

Prognostic value of Systemic Immune-Inflammation Index in head and neck cancer

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ABSTRACT

Aims: This study aimed to evaluate the prognostic value of the Systemic Immune-Inflammation Index (SII) in patients with head and neck cancer and its association with survival outcomes including disease-free survival (DFS) and overall survival (OS).

Methods: The patients diagnosed with head and neck cancer were retrospectively analyzed. Patients were stratified into two groups based on the SII cut-off value (796): low SII (L-SII) and high SII (H-SII). Clinical, demographic, and treatment-related parameters were compared between the groups. Kaplan-Meier survival analysis and Cox regression were used for univariate and multivariate analyses of DFS and OS.

Results: Of the total number of patients included in the study (n=184), 67 with high SII (≥ 796) exhibited significantly higher recurrence rates (43.3% vs. 8.5%, $p < 0.001$) and higher mortality (26.9% vs. 11.1%, $p = 0.006$) compared to those with low SII. Median DFS was shorter in the H-SII group (13.7 vs. 18.7 months), although the difference was not statistically significant ($p = 0.25$). In multivariate Cox analysis, advanced stage (HR: 3.00, 95% CI: 1.38-6.50, $p = 0.005$), ECOG ≥ 2 (HR: 3.72, 95% CI: 1.35-10.22, $p = 0.01$), and high SII (HR: 1.86, 95% CI: 1.01-3.16, $p = 0.05$) were independently associated with worse OS. Although high SII was not an independent predictor for DFS, it showed a clear trend toward worse outcomes (HR: 1.56, 95% CI: 0.72-3.34, $p = 0.25$).

Conclusion: High SII levels were associated with worse clinical outcomes and significantly higher rates of recurrence and mortality. While SII was an independent prognostic factor for OS, its effect on DFS did not reach statistical significance. These findings support the potential utility of SII as a simple, inflammation-based prognostic biomarker in head and neck cancers.

Keywords: Head and neck cancer, Systemic Immune-Inflammation Index, overall survival, progression-free survival, disease-free survival

INTRODUCTION

Head and neck cancer (HNC) encompasses a range of malignancies originating in the nasopharynx, larynx, oropharynx, hypopharynx, oral cavity, salivary glands, and paranasal sinuses and is a significant global health issue.¹ The treatment approach for HNC varies based on stage and location. While early-stage disease is typically treated with surgery or radiotherapy, induction chemotherapy is generally reserved for selected cases with locally advanced tumors. In recurrent or metastatic settings, systemic therapy aims to prolong survival and manage symptoms, although curative treatment is generally not feasible.

Optimal decision-making, treatment planning, and posttreatment response assessment for HNC patients require a multidisciplinary approach involving surgeons, medical oncologists, and radiation oncologists, as well as dentists, speech/swallowing pathologists, dietitians, psychosocial oncologists, prosthodontists, and rehabilitation therapists. Multidisciplinary tumor boards significantly impact

diagnostic and treatment decisions for many patients with newly diagnosed HNC.²

Despite advancements in multidisciplinary care, prognostic standards still fall short, leading to divergent survival rates among patients with identical tumor-node-metastasis (TNM) stages. Research has focused on prognostic factors aiding clinicians in identifying individuals with elevated susceptibility to HNC recurrence and mortality.³ Recognized prognostic factors in HNC include TNM staging, extranodal spread, HPV status, and patient attributes such as age, performance status, and history of smoking and alcohol consumption.⁴

Patient immunity and systemic inflammation play pivotal roles in angiogenesis and cancer progression, high neutrophil and platelet counts promote angiogenesis and tumor progression, while lymphopenia indicates impaired antitumor immunity.⁵ Studies have revealed associations between inflammation markers such as the neutrophil-to-lymphocyte ratio,

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lymphocyte-to-monocyte ratio, platelet-to-lymphocyte ratio, and C-reactive protein/albumin ratio-and cancer prognosis and survival.⁶⁻⁹ These findings underscore the significance of considering inflammatory markers in prognostic evaluation and treatment strategies for cancer patients.

A systematic review and meta-analysis encompassing 100 studies with 40,559 patients investigated the Systemic Immune-Inflammation Index (SII) as a prognostic determinant in various malignant solid tumors and revealed that elevated SII levels detrimentally impacted overall survival.¹⁰

While TNM staging and HPV status remain important prognostic indicators, additional biomarkers may help refine risk stratification in heterogeneous HNC populations. The present study investigates the impact of pretreatment SII values on survival outcomes in patients diagnosed with HNC. The study hypothesizes that high pretreatment SII is associated with poor disease-free survival (DFS) and overall survival (OS) in patients with HNC.

METHODS

The study was approved by the Ankara Etlik City Hospital Scientific Researches Evaluation and Ethics Committee (Date: 15.05.2024, Decision No: AEŞH-BADEK-2024-432). The study was conducted in accordance with the ethical principles set forth in the 1975 Declaration of Helsinki for the conduct of research.

We retrospectively analyzed patient records and electronic health data from individuals who were diagnosed with HNC and admitted to the Medical Oncology Clinic of Ankara Dışkapı Training and Research Hospital and the Medical Oncology Clinic of Ankara Etlik City Hospital between January 2017 and March 2024.

Although head and neck cancer is often considered a single entity, it encompasses a wide spectrum of malignancies with distinct biological behaviors, etiologies, and treatment responses. Nasopharyngeal carcinomas are strongly associated with Epstein-Barr Virus and exhibit unique epidemiologic and therapeutic characteristics, including a high sensitivity to radiotherapy. Similarly, salivary gland tumors comprise a heterogeneous group of histological subtypes, such as adenoid cystic and mucoepidermoid carcinomas, which differ significantly from squamous cell carcinomas in terms of progression patterns, treatment strategies, and prognosis. To ensure a homogeneous study population and to accurately evaluate the prognostic significance of the SII, patients with nasopharyngeal and salivary gland malignancies were excluded from the analysis. The following criteria were utilised for the exclusion of patients: the presence of active infections, autoimmune disorders (e.g. Behcet's disease or Hashimoto's thyroiditis), haemoglobinopathies, haematological conditions such as sickle cell anaemia, coagulation disorders, liver disorders, renal diseases, the use of corticosteroids during treatment, and incomplete baseline blood test results (Figure 1).

Standardized protocols were used across participating centers for Eastern Cooperative Oncology Group (ECOG) performance scoring, laboratory testing, and staging. We examined various parameters, including smoking habits,

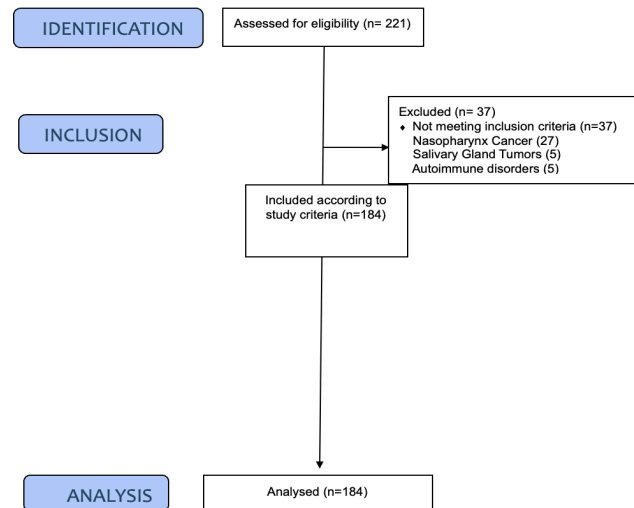


Figure 1. STROBE flow diagram

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

sex distribution, tumor localization, tumor stage [according to the American Joint Committee on Cancer TNM Staging Guidelines, 8th Edition (AJCC 2017)], treatment modalities, and the impact of radiotherapy, chemotherapy, surgery, and their combination on patient survival. We also explored the relationship between pretreatment SII values and survival outcomes. Performance status was assessed using the ECOG Performance Scale.¹¹

SII Evaluation

SII was calculated using blood samples collected within seven days prior to the initiation of any treatment. The index was calculated using granulocytes as a proxy for platelet (P), neutrophil (N), and lymphocyte (L) counts with the following formula: $SII = \text{absolute P} \times \text{absolute N} / \text{absolute L}$. The receiver operating characteristic (ROC) analysis was used to determine the optimal cut-off values for classifying the SII as low (LSII) or high (HSII) for predicting overall survival. The LSII and HSII were defined as values below and above the cut-off point, respectively.

Statistical Analysis

The primary endpoint was OS defined as the interval between the start of treatment and the date of death or last visit. The secondary endpoint was DFS, defined as the time from treatment initiation to recurrence, death, or last follow-up, reflecting curative-intent outcomes. Quantitative variables are expressed as the means and ranges, while categorical variables are expressed as percentage frequency distributions. Pearson's χ^2 test was used to compare demographic characteristics between groups.

Kaplan-Meier survival curves were used to estimate survival outcomes, and log-rank tests were performed for intergroup comparisons. The Cox regression model identified independent risk factors associated with DFS and OS in univariate analyses. Significant variables from univariate analysis were included in multivariate Cox analysis. A two-tailed $p < 0.05$ was considered to indicate statistical significance. Statistical analyses were performed using the Bluesky statistical (Version 10.3.2) program.

RESULTS

Of the 184 patients, 156 (84.8%) were male, and 28 (15.2%) were female. The median age was 63 years (range 32-91). The tumor locations included the larynx (51.6%), oral cavity (23.4%), oropharynx (10.9%), hypopharynx (9.8%), and paranasal sinuses (3.8%). Staging classified 1.6% as stage I, 13.6% as stage II, 33.7% as stage III, 32.6% as stage IVA, 13.6% as stage IVB, and 4.9% as stage IVC. There was no significant difference in demographic characteristics between the LSII and HSII groups ([Table 1](#)).

The ROC analysis was conducted to ascertain the most suitable cut-off values for the classification of SII as low (LSII) or high (HSII). The cut-off point was determined to be 796. The area under the curve (AUC) was determined to be 0.808 (95% CI: 0.697-0.952), $p < 0.001$, with a specificity of 74.4% and sensitivity of 74.5% ([Figure 2](#)).

In the comparison of treatment and survival outcomes according to SII groups, no statistically significant differences were observed in the distribution of primary treatment modalities, including surgery, concurrent chemoradiotherapy

Table 1. Clinical and demographical parameters				
Parameters	Whole cohort (n=184)	L-SII (<796) (n=117)	H-SII (≥796) (n=67)	p-value
Sex n (%)				
Male	156 (84.8)	100 (85.5)	56 (83.6)	0.73
Female	28 (15.2)	17 (14.5)	11 (16.4)	
Age (years)				
Median (min-max)	63.0 (32-91)	63 (25-90)	61 (32-91)	0.27*
Age groups n (%)				
<65 years	107 (58.2)	65 (55.6)	42 (62.7)	0.34
≥65 years	77 (41.8)	52 (44.4)	25 (37.3)	
Smoking n (%)				
Current smoker	156 (84.8)	101 (86.3)	55 (82.1)	0.44
Never smoke	28 (15.2)	16 (33.7)	12 (17.9)	
ECOG PS n (%)				
0	100 (54.3)	67 (57.3)	33 (49.3)	0.22
1	73 (39.7)	45 (38.5)	28 (41.8)	
2≤	11 (6.0)	5 (4.2)	6 (8.9)	
Primer n (%)				
Larynx	95 (51.6)	68 (58.1)	27 (40.3)	0.16
Oral cavity	43 (23.4)	23 (19.7)	20 (29.9)	
Oropharynx	20 (10.9)	13 (11.1)	7 (10.4)	
Hypopharynx	18 (9.8)	9 (7.7)	9 (13.4)	
Paranasal sinuses	7 (3.8)	3 (2.6)	4 (6.0)	
Stage n (%)				
I	3 (1.6)	2 (1.7)	1 (1.5)	0.08
II	25 (13.6)	13 (11.1)	12 (17.9)	
III	62 (33.7)	47 (40.2)	15 (22.4)	
IVA	60 (32.6)	38 (32.5)	22 (32.8)	
IVB	25 (13.6)	11 (9.4)	14 (20.9)	
IVC	9 (4.9)	6 (5.1)	3 (4.5)	
Extranodal extension n (%)				
Yes	37 (20.1)	18 (15.4)	19 (28.4)	0.03
No	147 (79.9)	99 (84.6)	48 (71.6)	
HPV status n (%)				
Not evaluated	159 (86.4)	102 (87.2)	57 (85.1)	0.80
Positive	9 (4.9)	6 (5.1)	3 (4.5)	
Negative	16 (8.7)	9 (7.7)	7 (10.4)	
Pearson X² test, *: Mann-Whitney U test, SII: Systemic Immune-Inflammation Index, min: Minimum, max: Maximum, ECOG: Eastern Cooperative Oncology Group, PS: Performance status, HPV: Human papillomavirus				

Pearson χ^2 test, *: Mann-Whitney U test, SII: Systemic Immune-Inflammation Index, min: Minimum, max: Maximum, ECOG: Eastern Cooperative Oncology Group, PS: Performance status, HPV: Human papillomavirus

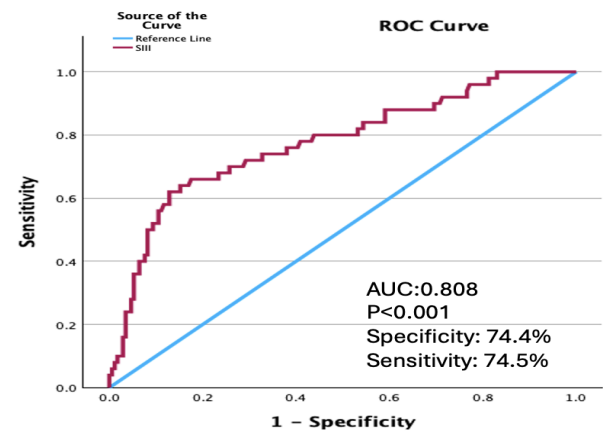


Figure 2. ROC curve according to the SII
ROC: Receiver operating characteristic, SII: Systemic Immune-Inflammation Index

(CCRT), induction chemotherapy followed by CCRT, palliative chemotherapy, radiotherapy alone, or no treatment ($p=0.21$). Although the proportion of patients receiving adjuvant chemotherapy was higher in the high SII group (29.9%) compared to the low SII group (17.9%), this difference did not reach statistical significance ($p=0.06$). Notably, disease recurrence was significantly more common in the high SII group (43.3%) than in the low SII group (8.5%) ($p<0.001$). Similarly, mortality was higher in the high SII group (26.9% vs. 11.1%, $p=0.006$) (Table 2).

Local/regional recurrence or metastasis occurred in 21.2% of patients: 10 in the LSII arm and 29 in the HSII arm. The median DFS was 18.7 months in the LSII arm and 13.7 months in the HSII arm ($p=0.25$) (Figure 3). During follow-up, 31 patients died (13 in the LSII arm and 18 in the HSII arm). The

estimated median OS was 103.8 months in the LSII arm and 80.3 months in the HSII arm ($p=0.035$) (Figure 4).

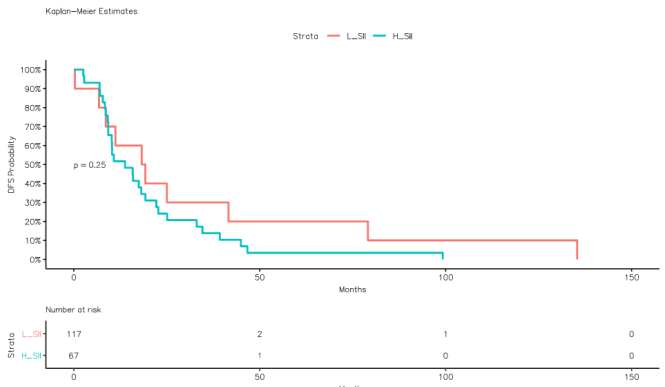


Figure 3. Kaplan-Meier estimates of disease-free survival according to the SII
SII: Systemic Immune-Inflammation Index

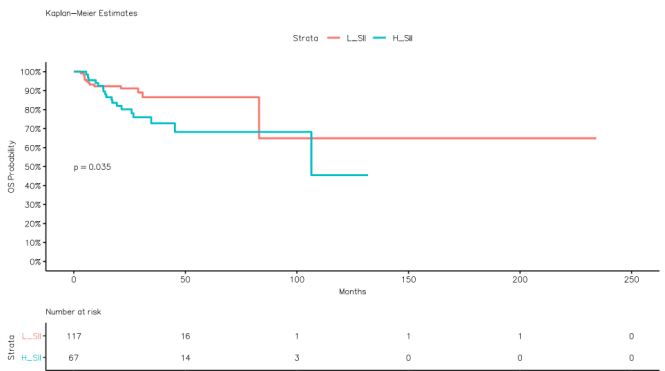


Figure 4. Kaplan-Meier estimates of overall survival according to the SII
SII: Systemic Immune-Inflammation Index

Table 2. Treatment and survival parameters				
Parameters	Whole cohort (n=184)	L-SII (<796) (n=117)	H-SII (≥796) (n=67)	p-value
Primary treatment n (%)				
Surgery	57 (31.0)	29 (24.8)	28 (41.8)	0.21
Concurrent	70 (38.0)	47 (40.2)	23 (34.3)	
Chemoradiotherapy (CC)	46 (25.0)	34 (29.1)	12 (17.9)	
Induction chemotherapy+CC	4 (2.2)	3 (2.6)	1 (1.5)	
Palliative chemotherapy	3 (1.6)	2 (66.7)	1 (1.5)	
Only radiotherapy	4 (2.2)	2 (1.7)	2 (3.0)	
None				
Adjuvant chemotherapy n (%)				
Yes	41 (22.3)	21 (17.9)	20 (29.9)	0.06
No	73 (39.7)	96 (82.1)	47 (70.1)	
Recurrence n (%)				
Yes	39 (21.2)	10 (8.5)	29 (43.3)	<0.001
No	145 (78.8)	107 (91.5)	38 (56.7)	
Median DFS (range) (months)	15.8 (8.6-NR)	18.7 (8.6-NR)	13.7 (10.2-22.2)	0.25*
Exitus n (%)				
Yes	31 (16.8)	13 (11.1)	18 (26.9)	0.006
No	153 (83.2)	104 (88.9)	49 (73.1)	
Median OS (range) (months)	103.8 (38.7-168.8)	103.8 (16.8-190.8)	80.3 (7.8-153.1)	0.14*
Median follow up) (months)	21.6	19.5	22.8	
Pearson X² test, *: Log-rank test, SII: Systemic Immune-Inflammation Index, PS: Performance status, DFS: Disease-free survival, OS: Overall survival				

In the univariate Cox regression analysis for DFS, older age (≥ 65), smoking status, advanced stage (stage IV), and higher ECOG performance score (≥ 2) were associated with poorer outcomes. However, in the multivariate model, age ≥ 65 (HR: 0.41, 95% CI: 0.18-0.94, $p=0.03$), current smoking (HR: 3.44, 95% CI: 1.00-11.78, $p=0.04$), and advanced stage (HR: 3.00, 95% CI: 1.38-6.50, $p=0.005$) remained independent predictors of shorter DFS. ECOG performance status and SII were not statistically significant in the multivariate analysis for DFS (Table 3).

Parameters	Univariate analyses		Multivariate analyses	
	HR (95% CI)	p	HR (95% CI)	p
Sex				
Female	Ref	0.10		
Male	1.93 (0.87-4.29)			
Age				
<65 age	Ref	0.03	0.41 (0.18-0.94)	0.03
≥65 age	0.45 (0.21-0.94)			
Smoking				
Never	Ref	0.01	3.44 (1.00-11.78)	0.04
Current	2.05 (0.95-4.41)			
Stage				
≤III	Ref	0.02	3.00 (1.38-6.50)	0.005
IV	2.18 (1.12-4.25)			
Extranodal extension				
No	Ref	0.02	0.89 (0.28-2.77)	0.84
Yes	2.40 (1.13-5.11)			
ECOG PS				
0-1	Ref	0.14		
2≤	2.46 (0.72-8.38)			
SII				
<796	Ref	0.25		
≥796	1.56 (0.72-3.34)			
Cox regression analyse, HR and 95% CI, DFS: Disease-free survival, HR: Hazard ratios, CI: Confidence intervals, ECOG: Eastern Cooperative Oncology Group, PS: Performance status, SII: Systemic Immune-Inflammation Index				

Cox regression analysis, HR and 95% CI, DFS: Disease-free survival, HR: Hazard ratios, CI: Confidence intervals, ECOG: Eastern Cooperative Oncology Group, PS: Performance status, SII: Systemic Immune-Inflammation Index

For OS, univariate analysis revealed that advanced stage, ECOG ≥ 2 , and high SII (>796) were significantly associated with worse outcomes. These associations persisted in multivariate analysis, where advanced stage (HR: 2.77, 95% CI: 1.24-6.15, $p=0.01$), ECOG ≥ 2 (HR: 3.72, 95% CI: 1.35-10.22, $p=0.01$), and high SII (HR: 1.86, 95% CI: 1.01-3.16, $p=0.05$) were identified as independent negative prognostic factors for OS (Table 4).

DISCUSSION

Many studies have investigated the relationships between stage, performance status, treatment protocol, and prognosis in HNC patients, identifying these parameters as important prognostic markers for overall survival.¹²⁻¹⁵ Similar to the literature, our study revealed significant relationships between stage, ECOG performance status, and overall survival.

Parameters	Univariate analyses		Multivariate analyses	
	HR (95% CI)	p	HR (95% CI)	p
Sex				
Female	Ref	0.92		
Male	1.04 (0.40-2.73)			
Age				
<65 age	Ref	0.19		
≥65 age	0.60 (0.28-1.29)			
Smoking				
Never	Ref	0.66		
Current	0.79 (0.27-2.26)			
Stage				
≤III	Ref	0.01	2.77 (1.24-6.15)	0.01
IV	2.67 (1.22-5.83)			
Extranodal extension				
No	Ref	<0.001	3.42 (1.47-7.93)	0.004
Yes	4.86 (2.38-9.90)			
ECOG PS				
0-1	Ref	0.004	3.72 (1.35-10.22)	0.01
2≤	4.10(1.55-10.80)			
SII				
<796	Ref	0.03	1.86 (1.01-3.16)	0.05
≥796	2.13 (1.03-4.39)			
Cox regression analyse, HR and 95% CI, OS: Overall survival, HR: Hazard ratios, CI: Confidence intervals, ECOG: Eastern Cooperative Oncology Group, PS: Performance status, SII: Systemic Immune-Inflammation Index				

Cox regression analysis, HR and 95% CI, OS: Overall survival, HR: Hazard ratios, CI: Confidence intervals, ECOG: Eastern Cooperative Oncology Group, PS: Performance status, SII: Systemic Immune-Inflammation Index

The five-year OS for patients with stage I-II disease is typically 70-90%, while patients with advanced disease (stage III-IV) have a worse prognosis.¹⁶ Our patient group included 84.8% with stage III-IV disease, with a 21.2% recurrence rate.

Smoking, a marker accepted as a prognostic factor in head and neck cancers, was evaluated in one study. According to the post hoc analysis, the 2-year PFS was significantly greater for patients who smoked less than 10 pack-years than for those who smoked 10 pack-years or more (92% vs. 57%; $p=0.0014$). There was also a statistically significant difference in 2-year OS, although not as markedly as PFS (93% vs. 86%; $p=0.040$).¹⁷ In our study, we observed a significant prognostic effect of smoking on DFS ($p=0.01$).

Many studies emphasize that extranodal (or extracapsular) extension is a negative prognostic factor in patients with HNC undergoing primary surgery.^{18,19} In our study, extranodal extension was positive in 20.1% of the patients. A significant negative prognostic effect on DFS and OS was observed in univariate analysis ($p=0.02$ and $p<0.001$, respectively). Multivariate analysis ($p=0.004$) revealed that this effect was maintained on OS.

Treatment of patients with HPV-associated oropharyngeal carcinoma is similar to that of HPV-negative patients, except in the context of clinical trials. Although testing for HPV associations provides prognostic information, there are

insufficient phase III data to modify treatment according to HPV status. At the same time, despite this excellent prognosis, positive margins and extracapsular extension may be associated with worse oncologic outcomes, including the risk of developing systemic disease.²⁰ In the present retrospective study, the effect of HPV on prognosis was not evaluated due to its absence from the pathology reports of the majority of patients.

High neutrophil or monocyte counts have been linked to poorer oncological outcomes not only in HNC but also in various other tumor types.²¹ Previous meta-analyses and studies have underscored the prognostic significance of associations between absolute neutrophil, lymphocyte, monocyte, and platelet counts. Consequently, there has been a growing emphasis on amalgamating these parameters and examining their combinations as potential biomarkers.²²⁻²⁴

While numerous studies have highlighted the association between markers of systemic inflammation and DFS and OS across various tumor types, there remains a lack of consensus regarding cut-off values specific to each cancer type. In a study by Rizzo et al.²⁵ comprising 925 HPV-negative HNSCC patients, the SII cut-off values for OS and DFS were <602 and >754, respectively. In our study, we determined the SII cut-off value for predicting survival to be 796. These varying cut-off values underscore the complexity of systemic inflammatory markers and highlight the need for further research to establish standardized thresholds tailored to specific tumor types.

In 2022, Wang et al.²⁶ conducted a meta-analysis involving 12 studies comprising 4369 HNC patients and revealed that elevated pretreatment SII values were correlated with worse OS, DFS. In a retrospective study by Zhou et al.²⁷ focusing on HNSCC patients, a high SII was identified as a prognostic factor associated with both OS and DFS in univariate analysis, although it did not emerge as an independent prognostic factor in multivariate analysis. In the present study, high SII was identified as an independent poor prognostic factor for OS in both univariate and multivariate analyses.

This finding aligns with previous studies suggesting that systemic inflammatory markers such as the SII are significant for cancer prognosis. An elevated SII likely reflects an enhanced inflammatory response and an immunosuppressive microenvironment, contributing to cancer progression.

Clinical Implications

The identification of a high SII as a prognostic marker for OS has important clinical implications. These findings suggest that patients with elevated SII values might benefit from more aggressive or tailored therapeutic strategies. For instance, these patients might be considered for closer surveillance or adjunctive treatments aimed at modulating the immune response. Additionally, the SII could be integrated into existing prognostic models to improve their accuracy and utility in clinical decision-making.

Our study also underscores the need for a multidisciplinary approach to the management of HNC. Given the complex interplay between inflammation, immunity, and cancer, collaboration among oncologists, immunologists, and other

specialists is crucial to optimize treatment outcomes. Further research into the underlying mechanisms by which the SII influences cancer progression could lead to novel therapeutic interventions targeting inflammatory pathways.

Limitations

While our study provides valuable insights, it is not without limitations. First, the retrospective design may introduce selection bias and limit the generalizability of our findings. Additionally, the single-center nature of the study may not reflect the broader population of HNC patients. Prospective, multicenter studies are needed to validate our results and confirm the prognostic value of the SII in diverse patient cohorts.

Due to the small number of patients receiving palliative chemotherapy (n=4), subgroup analysis by treatment intent was not feasible. Although a small number of patients received non-curative treatment, DFS was used as the secondary endpoint since most patients were treated with curative intent.

Another limitation is the lack of data on other potential confounding factors, such as HPV status, which is known to influence prognosis in HNC patients. HPV status, an important confounder especially for oropharyngeal tumors, was unavailable in most cases and therefore could not be included in the analysis. Future studies should consider including a comprehensive range of clinical and biological variables to provide a more nuanced understanding of the factors affecting prognosis.

CONCLUSION

As a result, the present study identified a high pretreatment SII value as an independent poor prognostic factor for OS in HNC patients. Although SII did not have a significant effect on DFS, its capacity to predict recurrence underscores its potential clinical utility. The incorporation of SII into routine prognostic assessments holds the potential to enhance risk stratification and to inform treatment strategies, thereby improving patient outcomes in HNC patients.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Ankara Etlik City Hospital Scientific Researches Evaluation and Ethics Committee (Date: 15.05.2024, Decision No: AEŞH-BADEK-2024-432).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Availability of Data and Materials

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

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