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Systemic Inflammatory Markers as Predictors of Postoperative Complications and Survival in Patients With Advanced Head and Neck Squamous Cell Carcinoma Undergoing Free-Flap Reconstruction

Andro Košec, MD, PhD, [*] *Darko Solter, MD, PhD,* [*] *Ana Ribić, MD,* [†] *Mislav Knežević, MD,* [†] *Davor Vagić, MD, PhD,* [‡] *and Alan Pegan, MD, PhD* [§]

Purpose: The aim of this study was to determine the prognostic value of systemic inflammatory indices as factors for postoperative complications and survival in patients with advanced stages of p16-negative head and neck squamous cell carcinoma undergoing free-flap reconstruction.

Methods: This was a retrospective cohort study. The primary predictor variables were inflammatory markers such as neutrophil, lymphocyte, monocyte, and platelet count, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio, lymphocyte-monocyte ratio, derived NLR, systemic immune-inflammatory index, and systemic inflammatory marker index (SIM). Multivariate regression analyses were used to measure the associations between systemic inflammatory indices and overall and disease-free survival as a primary outcome and occurrence of postoperative complications as a secondary outcome measure.

Results: The sample was composed of 69 male (76.67%) and 21 female (23.33%) patients, with an average age of 61.15 ± 9.79 years. The median follow-up time was 24 months, and 73 of 91 (66.43%) patients were alive during the median follow-up.

Overall disease survival correlated with systemic immune-inflammation ($P = .022$, cutoff >1,005.3, sensitivity 67.1%, and specificity 70.6%) and SIM ($P = .0001$, cutoff >4.05, sensitivity 90.4%, and specificity 41.2%), preoperative platelets ($P = .036$, cutoff <194, sensitivity 28.8%, and specificity 94.1%), and postoperative lymphocytes ($P = .012$, cutoff <0.6, sensitivity 38%, and specificity 76.5%), whereas increased SIM ($P = .042$, cutoff >4.05, sensitivity 91.3%, and specificity 38.1%), NLR ($P = .031$, cutoff >13.2, sensitivity 56.9%, and specificity 60%), and preoperative platelets ($P = .006$, cutoff <244, sensitivity 52.3%, and

[*]Assistant Professor, Department of Otorhinolaryngology and Head and Neck Surgery, University Hospital Centre Sestre milosrdnice, Zagreb, Croatia; University of Zagreb School of Medicine, Zagreb, Croatia.

†Resident, Department of Otorhinolaryngology and Head and Neck Surgery, University Hospital Centre Sestre milosrdnice, Zagreb, Croatia.

‡Department Head and Tenured Professor, Department of Otorhinolaryngology and Head and Neck Surgery, University Hospital Centre Sestre milosrdnice, Zagreb, Croatia; University of Zagreb School of Medicine, Zagreb, Croatia.

§Associate Professor, Department of Otorhinolaryngology and Head and Neck Surgery, University Hospital Centre Sestre milosrdnice, Zagreb, Croatia; University of Zagreb School of Medicine, Zagreb, Croatia.

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Address correspondence and reprint requests to Dr Košec, Department of Otorhinolaryngology and Head and Neck Surgery, University Hospital Center Sestre milosrdnice, Vinogradska cesta 29, Zagreb, Croatia; e-mail: andro.kosec@yahoo.com

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specificity 76%) were associated with adverse disease-free survival. The cumulative postoperative complication rate was 34.5%, of which 13.3% accounted for major complications, whereas derived NLR ($P = .013$, degrees of freedom 1, χ^2 test 6.161, cutoff >2.3) and postoperative lymphocytes ($P = .009$, DF 1, χ^2 test 6.756, cutoff <1) correlated with occurrence of complications.

Conclusions: Inflammatory indices as measures of inflammation-related systemic dysfunction may be associated with adverse survival in patients with head and neck squamous cell carcinoma and occurrence of postoperative complications and with specific cutoff values.

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Head and neck squamous cell carcinoma (HNSCC) accounts for over 90% of all head and neck cancers, arising from mucosal surfaces of the oral cavity, oropharynx, and larynx. HNSCC incidence in Europe is especially high in France, Hungary, Slovakia, and Slovenia.[1] According to the American Cancer Society, 53,260 new cases of oral cavity and oropharyngeal carcinoma are expected in 2021, accounting for 3% of all expected US cancer cases.[2] Well-known risk factors with synergistic effect are sustained exposure to tobacco and tobacco-like products and alcohol consumption.[3,4] The latest, 8th edition of American Joint Committee on Cancer Staging Manual now lists human papillomavirus-associated oropharyngeal cancer as a separate entity, but the TNM Classification of Malignant Tumours staging alone cannot accurately predict postoperative outcomes in patients with HNSCC.[5]

The immune system can have both an active protective role in suppression of malignant transformation and in promoting tumor growth.[6] The host inflammatory response may influence the progression and development of malignancies consequently creating a tumor microenvironment and a complex interplay of host-derived and tumor-derived cytokines generating smolder chronic-like inflammation.[6,7] Many literature reports have recently focused on this issue, especially for solid tumors, such as lung cancer, brain tumors, colorectal cancer, breast cancer, melanoma, and gastric cancer.[8,9,10,11]

To date, many inflammatory markers such as neutrophil, lymphocyte, monocyte, and platelet count, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio, lymphocyte-monocyte ratio, derived NLR (dNLR), systemic inflammatory marker index (SIM), systemic immune-inflammatory index (SII), and Glasgow prognostic score have been analyzed as potential predictive biomarkers that would supplement the current TNM staging and improve data on establishing an accurate prognosis.[6,12-16] Published data report increases in neutrophil, monocyte, and platelet counts to be linked with adverse disease outcome, alongside decrease in lymphocyte counts.[17-19]

Exact mechanisms driving the effects of peripheral blood cells on tumorigenesis have yet to be elucidated, as are their cutoff values to be used effectively in a clinical setting. The NLR, lymphocyte-monocyte ratio, and SIM were identified as significant prognostic indicators in HNSCC.[10] Head and neck reconstruction is also burdened with risk for postoperative complication greatly compromising the patient's quality of life.[20,21]

The aim of this study was to analyze the prognostic value of systemic inflammatory markers in patients with advanced stages of p16-negative HNSCC undergoing free-flap reconstruction. The investigators hypothesize that certain values of systemic inflammatory markers may correlate with postoperative complications and survival. The specific aims of the study were as follows: *1)* to identify associations between systemic inflammatory values and overall survival (OS) and disease-free survival (DFS) as a primary end point and *2)* occurrence of postoperative complications within a 14-day postoperative follow-up interval as a secondary end point.

Patients and Methods

STUDY DESIGN

To address the research purpose, the investigators designed and implemented a retrospective cohort study including patients with HNSCC undergoing surgical treatment and simultaneous microvascular free-flap reconstruction at a tertiary surgical center between January 2015 and December 2017. All patients received adjuvant (chemo)radiotherapy treatment. The study was approved by the University Hospital Center Bioethical Board adhering to the Helsinki Declaration Revision of 1989, and written informed consent was obtained from all the participants. The inclusion criteria were as follows: *1)* patients aged 18 to 80 years, *2)* patients with SCC of the oral cavity, oropharynx, hypopharynx, larynx, and the cervical esophagus, *3)* advanced stage (IVa and IVb) disease, *4)* no prior oncological or surgical treatment, *5)* no inflammatory or hematological disorder affecting the peripheral cell count, *6)* complete medical history, and *7)* minimum follow-up period of 1 year.

The exclusion criteria were as follows: *1)* patients with p16-positive oropharyngeal carcinoma, *2)* active preoperative inflammatory disease or infection, *3)*

Table 1. SUMMARY OF DESCRIPTIVE STATISTICS

Patients	n = 90
Average Age (±SD) in Yrs	61,15 ± 9,79
Gender (N)	
Male	69 (76.6%)
Female	21 (23.4%)
Primary tumor location (N)	
Oropharynx	34 (37.8%)
Hypopharynx	12 (13.3%)
Hypopharynx and cervical esophagus	1 (1.1%)
Larynx	3 (3.3%)
Tongue and base of mouth	37 (41.1%)
Paranasal sinus	2 (2.2%)
Temporal bone	1 (1.1%)
T category	
T1	14 (15.6%)
T2	1 (1.1%)
T3	31 (34.4%)
T4a	40 (44.4%)
T4b	4 (4.4%)
N category	
N0	31 (34.4%)
N1	10 (11.1%)
N2a	9 (10%)
N2b	11 (12.2%)
N2c	4 (4.4%)
N3	25 (27.8%)
TNM disease stage	
IVa	60 (66.7%)
IVb	30 (33.3%)
Flap type	
Anterolateral thigh (ALT)	20 (22.2%)
Radial forearm (RFFF)	33 (36.7%)
Deep circumflex illiac artery (DCIA)	8 (8.9%)
Jejunum	9 (10%)
Vertical rectus abdominis muscle (VRAM)	12 (13.3%)
Fibular osseocutaneous flap (FOCFF)	3 (3.3%)
Scapula	2 (2.2%)
Latissimus dorsi	3 (3.3%)
Major complications	13.3%
Flap failure	5.3%
Revision surgery required	9%
Minor complications	21.2%
Fistula formation	11.5%
Complications in the donor region	1.8%
Cumulative complication rate	34.5%

Abbreviation: SD, standard deviation.

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early disease stage, *4)* distant metastatic disease, and *5)* incomplete patient data and follow-up. In total, the study data included 90 patients.

STUDY VARIABLES

The peripheral blood samples were obtained within 2 weeks before surgery. The dNLR was defined as follows: baseline absolute neutrophil count/(baseline absolute lymphocyte count – baseline absolute neutrophil count) (cells/mm^3).[14] The SII was calculated as follows: baseline absolute neutrophil count × baseline absolute platelet count/baseline absolute lymphocyte count (cells/mm^3).[14] The SIM was calculated as follows: baseline absolute neutrophil count × baseline absolute monocyte count/baseline absolute lymphocyte count (cells/mm^3).[12]

Covariates were grouped into logical sets: age, sex, TNM category and disease stage, localization of tumor (oropharynx, hypopharynx, hypopharynx and cervical esophagus, larynx, tongue and base of mouth, paranasal sinus, temporal bone), type of free flap (anterolateral thigh, radial forearm, deep circumflex illiac artery, jejunum, vertical rectus abdominis muscle, fibular osseocutaneous flap, scapula, latissimus dorsi), inflammatory indices, presence of comorbidity (diabetes, hypertension, chronic liver disease, heart failure), smoking history, and alcohol history. The data were collected from preoperative and postoperative medical data, created through uniform administrative forms. In addition, other variables were covariates.

OUTCOME MEASURES

The initial survival follow-up point was the patient's arrival in the recovery room, and the end point was current patient survival status during regular monthly follow-up, with disease recurrence and death noted separately as binary censored values. Occurrence of postoperative complications up to 14 days after surgery was considered a secondary outcome measure, defined as the appearance of fistula, free-flap necrosis, stasis of the flap blood supply, and complications at the donor site or the operative region. The values were coded as binary. If one patient had several complications consecutively or simultaneously, they were noted as separate complications.

DATA ANALYSIS

Tested variables were noted using standard descriptors (arithmetic mean and standard deviation or median). Multivariate analyses were performed to assess the relationship between OS and DFS, occurrence of postoperative complications, and variables using multinomial logistic regression and Cox proportional hazards models.

Every variable that was significantly associated with survival (OS, DFS, or both) or postoperative complications was further analyzed with a receiver operating characteristic (ROC) analysis, and a cutoff value was identified using the Youden J index (measuring the

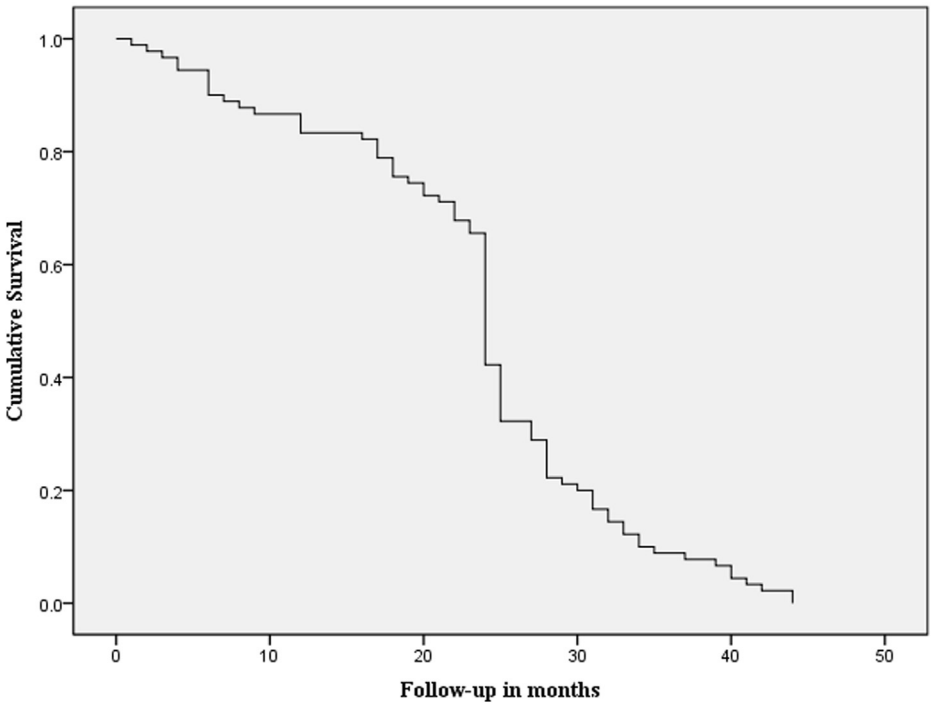

FIGURE 1. Overall survival in the patient cohort. The median follow-up time was 24 months.

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sensitivity and specificity of a dichotomous tested variable), and the patients were divided into low-risk (<the cutoff value) and high-risk subgroups (>the cutoff value). Associations between possible prognostic factors and survival were analyzed using Kaplan–Meier survival analysis using the log-rank test. All tests of statistical significance were performed using a two-sided 5% type I error rate. P values ≤ 0.05 were considered to be statistically significant. Statistical analysis was performed by MedCalc (Version 11.2.1 © 1993 to 2010. MedCalc Software bvba Software, Broekstraat 52, 9030 Mariakerke, Belgium).

Results

Of the 90 patients included, 69 were men (76.67%), and 21 were women (23.33%). Their average age was 61.15 years with a standard deviation of 9.79 years. The clinical characteristics of patients, including age, sex, tumor location, tumor category, tumor stage, are shown in Table 1. None of the patients diagnosed with HNSCC had distant metastatic disease. The study included 60 cases of stage IVa and 30 cases of stage IVb HNSSC. All the patients received postoperative oncologic treatment, with 41 patients receiving postoperative radiotherapy and 49 patients receiving postoperative chemoradiotherapy.

In this study, the median follow-up time was 24 months; 73 of 91 (66.43%) patients were alive during the median follow-up time (Fig 1).

The cumulative postoperative complication rate was 34.5%, of which 13.3% accounted for major complications, such as revision surgery and flap failure. The overall flap failure rate was 5.3%, corresponding to total necrosis and need for tissue removal. Fistula formation was noted in 11.5% of patients. Complications in the donor region occurred in 1.8% of patients (Table 1).

In our patient cohort, out of systemic inflammatory indices tested as predictors of postoperative complications, an increased dNLR and a decreased postoperative lymphocyte count correlated with occurrence of complications (multinomial regression df = 1, P = .013, χ^2 test = 6.161 and P = .009, χ^2 test = 6.756, respectively). The cutoff values identified by the ROC curve Youden J index having the highest sensitivity and specificity in correlating with postoperative complications were dNLR >2.3 (52.9% sensitivity and 32.88% specificity) and postoperative lymphocyte count <1 (94.1% sensitivity and 43.7% specificity) (Tables 2 and 3). Other variables were not significantly correlated with postoperative complications as the outcome variable (Table 2).

OS and DFS were used as outcome measures to further test the inflammatory indices identified as possible prognostic factors by Cox multivariate regression, whereas other variables were covariates. As expected, disease localization (P = .048) and advanced T category (P = .01) adversely affected OS and DFS.

Table 2. ANALYSIS OF ASSOCIATIONS BETWEEN INFLAMMATORY INDICES AS PRIMARY PREDICTOR VARIABLES AND OCCURRENCE OF POSTOPERATIVE COMPLICATIONS USING A MULTINOMIAL LOGISTIC REGRESSION MODEL

Primary Predictor Variables	Increased dNLR	Decreased Postoperative Lymphocyte Count	SII	SIM	NLR	Preop. Neutrophils	Preop. Lymphocytes	Preop. Leukocytes	Preop. Platelets	Preop. Monocytes	PLR	LMR	Postop. Neutrophils
Occurrence of postoperative complications													
Statistical significance *P*	**.013**	**0.009**	.698	.992	.650	.127	.969	.639	.389	.258	.969	.180	.253
DF, χ^2 test	1, 6.161	1, 6.756	1, 0.1511, 0.0		1, 0.218	1, 2.97	1, 0.002	1, 0.962	1, 0.734	1, 1.499	1, 0.0021, 2.369		1, 1.397
Youden J index (cutoff point)	>2.3	<1											

Bold indicates statistically significant values.

Abbreviations: dNLR, derived NLR; LMR, lymphocyte-monocyte ratio; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; SII, systemic immune-inflammatory index; SIM, systemic inflammatory marker index.

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Rising SII ($P = .022$), rising SIM ($P = .0001$), low preoperative platelet count ($P = .036$), and low postoperative lymphocyte count ($P = .012$) were associated with adverse overall disease survival (Table 4).

Cutoff values identified by the ROC curve and Youden J index having the highest sensitivity and specificity in correlating with overall disease survival were as follows: SII >1,005.3 (67.1% sensitivity and 70.6% specificity, 81.79% positive predictive value, and 52.17% negative predictive value), SIM >4.05 (90.4% sensitivity and 41.2% specificity, 75.15% positive predictive value, and 68.6% negative predictive value), preoperative platelet count <194 (28.8% sensitivity and 94.1% specificity, 90.57% positive predictive value, and 40.18% negative predictive value), and postoperative lymphocyte count <0.6 (38% sensitivity and 76.5% specificity, 76.1% positive predictive value, and 38.54% negative predictive value) (Table 5).

When analyzing the differences in survival subgroups related to the cutoff values, Kaplan–Meier survival curves comparing the low-SII (<1,005.3) and high-SII (≥1,005.3) subgroups showed a 2-year OS rate of 91% and 64% in low- and high-SII groups, respectively (Fig 2). When comparing the low-SIM (<4.05) and high-SIM (≥4.05) subgroups, the 2-year OS rate was 88% and 57% in low- and high-SIM groups, respectively (Fig 3). The preoperative platelet count showed 95% survival in the low-risk group (platelet count >194) and 78% in the high-risk group (platelet count <194) (Fig 4). Finally, postoperative lymphocyte groups showed an 83% 2-year survival rate in the low-risk group (Ly > 0.6) and 78% in the high-risk group (Ly < 0.6) (Fig 5).

Rising SIM ($P = .042$), rising NLR ($P = .031$), and low preoperative platelet count ($P = .006$) were negatively associated with DFS (Table 4).

All other variables were not significantly correlated with OS and DFS as the outcome variable.

The cutoff value identified by the ROC curve Youden J index having the highest sensitivity and specificity in correlating with adverse DFS was the SIM >4.05 (91.3% sensitivity and 38.1% specificity). The positive predictive value was 74.4%, and the negative predictive value was 69%. A Kaplan–Meier survival curve with a log-rank test comparing the low-SIM (<4.05) and high-SIM (≥4.05) subgroups showed the 2-year DFS rate was 85% and 47% in low- and high-SIM groups, respectively (Fig 6).

The cutoff ROC curve value identified for the NLR was >13.2 (56.9% sensitivity and 60% specificity). The positive predictive value was 73.7%, and the negative predictive value was 41.4%. A Kaplan–Meier survival curve with a log-rank test comparing the low-NLR (<13.2) and high-NLR (≥13.2) subgroups showed the 2-year DFS rate was 80% and 74% in low- and high-NLR groups, respectively (Fig 7).

Table 3. PREDICTIVE VALUES OF INFLAMMATORY MARKERS AND THEIR DERIVED INDICES WITH REGARD TO POSTOPERATIVE COMPLICATION OCCURRENCE

Variable	Cutoff Value	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
dNLR	>2.3	52.9	32.88	10.78 95% CI 4.198-21.635	81.98 95% CI 65.168-93.356
Decreased postoperative lymphocyte count	<1	94.1	43.7	20.41 95% CI 10.75-33.41	97.971 95% CI 86.36-99.99

Abbreviations: CI, confidence interval; dNLR, derived neutrophil-lymphocyte ratio.

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The ROC curve identified the preoperative platelet count cutoff value < 244 (52.31% sensitivity and 76% specificity). The positive predictive value was 81.1%, and the negative predictive value was 44.8%. A Kaplan–Meier survival curve with a log-rank test comparing the low–platelet count (>244) and high–platelet count (<244) subgroups showed the 2-year DFS rate was 90% and 74% in low– and high–preoperative platelet count groups, respectively (Fig 8).

Discussion

This study aimed to correlate systemic inflammatory marker values in patients with advanced stages of p16-negative HNSCC undergoing free-flap reconstruction with postoperative complications and survival. Inflammatory marker indices are combinations of these variables and may be specific to certain patient populations and tumor types. It is yet unknown whether specific cutoff values may be extrapolated to represent entire patient populations. However, they are particularly useful because they can be obtained through routine preoperative blood tests, are inexpensive, and are readily available for all patient populations. In addition, blood markers are not affected by any heterogeneity within the tumor.[14]

Our results suggest that an increased dNLR and a decreased postoperative lymphocyte count may significantly affect the occurrence of postoperative complications, whereas rising SII, rising SIM, decreased preoperative platelet count, and low postoperative lymphocyte count were negatively associated with overall disease survival.

Our results of postoperative complication rates are comparable to those reported in the literature, with regard to patients' characteristics and disease stages.[22,23] The sensitivity and specificity of the dNLR were low, but a postoperative lymphocyte count <1 showed a 94.1% sensitivity rate. An increased dNLR correlated with increased complication rates, suggesting that altered homeostasis affects the inflammatory process.

Wound healing may become disrupted because of increased chemotaxis and proteolysis, abnormal fibrin buildup, and inhibition of granulating tissue formation, and increased neutrophil activity has been correlated to adverse disease outcomes.[16,20,22] Tumor-infiltrating leukocytes regulate wound healing and different tumor growth stages, including growth and metastatic spread.[10] Aside from reactive oxygen and nitrogen species production, they can produce vascular endothelial growth factors and respond to transforming growth factor β, while also suppressing CD8+ T lymphocytes.[7,8,11-13] Monocytes and lymphocytes contribute to a therapy-resistant microenvironment through upregulating chemokine interactions and expression.[10] Platelets influence healing and malignant disease progression through releasing growth factors and inhibiting tumor lysis by aggregating around tumor cells.[7,14]

Existing knowledge on wound healing and the results of this study indicate that an increase in the dNLR corresponds to an increased neutrophil count and abnormal wound healing. Owing to the high sensitivity, decreased postoperative lymphocyte count in the peripheral blood in patients may be regarded as a potentially clinically useful variable in monitoring high-risk patients in the early postoperative period.[20,21,23]

Our results have linked several inflammatory indices with OS, calculated as cumulative disease-specific 2-year survival, and with DFS. The rising SII and SIM were associated with overall disease survival, regardless of adjuvant treatment protocols, as group treatment heterogeneity was low, and multivariate regression accounted for confounding factors. Increased SIM and NLR and decreased preoperative platelet count values were associated with adverse DFS. Similar results regarding the SIM were shown in several other studies, but no cutoff value was identified to date.[7,23] It has been shown repeatedly that patients with HNSCC have an elevated NLR compared to

Table 4. ANALYSIS OF ASSOCIATIONS BETWEEN INFLAMMATORY INDICES AS PRIMARY PREDICTOR VARIABLES AND 2-YEAR OVERALL AND DISEASE-FREE SURVIVAL USING A MULTIVARIATE COX REGRESSION MODEL

Primary Predictor Variables	Increased SII	Increased SIM	Low Preoperative Platelet Count	Low Postoperative Lymphocyte Count	dNLR	Increased NLR	Preoperative Neutrophils	Preoperative Lymphocytes	Preoperative Leukocytes	Preoperative Monocytes	PLR LMR	Postop. Neutrophils
Overall disease survival												
Statistical significance *P*	**.022**	**.0001**	**.036**	**.012**	.058	.090	.114	.151	.861	.171	.270 .230	.106
Youden J index (cutoff point)	>1,005.3	>4.05	<194	<0.6								
Disease-Free Survival												
Statistical significance *P*	.726	**.042**	**.006**	.307	.060	**.031**	.140	.151	.861	.070	.071 .300	.106
Youden J index (cutoff point)		>4.05	<244			>13.2						

Bold indicates statistically significant values.

Abbreviations: dNLR, derived NLR; LMR, lymphocyte-monocyte ratio; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; SII, systemic immune-inflammatory index; SIM, systemic inflammatory marker index.

healthy controls (>5) with regard to recurrence, tumor, and nodal stage in patients with p16-negative oropharyngeal carcinoma.[24,25] Our patient population comprised predominantly patients with oral and oropharyngeal cancer (67,8%), but excluded p16-positive patients to avoid bias as p16-positive patients have a different inflammatory response favoring leukocyte proliferation, with results pointing toward >2,3 as the optimal cutoff value, lower than previously suggested.[23]

Recently published results support high SII values predicting less favorable OS and DFS in patients with oral cavity squamous cell carcinoma after curative resection.[24] Our data suggest that using a cutoff value of 1,005.3, SII divides our patient population into two survival-related subgroups, with the low-risk group showing a survival rate of 91% and the other, high-risk group showing a survival rate of 64%, similar to published data advocating using SII as a risk stratification tool.[23,24] Mechanisms behind this may be neutrophil production of tumor necrosis factor-α, platelet production of growth factors that protect malignant cells against natural killer cell–induced cell death, and a blunted lymphocyte-mediated immune response against malignant cells.[25,26]

Our low-risk (<4.05) and high-risk (≥4.05) SIM subgroups showed an OS rate of 88% and 57%, respectively.[27] The SIM is an integrated indicator based on peripheral neutrophil, lymphocyte, and monocyte counts, developed to better reflect the inflammatory and immune status in HNSCC.[28] Our results were congruent with earlier data, confirming the SIM to be a reliable prognostic factor.[22,27]

Low preoperative platelet count (P = .036) and low postoperative lymphocyte count (P = .012) were also negatively associated with survival. Our data showed a 95% OS rate in the low-risk group (platelet count >194) and only 78% in the high-risk group (platelet count <194). In contrast with our results, one large meta-analysis suggests that an increased platelet count is associated with worse OS.[22] This is explained by the protumor effect of platelets, secreting interleukin-6 and increasing thrombopoietin synthesis in the liver, which results in paraneoplastic thrombocytosis. Platelets are activated by tumor cells, releasing soluble molecules, including ADP and thrombin.[29] However, published data do not unequivocally support high platelet count as a negative prognostic factor, and cutoff values for platelet count are inconsistent among individual studies, likely resulting in differing conclusions.[24,27,28] When examining the prognostic significance of the postoperative lymphocyte count using 0.6 as a cutoff value, subgroups showed an 83% 2-year survival rate in the low-risk group (Ly > 0.6) and 78% in the high-risk group (Ly < 0.6). Lymphocytes are mainly responsible for

Table 5. PREDICTIVE VALUES OF INFLAMMATORY MARKERS AND THEIR DERIVED INDICES WITH REGARD TO 2-YEAR OVERALL SURVIVAL AND DISEASE-FREE SURVIVAL

Variable	Cutoff Value	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
2-Yr Overall Survival					
SII	>1,005.3	67.1	70.6	81.79 95% CI 68.1-91.35	52.17 95% CI 36.03-67.98
SIM	>4.05	90.4	41.2	75.152 95% CI 63.54-84.6	68.57 95% CI 43.02-87.85
Low preoperative platelet count	<194	28.8	94.1	90.57 95% CI 68.26-99.1	40.18 95% CI 28.72-52.5
Low postoperative lymphocyte count	<0.6	38	76.5	76.09 95% CI 57.01-89.7	38.54 95% CI 26.28-51.98
Disease-Free survival					
SIM	>4.05	91.3	38.1	74.37 95% CI 62.83-83.9	69 95% CI 42.25-88.79
NLR	>13.2	56.9	60	73.67 95% CI 58.6-85.54	41.44 95% CI 26.79-57.29
Low preoperative platelet count	<244	52.31	76	81.09 95% CI 65.23-91.9	44.75 95% CI 30.9-59.25

Abbreviations: CI, confidence interval; NLR, neutrophil-lymphocyte ratio; SII, systemic immune-inflammatory index; SIM, systemic inflammatory marker index.

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immune-driven tumor suppression. By releasing interferon-γ and tumor necrosis factor-α, a high lymphocyte count has been shown to improve patient prognosis.[17,20,22,29]

The limitations of this study are its retrospective design, a heterogeneous sample, a relatively short follow-up time, and absence of multiple postsurgical sampling to verify the results over a longer

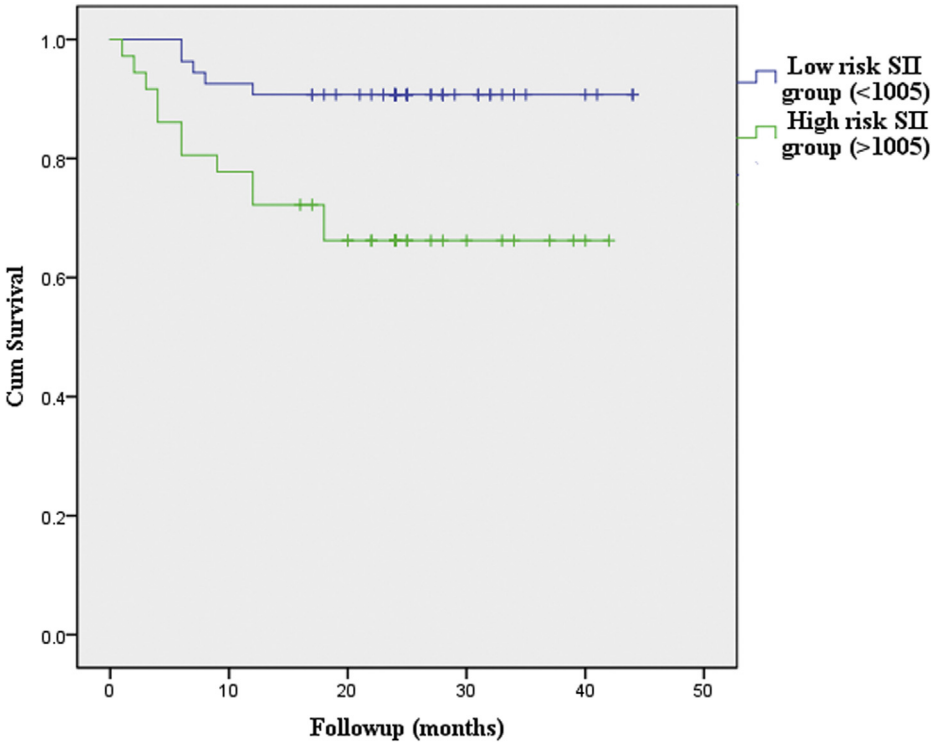

FIGURE 2. Systemic immune-inflammatory index (SII) and overall survival.

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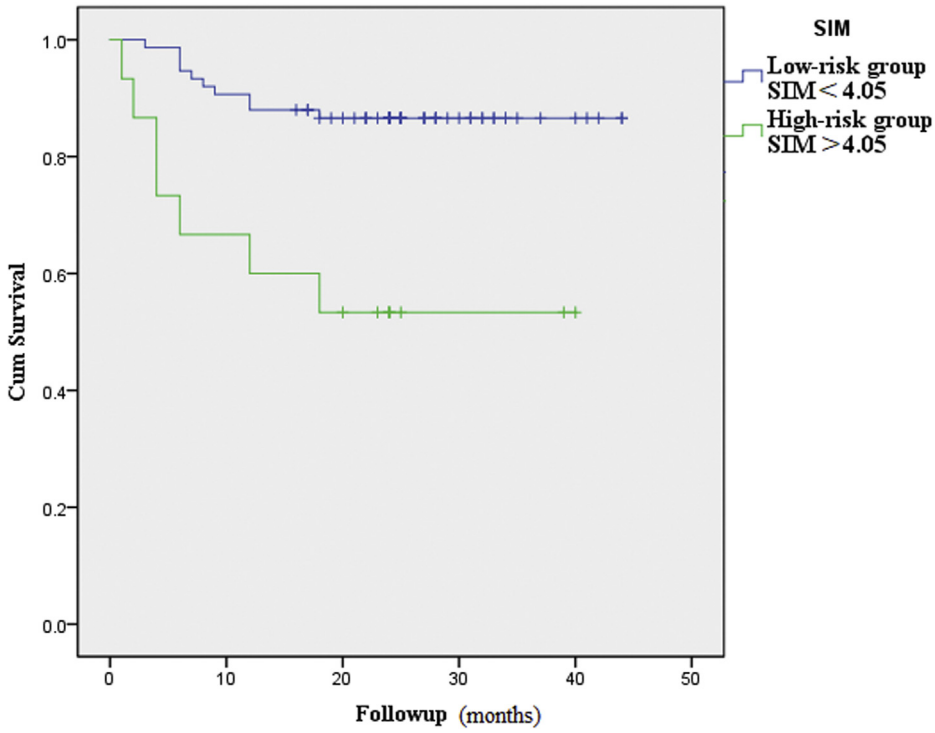

FIGURE 3. Systemic inflammatory marker index (SIM) and overall survival.

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period of time. Selection and sampling bias is reduced owing to the fact that all the patients in the study were in disease stage IV and underwent further postoperative oncologic treatment, with approximately half of patients receiving radiotherapy, as per National Comprehensive Cancer

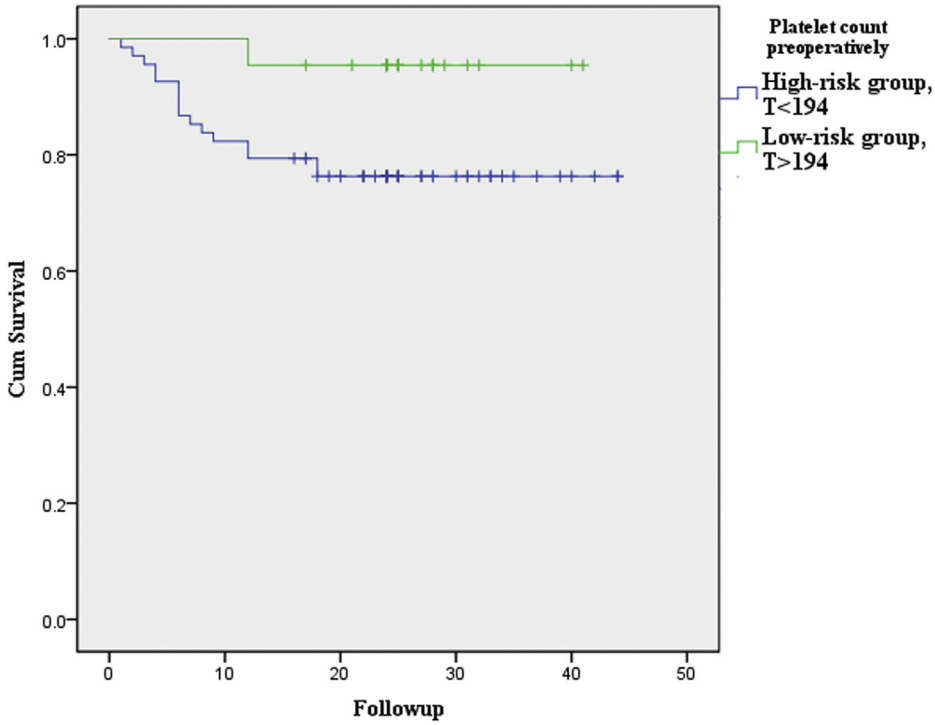

FIGURE 4. Preoperative platelet count and overall survival.

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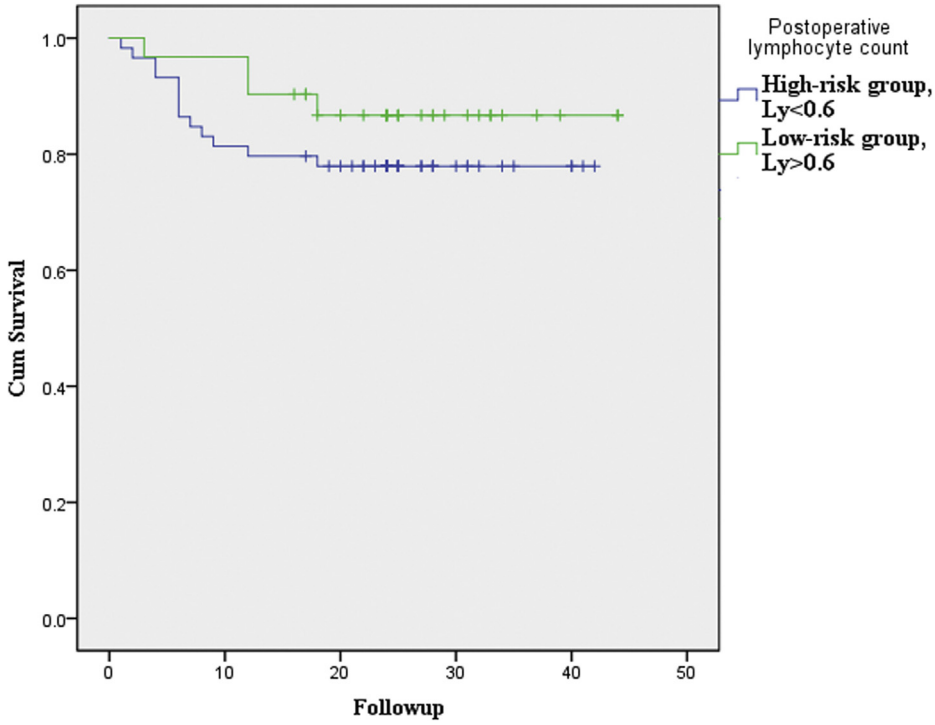

FIGURE 5. Postoperative lymphocyte count and overall survival.

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Network (NCCN) guidelines (41 patients), and the majority receiving chemoradiotherapy (49 patients). We accounted for patient heterogeneity by removing patients over the age of 80 years, who are not candidates for systemic chemotherapy, whereas the median follow-up time was

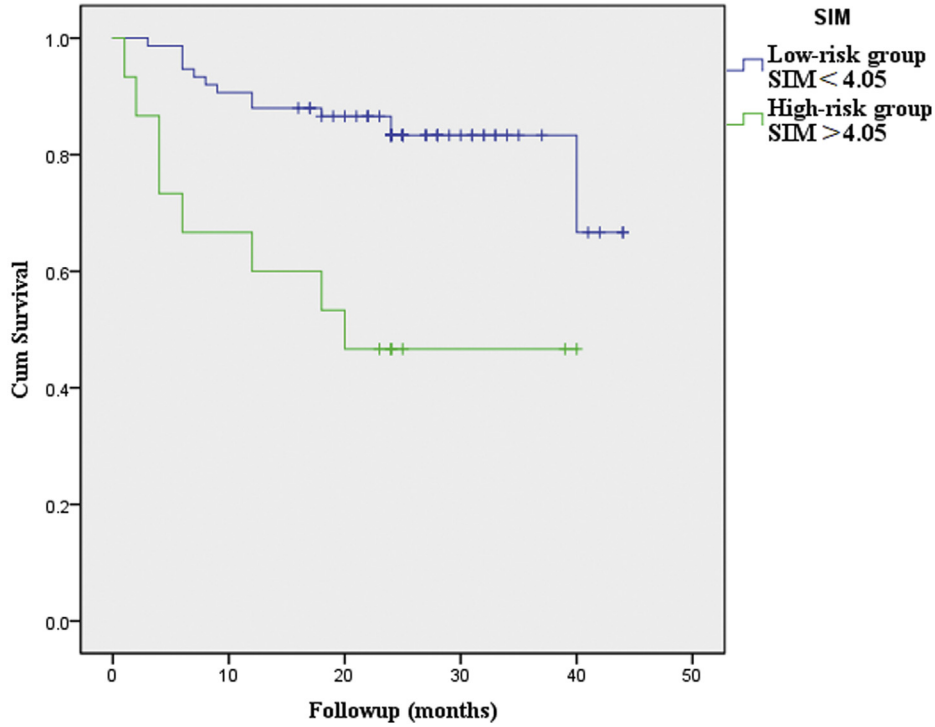

FIGURE 6. Systemic inflammatory marker index (SIM) and disease-free survival.

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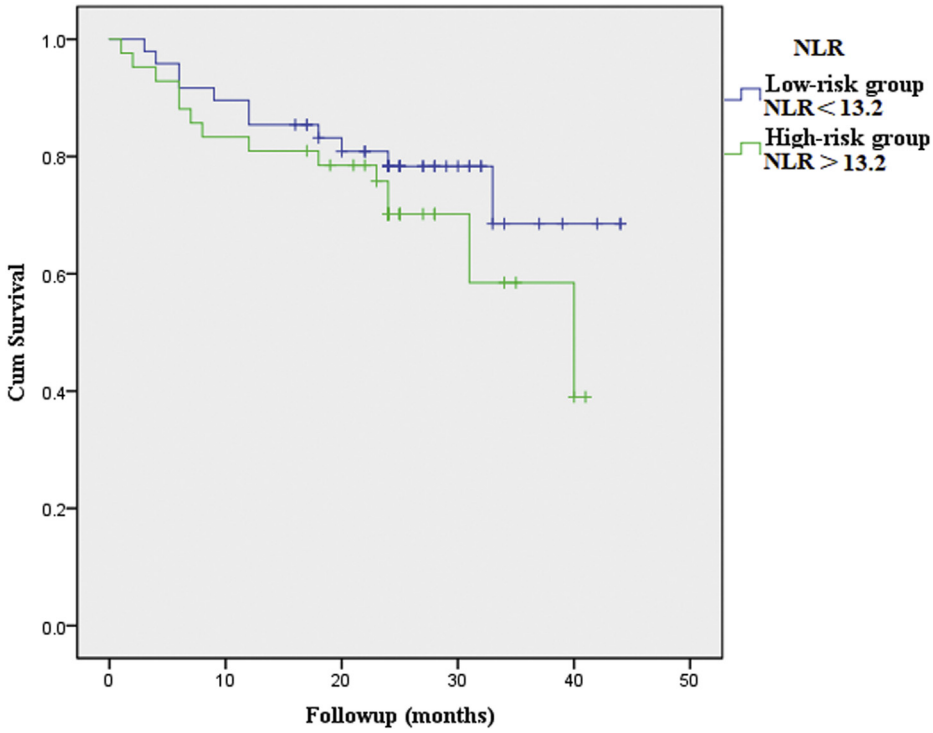

FIGURE 7. Neutrophil-lymphocyte ratio (NLR) and disease-free survival.

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24 months, reducing survival bias. Because the follow-up interval was relatively short, a survival bias related to some patients not receiving chemotherapy would be minimal, whereas the uniformity of data would allow for factors influencing short-term overall and disease-specific survival, such as

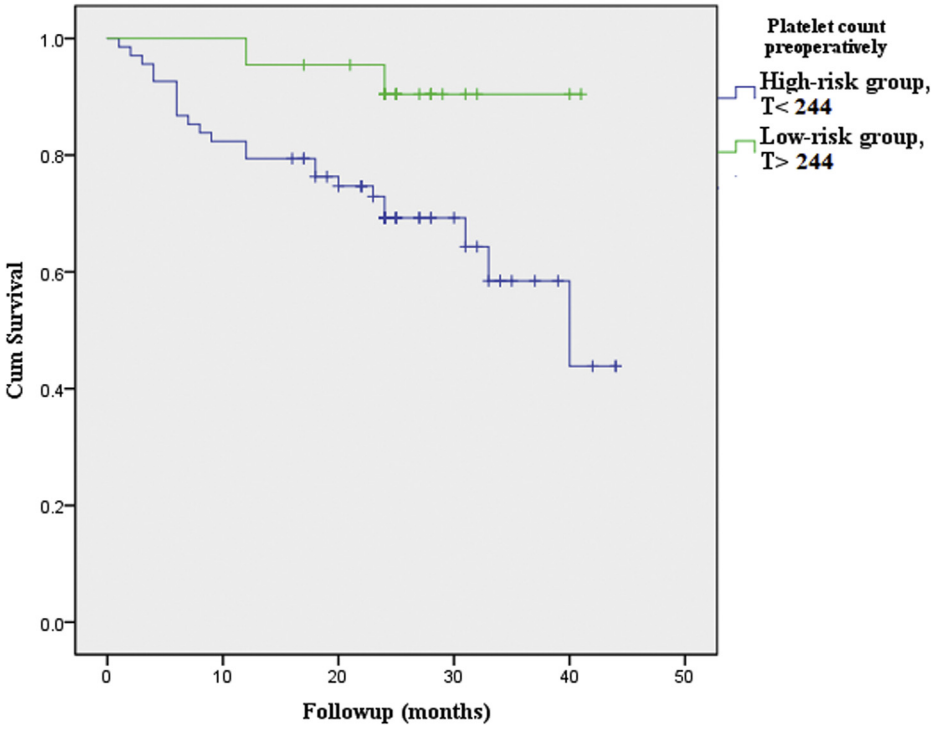

FIGURE 8. Preoperative platelet count and disease-free survival.

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inflammatory indices, to be more significant in the statistical analysis.

This retrospective cohort study identified several systemic inflammatory markers as possible predictors of postoperative complications and poor survival in patients with HNSSC undergoing microvascular reconstruction. An increased dNLR and a decreased postoperative lymphocyte count correlated with occurrence of complications, whereas increased SII and SIM, low preoperative platelet count, and low postoperative lymphocyte count were negatively associated with overall disease survival. Rising SIM, rising NLR, and low preoperative platelet count values were associated with lower DFS. This is a possible link between quantitative disruptions of inflammatory cells, complications, and adverse survival with specific cutoff values. These values may be useful for future analysis and verification in a multicenter study design.

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