Association of Systemic Inflammation Response Index With Long-Term Outcomes in Patients With Head and Neck Cancer Receiving Definitive Chemoradiation

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ABSTRACT

PURPOSE Systemic inflammation is an important factor for carcinogenesis and tumor progression. Systemic Inflammation Response Index (SIRI) was suggested as one of the peripheral blood biomarkers to assess the magnitude of inflammation. Herein, we aimed to evaluate the prognostic value of SIRI in head and neck cancer.

METHODS A single-institution database at a comprehensive cancer center was queried for patients with nonmetastatic head and neck cancer who underwent definitive chemoradiation between December 2011 and February 2024 with SIRI available for analysis. With the top quartile as a reference to evaluate high versus low SIRI, logistic multivariable analysis (MVA) was performed to identify variables associated with high SIRI. Cox MVA was performed to evaluate survival. Interaction term analysis was performed to evaluate whether there is a heterogeneous association of SIRI with outcomes stratified by p16 status.

RESULTS A total of 638 patients met our criteria. The median follow-up was 45.9 months (95% CI, 44.4 to 47.7). Using the top quartile cutoff of 3.22 for SIRI, those who were male, underweight, had poor performance status, and had advanced T staging were more likely to have high SIRI, whereas those with other racial background, p16-positive, and larynx primary site were less likely to have high SIRI. Those with high SIRI had worse overall survival (OS; adjusted hazard ratio [aHR], 1.59 [95% CI, 1.15 to 2.25], $P = .008$), but not PFS (aHR, 1.18 [95% CI, 0.86 to 1.61], $P = .320$). Interaction term analysis did not reach statistical significance ($P_{\text{interaction}} = .75$ for OS, 0.84 for PFS).

CONCLUSION Elevated SIRI was an independent, adverse prognostic factor for survival without heterogeneous association with outcomes based on p16 status. Further validation of SIRI would be warranted in future studies.

ACCOMPANYING CONTENT

Reflexivity Statement

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INTRODUCTION

Systemic inflammation and immune dysregulation are central to the biology of cancer progression.[1] Elevated neutrophil counts, among various peripheral blood biomarkers, have been associated with worse survival outcomes in multiple cancer types.[2] Tumor cells have been shown to release cytokines that stimulate the bone marrow to increase neutrophil production.[3-5] These neutrophils, in turn, release cytokines promoting angiogenesis and metastasis.[6,7] In patients with head and neck cancers specifically, elevated neutrophil counts have been found to be associated with adverse clinical outcomes.[2]

In head and neck squamous cell carcinoma (HNSCC), a malignancy characterized by diverse etiologies and heterogeneous clinical behaviors, there is a growing body of literature on the prognostic relevance of the host immune and inflammatory response. One such measure is the Systemic Inflammation Response Index (SIRI), a composite biomarker derived from peripheral blood counts calculated by multiplying neutrophil and monocyte counts and dividing by the lymphocyte count.[8] SIRI reflects the balance between pro- and anti-inflammatory immune cells and serves as a measure of systemic inflammatory response. As an integrative indicator of tumor-promoting inflammation and impaired immunosurveillance, elevated

CONTEXT

Key Objective
What is the prognostic role of Systemic Inflammation Response Index (SIRI) among patients with head and neck cancer treated with definitive chemoradiation, stratified by p16 status?

Knowledge Generated
In this single-institution study of over 600 patients with a median follow-up of nearly 4 years, elevated SIRI was an independent, adverse prognostic factor for survival without heterogeneous association with outcomes based on p16 status. Those with underweight, poor performance status, locally advanced disease, and p16-negative tumors were associated with high SIRI.

Relevance (*F. Rubagumya*)
Inflammatory biomarkers derived from routine complete blood counts offer a practical, low-cost approach to prognostic risk stratification in oncology. This study demonstrates that elevated SIRI is an independent adverse prognostic factor for overall survival following definitive chemoradiation. Notably, this prognostic impact was consistent regardless of p16/human papillomavirus status. These findings support prospective validation of SIRI as a clinically actionable biomarker to identify high-risk patients who may benefit from intensified surveillance or early supportive interventions such as nutritional optimisation.*

Plain Language Summary (*F. Rubagumya*)
Head and neck cancers are commonly treated with combined chemotherapy and radiation, yet patient outcomes vary widely. Inflammation, measurable through a routine blood test score called the SIRI, reflects the balance between immune cells that promote and suppress inflammation. In this study of 638 patients, those with high pre-treatment SIRI scores were significantly more likely to die compared to those with lower scores, regardless of whether their tumor was linked to human papillomavirus. These findings suggest that SIRI, derived from a standard blood test, could help clinicians identify higher-risk patients and guide decisions around closer monitoring or early supportive care.†

*Relevance section written by *JCO Oncology Advances* Associate Editor Fidel Rubagumya, MD, MMed, MPH.
†Plain Language Summary written by *JCO Oncology Advances* Associate Editor Fidel Rubagumya, MD, MMed, MPH.

SIRI has been associated with poor outcomes across multiple malignancies.[9-11]

HNSCC is particularly notable for its interplay between viral oncogenesis (eg, human papillomavirus [HPV]–associated oropharyngeal cancer), tobacco and alcohol exposures, and host physiologic status, including immune function and general health.[12,13] The prognostic landscape of HNSCC has evolved with the recognition that HPV-positive tumors tend to exhibit more favorable outcomes, whereas HPV-negative tumors are often associated with greater inflammatory responses and poorer prognosis.[14,15] Despite the increasing use of SIRI as a prognostic tool, its relevance across distinct biological subsets of HNSCC—including p16-positive and p16-negative disease—remains unclear.[9,13]

However, systemic inflammation is not solely a reflection of tumor biology. Emerging evidence suggests that patient-specific factors such as performance status, medical comorbidities, tobacco and alcohol consumption, and nutritional reserve may also influence inflammatory markers.[16-18] Elevated SIRI has been shown to be prognostic for poor outcomes among those with nonmalignant conditions, such as stroke and sepsis.[19,20] Understanding the clinicodemographic and tumor-specific correlates of elevated SIRI is therefore essential for contextualizing its prognostic value and guiding its integration into clinical decision making.

Although existing literature suggests that high SIRI levels may predict poor survival,[9,21,22] limited data have explored how SIRI relates to broader clinical end points such as progression-free survival, locoregional control, or distant recurrence in HNSCC. Even fewer studies have examined whether SIRI retains its prognostic utility across key molecular subtypes, such as HPV-related oropharyngeal cancer.[12,13]

To fill this knowledge gap and since SIRI has emerged as one of the well-investigated biomarkers in the literature for both patients with and without cancer as shown previously, our study selected SIRI as a biomarker of interest and aims to evaluate the clinical relevance of SIRI in a contemporary cohort of patients with HNSCC, with a specific focus on its prognostic implications across survival outcomes and its association with patient, tumor, and viral characteristics. By examining these questions within the framework of realworld clinical data, this investigation seeks to clarify the utility of SIRI as a host-based biomarker and contribute to a more nuanced understanding of inflammation-driven risk in HNSCC.

METHODS

This retrospective analysis was conducted under approval from the Institutional Review Board at The Ohio State University Comprehensive Cancer Center (protocol 2024C0084) and adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Patients diagnosed with nonmetastatic head and neck cancer who received definitive chemoradiotherapy between December 2011 and February 2024 were identified from our single institutional database. Eligibility required the availability of pretreatment SIRI values based on baseline complete blood count with differential results from peripheral blood. All included individuals underwent intensity-modulated radiation therapy to a total dose of 69.96-70 Gy delivered in 33-35 fractions. Patients who had surgery, radiation alone, or were treated with palliative intent were excluded. Those with unavailable SIRI data were also excluded.

In addition to baseline SIRI, clinical and demographic variables were collected for analysis, including age, gender, race, tobacco use history, primary tumor site, BMI, tumor (T) and nodal (N) stages based on American Joint Committee on Cancer 7th edition, p16 status, Eastern Cooperative Oncology Group performance status (ECOG PS), and concurrent chemotherapy regimen. All variables were incorporated into multivariable analyses (MVA), and missing data were categorized as unknown.

The primary end point was overall survival (OS), defined as time from diagnosis to death from any cause. The secondary end point was progression-free survival (PFS), defined as time from diagnosis to disease progression or death. Disease progression was evaluated using a multidisciplinary approach among radiologists, pathologists, surgeons, and medical and radiation oncologists. Follow-up with comprehensive clinical assessment was performed following the National Comprehensive Cancer Network guideline,[23] with typically positron emission tomography/computed tomography scan in 3 months after completing treatments.

Baseline variables were compared using Fisher's exact test. Frequency histogram was generated to visualize the distribution of SIRI values. Logistic regression was used to assess factors associated with elevated SIRI. High SIRI was denoted by values in the top quartile, whereas low SIRI included all other values. Top quartile value was used as a cutoff point based on similar studies showing the highest quartile being associated with the poorest outcomes.[24,25] Survival outcomes were analyzed using Kaplan-Meier curves and log-rank tests, with Cox proportional hazards models applied for MVA. Those who were lost to follow-up were censored when survival outcomes were evaluated.

To mitigate potential selection bias, propensity score matching was performed based on high versus low SIRI levels. Matching included all baseline variables and was executed using the nearest-neighbor approach at a 1:1 ratio without replacement and a caliper width of 0.2.[26] Interaction term analysis was performed, and if statistically significant, subgroup analyses were conducted to explore associations by p16 status.

All statistical tests were two-sided, and a *P* value <.05 was considered significant. Analyses were conducted using R (version 4.5.0, R Foundation for Statistical Computing).

RESULTS

A total of 638 patients met our criteria (516 men [80.9%]; median age 61 years [IQR, 55.0-68.0]; Table 1 and Fig 1). Most patients were Caucasian White (n = 572 [89.7%]), former smokers (n = 309 [48.4%]) with ECOG PS 0-1 (n = 582 [91.2%]), and overweight or obese BMI (n = 459 [71.9%]) who underwent chemoradiation with cisplatin (n = 398 [62.4%]) for oropharyngeal cancer (n = 424 [66.5%]). The median SIRI was 1.96 (IQR, 1.27-3.22; Fig 2). The median follow-up was 45.9 months (95% CI, 44.4 to 47.7).

Those who are male (adjusted odds ratio [aOR], 1.74 [95% CI, 1.03 to 3.06], *P* = .04), underweight (aOR, 3.78 [95% CI, 1.40 to 10.60], *P* = .009), had poor performance status (ECOG PS 1: aOR, 1.91 [95% CI, 1.25 to 2.93], *P* = .003; ECOG PS >1: aOR, 3.68 [95% CI, 1.77 to 7.70], *P* < .001), and had advanced T staging (aOR, 1.65 [95% CI, 1.11 to 2.47], *P* = .01) were more likely to have high SIRI, whereas those with other racial background (aOR, 0.28 [95% CI, 0.11 to 0.63], *P* = .004), p16-positive (aOR, 0.43 [95% CI, 0.21 to 0.86], *P* = .02), and larynx primary site (aOR, 0.28 [95% CI, 0.13 to 0.60], *P* = .001) were less likely to have high SIRI (Table 2).

Those with high SIRI had worse OS (adjusted hazard ratio [aHR], 1.59 [95% CI, 1.15 to 2.25], *P* = .008), but not PFS (aHR, 1.18 [95% CI, 0.86 to 1.61], *P* = .320; Table 3). Similar findings were observed in 147 matched pairs (OS: aHR, 1.63 [95% CI, 1.09 to 2.42], *P* = .017; PFS: aHR, 1.22 [95% CI, 0.85 to 1.74], *P* = .284; Table 1 and Figs 3 and 4). Interaction test was not statistically significant ($P_{interaction}$ = .75 for OS, .84 for PFS), and thus further subgroup analysis was not performed.

DISCUSSION

To our knowledge, this is the largest single-institution study including North American patients with nonmetastatic head and neck cancer with a median follow-up of nearly 4 years, suggesting that high systemic inflammation, quantified by the top SIRI quartile (≥3.22), was an independent adverse prognostic factor for OS in HNSCC.

TABLE 1. Baseline Characteristics

	Before Matching			After Matching		
	Low SIRI	High SIRI		Low SIRI	High SIRI	
Characteristic	No. (%)	No. (%)	*P*	No. (%)	No. (%)	*P*
Age, years			.22			.81
<65	307 (64.2)	94 (58.8)		91 (61.9)	88 (59.86)	
65 or older	171 (35.8)	66 (41.3)		56 (38.1)	59 (40.14)	
Gender			.11			.87
Female	96 (20.1)	26 (16.3)		21 (14.29)	23 (15.65)	
Male	382 (79.9)	134 (83.8)		126 (85.71)	124 (84.35)	
Race			.004			.54
White	419 (87.7)	153 (95.6)		143 (97.28)	140 (95.24)	
Other	59 (12.3)	7 (4.4)		4 (2.721)	7 (4.762)	
Smoking			.13			.95
Never	139 (29.1)	32 (20.0)		30 (20.41)	32 (21.77)	
Former	223 (46.7)	86 (53.8)		77 (52.38)	79 (53.74)	
Current	113 (34.2)	41 (25.6)		39 (26.53)	35 (23.81)	
Not available	3 (0.9)	1 (0.6)		1 (0.68)	1 (0.68)	
ECOG PS			<.001			.78
0	303 (63.4)	69 (43.1)		68 (46.26)	68 (46.26)	
1	143 (29.9)	67 (41.9)		63 (42.86)	62 (42.18)	
>1	27 (5.6)	21 (13.1)		13 (8.844)	16 (10.88)	
Not available	5 (1.0)	3 (1.9)		3 (2.041)	1 (0.68)	
Primary site			.47			.84
Oropharynx	316 (66.1)	108 (67.5)		100 (68.03)	99 (67.35)	
Larynx	120 (25.1)	34 (21.3)		33 (22.45)	31 (21.09)	
Other	42 (12.7)	18 (11.3)		14 (9.524)	17 (11.56)	
BMI			.007			.98
Normal	113 (23.6)	39 (24.4)		31 (21.09)	34 (23.13)	
Underweight	10 (2.1)	14 (8.8)		9 (6.122)	9 (6.122)	
Overweight	162 (33.9)	48 (30.0)		50 (34.01)	47 (31.97)	
Obese	190 (39.7)	59 (36.9)		57 (38.78)	57 (38.78)	
Not available	3 (0.6)	0 (0.0)		0 (0)	0 (0)	
T staging			.002			.64
1-2	318 (66.5)	84 (52.5)		77 (52.38)	82 (55.78)	
3-4	160 (33.5)	76 (47.5)		70 (47.62)	65 (44.22)	
N staging			.26			.33
0-1	173 (36.2)	66 (41.3)		48 (32.65)	57 (38.78)	
2-3	305 (63.8)	94 (58.8)		99 (67.35)	90 (61.22)	
p16			.06			.47
Negative	169 (35.4)	70 (43.8)		53 (36.05)	60 (40.82)	
Positive	309 (64.6)	90 (56.3)		94 (63.95)	87 (59.18)	
Chemotherapy			.5			.79
Cisplatin	304 (63.6)	94 (58.8)		83 (56.46)	89 (60.54)	
Carboplatin/Paclitaxel	165 (34.5)	62 (38.8)		60 (40.82)	54 (36.73)	
Other	9 (1.9)	4 (2.5)		4 (2.721)	4 (2.721)	

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; SIRI, Systemic Inflammation Response Index.

Since our interaction term analysis did not reach statistical significance, there was no heterogeneous association of SIRI with survival outcomes based on p16 status in our study. This aligns with prior work linking SIRI to mortality across malignancies at other sites, including nasopharyngeal, oral, and laryngeal cancers.[9,13,22]

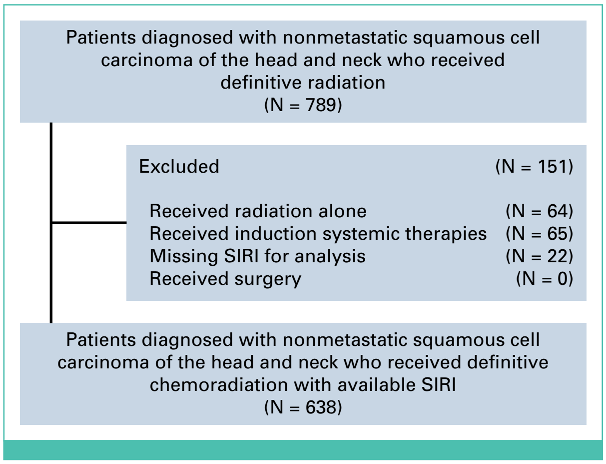

FIG 1. Patient flow chart. SIRI, Systemic Inflammation Response Index.

Although SIRI significantly predicted poor OS, it showed no association with PFS. Our finding contrasts with studies reporting that heightened inflammation contributes to tumor recurrence and shorter PFS in HNSCC. This can be explained because SIRI may reflect cachexia or infection susceptibility, leading to non–cancer-related deaths that affect OS more directly than recurrence or tumor progression.[27] In addition, in our study, patients with underweight BMI and poor performance status were likely to have high SIRI, and this finding may support the higher likelihood of non–cancer-related deaths. Neutrophil-derived cytokines such as IL-6 promote catabolism and immunosuppression,[2,28] accelerating noncancer deaths. Taken together, SIRI was incorporated as a key biomarker for machine learning–based risk stratification in a recent multicenter study,[29] and a single-institution, phase II clinical trial is currently ongoing to investigate prospectively whether such risk stratification may identify patients with head and neck cancer with poor prognosis and guide who may benefit from close surveillance for symptom management (ClinicalTrials.gov identifier: NCT05338905). Second, our cohort received definitive, curative-intent therapies, which may lead to a low number of tumor recurrences overall in our study. As a result, it might be too low to detect substantial differences based on SIRI values.

A lack of heterogeneous association of SIRI with outcomes based on p16 status in our study was notable, given an inherently different tumor biology between p16-positive and p16-negative tumors. For example, in p16-negative HNSCC, which is characterized by neutrophil-dominated inflammation and stromal remodeling, high SIRI may reflect poor prognosis.[3,30] Conversely, for p16-positive tumors that exhibit attenuated inflammatory responses and better immunogenicity, high SIRI may not be strongly associated with prognosis.[12] This aligns with findings that HPV-positive oropharyngeal cancers resist neutrophil-mediated angiogenesis and respond better to chemoradiation.[5,16,31] However, interaction term analysis did not reach statistical significance in our study, and it may in part be due to SIRI being associated with factors beyond tumor biology.

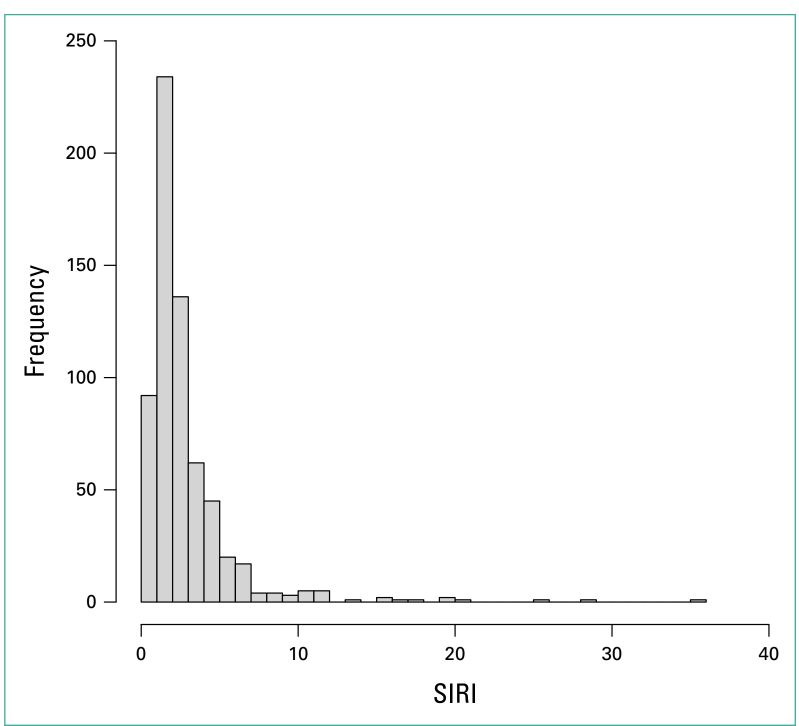

FIG 2. Frequency histogram representing the distribution of SIRI for the entire cohort. SIRI, Systemic Inflammation Response Index.

TABLE 2. Logistic Multivariable Analysis for Variables Associated With High SIRI

Characteristic	aOR	95% CI	*P*
Age, years			
Every increase by 1 year	1.02	1.00 to 1.04	.07
Gender			
Female	Reference		
Male	1.74	1.03 to 3.06	.04
Race			
White	Reference		
Other	0.28	0.11 to 0.63	.004
Smoking			
Never	Reference		
Former	1.24	0.75 to 2.05	.4
Current	1.18	0.63 to 2.20	.61
Not available	7.63	0.29 to 2.02e+02	.16
ECOG PS			
0	Reference		
1	1.91	1.25 to 2.93	.003
>1	3.68	1.77 to 7.70	<.001
Not available	4.87	0.81 to 29.23	.07
Primary site			
Oropharynx	Reference		
Larynx	0.28	0.13 to 0.60	.001
Other	0.55	0.24 to 1.20	.14
BMI			
Normal	Reference		
Underweight	3.78	1.40 to 10.60	.009
Overweight	0.88	0.52 to 1.52	.64
Obese	0.98	0.58 to 1.67	.93
Not available	<0.001	NA to 2.54e+26	.97
T staging			
1-2	Reference		
3-4	1.65	1.11 to 2.47	.01
N staging			
0-1	Reference		
2-3	0.89	0.55 to 1.45	.62
p16			
Negative	Reference		
Positive	0.43	0.21 to 0.86	.02
Chemotherapy			
Cisplatin	Reference		
Carboplatin/Paclitaxel	1.34	0.88 to 2.03	.17
Other	1.39	0.33 to 4.94	.63

Abbreviations: aOR, adjusted odds ratio; ECOG PS, Eastern Cooperative Oncology Group performance status; reference, reference group to which comparison groups were compared to calculate odds ratios; SIRI, Systemic Inflammation Response Index.

Logistic regression exemplified that high SIRI was independently associated with male sex, higher T stage, poorer performance status, and low BMI. Advanced T-stage tumors likely elevate SIRI by recruiting proinflammatory neutrophils via cytokine cascades such as VEGF and IL-6.[32] Low BMI contributes by worsening inflammation-induced immunosuppression, consistent with findings showing that SIRI's adverse prognostic value is accentuated in underweight patients with laryngeal cancer.[17] Consistent with literature, we found that lower BMI predicted occurrence of high SIRI, exemplifying potential vulnerability due to cachexia and immune dysregulation.[17,33] Worse performance status may amplify cytokine release, including CCR7, creating a feedback loop of inflammation and physiologic decline.[34]

Furthermore, in addition to patient demographics such as gender, BMI, and performance status, SIRI may also reflect broader socioeconomic and behavioral factors not typically captured in oncology data sets. Chronic stress, poor access to primary care, and food insecurity, for instance, have been shown to raise systemic inflammatory markers and potentially confound the link between SIRI and cancer outcomes.[35,36] SIRI may act as a proxy indicator for host vulnerability, extending beyond prior literature focused on cancer aggressiveness.[8] Furthermore, we identify a negative relationship between non-White race and SIRI. Clinically, SIRI ≥3.22 may identify high-risk patients who could benefit from early nutritional intervention and consideration of anti-inflammatory strategies.[28,33]

This study has limitations, including its single-center, retrospective design, which may limit generalizability. Validation studies would be needed to incorporate patients treated in other centers, since SIRI values may vary depending on different patient populations. As a result, limited generalizability may further explain discrepancies in results seen in our study versus other similar reports.[37] Given the single-institution, retrospective study design, there was also no prespecified sample size calculated a priori. Sample size and statistical power in our study may be insufficient to detect potentially clinically and statistically meaningful differences in outcomes. In particular, SIRI was analyzed with a top quartile as a cutoff in our study. Although the analysis should be ideally performed with SIRI as a continuous variable, we acknowledge that the SIRI distribution was highly right-skewed. There may not be sufficient statistical power since the sample size of patients with high SIRI may be too small.

In addition, there are other prognostic biomarkers such as neutrophil-lymphocyte ratio,[38] lymphocyte-monocyte ratio,[39] hemoglobin,[40] Systemic Immune-Inflammation Index,[41] Prognostic Nutritional Index,[42] and Gustave Roussy immune score[43] used for head and neck cancer. Other biomarkers were unavailable in our database for analysis, so comparison among these biomarkers was not feasible. Further studies would be needed to better evaluate the role of such biomarkers since the central focus of our study was not to compare various biomarkers and their prognostic abilities. Furthermore, disease progression was typically confirmed using radiographic evidence and pathologic confirmation whenever feasible. However, acceptable methods, such as

TABLE 3. Cox and Fine-Gray Multivariable Analysis for Survival

	Overall Survival			Progression-Free Survival		
Characteristic	aHR	95% CI	*P*	aHR	95% CI	*P*
SIRI						
Low	Reference			Reference		
High	1.59	1.13 to 2.25	.008	1.18	0.86 to 1.61	.32
Age, years						
Every increase by 1 year	1.03	1.01 to 1.05	<.001	1.03	1.01 to 1.04	<.001
Gender						
Female	Reference			Reference		
Male	1.61	1.08 to 2.41	.02	1.61	1.13 to 2.31	.009
Race						
White	Reference			Reference		
Other	0.93	0.56 to 1.57	.79	0.96	0.61 to 1.51	.87
Smoking						
Never	Reference			Reference		
Former	1.31	0.81 to 2.10	.27	1.27	0.84 to 1.91	.26
Current	2.03	1.21 to 3.43	.008	1.61	1.01 to 2.56	.05
Not available	2.28	0.22 to 24.04	.49	0.66	0.03 to 16.28	.8
ECOG PS						
0	Reference			Reference		
1	1.56	1.09 to 2.22	.01	1.42	1.04 to 1.94	.03
>1	3.89	2.45 to 6.20	<.001	2.85	1.85 to 4.38	<.001
Not available	0.84	0.27 to 2.66	.77	1.32	0.48 to 3.58	.59
Primary site						
Oropharynx	Reference			Reference		
Larynx	0.64	0.39 to 1.06	.08	0.68	0.43 to 1.08	.1
Other	0.81	0.48 to 1.38	.44	0.83	0.51 to 1.36	.46
BMI						
Normal	Reference			Reference		
Underweight	1.71	0.93 to 3.17	.09	1.72	0.98 to 3.02	.06
Overweight	0.82	0.55 to 1.21	.32	0.95	0.67 to 1.36	.8
Obese	0.8	0.53 to 1.23	.31	0.8	0.55 to 1.16	.24
Not available	1.39	0.11 to 17.35	.8	2.83	0.10 to 76.98	.54
T staging						
1-2	Reference			Reference		
3-4	1.36	0.99 to 1.88	.06	1.46	1.10 to 1.94	.009
N staging						
0-1	Reference			Reference		
2-3	1.59	1.08 to 2.32	.02	1.69	1.20 to 2.37	.003
p16						
Negative	Reference			Reference		
Positive	0.37	0.22 to 0.62	<.001	0.36	0.22 to 0.57	<.001
Chemotherapy						
Cisplatin	Reference			Reference		
Carboplatin/Paclitaxel	0.86	0.60 to 1.24	.42	0.84	0.61 to 1.16	.29
Other	1.29	0.54 to 3.06	.57	1.58	0.74 to 3.34	.24

Abbreviations: aHR, adjusted hazard ratio; ECOG PS, Eastern Cooperative Oncology Group performance status; reference, reference group to which comparison groups were compared to calculate hazard ratios; SIRI, Systemic Inflammation Response Index.

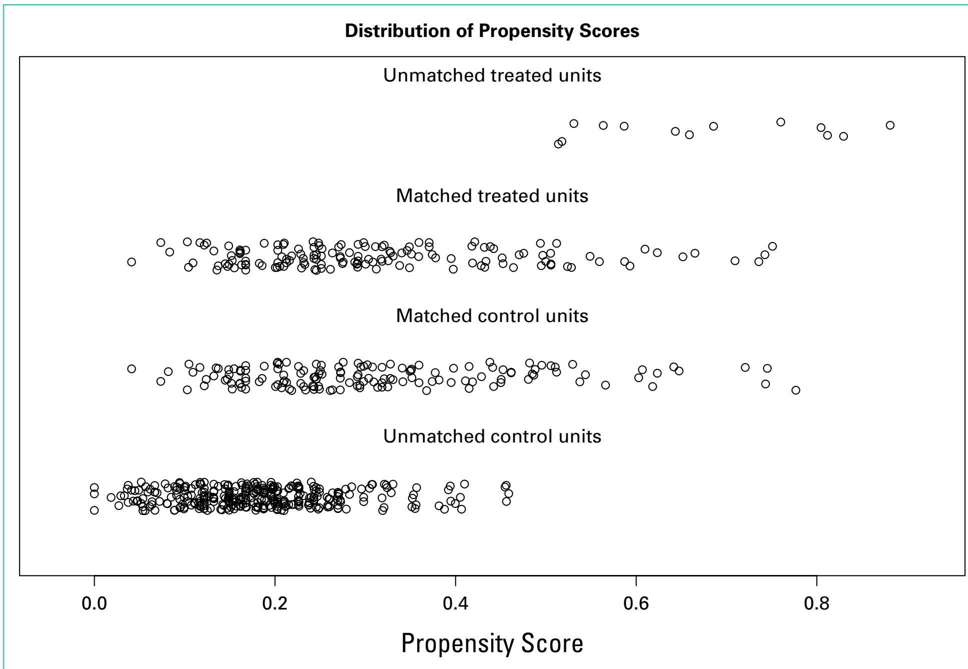

FIG 3. Jitter plot to visualize the overall distribution of propensity scores before and after matching Control units: low Systemic Inflammation Response Index cohort; treated units: high Systemic Inflammation Response Index cohort.

RECIST, might not have been consistently used in select patients (eg, patients may refuse further diagnostic imaging or biopsy confirmation despite clinical concerns of progression), and disease progression may be potentially misclassified in such cases. Despite the use of MVA and propensity score matching, selection bias may still exist. Although all baseline biomarkers were before the initiation of treatments, the exact dates of obtaining the peripheral blood samples were unavailable. Other clinically relevant variables, such as toxicity profiles and medical comorbidities, were unavailable for analysis. For example, SIRI has been shown to be associated with the history of stroke, the severity of stroke, and mortality among patients without cancer.[44,45] Inflammatory biomarkers were also shown to be associated with post-treatment secondary malignancy.[46] In addition, dynamic changes in blood biomarkers before, during, and after treatments were not available. For instance, persistently elevated inflammation biomarkers were suggested to be more prognostic rather than a single measurement of these biomarkers.[47] Racial subgroups in our study also had limited sample sizes for analysis, although racial differences in inflammatory biomarkers were

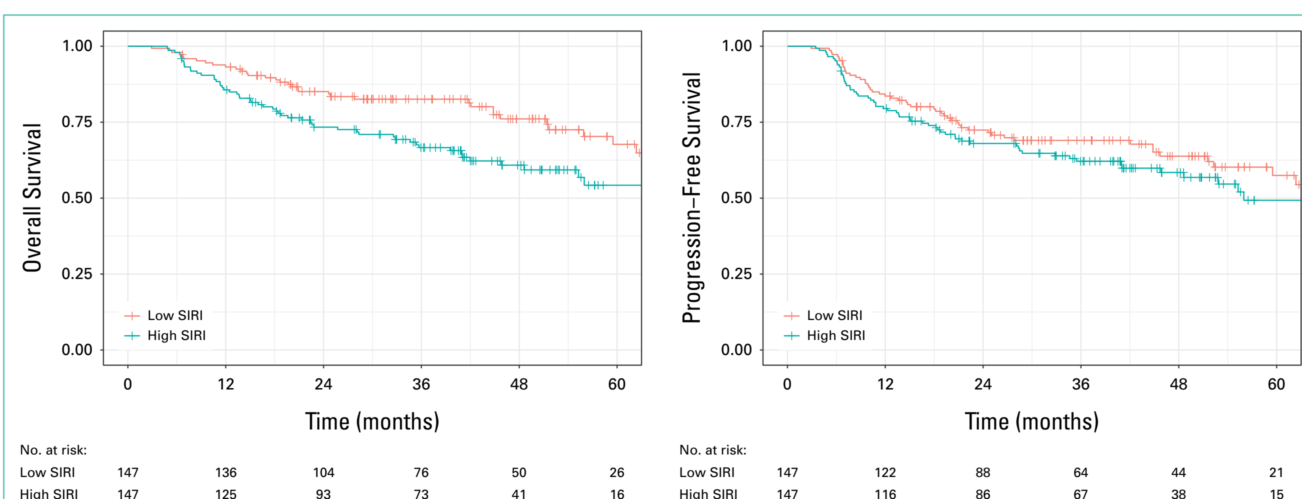

FIG 4. Kaplan-Meier plots for survival for the matched cohort. SIRI, Systemic Inflammation Response Index.

previously noted.[48] Furthermore, various studies used different cutoff values for SIRI, and further studies would be needed to investigate the optimal cutoff.

In conclusion, elevated SIRI was an independent, adverse prognostic factor for OS among patients with HNSCC without heterogeneous association with survival outcomes based on p16 status in our study. Those with underweight BMI, poor performance status, locally advanced disease, and p16-negative tumors were associated with high SIRI. Further validation of SIRI would be warranted in future studies.

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