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Research Article

Prognostic role of systemic immune-inflammation index in patients with nasopharyngeal cancer

Nazofarenks kanserli hastalarda sistemik immün-inflamasyon indeksinin prognostik rolü

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Abstract

Aim: This study aimed to evaluate the prognostic significance of the systemic immune-inflammation index (SII) in patients with nasopharyngeal carcinoma (NPC).

Material and Methods: This retrospective study included 42 patients diagnosed with NPC between January 2014 and January 2020. Clinical data, hematological parameters, and survival outcomes were collected. Disease stage was classified using the 8th edition of the American Joint Committee on Cancer (AJCC) Staging System. Pre-treatment SII values were calculated using complete blood count data (platelets × neutrophils / lymphocytes).

Results: The mean patient age was 54.0 ± 13.8 years, with a male predominance (66.7%). Most patients presented with advanced disease (AJCC Stage III–IV). Higher pre-treatment SII values were significantly associated with poorer overall survival (OS) and progression-free survival (PFS). Multivariate Cox regression analysis confirmed that elevated SII independently predicted reduced OS (HR: 1.06; 95% CI: 1.02–1.09; $p < 0.001$). ROC analysis identified optimal SII cut-off values of >610 for OS (sensitivity: 73.9%, specificity: 60.0%) and >580 for PFS (sensitivity: 75.0%, specificity: 57.1%). Kaplan–Meier analysis demonstrated significantly lower OS and PFS in patients with elevated SII (log-rank $p < 0.001$).

Conclusion: Elevated SII is a strong and independent prognostic marker for poor outcomes in NPC patients and may guide personalized clinical management.

Keywords: nasopharyngeal carcinoma, systemic immune-inflammation index, prognosis, survival analysis, inflammation

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Öz

Amaç: Bu çalışmanın amacı, nazofarenks karsinomlu (NPC) hastalarda sistemik immün-inflamasyon indeksinin (SII) prognostik önemini değerlendirmektir.

Gereç ve Yöntemler: Bu retrospektif çalışmaya Ocak 2014 ile Ocak 2020 arasında NPC tanısı alan 42 hasta dahil edildi. Klinik veriler, hematolojik parametreler ve sağkalım sonuçları toplandı. Hastalığın evresi, Amerikan Kanser Ortak Komitesi (AJCC) Evreleme Sisteminin 8. baskısı kullanılarak sınıflandırıldı. Tedavi öncesi SII değerleri, tam kan sayımı verileri (trombositler × nötrofiller / lenfositler) kullanılarak hesaplandı.

Bulgular: Hastaların ortalama yaşı 54,0 ± 13,8 yıl olup, erkek hastalar çoğunluktaydı (%66,7). Hastaların çoğunluğu ileri evrede (AJCC Evre III-IV) tanı aldı. Yüksek tedavi öncesi SII değerleri, anlamlı olarak daha kötü genel sağkalım (OS) ve progresyonsuz sağkalım (PFS) ile ilişkili bulundu. Çok değişkenli Cox regresyon analizinde, artmış SII'nin bağımsız olarak azalmış OS'yi öngördüğü gösterildi (HR: 1,06; %95 GA: 1,02–1,09; $p < 0,001$). ROC analizi ile OS için optimal SII eşik değeri >610 (%73,9 sensitivite, %60,0 spesifisite), PFS için >580 (%75,0 sensitivite, %57,1 spesifisite) olarak belirlendi. Kaplan-Meier analizinde yüksek SII olan hastaların OS ve PFS süreleri anlamlı derecede düşük bulundu (log-rank $p < 0,001$).

Sonuç: Artmış SII, NPC hastalarında kötü prognozun güçlü ve bağımsız bir belirtecidir ve kişiselleştirilmiş klinik tedavi yönetiminde yol gösterici olabilir.

Anahtar kelimeler: nazofarenks karsinomu, sistemik immün-inflamasyon indeksi, prognoz, sağkalım analizi, inflamasyon

Introduction

Nasopharyngeal carcinoma (NPC) is a malignant epithelial tumor of the nasopharynx with a distinct geographical distribution, particularly prevalent in East and Southeast Asia (1). It is also etiologically linked to Epstein–Barr virus (EBV) infection, and despite NPC's sensitivity to radiotherapy, a significant subset of patients still experience treatment failure. Indeed, up to one-third of NPC patients develop locoregional recurrence or distant metastasis after primary chemoradiotherapy, leading to poor survival outcomes (2). This variability in patient outcomes underlines the need for reliable prognostic biomarkers to improve risk stratification and guide individualized therapy in NPC (3).

Inflammation has increasingly been recognized as playing a pivotal role in cancer progression and metastasis (4). NPC is no exception: its tumor microenvironment is characterized by abundant inflammatory cell infiltration and elevated cytokine levels that promote tumor growth and spread (5). Consistent with this, clinical studies have shown that elevated systemic inflammation-based markers – such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) – are associated with worse survival in NPC patients (6-8). These findings suggest that the host's inflammatory response can significantly influence NPC progression and prognosis.

Among the various inflammation-related indices, the Systemic Immune-Inflammation Index (SII) has emerged as a novel composite prognostic indicator. SII is derived from peripheral blood neutrophil, platelet, and lymphocyte counts, reflecting the balance between host inflammatory response and immune status (9). High SII values have been linked to adverse outcomes in several solid tumors, and recent evidence indicates a similar prognostic impact in NPC. In fact, a meta-analysis of six studies found that NPC patients with an elevated pretreatment SII had significantly poorer overall and progression-free survival compared to those with low SII (10). This highlights SII as a promising candidate biomarker for risk stratification in nasopharyngeal carcinoma.

While previous research in Turkey has investigated the prognostic significance of SII in head and neck cancers, to our knowledge, no study has specifically addressed its role in Turkish patients with NPC cohorts. This study aimed to evaluate the prognostic role of the SII in patients with NPC.

Patients and Methods

This retrospective study was conducted on adult patients diagnosed with nasopharyngeal carcinoma who were followed at the Department of Otorhinolaryngology, Dicle University, between January 2014 and January 2020. The study was approved by the Dicle University Medical Faculty Ethics Committee for Non-Interventional Studies (25.09.2024 - No: 245) and was carried out in accordance with the relevant ethical guidelines and the Helsinki Declaration (2013 Brazil revision). The need for informed consent was waived under the approval of the Local Ethics Committee due to the retrospective design.

During the study period, a total of 96 patients followed

for NPC were retrospectively evaluated. Inclusion criteria included histopathologically confirmed NPC, receipt of either radiotherapy or chemotherapy, and availability of a complete blood count taken within two weeks prior to the initiation of treatment. All patients included in the study had a confirmed diagnosis of NPC, and their disease stage was classified using the 8th edition of the American Joint Committee on Cancer (AJCC) Staging System, which is specifically adapted for nasopharyngeal carcinoma. Additionally, all patients received routine intensity modulated radiotherapy. Exclusion criteria were: histological types other than squamous cell carcinoma, a previous malignancy, autoimmune or chronic inflammatory diseases, acute infections, and insufficient clinical data. Forty-two patients who met the exclusion and inclusion criteria were included in the analyses.

Data collection

The hospital's electronic information system and patient files were used to gather demographic and clinical data. The collected variables encompassed age, gender, ECOG performance status, T and N classifications, overall stage, anthropometric data (height and weight), treatment strategy, and pre-treatment hematologic parameters including neutrophils, lymphocytes, platelets, and monocytes. NLR was defined as the ratio of the absolute neutrophil count to the absolute lymphocyte count, and PLR as the ratio of the platelet count to the lymphocyte count, both derived from complete blood count values. SII was determined using the formula: platelet count × neutrophil count ÷ lymphocyte count (all in 10^9/L).

All patients were evaluated over a 5-year follow-up period. Overall survival (OS) was defined as the time from diagnosis to the date of last follow-up or death from any cause. Progression-free survival (PFS) was defined as the time from diagnosis to disease progression or death.

Statistical Analysis

All analyses were conducted using IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA) software. The normal distribution of numerical variables was assessed using the Kolmogorov-Smirnov test. Variables with a normal distribution were presented as mean ± standard deviation (SD), whereas non-normally distributed variables were expressed as median and interquartile range (IQR: 25th–75th percentiles). Categorical variables were presented as counts and percentages. To evaluate the prognostic relevance of potential factors, univariate Cox regression analyses were conducted. Variables with $p < 0.25$ were subsequently entered into a multivariate Cox regression model with 95% confidence intervals (CIs). ROC curve analysis was performed to evaluate the prognostic accuracy of SII, and the optimal cut-off point was determined using the Youden index, which identifies the value with the highest combined sensitivity and specificity. Survival outcomes were analyzed using the Kaplan–Meier method, and differences between groups were assessed with the log-rank test. A p-value < 0.05 was considered statistically significant in all analyses.

Results

The study included 42 patients with a mean age of 54.0 ± 13.8 years, of whom 28 were men (66.7%) and 14 were women (33.3%). The mean body mass index was 25.5 ± 4.3. T1–T2 staging was observed in 35.7% of patients, and N0–N1 in 31%, with most patients classified within AJCC stage III–IV. A total of 45.2% of patients received adjuvant chemotherapy (Table 1). The mean OS was 31 months, and the estimated OS for 1-, 3- and 5-year was were 81%, 62%, and 43%, respectively.

Univariate Cox regression analysis identified age, N stage, overall stage, and SII as statistically significant factors associated with overall survival. An increase in age was associated with a 1.27-fold higher risk of mortality (HR: 1.27; 95% CI: 1.02–1.53; p = 0.016). Similarly, patients with N stage 2–3 had a significantly increased risk of death compared to those with N stage 0–1, with a 2.45-fold elevated hazard (HR: 2.45; 95% CI: 1.06–5.70; p = 0.037). Patients with AJCC stage III–IV disease had a 1.88-fold increased risk of mortality compared to those with stage I–II (HR: 1.88; 95% CI: 1.20–2.95; p = 0.031). Additionally, higher SII values were significantly associated with worse survival outcomes (HR: 1.07; 95% CI: 1.03–1.10; p < 0.001) (Table 1).

Multivariate Cox regression analysis revealed that age, overall stage, and SII remained independent predictors of mortality. Age remained significant (HR: 1.29; 95% CI: 1.04–1.61; p = 0.018), as did advanced stage disease (HR: 1.93; 95% CI: 1.16–3.22; p = 0.012). SII also retained independent prognostic value, with each unit increase conferring a 1.06-fold increase in mortality risk (HR: 1.06; 95% CI: 1.02–1.09; p < 0.001) (Table 2).

ROC analysis showed that the SII had moderate discriminative ability for predicting OS (AUC: 0.684; 95% CI: 0.566–0.802) with an optimal cut-off value >610, yielding 73.9% sensitivity and 60.0% specificity. For PFS, the AUC was 0.662 (95% CI: 0.548–0.775), with an optimal cut-off value >580, sensitivity of 75.0%, and specificity of 57.1%. Both analyses were statistically significant (p < 0.001) (Table 3).

Kaplan–Meier analysis demonstrated significantly reduced OS and PFS in patients with elevated SII. Patients with SII > 610 had significantly worse OS compared to those with SII ≤ 610 (HR = 1.8; 95% CI = 1.3-2.2; log-rank p < 0.001). Similarly, patients with SII > 580 showed significantly shorter progression-free intervals (HR = 1.6; 95% CI = 1.2-1.9; log-rank p < 0.001) (Figure 1).

Table 1. Characteristics of the study population and univariate analysis of factors associated with overall survival.

			Survival	Univariable Regression	
	Alive n = 22	Deceased n = 20	HR	95% CI	p
Age, years	50.4 ± 14.6	58.3 ± 13.6	1.27	1.02-1.53	0.016*
Gender, n (%)					
Female	8 (36.4)	6 (30.0)	ref		
Male	14 (63.6)	14 (70.0)	1.44	0.55-3.76	0.454
BMI, kg/ m2	25.1 ± 3.5	25.7 ± 4.6	1.05	0.85-1.16	0.347
T stage, n (%)					
1-2	10 (45.5)	7 (35.0)	ref		
3-4	12 (54.5)	13 (65.0)	1.36	0.54-3.42	0.509
N stage, n (%)					
0-1	9 (40.9)	4 (20.0)	ref		
2-3	13 (59.1)	16 (80.0)	2.45	1.06-5.70	0.037*
AJCC stage					
I-II	7 (31.8)	4 (20.0)	ref		
III-IV	15 (68.2)	16 (80.0)	1.88	1.20-2.95	0.031*
Adjuvant chemotherapy, n (%)	10 (45.5)	9 (45.0)	1.27	0.61-2.63	0.523
NLR	2.2 ± 0.8	2.5 ± 0.7	1.52	1.12-2.05	0.018*
PLR	226.2 ± 44.8	243.7 ± 61.9	1.05	1.01-1.10	0.035*
SII	539.6 ± 142.4	688.3 ± 153.8	1.07	1.03-1.10	<0.001*

The data are expressed as the mean ± SD or IQR (25th–75th percentiles).or n (%).* indicates statistical significance at p < 0.05. AJCC, American Joint Committee on Cancer; BMI, Body Mass Index; CI, Confidence Interval; HR, Hazard Ratio; NLR, Neutrophil-To- Lymphocyte Ratio; PLR, Platelet-To-Lymphocyte Ratio; ref, Reference Category; SII, Systemic Immune-Inflammation Index; T stage, Primary Tumor Stage; N stage, Nodal Stage

Table 2. Independent predictors of mortality.

Variables	Multivariable Regression		
	HR	95% CI	p
	1.29	1.04-1.61	0.018*
AJCC stage			
I-II	ref		
III-IV	1.93	1.16-3.22	0.043*
SII	1.08	1.02-1.13	<0.001*

* indicates statistical significance at p < 0.05. AJCC, American Joint Committee on Cancer; BMI, Body Mass Index; CI, Confidence Interval; HR, Hazard Ratio; NLR, Neutrophil-To-Lymphocyte Ratio; PLR, Platelet-To-Lymphocyte Ratio; ref, Reference Category; SII, Systemic Immune-Inflammation Index; T stage, Primary Tumor Stage; N stage, Nodal Stage

Table 3. The diagnostic performance of the Systemic Immune-Inflammation Index in predicting overall survival (OS) and progression-free survival (PFS).

ROC Curve findings	OS	PFS
Area under the curve	0.684	0.662
Standard error	0.060	0.058
95% Confidence interval	0.566–0.802	0.548–0.775
P -value	<0,001*	<0,001*
Threshold value	>610	>580
Sensitivity (%)	73.9	75.0
Specificity (%)	60.0	57.1

* indicates statistical significance at p < 0.05. S>II, Systemic Immune-Inflammation Index.

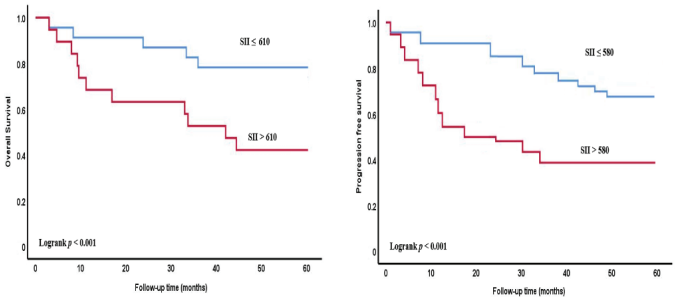

Figure 1. Axial magnetic resonance imaging (MRI) illustrating measurement of the interpeduncular angle (IPA).

The red lines indicate the angle formed between the medial aspects of the cerebral peduncles at the midbrain level.

Discussion

In this study, we found that an elevated pretreatment SII was associated with significantly poorer outcomes in NPC patients. Those with high SII values had lower OS and PFS rates compared to patients with low SII. Notably, our results indicate that SII can stratify NPC patients by risk. To the best of our knowledge, this is the first study to demonstrate the prognostic value of SII in the Turkish NPC patients.

Chronic inflammation is now recognized as a key driver in cancer progression, including NPC (10). NPC tumors often elicit

a systemic inflammatory response that correlates with disease severity. Inflammatory cells and mediators in the tumor microenvironment can promote angiogenesis, invasion, and immunosuppression, thereby facilitating tumor progression. For example, neutrophils – the most abundant immune cells in blood – can secrete pro-tumor factors (e.g. vascular endothelial growth factor, proteases) and suppress cytotoxic T-cell activity, fostering NPC invasion and metastasis (11). Conversely, lymphocytes (T cells, B cells, NK cells) are crucial for anti-tumor immunity; a reduction in lymphocyte count or function impairs immune surveillance and has been associated with worse outcomes in NPC (12, 13). Platelets also play a role by protecting tumor cells and aiding metastatic spread. Activated platelets release cytokines that support tumor cell extravasation and shield circulating cancer cells from NK cell–mediated lysis (14,15). Consistent with these mechanisms, clinical studies have observed that higher neutrophil and platelet counts (reflecting pro-tumor inflammation) and lower lymphocyte counts (reflecting weak immune response) are associated with more aggressive NPC and poorer survival (16-18). This link between systemic inflammation and NPC progression provides a rationale for investigating blood-derived inflammatory markers as prognostic indicators.

In the present study, both NLR and PLR were found to be associated with 5-year mortality. Among the inflammatory indices derived from blood counts, the NLR and PLR have been widely studied in NPC. These ratios serve as surrogates for the balance between pro-tumor inflammation and anti-tumor immunity. Numerous studies have confirmed that an elevated NLR or PLR is associated with advanced tumor burden and poorer survival outcomes in NPC (19-24). The prognostic value of NLR and PLR likely stems from their reflection of underlying biology: a high NLR indicates neutrophilia, which can promote tumor growth and suppress immunity, coupled with relative lymphopenia (impaired immune defense), while a high PLR indicates thrombocytosis (platelet-driven tumor progression) alongside lymphopenia.

By incorporating neutrophil and platelet counts together (rather than separately as in NLR or PLR), SII captures a broader spectrum of the systemic inflammatory response. This appears to translate into better risk stratification. Jiang et al. reported that in a cohort of over 300 NPC patients, SII had a higher area under the ROC curve for 3-year and 5-year survival than either NLR or PLR, indicating better discriminatory ability (21). In that study, all three indices showed significant associations with survival on univariate analysis, but SII emerged as the strongest independent predictor in multivariate modeling (hazard ratio for OS ~2.3 for high SII, compared to ~1.7 for NLR). Even after applying propensity score matching to balance baseline characteristics, SII remained an independent prognostic factor, whereas the predictive value of NLR and PLR was less pronounced. The authors concluded that "the prognostic value of SII is superior to PLR, NLR and MLR" in NPC (21). This finding has been echoed by others – a systemic review noted that composite indices like SII are more accurate in prognostic prediction than NLR or PLR in the NPC population (11,25). The enhanced performance of SII is biologically plausible: it simultaneously accounts for two tumor-promoting components (neutrophils and platelets) and the key tumor-fighting component (lymphocytes), thereby providing a more comprehensive measure of the immune-inflammatory balance. While NLR and PLR are useful and indeed prognostic in NPC, SII appears to yield superior prognostic information by virtue of its integrated formulation.

The results of the present study reinforce the prognostic significance of SII in NPC and align well with the existing body of literature. In our cohort, patients with higher SII experienced significantly worse outcomes, mirroring the adverse survival impact of elevated SII reported in prior studies (11,21,25). A 2022 meta-analysis pooling six studies (2169 patients) found that NPC patients with high SII had a 1.7-fold higher hazard of death and a ~1.6-fold higher risk of disease progression compared to those with low SII (10). Similarly, a 2023 systematic review including nine studies confirmed that SII is an independent predictor of both OS and PFS in NPC, with combined hazard ratios on the order of 1.7–1.8 for OS and 1.6–1.7 for PFS in favor of low SII (11). Xiong et al. reported that among 319 locally advanced NPC patients treated with chemoradiotherapy, those with high pretreatment SII had significantly shorter OS and PFS; furthermore, SII remained an independent predictor when controlling for clinicopathological factors (HR of 2.6 for OS and 1.3 for PFS) (26). These studies have identified optimal SII cut-off values in the mid-hundreds (generally ~400–700) to distinguish high- and low-risk patients. Despite these differences, the pattern is consistent: patients with SII above the optimal cut-off have markedly worse survival outcomes (including OS and disease-free/progression-free survival) compared to those below the cut-off. In the present study, the hazard ratios of SII for both OS and PFS were consistent with the existing literature. Notably, the magnitude of risk associated with high SII in our analysis (hazard ratios for OS and PFS) is comparable to that reported in earlier series and meta-analyses, lending credence to the reproducibility of this marker

across different populations. We also observed that SII provided independent prognostic value beyond the AJCC stage, which is consistent with most published data where SII remained significant in multivariable models (21).

Evidence from Turkey and other non-endemic regions echoes the prognostic significance of these markers, though published data are more limited. In a Turkish single-center study on NPC, patients with an elevated NLR (≥3) before treatment had substantially worse survival than those with lower NLR values (27). The same study and others also observed trends of higher PLR being associated with poorer outcomes, although NLR often emerged as the more significant predictor (27, 28). Until now, SII has not been extensively reported in Turkish NPC cohorts. This study contributes to the current evidence base by offering findings from a non-endemic population, indicating that the prognostic utility of SII is not exclusive to East Asian populations.

This study has several limitations that should be acknowledged. First, its retrospective design introduces potential selection bias and limits the ability to establish causal relationships. Although multivariate analyses were performed, unmeasured confounding factors may have influenced the results. Second, the sample size was relatively small, which may limit the statistical power and generalizability of the findings. Third, as a single-center study, the patient population may not fully represent broader demographic or geographic variations in nasopharyngeal carcinoma, particularly in non-endemic regions. Fourth, although SII was found to be a significant prognostic indicator, it can be influenced by non-cancer-related factors such as subclinical infections, concurrent inflammatory or hematologic conditions, and medication use, which may have affected pre-treatment blood counts. Finally, there remains no universally accepted cut-off value for SII in NPC; variability in thresholds across studies may impact its reproducibility and clinical applicability. Future multicenter prospective studies with larger and more diverse cohorts are needed to validate the prognostic utility of SII and to determine standardized reference values.

In conclusion, this study demonstrated that an elevated pre-treatment SII independently predicts poorer overall and progression-free survival outcomes in nasopharyngeal carcinoma patients. SII is an easily accessible, cost-effective biomarker that could improve risk stratification and guide clinical management.

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Conflicts of Interest

The authors declare they have no conflicts of interest.

Ethics Approval

The study was approved by the Dicle University Medical Faculty Ethics Committee for noninterventional studies (25.09.2024 - No: 245).

Informed Consent

The need for informed consent was waived under the approval of the Local Ethics Committee due to the retrospective design.

Availability of Data and Material

The data that support the findings of this study are available on request from the corresponding author.

Authors' contribution

Concept – G.K., Design- G.K., Data collection and/or processing - G.K. and B.H., Analysis and/or interpretation - G.K. and B.H., Writing – G.K., Critical review- B.H. All authors read and approved the final version of the manuscript.

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