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

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Running title: Systemic Inflammatory Markers as Predictors of Outcome in HNSCC

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Abstract

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 HNSCC undergoing free flap reconstruction.

Methods: A retrospective cohort study. The primary predictor variables were inflammatory markers; neutrophil, lymphocyte, monocyte, and platelet count, neutrophil-lymphocyte (NLR), platelet-lymphocyte (PLR), lymphocyte-monocyte (LMR), derived neutrophil-lymphocyte ratio (dNLR), systemic immune-inflammation (SII) 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 median follow-up.

Overall disease survival correlated with SII (p=0.022, cut-off >1005.3, sensitivity 67.1% and specificity 70.6%) and SIM (p=0.0001, cut-off >4.05, sensitivity 90.4% and specificity 41.2%), preoperative platelets (p=0.036, cut-off <194, sensitivity 28.8% and specificity 94.1%) and postoperative lymphocytes (p=0.012, cut-off <0.6, sensitivity 38% and specificity 76.5%), while increased SIM (p=0.042, cut-off >4.05, sensitivity 91.3% and specificity 38.1%), NLR (p=0.031, cut-off >13.2, sensitivity 56.9% and specificity 60%) and preoperative platelets (p=0.006, cut-off <244, sensitivity 52.3% and 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, while dNLR (p=0.013, DF 1, chi-square 6.161, cut-off >2.3) and postoperative lymphocytes (p=0.009, DF 1, chi-square 6.756, cut-off <1) correlated with occurrence of complications.

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

Keywords: inflammatory index; head and neck squamous cell carcinoma; free flap reconstruction; prognosis; outcome; complications

Introduction

Head and neck squamous cell carcinoma (HNSCC) accounts for over 90% of all head and neck cancer, 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 USA cancer cases.[2] Well known risk factors with synergistic effect are sustained exposure to tobacco, tobacco-like products and alcohol consumption.[3,4] The latest, 8th edition of AJCC Cancer Staging Manual now lists HPV-associated oropharyngeal cancer as a separate entity, but TNM 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 (TME) and a complex interplay of host-derived and tumor-derived cytokines generating smoulder 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, NLR, PLR, LMR, dNLR, SIM, SII and Glasgow Prognostic score have been analysed as potential predictive biomarkers that would supplement the current TNM staging and improve data on establishing an accurate prognosis.[6,12,13,14,15,16] Published data reports increases in neutrophil, monocyte and platelet counts to be linked with adverse disease outcome, alongside decrease in lymphocyte counts.[17,18,19]

Exact mechanisms driving the effects of peripheral blood cells on tumorigenesis have yet to be elucidated, as are their cut-off values to be used effectively in a clinical setting. The NLR, LMR 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 analyse 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: 1) to identify associations between systemic inflammatory values and overall (OS) and disease-free survival (DFS) as a primary end point, 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 head and neck squamous cell carcinoma undergoing surgical treatment and simultaneous microvascular free-flap reconstruction at a tertiary surgical centre 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. Inclusion criteria were: 1) patients aged 18–80 years, 2) patients with SCC of oral cavity, oropharynx, hypopharynx, larynx, and the cervical oesophagus, 3) advanced stage (IVa and IVb) disease, 4) no prior oncological or surgical treatment, 5) no inflammatory or haematological disorder affecting the peripheral cell count, 6) complete medical history, 7) minimum follow-up period of one year.

Exclusion criteria were: 1) patients with p16-positive oropharyngeal carcinoma, 2) active preoperative inflammatory disease or infection, 3) 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 prior to surgery. The derived neutrophil-lymphocyte ratio (dNLR) was defined as follows: baseline absolute neutrophil count / (baseline absolute lymphocyte count – baseline absolute neutrophil count) (cells/mm3). (14) The systemic immune-inflammatory index (SII) was calculated as follows: baseline absolute neutrophil count × baseline absolute platelet count / baseline absolute lymphocyte

count (cells/mm3). (14) The systemic inflammatory marker index (SIM) was calculated as follows: baseline absolute neutrophil count × baseline absolute monocyte count / baseline absolute lymphocyte count (cells/mm3).[12]

Covariates were grouped into logical sets; age, sex, TNM category and disease stage, localization of tumor (oropharynx, hypopharynx, hypopharynx and cervical oesophagus, larynx, tongue and base of mouth, paranasal sinus, temporal bone), type of free flap (anterolateral thigh (ALT), radial forearm (RFFF), deep circumflex illiac artery (DCIA), jejunum, vertical rectus abdominis muscle (VRAM), fibular osseocutaneous flap (FOCFF), 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 pre- and postoperative medical data, created through uniform administrative forms. and 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' post-surgery was considered a secondary outcome measure, defined as the appearance of fistula, free flap necrosis, stasis of the flap blood supply, 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 overall and disease-free survival, 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 analysed with a Receiver Operating Characteristic (ROC) analysis and a cut-off value was identified using the Youden J index (measuring the sensitivity and specificity of a dichotomous tested variable) and the patients were divided into low risk (< the cut-off value) and high risk subgroups (> the cut-off value). Associations between possible prognostic factors and survival were analysed 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 © 1993-2010. MedCalc Software bvba Software, Broekstraat 52, 9030 Mariakerke, Belgium).

Results

Of the 90 patients included, 69 were male (76.67 %), and 21 were female (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 of the patients received postoperative oncologic treatment, with 41 patients receiving postoperative radiotherapy, and 49 patients receiving postoperative chemoradiotherapy.

In this study median follow-up time was 24 months; 73 of 91 (66.43%) patients were alive during the median follow-up time (Figure 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, increased dNLR and decreased postoperative lymphocyte count correlated with occurrence of complications (multinomial regression df=1, p=0.013, chi-square=6.161 and p=0.009, chi-square=6.756, respectively). The cut-off 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), postoperative lymphocyte count <1 (94.1% sensitivity and 43.7% specificity) (Table 3). Other variables were not significantly correlated with postoperative complications as the outcome variable. (Table 2).

Overall survival and disease-free survival were used as outcome measures to further test the inflammatory indices identified as possible prognostic factors by Cox multivariate regression, while other variables were covariates. As expected, disease localization (p=0.048) and advanced T category (p=0.01) adversely affected overall and disease-free survival.

Rising SII (p=0.022), rising SIM (p=0.0001), low preoperative platelet count (p=0.036) and low postoperative lymphocyte count (p=0.012) were associated with adverse overall disease survival (Table 4).

Cut-off 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 >1005.3 (67.1% sensitivity and 70.6% specificity, 81.79% positive predictive value, 52.17% negative predictive value), SIM >4.05 (90.4% sensitivity and 41.2% specificity, 75.15% positive predictive value,

68.6% negative predictive value), preoperative platelet count <194 (28.8% sensitivity and 94.1% specificity, 90.57% positive predictive value, 40.18% negative predictive value), postoperative lymphocyte count <0.6 (38% sensitivity and 76.5% specificity, 76.1% positive predictive value, 38.54% negative predictive value) (Table 5).

When analysing the differences in survival subgroups related to the cut-off values, Kaplan–Meier survival curves comparing the low (<1005.3) and high (≥1005.3) SII subgroups, showed a 2-year overall survival rate of 91% and 64% in low- and high-SII groups, respectively (Figure 2). When comparing the low (<4.05) and high (≥4.05) SIM subgroups, the 2-year overall survival rate was 88% and 57% in low- and high-SIM groups, respectively (Figure 3). Preoperative platelet count showed 95% survival in the low risk group (platelet count >194), and 78% in the high risk group (platelet count <194) (Figure 4). Finally, postoperative lymphocyte groups showed a 83% 2-year survival rate in the low risk group (Ly >0.6), and 78% in the high risk group (Ly<0.6) (Figure 5).

Rising SIM (p=0.042), rising NLR (p=0.031) and low preoperative platelet count (p=0.006) were negatively associated with disease-free survival (Table 4).

All other variables were not significantly correlated with overall and disease-free survival as the outcome variable.

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

Cut-off ROC curve value identified for NLR was >13.2 (56.9% sensitivity and 60% specificity). Positive predictive value was 73.7%, and negative predictive value was 41.4%. A

Kaplan–Meier survival curve with a log-rank test comparing the low (<13.2) and high (≥13.2) NLR subgroups, showed the 2-year disease-free survival rate was 80% and 74% in low- and high-NLR groups, respectively (Figure 7).

ROC curve identified preoperative platelet count cut-off value <244 (52.31% sensitivity and 76% specificity). Positive predictive value was 81.1%, and negative predictive value was 44.8%. A Kaplan–Meier survival curve with a log-rank test comparing the low (>244) and high (<244) platelet count subgroups, showed the 2-year disease-free survival rate was 90% and 74% in low- and high-preoperative platelet count groups, respectively (Figure 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 cut-off values may be extrapolated to represent entire patient populations. However, they are particularly useful because they can be obtained through routine pre-operative blood tests, are inexpensive and readily available for all patient populations. In addition, blood markers are not affected by any heterogeneity within the tumor.[14]

Our results suggest that increased dNLR and decreased postoperative lymphocyte count may significantly affect the occurrence of postoperative complications, while rising SII, SIM and 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 regards to patients' characteristics and disease stages.[22,23] The sensitivity and specificity of dNLR were low, but a postoperative lymphocyte count <1 showed a 94.1%

sensitivity rate. Increased dNLR correlated with increased complication rates, suggesting that altered homeostasis affects the inflammatory process.

Wound healing may become disrupted due to 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 (VEGFA) and respond to transforming growth factor β (TGF-β), while also supressing CD8+ T lymphocytes.[7,8,11,12,13] 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 dNLR corresponds to an increased neutrophil count and abnormal wound healing. Due 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 overall survival, calculated as cumulative disease-specific 2-year survival, and with disease-free survival. Rising SII and SIM were associated with overall disease survival, regardless of adjuvant treatment protocols, since 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 disease-free survival. Similar results regarding SIM were shown in several other studies, but no cut-off value was identified to date.[7,23] It has been shown repeatedly that HNSCC patients have elevated NLR compared to healthy controls (>5) with

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

Recently published results support high SII values predicting less favorable overall survival and disease-free survival in patients with oral cavity squamous cell carcinoma after curative resection.[24] Our data suggests that using a cut-off value of 1005.3, 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 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 overall survival rate of 88% and 57% respectively.[27] 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 SIM to be a reliable prognostic factor.[22,27]

Low preoperative platelet count (p=0.036) and low postoperative lymphocyte count (p=0.012) were also negatively associated with survival. Our data showed a 95% overall survival 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 overall survival.[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 cut-off values for platelet count are inconsistent among individual studies, likely resulting in differing conclusions.[24,27,28] When examining the prognostic significance of postoperative lymphocyte count using 0.6 as a cut-off 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 immune-driven tumor suppression. By releasing interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-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 period of time. Selection and sampling bias is reduced due to the fact that all of 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 NCCN guidelines (41 patients), while the majority receiving chemoradiotherapy (49 patients). We accounted for patient heterogeneity by removing patients over the age of 80, that are not candidates for systemic chemotherapy, while the median follow-up time was 24 months, reducing survival bias. Since the follow-up interval was relatively short, a survival bias related to some patients not receiving chemotherapy would be minimal, while the uniformity of data would allow for factors influencing short-term overall and disease specific survival, such as inflammatory indices to be more significant in the statistical analysis.

Conclusion

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. Increased dNLR and decreased postoperative lymphocyte count correlated with occurrence of complications, while 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 disease-free survival. This is a possible link between quantitative disruptions of inflammatory cells, complications and adverse survival with specific cut-off values. These values may be useful for future analysis and verification in a multicentre study design.

Conflict of Interest

The authors have no conflict of interest to declare.

Financial Disclosure

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Ethical approval

This retrospective observational cohort study and its protocol were approved by the University Hospital Center Sestre milosrdnice Bioethics Board, adhering to the Helsinki Declaration of 1983.

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Figures and Legends

Figure 1. Overall survival in the patient cohort. Median follow-up time was 24 months.

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

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

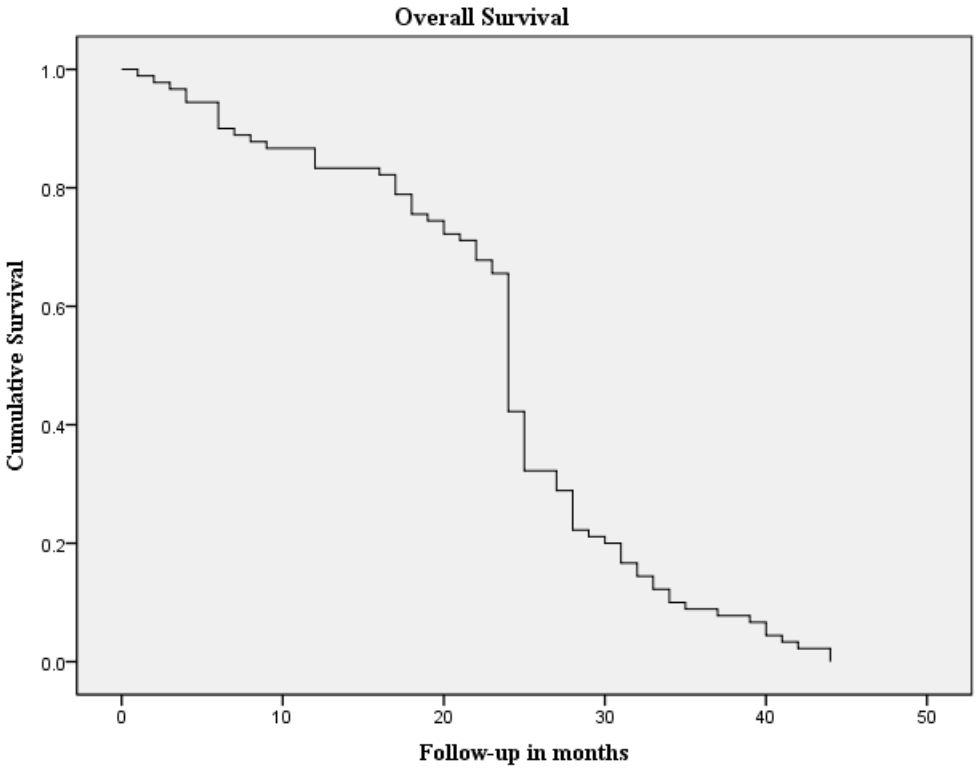
Figure 4. Preoperative platelet count and overall survival.

Figure 5. Postoperative lymphocyte count and overall survival.

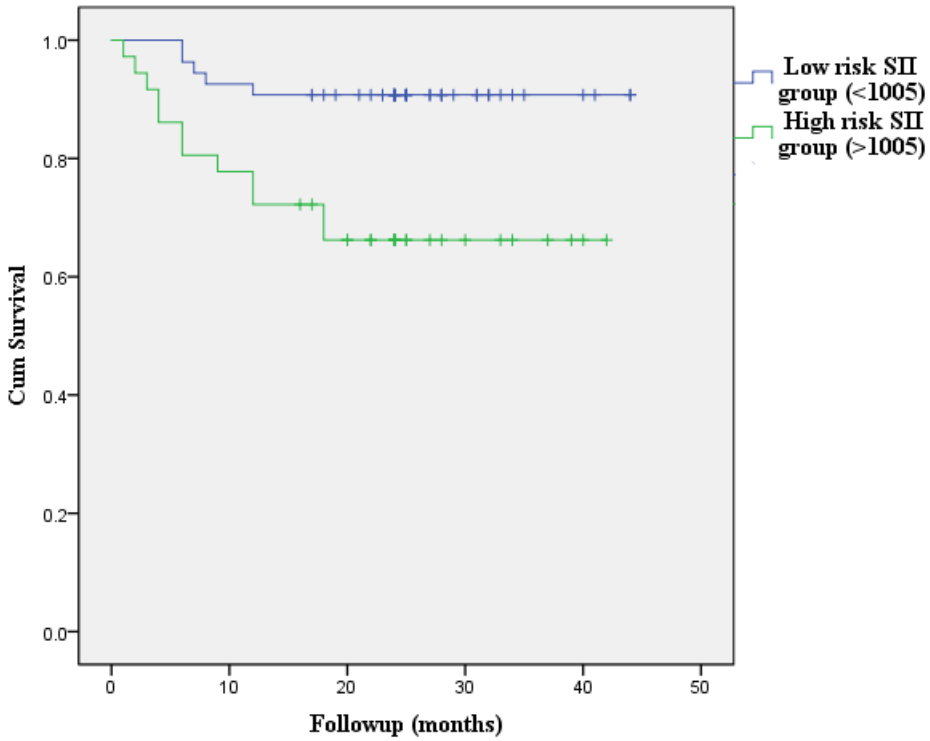
Figure 6. Systemic inflammatory marker (SIM) and disease-free survival.

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

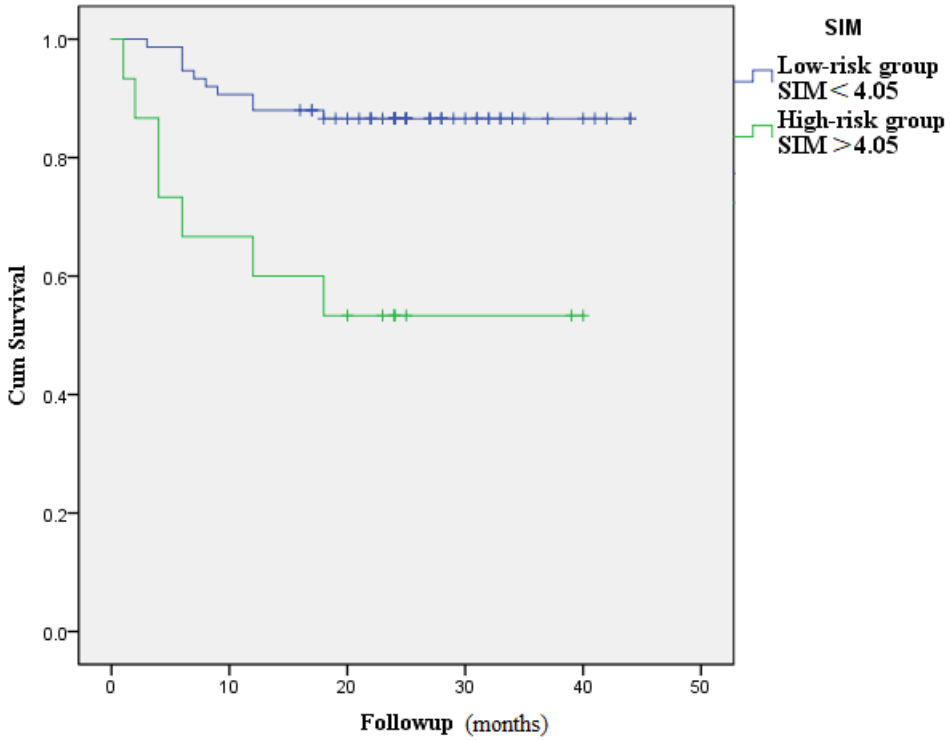
Figure 8. Preoperative platelet count and disease-free survival.

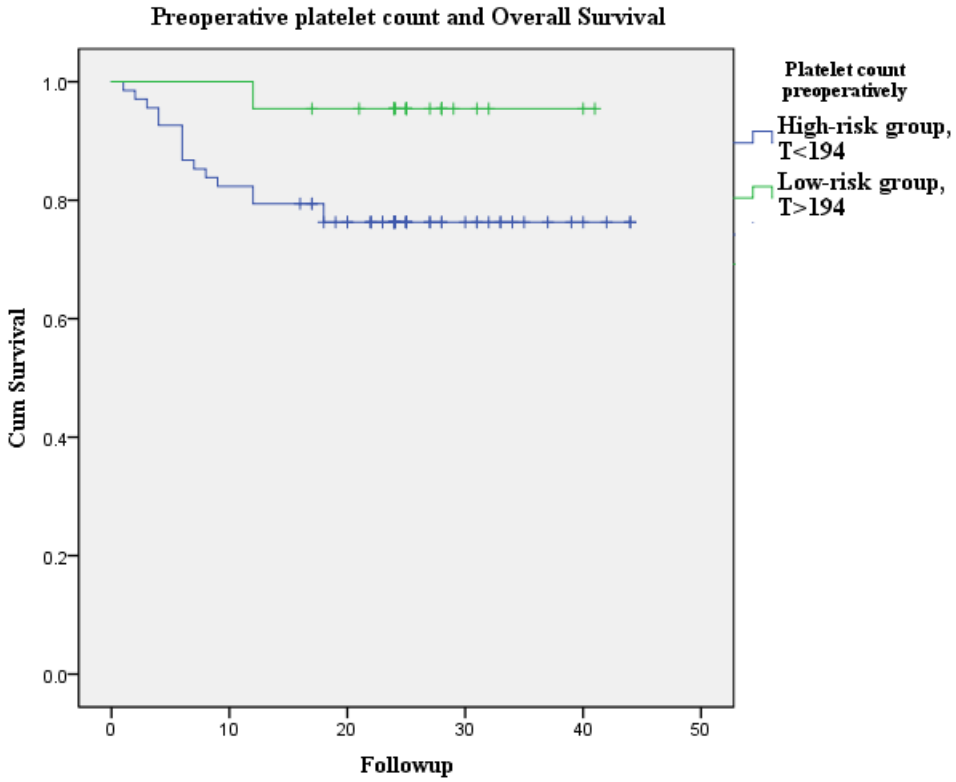

Overall Survival
Cumulative Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
Follow-up in months

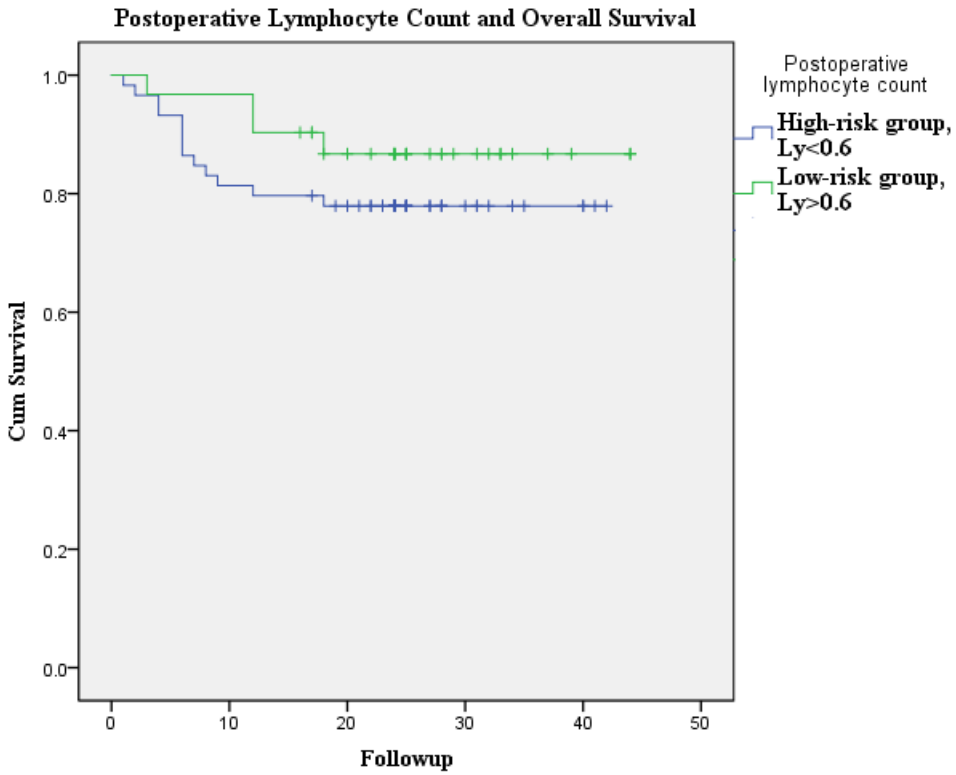
Systemic immune-inflammatory index (SII) and Overall Survival



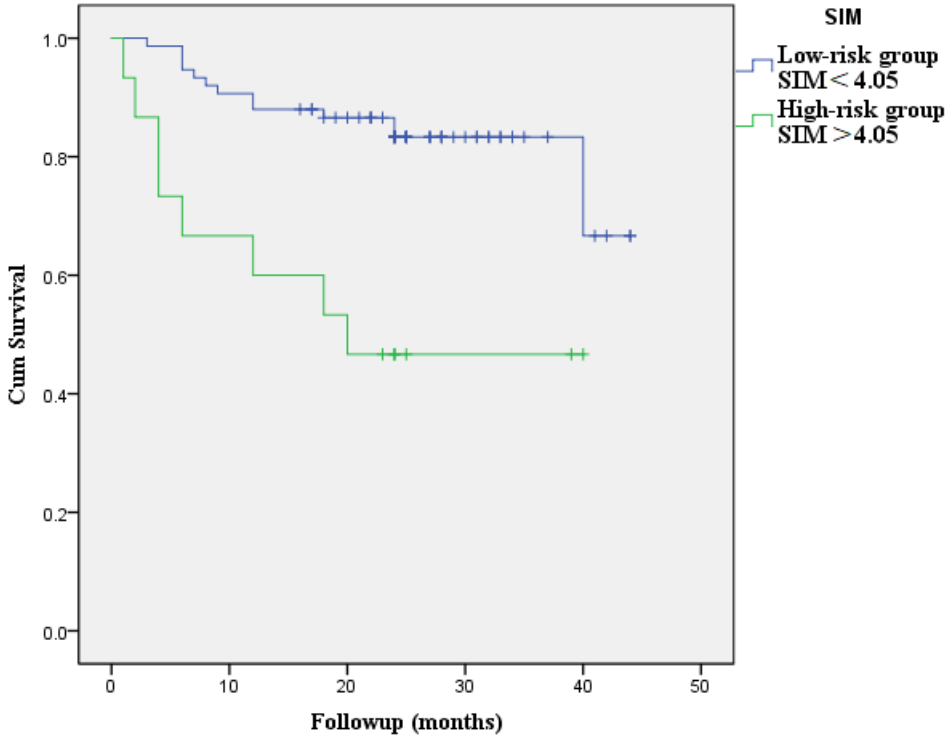
Systemic inflammatory marker (SIM) and Overall Survival



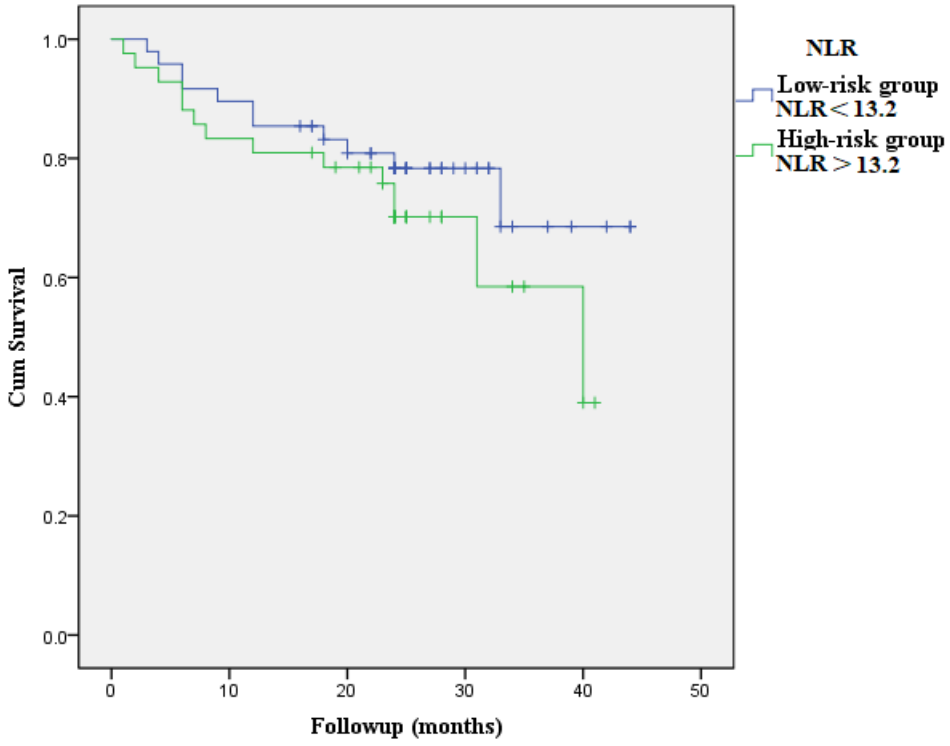

Preoperative platelet count and Overall Survival
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
Followup
Platelet count preoperatively
High-risk group, T<194
Low-risk group, T>194

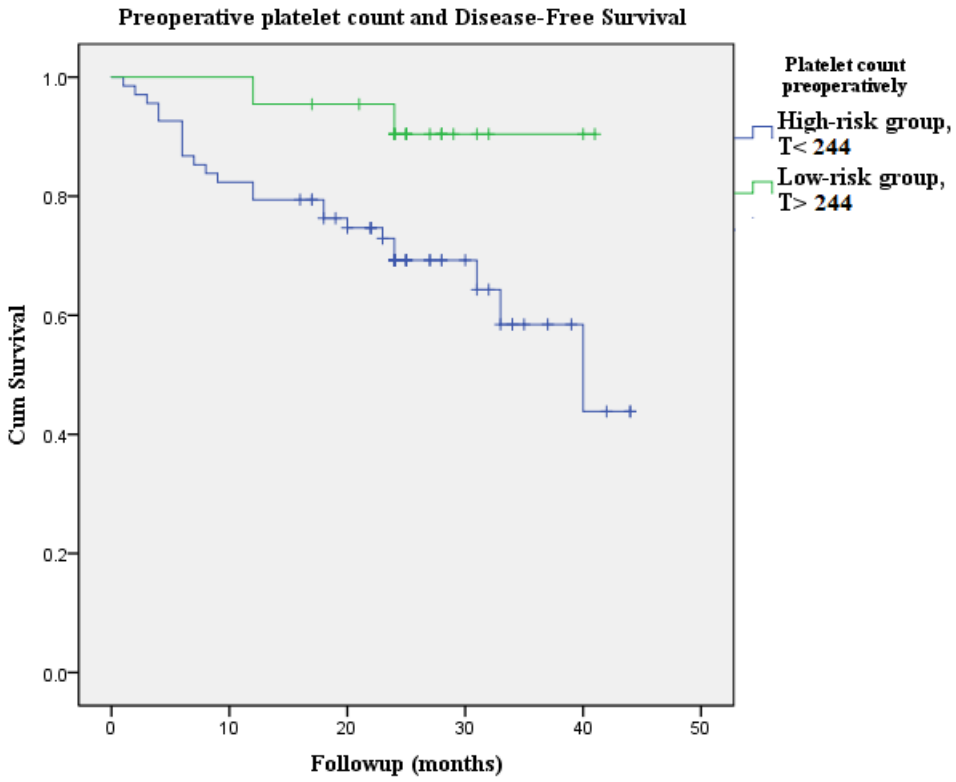

Postoperative Lymphocyte Count and Overall Survival
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
Followup
Postoperative lymphocyte count
High-risk group, Ly<0.6
Low-risk group, Ly>0.6

Systemic inflammatory marker (SIM) and Disease-free Survival



Neutrophil-lymphocyte ratio (NLR) and Disease-free Survival




Preoperative platelet count and Disease-Free Survival
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
Followup (months)
Platelet count preoperatively
High-risk group, T< 244
Low-risk group, T> 244

Tables and Legends

Table 1. Summary of descriptive statistics.

Patients	**n = 90**
Average age (±SD) in years	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%

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*	**0.013**	**0.009**	0.698	0.992	0.650	0.127	0.969	0.639	0.389	0.258	0.969	0.180	0.253
DF, chi-square	1, 6.161	1, 6.756	1, 0.151	1, 0.0	1, 0.218	1, 2.97	1, 0.002	1, 0.962	1, 0.734	1, 1.499	1, 0.002	1, 2.369	1, 1.397
Youden J index (cut-off point)	>2.3	<1											

Table 3. Predictive values of inflammatory markers and their derived indices with regard to postoperative complication occurrence.

Variable	**Cut-off 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

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*	**0.022**	**0.0001**	**0.036**	**0.012**	0.058	0.090	0.114	0.151	0.861	0.171	0.270	0.230	0.106
Youden J index (cut-off point)	>1005.3	>4.05	<194	<0.6									

Disease-free Survival													
Statistical significance *P*	0.726	**0.042**	**0.006**	0.307	0.060	**0.031**	0.140	0.151	0.861	0.070	0.071	0.300	0.106
Youden J index (cut-off point)		>4.05	<244			>13.2							

Table 5. Predictive values of inflammatory markers and their derived indices with regard to 2-year overall survival and disease-free survival.

Variable	Cut-off value	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
2-year overall survival					
SII	>1005.3	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	69

				95% CI 62.83-83.9	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