yielding an AUC of 0.74 and balanced sensitivity and specificity around 69% (12). Bauzá et al. further demonstrated that an NLR cut-off of 2.2 (AUC 0.802; sensitivity 76%, specificity 70%) could differentiate patients with testicular tumors from those with benign conditions (13). Collectively, these studies report cut-off values between 2.0–3.4, which closely align with our threshold of 3.14, underscoring the reproducibility of NLR as a marker of advanced disease. It should be noted that the AUC values observed in this study were below 0.85, indicating moderate rather than high diagnostic performance, and supporting the role of inflammatory indices as complementary rather than standalone diagnostic tools.

SII has also been examined in TGCTs. Wang et al. identified an SII cut-off near 1000, significantly associated with poor prognostic features, while another study proposed a threshold of 881.24 as predictive of disease status (5). Our SII cut-off of ~682 is slightly lower but still consistent with the overall literature, with comparable discriminative accuracy. Furthermore, metastatic GCT cohorts have shown that both NLR and SII carry prognostic value in predicting progression-free and overall survival, although they do not outperform established IGCCCG (International Germ Cell Cancer Collaborative Group) classification when adjusted in multivariable models (11).

In contrast, evidence regarding SIRI and AISI in testicular cancer is essentially absent. Our study therefore represents, to the best of our knowledge, the first attempt to define ROC-based cut-off thresholds for these indices in this malignancy. Nevertheless, findings from other cancers strongly support their clinical relevance. For example, Yu et al. demonstrated that high SIRI values independently predicted worse survival outcomes in patients with upper tract urothelial carcinoma, particularly when combined with tumor multifocality (14). Cai et al. reported that elevated preoperative SIRI significantly correlated with inferior survival in resectable colorectal cancer (15), while Yilmaz et al. found SIRI to be a stronger independent predictor of recurrence and overall survival than NLR, PLR, or SII in bladder cancer patients undergoing cystectomy (16). AISI, though less extensively studied, has also been shown to reflect advanced disease and poor prognosis in multiple solid tumors, further supporting its potential role in urologic oncology.

Taken together, our findings extend previous literature by confirming the diagnostic value of established indices (NLR, PLR, LMR, SII) while introducing SIRI and AISI as novel markers in testicular cancer. From a clinical perspective, the addition of these readily obtainable, cost-effective biomarkers may complement traditional serum tumor markers (AFP, β-hCG, LDH), which are not always elevated, thereby enhancing risk stratification at diagnosis. The strengths of our study include the simultaneous evaluation of all six indices in a contemporary cohort and the establishment of cut-off thresholds through ROC analysis. This study has several limitations, including its retrospective, single-center design and the lack of external validation of the proposed cut-off values. Although SMOTE was applied as a secondary sensitivity analysis to address class imbalance, synthetic oversampling may increase the risk of overfitting and limit the generalizability of the results. Therefore, diagnostic performance estimates, particularly those derived from SMOTE-adjusted analyses should be interpreted with caution. External validation in larger, multicenter cohorts is warranted to confirm the reproducibility of these findings and to determine whether integrating inflammatory indices with established IGCCCG prognostic classification improves predictive accuracy.

CONCLUSIONS

In summary, our data confirm the association of elevated NLR, PLR, and SII and reduced LMR with metastatic testicular cancer, consistent with previous studies, while also presenting the initial evidence that SIRI and AISI may serve as novel, clinically useful biomarkers at the initial diagnosis of metastatic testicular cancer. These indices are not intended to replace the established IGCCCG prognostic classification but may provide complementary information to enhance risk stratification at diagnosis.

REFERENCES

1. Patrikidou A, Cazzaniga W, Berney D, et al. European Association of Urology guidelines on testicular cancer: 2023 update. *Eur urol* 2023;84:289-301. https://doi.org/10.1016/j.eururo.2023.04.010
2. Gilligan T, Lin DW, Adra N, et al. NCCN Guidelines® Insights: Testicular cancer, version 2.2025: Featured updates to the NCCN guidelines. *J Natl Compr Canc Netw* 2025;23. https://doi.org/10.6004/jnccn.2025.0018
3. Akkız H, Şimşek H, Balcı D, et al. Inflammation and cancer: Molecular mechanisms and clinical consequences. *Front Oncol* 2025;15:1564572. https://doi.org/10.3389/fonc.2025.1564572
4. Greten FR, Grivennikov SI. Inflammation and cancer: Triggers, mechanisms, and consequences. *Immunity* 2019;51:27-41. https://doi.org/10.1016/j.immuni.2019.06.025
5. Wang S, Yang X, Yu Z, et al. The values of systemic immune-inflammation index and neutrophil-lymphocyte ratio in predicting testicular germ cell tumors: A retrospective clinical study. *Front Oncol* 2022;12:893877. https://doi.org/10.3389/fonc.2022.893877
6. Kwon WA, Joung JY, Lee JE, et al. Neutrophil-to-lymphocyte ratio independently predicts advanced pathological staging and poorer survival outcomes in testicular cancer. *Investig Clin Urol* 2019;60:176-83. https://doi.org/10.4111/icu.2019.60.3.176
7. Mjaess G, Chebel R, Karam A, et al. Prognostic role of neutrophil-to-lymphocyte ratio (NLR) in urological tumors: An umbrella review of evidence from systematic reviews and meta-analyses. *Acta Oncol* 2021;60:704-13. https://doi.org/10.1080/0284186X.2021.1886323
8. Zhang S, Ni Q. Prognostic role of the pretreatment systemic immune-inflammation index in patients with glioma: A meta-analysis. *Front Neurol* 2023;14:1094364. https://doi.org/10.3389/fneur.2023.1094364
9. Arda E, Arikan G, Akdere H, et al. Predictive and prognostic impact of preoperative complete blood count based systemic inflammatory markers in testicular cancer. *Int Braz J Urol* 2020;46:216-23. https://doi.org/10.1590/s1677-5538.ibju.2018.0820
10. Ilktac A, Dogan B, Ersoz C, et al. The relationship of neutrophil to lymphocyte ratio with testicular cancer. *Int Braz J Urol* 2020;46:101-7. https://doi.org/10.1590/s1677-5538.ibju.2019.0321
11. Yuksel OH, Verit A, Sahin A, et al. White blood cell counts and neutrophil to lymphocyte ratio in the diagnosis of testicular cancer: A simple secondary serum tumor marker. Int Braz J Urol 2016;42:53-9. https://doi.org/10.1590/S1677-5538.IBJU.2014.0593
12. Quetglas JL, Fernández AT, Bertolo R, et al. Neutrophil to lymphocyte ratio: A testicular cancer diagnostic tool: Neutrophil to lymphocyte ratio: A testicular cancer diagnostic tool. *Annals of Mediterranean Surgery* 2020;3:3-12. https://doi.org/10.22307/2603.8706.2020.01.002
13. Fankhauser CD, Sander S, Roth L, et al. Systemic inflammatory markers have independent prognostic value in patients with metastatic testicular germ cell tumours undergoing first-line chemotherapy. *Br J Cancer* 2018;118:825-30. https://doi.org/10.1038/bjc.2017.467
14. Yu LC, Wang CA, Hu CY, et al. Preoperative systemic inflammation response index enhances the prognostic value of tumor multifocalityin upper tract urothelial carcinoma. *Oncol Lett* 2024;28:436. https://doi.org/10.3892/ol.2024.14569

15. Cai H, Chen Y, Zhang Q, et al. High preoperative CEA and systemic inflammation response index (C-SIRI) predict unfavorable survival of resectable colorectal cancer. *World J Surg Oncol* 2023;21:178. https://doi.org/10.1186/s12957-023-03056-z
16. Yilmaz H, Cinar NB, Avci IE, et al. The systemic inflammation response index: An independent predictive factor for survival outcomes of bladder cancer stronger than other inflammatory markers. InUrologic oncology: Seminars and original investigations. *Urol Oncol* 2023;5:256-el. https://doi.org/10.1016/j.urolonc.2022.11.011

FIGURES AND TABLES

Figure 1. Receiver operating characteristic (ROC) curves of six systemic inflammatory indices for predicting metastatic disease at diagnosis (A) pre-SMOTE; and (b) post-SMOTE analysis. SMOTE: synthetic minority oversampling technique.

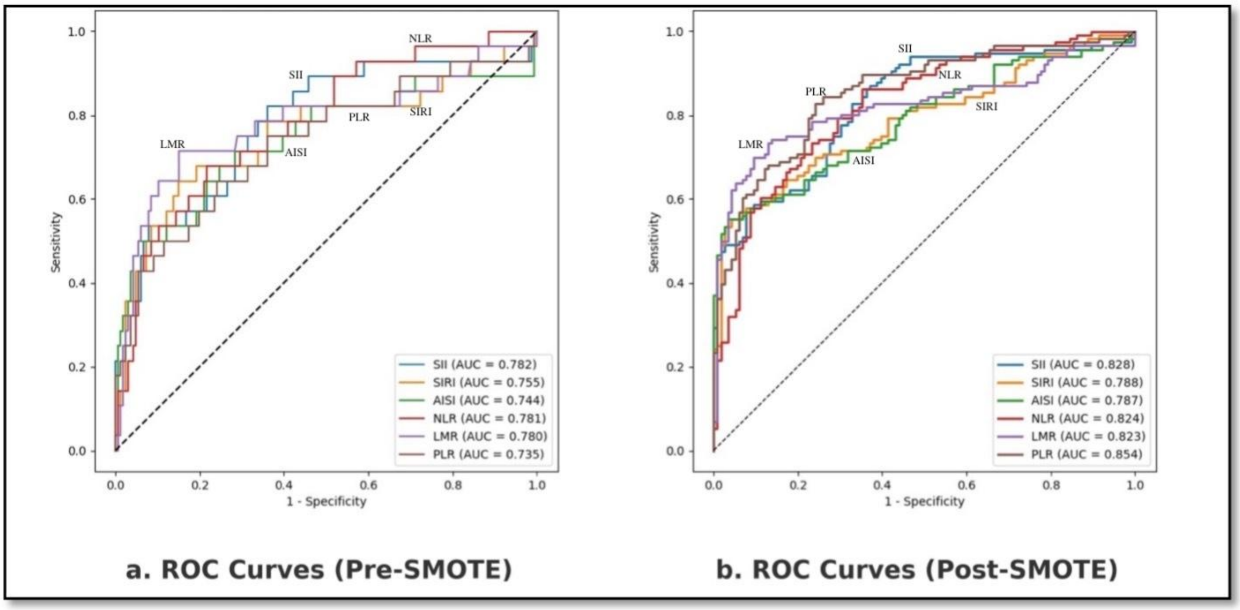

Table 1. **Baseline demographic, hematologic, biochemical, and pathologic characteristics of patients with testicular germ cell tumors**

Variable	Median (IQR)
Age (years)	31.00 (25.00–39.00)
Tumor diameter (mm)	20.00 (6.12–54.41)
β-hCG	1.20 (0.20–16.00)
AFP	3.69 (1.89–36.10)
LDH	234.00 (187.00–318.00)
SII	608.04 (442.08–947.56)
SIRI	1.65 (1.01–2.43)
AISI	415.90 (237.65–680.11)
NLR	2.38 (1.82–3.29)
LMR	3.36 (2.59–4.39)
PLR	120.17 (91.20–160.94)
Histology, n	
Seminoma	84
Non-seminoma	110

T stage, n	
T1	99
T2	80
T3	15
T4	0
Metastasis (at initial diagnosis), n	
No	166
Yes	28

AFP: alpha-fetoprotein; AISI: Aggregate Index of Systemic Inflammation; HCG: human chorionic gonadotropin; LDH: lactate dehydrogenas; LMR: lymphocyte-to-monocyte ratio; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SII: Systemic Immune-Inflammation Index; SIRI: Systemic Inflammation Response Index.

Table 2. Comparison of systemic inflammatory indices between metastatic and non-metastatic testicular cancer patients at diagnosis

Variable	**Non-metastatic (n=166)**	**Metastatic (n=28)**	**p**
SII	565.26 (426.49–840.08)	1288.09 (747.22–2308.39)	<0.001
SIRI	1.56 (0.97–2.20)	3.61 (1.82–5.63)	<0.001
AISI	389.47 (232.16–629.03)	1037.64 (470.93–2180.22)	<0.001
NLR	2.28 (1.73–2.96)	4.12 (2.49–6.19)	<0.001
LMR	3.57 (2.78–4.44)	2.10 (1.50–2.94)	<0.001
PLR	112.08 (87.74–143.79)	173.01 (125.25–231.65)	<0.001

AISI: Aggregate Index of Systemic Inflammation; LMR: lymphocyte-to-monocyte ratio; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SII: Systemic Immune-Inflammation Index; SIRI: Systemic Inflammation Response Index.

Table 3. Combined univariate and multivariable logistic regression analyses of systemic inflammatory indices for predicting metastatic disease at initial diagnosis

Univariate				Multivariate				
Model	**Odds Ratio (Before SMOTE)**	**95% CI**	**p-value**	**Model**	**Variable**	**Odds Ratio**	**95% CI**	**p-value**
AISI	1.00	1.00–1.00	**<0.001**	**AISI**		1.00	1.00–1.00	**0.0006**
					Age	0.95	0.90–1.00	0.0543
					LVI	2.19	0.56–8.65	0.2614
					Stage	1.78	0.64–4.96	0.2697
NLR	1.47	1.23–1.76	**<0.001**	**NLR**		1.47	1.20–1.80	**0.0002**
					Age	0.94	0.90–0.99	**0.0293**
					LVI	2.25	0.56–8.98	0.2512
					Stage	1.85	0.66–5.22	0.2436
PLR	1.01	1.00–1.01	**<0.001**	**PLR**		1.01	1.01–1.02	**0.0002**
					Age	0.95	0.91–1.00	0.0533
					LVI	2.31	0.60–8.84	0.2227
					Stage	1.81	0.66–4.98	0.2488
SII	1.00	1.00–1.00	**<0.001**	**SII**		1.00	1.00–1.00	**<0.0001**
					Age	0.95	0.90–1.00	**0.0462**
					LVI	1.82	0.44–7.47	0.4052
					Stage	1.86	0.65–5.36	0.2479
SIRI	1.43	1.17–1.74	**0.0004**	**SIRI**		1.37	1.12–1.66	**0.0017**
					Age	0.94	0.90–0.99	**0.0269**
					LVI	2.67	0.68–10.41	0.1572
					Stage	1.66	0.60–4.60	0.3298
LMR	0.73	0.52–1.01	0.063	**LMR**		0.80	0.57-1.13	0.2091
					Age	0.96	0.91-1	**0.0487**
					LVI	2.35	0.68-8.19	0.1782
					Stage	1.95	0.76-4.96	0.1637

AISI: Aggregate Index of Systemic Inflammation; CI: confidence interval; LMR: lymphocyte-to-monocyte ratio; LVI: lymphovascular invasion; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SII: Systemic Immune-Inflammation Index; SIRI: Systemic Inflammation Response Index.

Table 4. Optimal cutoff values and diagnostic performance (sensitivity, specificity, PPV, NPV) of inflammatory indices before and after SMOTE adjustment

Variable	PRE-SMOTE					POST-SMOTE				
	Cut-off	Sensitivity	Specificity	PPV	NPV	Cut-off	Sensitivity	Specificity	PPV	NPV
SII	682.07	0.82	0.63	0.28	0.95	669.14	0.83	0.64	0.28	0.95
SIRI	2.84	0.64	0.84	0.40	0.93	2.67	0.66	0.85	0.43	0.93
AISI	1222.66	0.50	0.94	0.58	0.91	1143.88	0.52	0.92	0.52	0.91
NLR	3.14	0.67	0.78	0.34	0.93	2.97	0.68	0.78	0.35	0.93
LMR	2.68	0.46	0.72	0.21	0.90	2.64	0.54	0.75	0.28	0.91
PLR	152.25	0.64	0.75	0.31	0.93	146.23	0.65	0.75	0.31	0.93

AISI: Aggregate Index of Systemic Inflammation; CI: confidence interval; LMR: lymphocyte-to-monocyte ratio; LVI: lymphovascular invasion; NLR: neutrophil-to-lymphocyte ratio; NPV: negative predictive value; PLR: platelet-to-lymphocyte ratio; PPV: positive predictive value SII: Systemic Immune-Inflammation Index; SIRI: Systemic Inflammation Response Index.