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Systemic Inflammation is Associated with Disease Extent and Survival in Oral Cavity Squamous Cell Carcinoma

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Abstract

Background: Although systemic immune-inflammation index (SII) correlates with patient survival in various solid malignancies limited information is available in the setting of oral cavity squamous cell carcinoma (OCSCC).

Methods: We retrospectively reviewed 222 patients who underwent a resection of curative intent for patients with OCSCC. SII was determined prior to surgical resection as platelet count × neutrophil count/ lymphocyte count.

Results: At a median follow-up of 30.6 months, 2-year disease-free survival (DFS) and overall survival (OS) rates were 63.9% and 76.4%, respectively. A high SII (>1047) was associated with poor performance status and disease extent. A low SII was independently associated with improved DFS (HR: 0.440, *p*p=0.007) rates.

Conclusions: SII values at diagnosis were associated with patient performance status, disease extent at the time of diagnosis, improved disease control rates, and improved patient survival.

Keywords

Inflammation, oral cavity, squamous cell carcinoma, SII

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Conclusions: SII values at diagnosis were associated with patient performance status, disease extent at the time of diagnosis, improved disease control rates, and improved patient survival.

Introduction

The management of oral cavity squamous cell carcinoma (OCSCC) is complex with difficult decision making on the part of the multidisciplinary oncologic team.[1] The extent of upfront resection can be permanently disfiguring and is associated with functional deficits limiting quality of life. Post-operative management including the employment of aggressive adjuvant radiotherapy or concurrent chemoradiotherapy is associated with high rates of acute toxicity and long-term complications.[2] The recently reported Keynote-048 investigating the role of pembrolizumab in recurrent or metastatic head and neck squamous cell carcinoma has demonstrated only marginally improved overall survival benefit without improvement of progression free survival.[3] This has led to the revisiting of the interaction of head and neck squamous cell carcinoma and the tumor microenvironment to select for therapeutic advantages.

The tumor microenvironment continues to be an active area of investigation as the interaction of cancer and the immune system is an evolving area of therapeutic implication.[4-5] Mounting evidence has demonstrated that immune and inflammatory cells play a prominent role in cancer growth, invasion, chemoresistance, and metastasis.[6] Although our understanding of the exact mechanism and interactions of the immune system and cancer progression continues to evolve, existing data strongly suggests that host immune-inflammatory factors play a vital role in disease progression and patient survival.[7] Hyperinflammatory states that develop in settings such as poorly controlled diabetes, obesity, and chronic infectious processes are also associated with worse cancer outcomes even when controlled for other clinicopathologic factors.[8-9] Similarly, immunocompromised states such as those associated with hereditary immunodeficiency and acquired immunosuppression associated with solid organ and bone marrow transplants are similarly associated with increased cancer incidence, accelerated cancer growth, and poor overall survival.[10]

Conventional clinicopathologic parameters including TNM stages, tumor grade, and patient performance status fail to account for host immune-inflammatory factors in evaluating the patient prognosis and selecting an optimal treatment paradigm. While positive surgical margins and extracapsular extension (ECE) have been identified as independent indications for post-operative chemoradiotherapy in patients with OCSCC, little attention is payed to host immune-inflammation factors to predict survival and select for patients in which treatment escalation may be beneficial.[11] Recently, a growing body of evidence has suggested that the systemic immune-inflammation index (SII) is a powerful tool in predicting disease extent and patient survival.[12] SII — calculated as platelet count x neutrophil/lymphocyte count — is a quantifiable factor hypothesized to describe the interplay of the immune system and tumor.[13] At the time of diagnosis, SII appears to have prognostic value in multiple solid malignancies including lung cancer and cancers of the gastrointestinal tract; however, limited data exists on its prognostic implications of patients with OCSCC.[13-17]

In the present study, we sought to determine the optimal cutoff of preoperative SII and the prognostic implications of this tool on disease progression and survival in patients with OCSCC undergoing curative resection.

Materials and Methods

Study Population: We undertook a retrospective review of patients with OCSCC who underwent curative resection at the University of Nebraska Medical Center from 2010-2019. Clinical data were obtained from the electronic medical record. Patients were included if they had a CBC with differential within 45 days prior to their resection and did not have active infections, inflammatory disease, or steroid use within a 4 week period before their blood draw. Patients presenting with recurrent or distant metastatic OCSCC, non-SCC histological diagnosis, or who were treated with neoadjuvant or primary chemoradiotherapy were excluded. This study was approved by our IRB (#572-20-EP).

Staging and Workup: Patients underwent work-up at the discretion of their evaluating surgeon which included physical examination, biopsy, and cross-sectional imaging (CT and PET-CT imaging). Pathologic data was obtained from the pathology reports. Pathologic TNM classification data was updated based on guidelines set forth by the AJCC 8th edition. When no neck dissection was performed, the N classification of cN0 was used.

SII Calculation: SII was determined using a CBC with differential drawn closest to (but prior to) surgical resection. As defined previously, SII was calculated as platelet count x neutrophil/lymphocyte count on a preoperative CBC with differential. An optimal cutoff of SII was determined using a receiver operating characteristic (ROC)

curve that maximized the area under the curve (AUC).

Resection and Adjuvant Therapy: In all patients the initial resection of the primary tumor was performed with curative intention, with objective clinical margins greater than 1 cm. Following resection, all cases were reviewed at a multidisciplinary tumor board at which time consensus recommendations for adjuvant therapy were reached. The indications for adjuvant concurrent chemoradiotherapy were strictly presence of extracapsular extension (ECE) or a positive surgical margin (SM) while intermediate risk factors for recurrence prompted adjuvant radiotherapy and included recurrent disease, close SM, perineural invasion (PNI), T3 or T4 disease, and nodal involvement.[11] The dose and fractionation of adjuvant radiotherapy was at the discretion of the managing radiation oncologists, but predominantly included comprehensive oral cavity and cervical lymph node coverage.

Statistical Analysis: The date and site(s) of relapse were defined at the first observation documented on either clinical exam or imaging. The duration of freedom from locoregional recurrence (FFLRR) was defined as the date of surgical resection to the date of locoregional recurrence (even if this was not the site of first relapse). Subjects known to be recurrence free at last follow-up were treated as censored events. The duration of disease-free survival (DFS) was measured from the date of surgical resection to the date of relapse or death. Subjects known to be recurrence free and alive at last follow-up were treated as censored events. The duration of overall survival (OS) was measured from the date of diagnosis to the date of death, patients lost to follow-up prior to death were censored. The duration of disease-specific survival (DSS) was measured from date of diagnosis to the date of death if the death was attributable to the disease process including treatment related complications; otherwise, the case was censored. Relationships between parameters were examined using the Chi-squared test. Factors associated with FFLRR, DFS, OS, and DSS were determined with the log-rank test and Kaplan-Meier curves. Hazard ratios were computed with the Cox proportional hazards model. P-values less than 0.05 were considered to be significant. Univariate and multivariate Cox regression analyses of potential factors affecting patients' outcome were performed. No-multicollinearity of the grouped co-variates was checked. Factors analyzed for an association with recurrence and survival outcomes in the Cox regression analysis included: sex (male vs female), age (<65 vs ≥65 years), Eastern Cooperative Oncology Group (ECOG) performance status (0-1 vs 2-3), smoking history (non-smoker vs. former or active smoker), size of primary disease (<20 mm vs >20 mm), SM (negative vs positive), and presence vs absence of LVSI, PNI, cortical bone involvement, and ECE. Statistical analysis was performed using SPSS software, version 26 (IBM Corp., Armonk, NY).

Results

From 2010 to 2019, 222 patients underwent a curative resection with stage I-IVB OCSCC at our institution who met the inclusion criteria (see Table 1 for baseline patient characteristics). The median age at the time of diagnosis was 63 years (range: 22-94). The median follow-up for all patients was 23.0 months (range: 1.1-116.6 months) and 30.6 months (range: 1.5-116.6 months) for patients alive at last contact. Fifty-one patients (23.0%) underwent adjuvant radiotherapy and 37 patients (16.7%) underwent adjuvant chemoradiotherapy.

During the follow-up period, 60 patients (27.0%) developed recurrent disease of which 13 patients (21.7%) developed metastatic disease. During the follow-up period, 82 patients (36.9%) died of which 46 (56.1%) were attributed to disease progression or treatment associated complication. The 2-year FFLRR, DFS, OS, and DSS rates were 82.6%, 83.9%, 76.4%, and 81.6%, respectively.

We examined SII as a prognostic indicator of outcomes in this patient population. The median SII was 637 (range: 34.9-23,400.0). The optimal cut-off point of 1047 was determined using a receiver operating characteristic (ROC) curve with 2-year OS as the endpoint (Figure 1). The area under the curve (AUC) for OS was 0.674 (95% CI: 0.583-0.765, $p<0.001$). We divided all patients into high-level group and low-level group based on the SII cut-off value of 1047. As shown in Table 2, 173 patients (77.9%) had SII <1047 and, and 49 patients (22.1%) had SII >1047. A high SII was associated with worse patient related factors such as ECOG performance status ≥2 (28.6% vs 8.7%, $p<0.001$), and increased disease extent including size of primary disease >20 mm (69.4% vs 45.7%, $p=0.003$), DOI >10 mm (59.2% vs 28.9%, $p<0.001$), PNI (53.1% vs 27.2%, $p<0.001$), and ECE (32.7% vs 15.6%, $p=0.008$).

SII assessed prior to curative resection was an important prognostic factor for FFLRR, DFS, OS, and DSS as identified in both univariate (Table 3) and multivariate analyses (Table 4). Patients who presented with a low SII (<1047) had a lower rates of locoregional recurrence when compared with patients with a high SII (>1047), with an average (median not met) FFLRR of 94.8 months versus 66.7 months, respectively (unadjusted HR: 0.355, 95% CI: 0.175-0.72, $p=0.004$) (see Figure 2). The two-year FFLRR rate was 85.5% in patients with

Table 1. Baseline patient characteristics

Characteristic	No. (%)
Age (years)	
<65	124 (55.9%)
≥65	98 (44.1%)
Sex	
Male	126 (56.8%)
Female	96 (43.2%)
Race	
Caucasian	209 (94.1%)
African American	6 (2.7%)
Asian	2 (0.9%)
Other	5 (2.3%)
ECOG PS	
0	80 (36.0%)
1	113 (50.9%)
2	20 (9.0%)
3	9 (4.1%)
Smoking history	
<40 pack years	50 (22.5%)
≥40 pack years	172 (77.5%)
Subsite	
Oral tongue	115 (51.8%)
Floor of mouth	36 (16.2%)
Alveolar ridge	34 (15.3%)
Buccal mucosa	14 (6.3%)
Retromolar trigone	9 (4.1%)
Lip	7 (3.2%)
Hard palate	7 (3.2%)
Grade	
1	86 (38.7%)
2	119 (53.6%)
3	17 (7.7%)
Further pathologic findings	
LVSI	19 (8.6%)
PNI	73 (32.9%)
Cortical bone invasion	43 (19.4%)
ECE	43 (19.4%)
Positive margin	9 (4.1%)
Group stage	
I	63 (28.4%)
II	38 (17.1%)
III	31 (14.0%)
IVA	47 (21.2%)
IVB	43 (19.4%)
Adjuvant management	
None	134 (60.4%)
RT	51 (23.0%)
CRT	37 (16.7%)

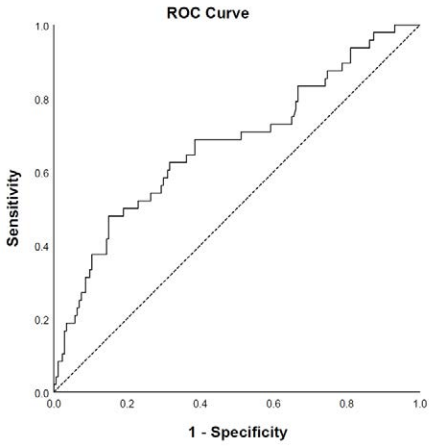

Figure 1. Receiver Operator Curve (ROC) analysis of the prognostic power of the systemic immune-inflammation index (SII) on overall survival (OS). An SII of 1047 was identified as optimally prognostic for OS (Area 0.654, p=0.011).

Table 2. Associations between the systemic immune-inflammatory index (SII) and patient clinicopathologic factors.

Factor	SII High (≥1047) (n=49)	SII Low (<1047) (n=173)	Total (n=222)	P-value
Age				0.272
<65 years	24 (49.0%)	100 (57.8%)	124 (55.9%)	
≥65 years	25 (51.0%)	73 (42.2%)	98 (44.1%)	
Sex				0.698
Male	29 (59.2%)	97 (56.1%)	126 (56.8%)	
Female	20 (40.8%)	76 (43.9%)	96 (43.2%)	
ECOG PS				<0.001
<2	35 (71.4%)	158 (91.3%)	193 (86.9%)	
≥2	14 (28.6%)	15 (8.7%)	29 (13.1%)	
Smoking history				0.688
Non-smoker	10 (20.4%)	40 (23.1%)	50 (22.5%)	
Former or active smoker	39 (79.6%)	133 (76.9%)	172 (77.5%)	
Size of primary				0.003
≤20 mm	15 (30.6%)	94 (54.3%)	109 (49.1%)	
>20 mm	34 (69.4%)	79 (45.7%)	113 (50.9%)	
DOI				<0.001
≤10 mm	20 (40.8%)	123 (71.1%)	143 (64.4%)	
>10 mm	29 (59.2%)	50 (28.9%)	79 (35.6%)	
Surgical margin				0.991
Negative	47 (95.9%)	166 (96.0%)	213 (95.9%)	
Positive	2 (4.1%)	7 (4.0%)	9 (4.1%)	
Grade				0.186
1	15 (30.6%)	71 (41.0%)	86 (38.7%)	
2-3	34 (69.4%)	102 (59.0%)	136 (61.3%)	
LVSI				0.105
Absent	42 (85.7%)	161 (93.1%)	203 (91.4%)	
Present	7 (14.3%)	12 (6.9%)	19 (8.6%)	
PNI				<0.001
Absent	23 (46.9%)	126 (72.8%)	149 (67.1%)	
Present	26 (53.1%)	47 (27.2%)	73 (32.9%)	
Cortical bone invasion				0.065
Absent	35 (71.4%)	144 (83.2%)	179 (80.6%)	
Present	14 (28.6%)	29 (16.8%)	43 (19.4%)	
ECE				0.008
Absent	33 (67.3%)	146 (84.4%)	179 (80.6%)	
Present	16 (32.7%)	27 (15.6%)	43 (19.4%)	

Abbreviations: SII, systemic immune-inflammatory index; ECOG PS, Eastern cooperative oncology group performance status; DOI, depth of invasion; LVSI, lymphovascular space invasion; PNI, perineural invasion; ECE, extracapsular extension.

a low SII and 71.1% in patients with a high SII (p=0.230). A low SII was associated with improved DFS with a median DFS of 68.0 months compared to 12.1 months for patients with a high SII (unadjusted HR: 0.316, 95% CI: 0.208-0.480, p<0.001). The two-year DFS rates of patients with a low versus high SII was 72.7% versus 31.9% (p<0.001). A low SII was also associated with improved OS with a median OS of 107.4 months compared to 23.1 months for patients with a high SII (unadjusted HR: 0.352, 95% CI: 0.221-0.560, p<0.001). The two-year OS rates of patients with a low versus high SII was 84.1% versus 48.3% (p<0.001). A low SII was associated with improved DSS with an average (median not met) DSS of 100.8 months compared to 60.5 months for patients with a high SII (unadjusted HR: 0.289, 95% CI: 0.159-0.526, p<0.001). The two-year DSS rates of patients with a low versus high SII was 87.2% versus 58.6% (p=0.004).

On multivariate analysis, a low SII was independently associated with an improved FFLRR (HR: 0.382, 95% CI: 0.21-0.694, p=0.002), DFS (HR: 0.440, 95% CI: 0.286-0.679, p<0.001), OS (HR: 0.516, 95% CI: 0.319-0.836, p=0.007) and DSS (HR: 0.416, 95% CI: 0.222-0.781, p=0.006) (see Table 4). Other factors associated with OS on multivariate analysis included size of primary disease >20 mm (HR: 1.944, 95% CI: 1.147-3.295, p=0.014), presence of LVSI (HR: 2.067, 95% CI: 1.11-3.85, p=0.022), presence of PNI (HR: 2.251, 95% CI: 1.348-3.759, p=0.002), ECOG performance status ≥2 (HR: 2.649, 95% CI: 1.574-4.458, p<0.001), and a final positive margin (HR: 5.042, 95% CI: 2.198-11.563, p<0.001). See Table 4 for factors associated on multivariate analysis with FFLRR, DFS, and DSS.

Discussion

The interplay of the immune-inflammatory system with the extent of disease at time of resection and patient outcomes may be represented by the systemic immune-inflammation index. We found that an elevated SII was strongly associated with increased extent of OCSCC at the time of resection as represented by size of primary disease >20 mm, DOI >10 mm, PNI, and ECE. Additionally, an elevated SII was associated with worse patient performance status as represented by ECOG performance status ≥2. With these associations controlled on multivariate analysis, a high SII remained strongly prognostic for FFLRR, DFS, OS, and DSS. To our knowledge, these findings represent the first publication of the prognostic implication of SII on both oncologic and survival outcomes of patients with OCSCC in a predominantly Caucasian population. Additionally, our findings add to the current understanding of the association between SII and disease extent by reporting the association with individual pathologic findings rather than simply grouped TNM staging.[15-17]

Table 3. Factors associated (p<0.05) on univariate analysis with freedom from locoregional recurrence (FFLRR), disease-free survival (DFS), overall survival (OS), and disease-specific survival (DSS).

Characteristic	HR	95% CI	P-value
FFLRR			
SII <1047	0.355	0.175-0.72	0.004
Age ≥65	1.797	1.034-3.125	0.038
DOI >10 mm	2.262	1.308-3.911	0.003
ECE	2.409	1.352-4.292	0.003
Size of primary >20 mm	2.418	1.370-4.268	0.002
LVSI	2.539	1.138-5.662	0.023
PNI	2.553	1.471-4.431	0.001
ECOG ≥2	2.708	1.388-5.281	0.003
Positive margin	3.455	1.234-9.676	0.018
DFS			
SII <1047	0.316	0.208-0.480	<0.001
Age ≥65	1.580	1.061-2.351	0.024
ECE	2.380	1.572-3.601	<0.001
DOI >10 mm	2.443	1.644-3.629	<0.001
LVSI	2.449	1.411-4.251	0.001
Size of primary >20 mm	2.871	1.887-4.369	<0.001
ECOG ≥2	2.971	1.885-4.681	<0.001
PNI	3.002	2.016-4.469	<0.001
Positive margin	3.127	1.509-6.481	0.002
OS			
SII <1047	0.352	0.221-0.560	<0.001
Cortical bone involvement	2.133	1.311-3.470	0.002
ECE	3.061	1.953-4.799	<0.001
DOI >10 mm	3.165	2.028-4.938	<0.001
Size of primary >20 mm	3.311	2.057-5.330	<0.001
LVSI	3.390	1.893-6.071	<0.001
ECOG ≥2	3.567	2.165-5.878	<0.001
PNI	4.128	2.635-6.468	<0.001
Positive margin	4.560	2.079-10.001	<0.001
DSS			
SII <1047	0.289	0.159-0.526	<0.001
Grade 2-3	1.955	1.011-3.781	0.046
ECOG ≥2	3.004	1.524-5.920	0.001
Cortical bone involvement	3.270	1.802-5.936	<0.001
LVSI	4.189	2.060-8.516	<0.001
DOI >10 mm	4.199	2.293-7.688	<0.001
ECE	5.244	2.935-9.370	<0.001
Size of primary >20 mm	5.594	2.686-11.649	<0.001
PNI	6.595	3.493-12.452	<0.001
Positive margin	7.952	3.509-18.020	<0.001

Abbreviations: SII, systemic immune-inflammatory index; FFLRR, freedom from locoregional recurrence; DFS, disease-free survival; OS, overall survival; DSS; disease-specific survival; ECOG PS, Eastern cooperative oncology group performance status; DOI, depth of invasion; LVSI, lymphovascular space invasion; PNI, perineural invasion; ECE, extracapsular extension.

Table 4. Factors associated (p<0.05) with freedom from locoregional recurrence (FFLRR), disease-free survival (DFS), overall survival (OS), and disease-specific survival (DSS) in the cox regression model.

Characteristic	HR	95% CI	P-value
FFLRR			
SII <1047	0.382	0.210-0.694	0.002
ECE	2.409	1.352-4.292	0.003
Positive margin	3.047	1.060-8.754	0.039
DFS			
SII <1047	0.440	0.286-0.679	<0.001
Age ≥65	1.548	1.035-2.315	0.033
Size of primary >20 mm	1.865	1.184-2.938	0.007
ECOG ≥2	1.974	1.231-3.167	0.005
PNI	2.018	1.306-3.116	0.002
OS			
SII <1047	0.516	0.319-0.836	0.007
Size of primary >20 mm	1.944	1.147-3.295	0.014
LVSI	2.067	1.110-3.850	0.022
PNI	2.251	1.348-3.759	0.002
ECOG ≥2	2.649	1.574-4.458	<0.001
Positive margin	5.042	2.198-11.563	<0.001
DSS			
SII <1047	0.416	0.222-0.781	0.006
Size of primary >20 mm	2.902	1.334-6.311	0.007
PNI	4.098	2.084-8.060	<0.001
Positive margin	9.617	4.042-22.886	<0.001

Abbreviations: SII, systemic immune-inflammatory index; FFLRR, freedom from locoregional recurrence; DFS, disease-free survival; OS, overall survival; DSS; disease-specific survival; ECOG PS, Eastern cooperative oncology group performance status; DOI, depth of invasion; LVSI, lymphovascular space invasion; PNI, perineural invasion; ECE, extracapsular extension.

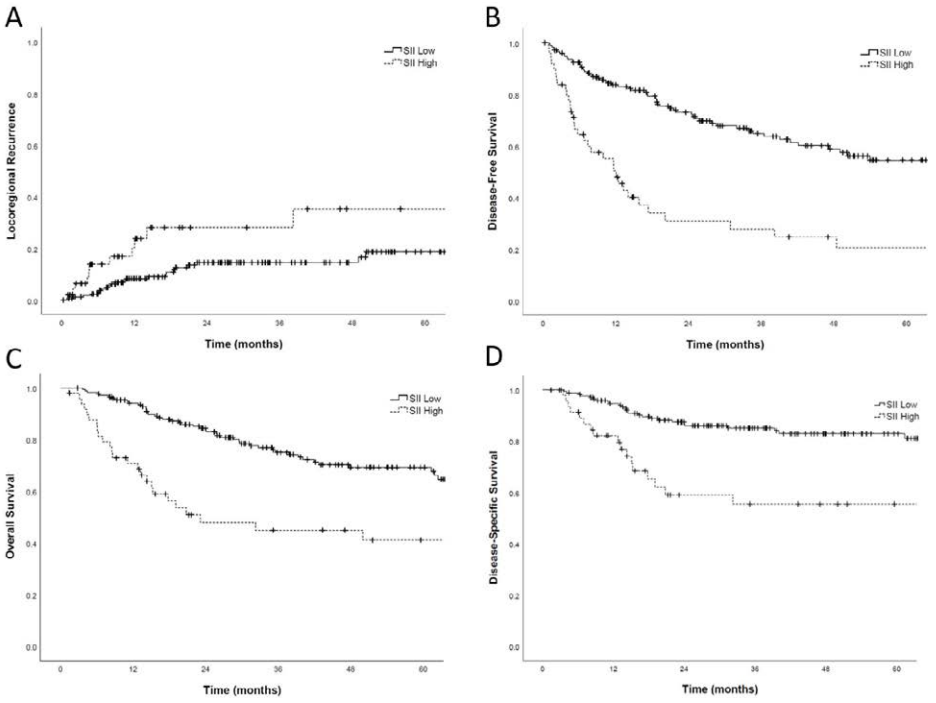

Figure 2. Systemic immune-inflammation index (SII) of a cut-off value of 1047 was associated with (A) an improved LRR rate (p=0.004), (B) an improved disease-free survival (p<0.001), (C) an improved overall survival (p<0.001), and (D) an improved disease-specific survival (p<0.001).

The prognostic implication of SII in patients with OCSCC has previously been described in multiple cohorts which have similarly demonstrated the association between a high SII and worse OS and DFS.[15-17] They similarly identified that an elevated SII was associated with increased disease extent as represented by both T and N staging. Additionally, we found that SII was associated with FFLRR and DSS suggesting that SII may be prognostic for disease control rather than simply a surrogate for patient frailty or comorbidity.

In our cohort, we identified an optimal SII cutoff of 1047, while cutoff values of SII for patients with OCSCC among previously published literature ranges from 484.5 to 569.[15-17] Heterogeneous populations, treatment paradigm, disease site, and patient selection factors might explain variance. It is not beyond our notice that the previously published studies included predominantly Asian populations while our cohort was predominantly Caucasian. This discrepancy exists in other disease sites including non-small cell lung cancer in which SII cut off values of 521-660 were prognostic for OS in Asian populations while a cut-off value of 1270 was prognostic for OS in a European population.[18-20] Cultural or racial differences might influence the optimal SII cut-off value for survival.

We have identified an association of SII with disease extent at the time of resection and with treatment outcomes; however, little data exists delineating the role of SII to predict for a therapeutic advantage with differing treatment options. The interaction of surgery, radiotherapy, and systemic therapy including chemotherapy and immunotherapy with the immune system is an evolving area of study. Further investigation into the role of SII as a predictor of treatment response is needed.

While personalized medicine is associated with increased costs to patients and the healthcare system, SII remains a low cost and a potentially powerful prognostic tool. SII can be easily calculated at the time of diagnosis after collecting a CBC with differential.[12] This prognostic information has the potential to guide definitive and adjuvant management. Furthermore, improved control of contributing comorbidities may be of particular importance in patients presenting with an elevated SII to improve oncologic outcomes, although additional data is needed in this area.

Limitations of this study include its relatively small sample size and retrospective nature. Furthermore, preoperative SII is captured at a single time point and does not control for all possible factors contributing to temporal inflammation, and is therefore is a limited surrogate for patient inflammation.

However, this adds to the increasing body of evidence correlating the role of systemic inflammation with other solid tumors such as lung cancer outcomes. Notwithstanding the aforementioned limitations, these findings warrant further investigation into both the prognostic and predictive value of SII in OCSCC. We plan to expand our study to other head neck squamous cell carcinoma such as oropharyngeal and laryngeal SCC.

Conclusion

In the present study we demonstrate that SII is strongly associated with the extent of OCSCC at the time of resection and is powerfully prognostic for FFLRR, DFS, OS, and DSS. These findings add to the previously published knowledge of the value of SII in this setting. Both the inexpensive nature of obtaining an SII and the prognostic value not accounted for in other patient clinicopathologic factors warrants further investigation into SII as an oncologic biomarker in the clinical setting. ■

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