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# The Role of HALP Score and Other Inflammatory Indices in Risk Stratification for Testicular Germ Cell Tumors

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

Systemic inflammatory and immuno-nutritional indices such as neutrophil-to-lymphocyte ratio and systemic immune-inflammation index (SII) have been associated with advanced disease in testicular cancer. However, comparative data regarding the predictive power of various indices remain limited. This study demonstrates that hemoglobin, albumin, lymphocyte and platelet, SII, and inflammatory burden index are independent predictors of advanced-stage testicular germ cell tumors. By identifying the most accurate and accessible biomarkers, this research enhances the utility of inflammation- and nutrition-based scores in clinical risk stratification.

## Abstract

**Objective:** Systemic inflammatory and immuno-nutritional indices have emerged as promising tools in cancer prognosis. This study aimed to evaluate the predictive value of hemoglobin, albumin, lymphocyte and platelet (HALP), neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), C-reactive protein lymphocyte ratio (CLR), inflammatory burden index (IBI), and systemic inflammation response index (SIRI) for advanced-stage disease in testicular germ cell tumors (TGCTs).

**Materials and Methods:** We retrospectively analyzed 143 patients with TGCTs who underwent orchiectomy between 2015 and 2023. Preoperative laboratory values were used to calculate HALP, NLR, SII, CLR, IBI, and SIRI. Associations with clinical stage were examined using Kruskal-Wallis tests, logistic regression, and ROC curve analysis.

**Results:** Higher values of HALP, SII, CLR, NLR, and IBI were significantly associated with advanced clinical stages ($p<0.001$), while SIRI showed limited predictive value. HALP demonstrated the highest discriminative ability [area under the curve (AUC)=0.742], followed by SII (AUC=0.731) and IBI (AUC=0.676). Multivariable logistic regression identified HALP, CLR, and IBI as independent predictors of advanced disease.

**Conclusion:** HALP, SII, CLR, and IBI are accessible, cost-effective biomarkers with significant potential for risk stratification in TGCTs. These indices may support clinical decision-making by identifying patients at risk for advanced-stage disease.

**Keywords:** Testicular germ cell tumors, HALP score, systemic inflammatory index, inflammatory burden index, immuno-nutritional markers

## Introduction

Testicular cancer is the most common malignancy among men aged 15 to 40 years, representing approximately 1% of all male cancers globally (1). Although the disease is rare, its incidence has been steadily increasing, particularly in developed regions, making it a critical area of oncological research (2,3). Despite the high cure rates achieved with multimodal treatments, including orchiectomy and cisplatin-based chemotherapy, patients with advanced or recurrent disease often face poorer outcomes (3,4). This underscores the need for enhanced prognostic tools to stratify patients effectively and guide clinical decision-making (5).

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Cancer is recognized not only for causing localized symptoms in the affected organ but also for inducing systemic manifestations, which are indicative of the inflammatory processes associated with malignancy (6). Inflammation plays a pivotal role in regulating oncogenesis and neoplastic proliferation, particularly during the resistance phase, a critical period for the immune system to exhibit its functional efficacy (7). However, excessive or dysregulated immune responses may lead to immunopathological damage, resulting in necrosis. This can transition into the tolerance phase, which is characterized by systemic symptoms (6). During this phase, macrophages and other myeloid-derived cells, such as neutrophils, are central to the pathophysiology (8). These cells secrete cytokines, chemokines, and reactive oxygen species, which not only promote immunosuppression and the progression of neoplastic cells but also contribute to systemic effects (6). A comprehensive understanding of these "repair" phenomena sheds light on the pathogenesis of thrombophilia, anemia, sarcopenia, and disruptions in iron metabolism frequently observed in patients with advanced-stage malignancies (9).

The role of systemic inflammation in cancer development and progression has been well-documented. Chronic inflammation fosters processes such as tumor initiation, angiogenesis, immune evasion, and metastasis (10-12). In the context of testicular germ cell tumors (TGCTs), systemic inflammatory markers such as neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), and systemic inflammation response index (SIRI) have shown significant associations with disease burden and progression. Elevated levels of these indices have been linked to advanced tumor stages and poorer survival outcomes (13-15). In addition, indices such as inflammatory burden index (IBI) and C-reactive protein (CRP) lymphocyte ratio (CLR) -though less commonly investigated in testicular tumors- have been associated with advanced cancer stages and poor prognosis in other malignancies, including lung, colorectal, and gastrointestinal cancers (16,17).

Similarly, nutritional status plays a critical role in modulating cancer progression and patient survival (18,19). Comprehensive immuno-nutritional indices, such as the hemoglobin, albumin, lymphocyte, and platelet (HALP) score and the prognostic nutritional index, provide a robust assessment of systemic inflammation and nutritional health. Previous research has shown that HALP scores were significantly lower in patients with testicular cancer compared to healthy individuals (20). Studies have demonstrated that lower values of these indices correlate with advanced disease stages and larger tumor sizes, further supporting their potential utility as non-invasive, easily accessible tools for risk stratification (21,22).

This study aims to evaluate the relative prognostic significance of inflammatory and immuno-nutritional indices in testicular cancer. By comparing the predictive capabilities of these parameters, this research seeks to determine whether inflammatory or nutritional markers offer superior utility in understanding disease progression.

## Materials and Methods

This study protocol was reviewed and approved by Haydarpaşa Numune Training and Research Hospital, Scientific Research Ethics Committee on September 17 2024, approval number HNEAH-BAEK/KK/2024/119. Study activities adhered to the principles outlined in the Declaration of Helsinki. All participating patients, who agreed to the anonymous use of their data, signed the informed consent in writing.

Two hundred and fifty-two patients who had orchiectomy surgery at our tertiary referral urooncology clinic between January 2015 and December 2023, were enrolled. 109 patients with benign pathology (n=45), undescended testicle (n=25), non-germ cell testicular tumors (n=21), testicular torsion (n=14), or surgical castration (n=4) were excluded from the study. Following these exclusions, our study group comprised 143 patients.

Demographic information (age) and clinical parameters were collected. The data of orchiectomy surgery, postoperative pathology results, stage, primary type, tumor size, presence of rete testes invasion and presence of lympho-vascular invasion (LVI) were collected from the hospital database. The staging has been carried out according to the testicular cancer section of the TNM classification of malignant tumors, Union for International Cancer Control, 8$^{th}$ edition (23). Preoperative biochemical markers, including CRP (mg/L), albumin (g/L) and complete blood count values (hemoglobin, lymphocyte, monocyte, neutrophil, platelet) were recorded within a two-week window surrounding surgery. The following calculated indices were derived from the collected data: hemoglobin x albumin x lymphocyte/platelet as HALP, neutrophil/lymphocyte as NLR, CRP/lymphocyte as CLR, CRP x NLR as IBI, monocyte x NLR as SIRI, platelet x NLR as SII.

### Statistical Analysis

Statistical analyses were performed using IBM SPSS version 25 (IBM Corp, Armonk, NY, USA). Continuous variables were expressed as median (interquartile range) according to the data distribution. Categorical variables were presented as frequencies and percentages.

The Kruskal-Wallis test was used to compare non-parametric continuous variables across groups. Pairwise comparisons were performed using the Mann-Whitney U test. Chi-square tests were applied to analyze categorical variables. Logistic regression analysis was employed to evaluate the association between clinicopathological parameters and inflammatory/immuno-

nutritional scores. Odds ratios (OR) with 95% confidence intervals (CI) were calculated.

Receiver operating characteristic (ROC) curve analysis was conducted to assess the discriminative ability of inflammatory and immuno-nutritional scores for advanced clinical stages. The area under the curve (AUC), optimal cut-off values, sensitivity, and specificity were reported. Logistic regression analysis was performed to identify independent predictors of advanced disease, with results expressed as adjusted odds ratios (aOR) and 95% CIs. A p-value of <0.05 was considered statistically significant for all analyses.

## Results

A total of 143 patients were included in the study, with a median age of 36 years (interquartile range: 28-43). Among the cohort, 61 patients (42.7%) were diagnosed with seminoma, while 82 patients (57.3%) had non-seminomatous germ cell tumors. Clinical stage distribution revealed that 76 patients (53.9%) were in stage I, 34 (24.1%) in stage II, and 31 (22%) in stage III. Tumor size was ≥4 cm in 83 patients (59.3%) and <4 cm in 57 patients (40.7%). Rete testis invasion was observed in 86 patients (60.1%), while LVI was present in 65 patients (45.5%) (Table 1).

Patients with higher clinical stages exhibited a higher prevalence of pathological risk factors. Logistic regression analysis identified that rete testis invasion significantly increased the likelihood of advanced disease (stage II/III) with an OR of 2.611 (95% CI: 1.290-5.286, p=0.008). Similarly, LVI was significantly associated with advanced disease stages, with an OR of 2.128 (95% CI: 1.083-4.182, p=0.028) (Table 2).

Inflammatory and immuno-nutritional scores demonstrated significant differences across clinical stages. Median HALP scores were significantly lower in stage I [34.64 (24.85-57.84)] compared to stages II and III (p<0.001). Similarly, median SII scores were markedly higher in stage III [1378.36 (806-1883.43)] compared to stage I [804.55 (643.37-1037.33), p<0.001]. Other markers, including IBI, CLR, and NLR, also showed significant upward trends with advancing disease stages (p<0.05). However, the SIRI did not exhibit statistically significant differences among the stages (p=0.193), indicating a less robust role of SIRI in differentiating disease severity (Table 3).

ROC curve analysis revealed that HALP and SII scores had the highest discriminative abilities for advanced clinical stages, with

**Table 1. Clinicopathological characteristics of patients**

| Variables | Number of patients, n=143 (%) |
|---|---|
| Age | 36.8 (18-69) |
| **Tumor type** | |
| Seminoma | 61 (42.7) |
| NSGCT | 82 (57.3) |
| **Clinical stage** | |
| I | 76 (53.9) |
| II | 34 (24.1) |
| III | 31(22) |
| **Tumor size** | |
| <4 cm | 57 (40.7) |
| ≥4 cm | 83 (59.3) |
| **Rete testes invasion** | |
| Yes | 86 (60.1) |
| No | 57 (39.9) |
| **Lymphovascular invasion** | |
| Yes | 65 (45.5) |
| None | 78 (54.5) |

NSGCT: Non-seminomatous germ cell tumors

**Table 2. Epidemiological and pathological characteristics**

| Variables | Stage I (n=76) | Stage II (n=34) | Stage III (n=31) | p[1] | |
|---|---|---|---|---|---|
| Age[2] | 38.2 (20-69) | 34.6 (22-64) | 35.9 (18-62) | 0.227 | |
| Variables | Stage I n (%) | Stage II n (%) | Stage III n (%) | OR (95% CI) | p[3] |
| **Tumor size** | | | | | |
| <4 cm | 31 (41.9) | 13 (39.4) | 13 (41.9) | 0.949 (0.481-1.873) | 0.880 |
| ≥4 cm | 43 (58.1) | 20 (60.6) | 18 (58.1) | | |
| **Rete testes invasion** | | | | | |
| Yes | 38 (50) | 25 (73.5) | 22 (71) | 2.611 (1.290-5.286) | **0.008** |
| No | 38 (50) | 9 (26.5) | 9 (29) | | |
| **Lymphovascular invasion** | | | | | |
| Yes | 28 (36.8) | 15 (44.1) | 21 (67.7) | 2.128 (1.083-4.182) | **0.028** |
| None | 48 (63.2) | 19 (55.9) | 10 (32.3) | | |

[1]Kruskall-Wallis, [2]Mean (minimum-maximum), [3]Logistic regression, OR: Crude odds ratio, CI: Confidence interval

AUC values of 0.742 and 0.731, respectively (p<0.001 for both). HALP demonstrated a sensitivity of 61.3% and specificity of 84.5% at a cut-off value of 38.39, while SII showed a sensitivity of 54.8% and specificity of 90% at a cut-off value of 1346.75. Other markers, including IBI, CLR, and NLR, also demonstrated moderate discriminative abilities, with respective AUC values of 0.676, 0.646, and 0.698 (Table 4, Figure 1).

Significant associations were observed between inflammatory and immuno-nutritional scores and clinical stage. Patients with advanced stages (stage II/III) demonstrated higher levels of HALP, SII, IBI, CLR, and NLR (p<0.001 for all). HALP scores were notably higher in patients with stage I disease, indicating its association with better nutritional and inflammatory status in less advanced stages. Tumor size (≥4 cm), LVI, and rete testis invasion were associated with elevated inflammatory markers; however, these associations did not achieve statistical significance for all scores. Tumor size (≥4 cm) is associated with lower levels of HALP (p=0.049). LVI and rete testis invasion were associated with lower levels of HALP, however, this association did not achieve statistical significance (Table 5).

The significant predictive power of inflammatory and immuno-nutritional scores demonstrates the risk of developing clinically advanced disease. Both crude (OR1) and aOR (OR2) indicate a strong association between elevated score levels and increased risk, even after controlling for tumor size (≥4 cm), LVI, and rete testis invasion. Logistic regression analysis identified HALP (OR: 4.4, 95% CI: 1.919-10.089, p<0.001), SII (OR: 3.778, 95% CI: 1.532-9.313, p=0.004), CLR (OR: 5.043, 95% CI: 1.986-12.806, p<0.001), IBI (OR: 2.22, 95% CI: 1.046-4.721, p=0.035), and NLR (OR: 3.12, 95% CI: 1.234-7.876, p=0.021) as independent predictors of advanced clinical disease. These findings underscore the utility of inflammatory and immuno-nutritional scores, including HALP, SII, CLR, IBI, and NLR, in stratifying patients by disease severity. The IBI showed the highest adjusted OR (OR2=11.504, 95% CI: 3.508-37.725, p<0.001), emphasizing its robust predictive value. Similarly, the CLR and HALP also demonstrated strong associations, with adjusted ORs of 6.687 (95% CI: 2.446-18.278, p<0.001) and 5.079 (95% CI: 2.074-12.436, p<0.001), respectively. SII and NLR also showed significant adjusted odds, indicating their relevance in predicting disease progression, with SII (OR2=4.339, p=0.003) and NLR (OR2=3.581, p<0.001). These findings underscore the utility of these scores as non-invasive tools for risk stratification and clinical decision-making in patients with germ cell tumors (Table 6).

## Discussion

This study investigates the prognostic significance of systemic inflammatory and immuno-nutritional indices in TGCTs, highlighting their potential role in risk stratification and clinical decision-making. By evaluating key markers such as HALP, SII, NLR, CLR, and IBI, this research contributes to the growing evidence supporting the integration of inflammatory and nutritional biomarkers into oncological practice.

Results from this study demonstrate that elevated levels of HALP, SII, CLR, IBI, and NLR are significantly associated with advanced

**Table 3. Inflammatory and Immuno-nutritional scores for GCT staging**

| Scores | Stage I | Stage II | Stage III | p[1] |
|---|---|---|---|---|
| **HALP** | 59.37 (21.46) | 62.73 (29.11) | 62.73 (20.92) | **<0.001** |
| **SII** | 920.72 (528.80) | 1087.99 (1426.76) | 1628.35 (1232.10) | **<0.001** |
| **SIRI** | 1.49 (1.08) | 2.06 (3.34) | 2.00 (1.46) | 0.193 |
| **IBI** | 10.68 (53.62) | 13.46 (27.82) | 22.19 (38.18) | **0.001** |
| **CLR** | 1.67 (6.76) | 2.06 (2.64) | 3.20 (5.23) | **0.002** |
| **NLR** | 2.68 (1.54) | 3.07 (2.36) | 4.88 (4.19) | **0.003** |

[1]Mann-Whitney U test, HALP: Hemoglobin, albumin, lymphocytes and platelets score, NLR: Neutrophil lymphocyte ratio, SII: Systemic inflammatory index, SIRI: Systemic inflammation response index, IBI: Inflammatory burden index, CLR: C-reactive protein lymphocyte ratio, GCT: Germ cell tumor

**Table 4. The discriminating potential of the assessed inflammatory and immuno-nutritional scores**

| Scores | Cut-off points | AUC | p | 95% CI | Specifity (%) | Sensitivity (%) |
|---|---|---|---|---|---|---|
| **HALP** | 38.39 | 0.742 | **0.000** | 64.2-84.2 | 84.5 | 61.3 |
| **SII** | 1346.75 | 0.731 | **0.000** | 62.1-84.2 | 90 | 54.8 |
| **IBI** | 11.26 | 0.676 | **0.001** | 56.8-78.5 | 88.2 | 41.9 |
| **CLR** | 2.08 | 0.646 | **0.009** | 53.6-75.6 | 86.4 | 41.9 |
| **NLR** | 2.71 | 0.698 | **0.000** | 58.7-80.9 | 66.4 | 71 |

HALP: Hemoglobin, albumin, lymphocytes and platelets score, NLR: Neutrophil lymphocyte ratio, SII: Systemic inflammatory index, IBI: Inflammatory burden index, CLR: C-reactive protein lymphocyte ratio, AUC: Area under curve, CI: Confidence interval

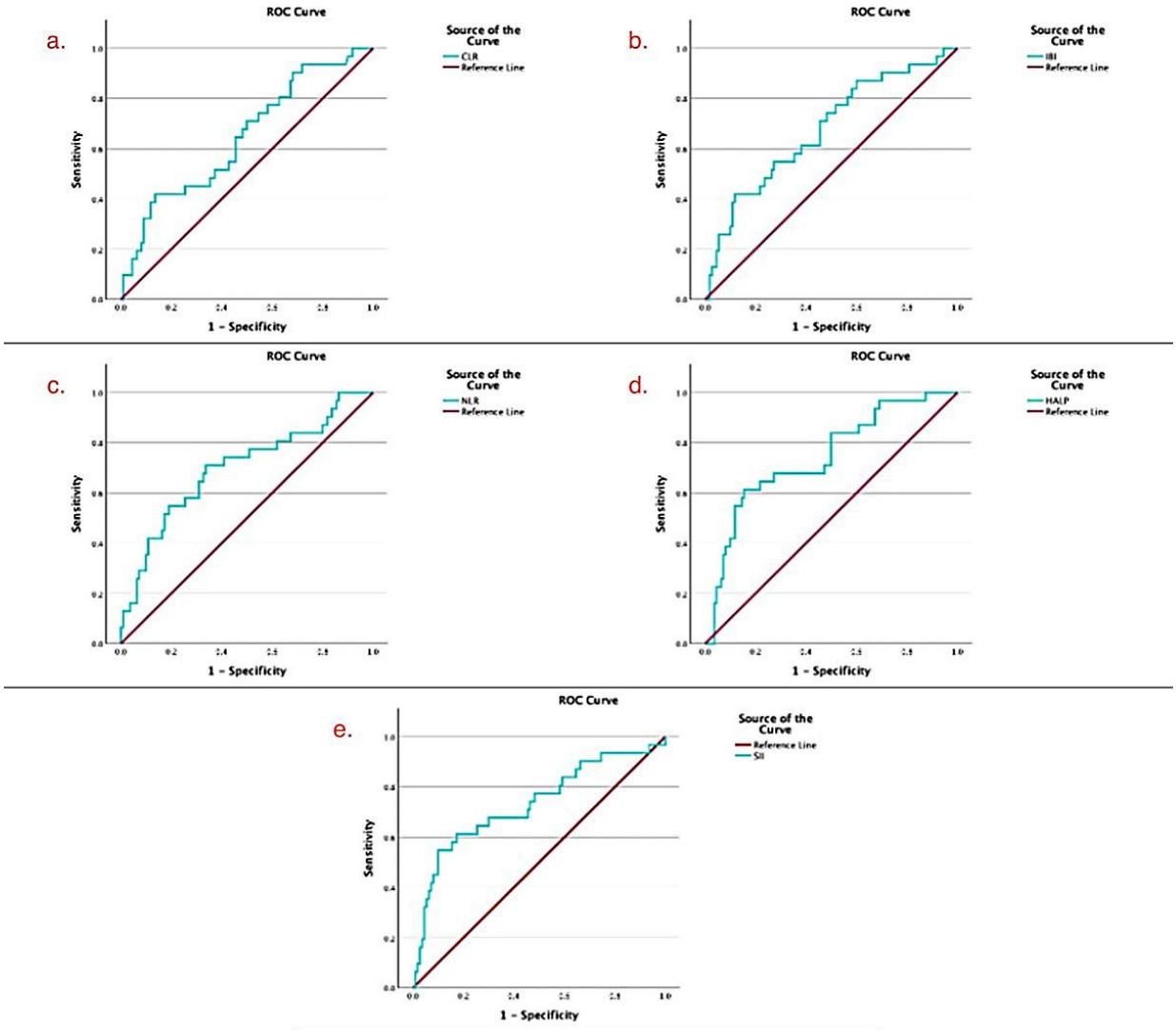


**Figure 1.** ROC curves for CLR (a). Roc plot for IBI (b). Roc plot for NLR (c). Roc plot for HALP (d). Roc plot for SII (e)

ROC: Receiver operating characteristic, HALP: Hemoglobin, albumin, lymphocytes and platelets score, NLR: Neutrophil lymphocyte ratio, SII: Systemic inflammatory index, IBI: Inflammatory burden index, CLR: CRP lymphocyte ratio. The red line represents the reference line for a non-discriminatory test

disease stages, whereas SIRI showed limited discriminatory power. Among these markers, HALP and SII exhibited the highest predictive accuracy, as evidenced by ROC curve analysis. Logistic regression further identified HALP, CLR, and IBI as independent predictors of advanced-stage TGCTs. These findings underscore the relevance of inflammatory and immuno-nutritional indices in stratifying patients and guiding treatment decisions.

Inflammation plays a pivotal role in all stages of tumor development and progression. It also significantly influences the tumor immune microenvironment and treatment response. Elevated neutrophil counts are associated with the release of tumor-promoting factors, including reactive oxygen species, arginase, inflammatory cytokines, tumor or vascular growth factors, and metalloproteinases, which may contribute to cancer progression and metastasis. Conversely, reduced lymphocyte counts are linked to impaired anti-tumor immune responses, including diminished $CD8^+$ T-cell cytotoxicity and compromised $CD4^+$ helper T-cell functions. Platelets play a multifaceted role in cancer progression by releasing cytokines, such as platelet-derived growth factor and platelet-reactive protein, which facilitate hematogenous dissemination and invasion. Monocytes are precursors to tumor-associated macrophages, which are implicated in immune suppression, angiogenesis, and metastasis. Their role in inflammation-mediated cancer progression is well-established (11,24,25). As a marker of systemic inflammation, elevated CRP levels signify a heightened inflammatory response often triggered by cytokines secreted by tumors. High CRP levels have been associated with advanced disease stages (15). Considering the significant influence of nutritional status on tumor immunotherapy, numerous studies

**Table 5. The association between different clinicopathological parameters and immuno-nutritional/ inflammatory scores**

| Parameters | HALP, n (%) | | | SII, n (%) | | | IBI, n (%) | | | CLR, n (%) | | | NLR, n (%) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Low | High | p | Low | High | p | Low | High | p | Low | High | p | Low | High | p |
| **Clinical stage** | | | | | | | | | | | | | | | |
| Stage I | 10 | 66 | | 68 (89) | 8 (11) | | 72 (95) | 4 (5) | | 69 (91) | 7 (9) | | 53 (70) | 23 (30) | |
| Stage II | 7 | 27 | **<0.001** | 31 (91) | 3 (9) | **<0.001** | 25 (74) | 9 (26) | **<0.001** | 25 (74) | 9 (26) | **<0.001** | 20 (59) | 14 (41) | **<0.001** |
| Stage III | 19 | 12 | | 14 (45) | 17 (55) | | 18 (58) | 13 (42) | | 18 (58) | 13 (42) | | 9 (29) | 22 (71) | |
| **Tumor size** | | | | | | | | | | | | | | | |
| <4 cm | 10 | 47 | **0.049** | 47 (83) | 10 (17) | 0.352 | 47 (83) | 10 (17) | 0.488 | 46 (81) | 11 (19) | 0.451 | 37 (65) | 20 (35) | 0.138 |
| ≥4 cm | 26 | 57 | | 65 (78) | 18 (22) | | 67 (81) | 16 (19) | | 65 (78) | 18 (22) | | 45 (54) | 38 (46) | |
| LVI | | | | | | | | | | | | | | | |
| Yes | 19 | 46 | 0.204 | 52 (80) | 13 (20) | 0.537 | 54 (83) | 11 (17) | 0.447 | 52 (80) | 13 (20) | 0.554 | 38 (59) | 27 (41) | 0.543 |
| No | 17 | 61 | | 63 (81) | 15 (19) | | 63 (81) | 15 (19) | | 62 (80) | 16 (20) | | 46 (59) | 32 (41) | |
| **Rete testes invasion** | | | | | | | | | | | | | | | |
| Yes | 23 | 63 | 0.371 | 69 (80) | 17 (20) | 0.561 | 70 (81) | 16 (19) | 0.528 | 70 (81) | 16 (19) | 0.342 | 50 (58) | 36 (42) | 0.498 |
| No | 13 | 44 | | 46 (81) | 11 (19) | | 47 (83) | 10 (17) | | 44 (77) | 13 (23) | | 34 (60) | 23 (40) | |

HALP: Hemoglobin, albumin, lymphocytes and platelets score, NLR: Neutrophil lymphocyte ratio, SII: Systemic inflammatory index, IBI: Inflammatory burden index, CLR: C-reactive protein lymphocyte ratio, LVI: Lymphovascular invasion. Cut-off values; HALP 38.39, SII 1346.75, IBI 11.26, CLR 2.08, NLR 2.71; $\chi 2$ test

**Table 6. The risk of developing clinically advanced disease in relation to the levels of inflammatory and immuno-nutritional scores**

| Variables | OR1 (95% CI) | p | OR2 (95% CI) | p |
|---|---|---|---|---|
| **HALP** | 4.4 (1.919-10.089) | **<0.001** | 5.079 (2.074-12.436) | **<0.001** |
| **SII** | 3.778 (1.532-9.313) | **0.004** | 4.339 (1.672-11.266) | **0.003** |
| **IBI** | 9.209 (2.974-28.519) | **<0.001** | 11.504 (3.508-37.725) | **<0.001** |
| **CLR** | 5.043 (1.986-12.806) | **<0.001** | 6.687 (2.446-18.278) | **<0.001** |
| **NLR** | 2.861 (1.432-5.714) | **0.003** | 3.581 (1.675-7.655) | **<0.001** |

HALP: Hemoglobin, albumin, lymphocytes and platelets score, NLR: Neutrophil lymphocyte ratio, SII: Systemic inflammatory index, IBI: Inflammatory burden index, CLR: C-reactive protein lymphocyte ratio, OR1: Crude odds ratio, OR2 is adjusted to tumor size (greater than 4 cm), presence of LVI and presence of rete testis invasion, CI: Confidence interval, LVI: Lymphovascular invasion

have investigated the relationship between nutrition-related factors and prognosis (26,27). Markers of malnutrition, such as low albumin and hemoglobin levels, have been associated with poor clinical outcomes (21).

The NLR is a widely used systemic inflammatory biomarker reflecting the balance between neutrophils, which promote inflammation and tumor progression, and lymphocytes, which mediate anti-tumor immune responses. Elevated NLR values have been consistently associated with poor prognosis in several cancers, including testicular cancer (14,28,29). In our study, NLR significantly increased with advancing clinical stages of testicular GCTs, particularly in seminoma patients, aligning with prior findings linking high NLR to poor overall survival (OS) and progression-free survival (PFS) (15,28). Moreover, NLR has been shown to predict higher metastatic potential and poor chemotherapy responses, reinforcing its value as a predictive marker of disease progression and treatment outcomes (22,29). In this study, SII demonstrated significant differences across clinical stages, with higher values correlating with advanced-stage disease. This observation is consistent with prior research identifying SII as a strong predictor of adverse outcomes, including OS and PFS, in multiple cancers (30). Compared to NLR, SII's inclusion of platelet counts may provide a more comprehensive representation of the inflammatory milieu, potentially enhancing its prognostic utility. In contrast, the SIRI did not exhibit significant stage-dependent variations in our cohort, suggesting limited discriminatory power in testicular cancer. While SIRI has shown promise in other malignancies, its role in GCTs appears supplementary, possibly enhancing predictive accuracy when used in conjunction with other indices like NLR or SII (15). Collectively, our findings reinforce the utility of NLR and SII as robust, accessible, and cost-effective markers for predicting disease progression in testicular cancer, with SII emerging as the more comprehensive index in this context.

The HALP score, integrating HALP levels, reflects both the nutritional and inflammatory status of cancer patients. In this study, lower HALP scores were strongly associated with advanced clinical stages of testicular GCTs. These findings align with previous research demonstrating HALP's utility in stratifying cancer patients based on disease severity. For

instance, Bumbasirevic et al. (21) reported that HALP scores below 42.56 were predictive of advanced disease, with a four-fold increased risk for stages II and III compared to stage I. Comparatively, HALP has been shown to outperform NLR and PLR in malignancies, such as renal cell carcinoma and bladder cancer, where it predicts survival and enhances prognostic accuracy when integrated into multivariate models (31,32). In testicular cancer, HALP's ability to reflect both systemic inflammation and nutritional deficiencies provides valuable prognostic insights, particularly for guiding treatment decisions and follow-up strategies in advanced-stage patients (21).

The CLR and IBI are less studied in testicular cancer but have demonstrated prognostic significance in other malignancies. In cancers such as colorectal and bladder cancer, elevated CLR values correlate with advanced stages and poorer survival outcomes (17,33). While CLR showed moderate predictive value in this study, its utility may be enhanced when combined with indices like NLR or HALP. Studies in non-small cell lung and gastrointestinal cancers have identified IBI as a strong predictor of survival and adverse outcomes, such as prolonged hospitalization and cachexia (16,34). Although IBI's performance in our testicular cancer cohort was less pronounced, its integration with other markers could provide additional prognostic value.

Among the indices evaluated, SII and HALP emerged as the most comprehensive predictors of testicular cancer progression, followed closely by NLR. SII's broader inflammatory context and HALP's integration of nutritional parameters make them particularly valuable for risk stratification, and treatment planning. In clinical practice, NLR serves as a quick and accessible marker for inflammation. SII provides a broader measure of systemic inflammation, offering enhanced prognostic utility. HALP adds critical insights into the patient's nutritional and immune status, complementing the inflammatory data from NLR and SII. While CLR and IBI demonstrated limited standalone utility in this study, their incorporation into multivariate models could refine prognostic accuracy, particularly in advanced-stage GCTs. These markers, collectively, hold promise for guiding individualized treatment approaches, optimizing follow-up strategies, and improving outcomes in testicular cancer patients.

This study provides valuable insights into the prognostic utility of systemic inflammatory and immuno-nutritional indices in risk stratification for TGCTs. A key strength of this research lies in its comprehensive analysis of multiple biomarkers, including HALP, SII, CLR, IBI, and NLR, using a well-defined cohort and robust statistical methods. The identification of HALP and SII as the most potent predictors of advanced disease underscores their potential role in enhancing clinical decision-making.

### Study Limitations

However, several limitations must be acknowledged. The retrospective design introduces inherent biases, and the absence of a healthy control group limits broader generalizability. Another limitation is that a considerable proportion of the study cohort presented with adverse pathological features such as large tumor size, rete testis invasion, and lymphovascular invasion, which may have influenced the stage distribution and biomarker associations.

## Conclusion

Additionally, while the study establishes strong associations, the underlying biological mechanisms linking these markers to tumor progression warrant further investigation. Despite these limitations, this study contributes to the growing body of evidence supporting the integration of inflammatory and nutritional markers into routine oncological practice. Future prospective studies are essential to validate these findings and explore their applicability in personalized treatment strategies for testicular cancer patients.

### Ethics

**Ethics Committee Approval:** This study protocol was reviewed and approved by Haydarpaşa Numune Training and Research Hospital, Scientific Research Ethics Committee on September 17 2024, approval number HNEAH-BAEK/KK/2024/119.

**Informed Consent:** All participating patients, who agreed to the anonymous use of their data, signed the informed consent in writing.

### Footnotes

### Authorship Contributions

Surgical and Medical Practices: K.K., R.K., E.K., Ç.T., Concept: K.K., R.K., E.K., Design: K.K., R.K., E.K., Data Collection or Processing: B.B.G., Analysis or Interpretation: K.K., R.K., Literature Search: K.K., Ç.T., Writing: K.K., E.K., Ç.T., Ö.E.Y.

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