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Pretreatment peripheral blood leukocytes are independent predictors of survival in oral cavity cancer

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Abstract

Background—Inflammation and immune surveillance evasion are cancer hallmarks. Peripheral blood leukocytes (PBLs) represent both. The aim of this study is to examine PBLs as predictors of outcomes in oral cavity squamous cell carcinoma (OSCC), and to find specific cutoffs with the goal of including PBLs as host factor in patients' preoperative risk assessment.

Methods—Previously established head and neck squamous cell carcinoma (HNSCC) cutoffs were examined in an independent cohort of 1369 OSCC patients. Then optimal OSCC cutoffs were found and validated in the subset of patients with OSCC (n = 119) from the external HNSCC cohort. The PBLs analyzed were neutrophils, monocytes and lymphocytes individually, neutrophil-to-lymphocyte ratio (NLR), and a combined index using all PBLs called Systematic Inflammation Response Index (SIRI).

Results—All parameters were significant predictors of survival using previous cutoffs. However, OSCC cutoffs stratified survival outcomes better. Considering neutrophils $4.8 \times 10^9/L$ as reference, patients with $4.8\text{--}9.1 \times 10^9/L$ neutrophils had 1.536 times higher risk of death (95% CI: 1.295–1.822), and patients with $9.1 \times 10^9/L$ had 3.076 times higher risk (95% CI: 2.170–4.360). All PBLs maintained independent prognostic capacity in multivariable analysis. Neutrophils, NLR, and SIRI were significant predictors of survival when validating OSCC cutoffs in the external validation cohort.

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Cristina Valero: conception and design, collection and assembly of data, data analysis and interpretation, writing, editing. **Daniella K. Zanoni:** data curation and analysis, review. **Marlana R. McGill:** data curation and analysis, project administration. **Ian Ganly:** methodology, supervision, review. **Luc G.T. Morris:** methodology, supervision, review. **Miquel Quer:** supervision, review. **Jatin P. Shah:** supervision, review. **Richard J. Wong:** supervision, review. **Xavier León:** conception and design, data analysis and interpretation, review. **Snehal G. Patel:** conception and design, supervision, writing, editing, review.

Conflict of interest: The authors declare no conflicts of interest pertinent to this work.

Conclusions—Pretreatment peripheral blood neutrophils, NLR and SIRI are the most robust independent predictors of overall survival amongst all PBLs in OSCC. We report externally validated cutoffs that demonstrate the feasibility of including PBLs as host features in the preoperative prognostication of OSCC.

Precis for use in the Table of Contents:

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Keywords

Neutrophils; Monocytes; Lymphocytes; NLR; SIRI; Mouth Neoplasms; Biomarkers

INTRODUCTION

Inflammation and immune surveillance have been recently established as cancer hallmarks, emphasizing the role of the host when analyzing the complexity of cancer, its treatment, and outcomes. Inflammation promotes tumor initiation and progression. Immune surveillance evasion reflects the immune system's failure to detect and eradicate tumor cells, allowing cancer to develop and spread.¹⁻³ It has been shown in different tumor models that higher infiltration by neutrophils and macrophages in the tumor microenvironment is associated with worse oncological outcomes.⁴⁻⁷ On the contrary, higher lymphocyte infiltration is associated with better outcomes.⁸

At a systemic level, the same correlations have been studied in the peripheral blood. The most analyzed parameters in the literature are the pretreatment absolute count of neutrophils, monocytes, and lymphocytes, as well as the ratio between neutrophils and lymphocytes (NLR). These have been reported to be strong predictors of outcomes in a wide range of tumor models, including head and neck tumors.⁹⁻²⁰ Moreover, to integrate the influence of all these variables, Qi et al. have recently proposed an index called Systemic Inflammation Response Index (SIRI), which combines all the leukocytes of interest (neutrophils, monocytes, and lymphocytes), showing that it has prognostic capacity in pancreatic cancer.²¹

Multiple studies have been published analyzing the prognostic capacity of pretreatment peripheral blood leukocytes (PBLs) using different cutoffs found with different methods. However, a limited number of studies aimed to validate established cutoffs or define universal cutoffs that can be used on a daily clinical basis when preoperatively assessing patient's risk for worse outcomes.²²

A previous study showed that higher pretreatment peripheral neutrophils, monocytes, NLR, and lower lymphocytes are associated with worse outcomes in head and neck squamous cell carcinomas (HNSCC).²³ The previous cohort included patients treated both surgically and

non-surgically, and tumors from different head and neck sites, with a limited number of patients with oral cavity tumors (n = 119, 14.4%).

Since oral cavity cancer is mainly treated surgically and is a distinct entity, the first aim of this study is to examine the role of PBLs as predictors of outcomes in an independent cohort of patients with oral cavity squamous cell carcinoma (OSCC). The second aim is to find the optimal cutoffs for OSCC, with the goal of analyzing the feasibility of including PBLs as host features in the preoperative assessment of prognosis for OSCC patients.

MATERIALS AND METHODS

The previous study was performed in 824 patients with biopsy-proven squamous cell carcinoma of the oral cavity, oropharynx, larynx, and hypopharynx diagnosed and treated in Hospital de la Santa Creu i Sant Pau (HSCSP) from 2000 to 2012. Optimal cutoffs for each PBL were found using a recursive-partitioning analysis (RPA), with disease-specific survival (DSS) as the outcome of interest.²³

We first validated these previously reported cutoffs in 1369 patients with OSCC treated at Memorial Sloan Kettering Cancer Center (MSK) from 1998 to 2015 (Group A: test set). The cohort was selected from MSK's departmental database of patients who had a biopsy-proven invasive OSCC treated with primary surgery. Exclusion criteria were synchronous HNSCC, prior treatment of the reference carcinoma, distant metastasis at presentation, and prior history of non-endocrine head and neck cancer. Patients without available leukocyte counts within a month prior to start of treatment were excluded (n = 8). The retrospective study design was approved by MSK's Institutional Review Board.

Optimal cutoffs for the MSK OSCC cohort were identified using an RPA (CART-method) with overall survival (OS) as outcome of interest.²⁴ Recursive-partitioning analyses create a decision tree by finding the optimal cutoffs of the independent variable (leukocyte counts in this study) that will classify the cohort into groups with significant differences in the dependent variable (overall survival in this study). This method provides different number of cutoffs for each independent variable tested depending on the stratification that will more accurately group the cohort in terms of the dependent variable. The PBLs analyzed were the absolute counts of neutrophils, monocytes, and lymphocytes, NLR, and SIRI, the recently published index that combines the 3 absolute counts using the following formula: neutrophils*monocytes/lymphocytes. The established cutoffs from both studies are shown in Supplementary Table 1.

A multivariable analysis for each PBL as predictor of OS was conducted including the clinicopathologic characteristics that were significant in the univariable analysis and the PBL categories obtained with the RPA as independent variables.

The cutoffs identified in the test set (Group A) were externally validated in the subset of 119 patients with OSCC from the previous HSCSP cohort (Group B: validation set). The study was approved by HSCSP's Institutional Review Board. The description of clinicopathologic characteristics and the comparison between Group A and Group B are shown in Table 1. Median values of each PBL for both groups are shown in Supplementary Table 2. The

average count of each PBL according to the clinicopathologic characteristics are shown in Supplementary Table 3.

Student's t-test, Pearson's chi-squared test, or Fisher's exact test were used to compare the clinicopathologic characteristics. We evaluated the relationship between the leukocyte counts and patient characteristics using student's t test or 1-way ANOVA. Survival curves were calculated according to the Kaplan-Meier method, and differences in survival were compared using the log-rank test. Hazard ratios were calculated according to Cox's proportional hazard regression model, also used to perform the multivariable analyses. A *P* value of less than 0.05 was considered statistically significant. All statistical analyses were conducted using SPSS (v25.0, IBM Corporation; Somers, NY) and Stata (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

RESULTS

Description of the test set (Group A; n = 1369)

The clinicopathologic characteristics of the cohort are shown in Table 1 (**Group A**). The mean age was 62 years (range 18–100), and 56.2% were men. History of tobacco and alcohol use was reported by 62.5% and 69.5%, respectively. Comorbidities were recorded according to the Washington University Head and Neck Comorbidity Index (WUHNCI), with 28.6% of the patients having a WUHNCI ≥ 1 at time of diagnosis.²⁵ The most common primary tumor subsite was tongue (53.6%). A total of 47.5% of patients had an advanced pathological stage (III–IV), according to American Joint Committee on Cancer 8th Edition TNM classification.²⁶ Median follow-up time was 39 months (range, 1–221). Five-year OS and DSS were 64.1% and 79.8%, respectively.

Validation of the previous cutoffs in the test set (Group A)

We first analyzed the 5-year OS and DSS in the MSK cohort (n = 1369) using the previously published cutoffs (Supplementary Table 4).²³ All PBLs were significant predictors of OS. Regarding DSS, neutrophils and NLR were significant predictors of outcomes (*P* < 0.001) and monocytes showed nearly significant differences (*P* = 0.099). Neutrophils showed the best discrimination for both OS and DSS. Survival curves according to neutrophil count categories defined by the previous cutoffs are shown in Supplementary Figure 1.

Optimal PBL cutoffs for the test set (Group A; n = 1369)

Differences in OS and DSS using the optimal cutoffs found in our test cohort were analyzed (Table 2). All PBLs categorized by the new cutoffs were found to be good predictors of outcomes for both OS and DSS. Only the absolute count of lymphocytes showed no significant differences in DSS (*P* = 0.246).

Again, neutrophils seemed to be the variable with the best discrimination for OS and DSS, with a 1.5 times higher risk of death (overall and disease-specific) in patients with $4.8\text{--}9.1 \times 10^9/\text{L}$ neutrophils and a 3 times higher risk in patients with $> 9.1 \times 10^9/\text{L}$ compared to patients with neutrophils $< 4.8 \times 10^9/\text{L}$ (*P* < 0.001). Survival curves according to the neutrophil count categories defined by the new cutoffs are shown in Figure 1. OS curves for

the other PBLs are shown in Figure 2, and DSS curves are shown in Supplementary Figure 2. Additionally, receiver operating characteristic (ROC) curves for all the parameters analyzed are shown in Supplementary Figure 3.

Finally, we carried out an individual multivariable analysis for each PBL as predictors of OS. All PBLs maintained their prognostic capacity in the multivariable analysis and were therefore independent prognostic factors. The multivariable analysis including SIRI is shown in Table 3. The multivariable analyses for neutrophils, monocytes, lymphocytes, and NLR are not shown.

Validation of the new cutoffs in the validation set (Group B; n = 119)

In order to validate the new OSCC cutoffs identified upon analysis of the test set (Group A), the cutoffs were tested in the validation set (Group B), which was formed by the subset of patients from HSCSP that had OSCC (n = 119, 14.4%). The clinicopathologic characteristics are shown in Table 1 (**Group B**). Compared to the MSK OSCC cohort (Group A), the validation set (Group B) had a higher percentage of males, patients were older, had more comorbidities, and had higher stage tumors. Regarding treatment, Group A's inclusion criteria only considered primary surgically treated patients. On the other hand, Group B considered all treatment modalities, where 25% of patients were treated non-surgically, and 6% of patients had palliative treatment.

We analyzed if there were differences in OS using the new cutoffs from Group A in the validation set (Group B). The cutoffs for neutrophils, NLR, and SIRI reached statistically significant differences ($P < 0.001$). Monocytes and lymphocytes did not, even though there were trends for both. Among all parameters analyzed, SIRI was the factor that had the best balance in the number of patients included in each category using the new cutoffs, emphasizing that patients in the highest category (SIRI = 1.9) had 3.069 times higher risk of death (95% CI: 1.655–5.691), compared to patients in the lowest category (SIRI = 1.0) (Table 4). Survival curves are shown in Supplementary Figure 4.

DISCUSSION

It has been shown in several studies that PBLs predict oncological outcomes in various tumor models, including OSCC.^{9–20} However, these biomarkers have not gained acceptance for routine use in preoperative prognostication. To add a new factor as a widely used prognostic indicator, the variable must be universally evaluable, easily available, reproducible, have a low cost, and be easy to standardize. PBLs meet all these criteria. The main challenge is to set the optimal cutoffs that can be used universally. To our knowledge, only Cho et al. have tried to set the optimal cutoffs for HNSCC.²² Our aim was to establish the utility of pretreatment PBLs as prognostic factors in OSCC and to find optimal cutoffs that can be translated to routine clinical use.

To evaluate the prognostic capacity of PBLs in OSCC, the previously published cutoffs for HNSCC accurately predicted OS in the test set (Group A). When analyzing DSS, lymphocytes did not show a significant prognostic capacity. This correlated with the previous findings, where lymphocytes had a limited prognostic capacity.

Since OSCC is a separate entity among HNSCC, and is mainly treated with primary surgery, we believe that specific cutoffs for OSCC should be established. In the previous study, there were limited OSCC within the cohort (n = 119, 14.4%), and only 70% of them were primarily surgically treated.²³ Therefore, we decided to define optimal cutoffs for OSCC in a large series of 1369 OSCC treated with primary surgery.

Additionally, we included SIRI in the analyses, an index defined by Qi et al., which combines all PBLs.²¹ We agree with these authors that incorporating the value added by each leukocyte count makes an even more integrative biomarker than analyzing the individual counts. A limited number of studies have been published analyzing the prognostic capacity of SIRI.^{27–31} To the best of our knowledge, this is the first study analyzing SIRI as a prognostic factor in a large series of OSCC.

When analyzing the prognostic capacity of PBLs using the new cutoffs, we obtained similar results to the previous study.²³ Neutrophils, monocytes, NLR, and SIRI were consistent predictors of OS and DSS. Lymphocytes showed a more limited predictive capacity in terms of DSS.

If we compare the optimal cutoffs for the test set (Group A) with the previous cutoffs for HNSCC (Supplementary Table 1), the results for neutrophils were similar. However, for lymphocytes and monocytes, the cutoffs were lower in the OSCC cohort. It follows that NLR cutoffs were higher in the OSCC cohort. Interestingly, the NLR cutoffs were very similar to the optimal NLR cutoffs defined by Cho et al. (2 and 6 vs 2.9 and 5.7 in our study, respectively).²²

Finally, we validated the cutoffs identified in the test set (Group A) using an independent subset of patients with OSCC (Group B) from the previous study. Only neutrophils, NLR, and SIRI predicted outcomes in the validation cohort. To explain the lack of validation of monocytes and lymphocytes, we compared the median values of the PBLs between the 2 groups (Supplementary Table 2). The test cohort (Group A) had a higher median for neutrophils and a lower median for monocytes and lymphocytes. These lower thresholds for monocytes and lymphocytes meant that only 8 patients were eligible in the lowest monocyte category, and 1 patient was eligible in the lowest lymphocyte category. This limited number of patients may explain why the results are not significant, even though we observed the expected trend. The discrepancies in the median values of the leukocytes may also explain the differences in the cutoffs found between the 2 groups.

Baseline differences in PBLs exist depending on clinical characteristics such as age. Valiathan et al. showed that neutrophil and monocyte counts increase with aging, and lymphocyte counts decrease.³² We have seen correlations between PBLs and patient's clinicopathologic characteristics such as age, sex, history of tobacco and/or alcohol consumption, comorbidities, subsite, stage, and histological grade (Supplementary Table 3). As shown in Table 1, there were differences in these clinicopathologic characteristics between the 2 groups that can account for the different cutoffs and median values. These differences between populations are emblematic of the challenge in establishing universal cutoffs for the less robust predictors such as monocytes and lymphocytes. It is also

conceivable that the prognostic influence of leukocytes may be driven by the associations between leukocytes and clinicopathologic characteristics. However, we have shown that all PBLs maintained independent prognostic capacity for OS when analyzed in multivariable analyses including clinicopathologic characteristics.

This study has inherent limitations due to its retrospective nature, and since PBLs values were only analyzed at a single time point prior to initial treatment. PBLs values can be influenced by multiple factors, such as infections, treatment with steroids, or hematologic malignancies. These could not be controlled in this study, and a single snap-shot assessment may not be truly representative of the patient's immune status. Notwithstanding these limitations, our observations are consistent with previously published studies.

The current staging system for OSCC only considers tumor features. Even though risk stratification of patients is overall accurate, there is considerable heterogeneity within staging groups, especially with increasing stage.³³ Differences in host characteristics can partially explain this heterogeneity. Inflammation and immune system evasion are fundamental pillars when trying to understand carcinogenesis, tumor progression, and oncological outcomes. The interplay between these opposing forces is an important host feature that can be easily evaluated using pretreatment PBLs.

Studies developing nomograms including PBLs to predict outcomes in OSCC have recently been used to stratify patients considering both tumor and host factors. However, none of the studies performed an external validation.^{34, 35} The results of our study provide the basis for considering inclusion of PBLs in the preoperative assessment of prognosis in patients with OSCC using a larger cohort of patients, and aims to further analyze and externally validate the feasibility of including PBLs as host factors in a nomogram-based system.³⁶

CONCLUSIONS

Pretreatment peripheral blood neutrophils, NLR and SIRI are the most robust independent predictors of OS amongst all PBLs in OSCC. We report externally validated cutoffs that demonstrate the feasibility of including PBLs as host features in the preoperative prognostication of OSCC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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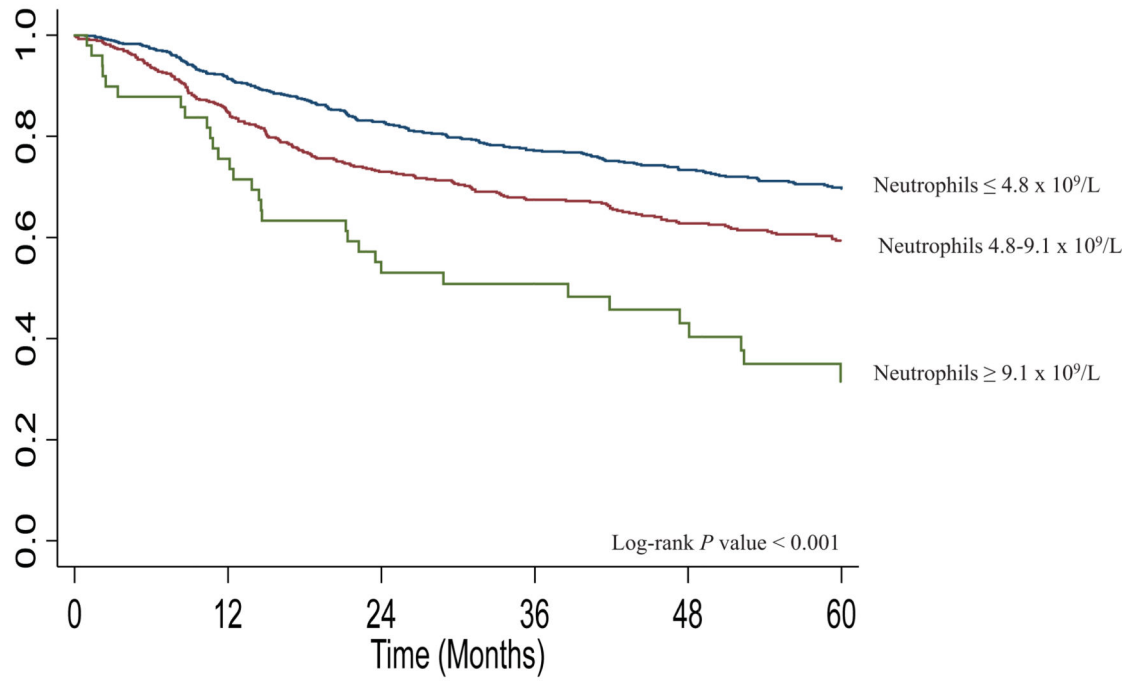
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A

Overall Survival



	Number at risk					
	0	12	24	36	48	60
Neutrophils $\leq 4.8 \times 10^9/L$	770	672	580	487	391	303
Neutrophils $4.8-9.1 \times 10^9/L$	549	437	354	290	245	189
Neutrophils $\geq 9.1 \times 10^9/L$	50	37	25	20	16	9

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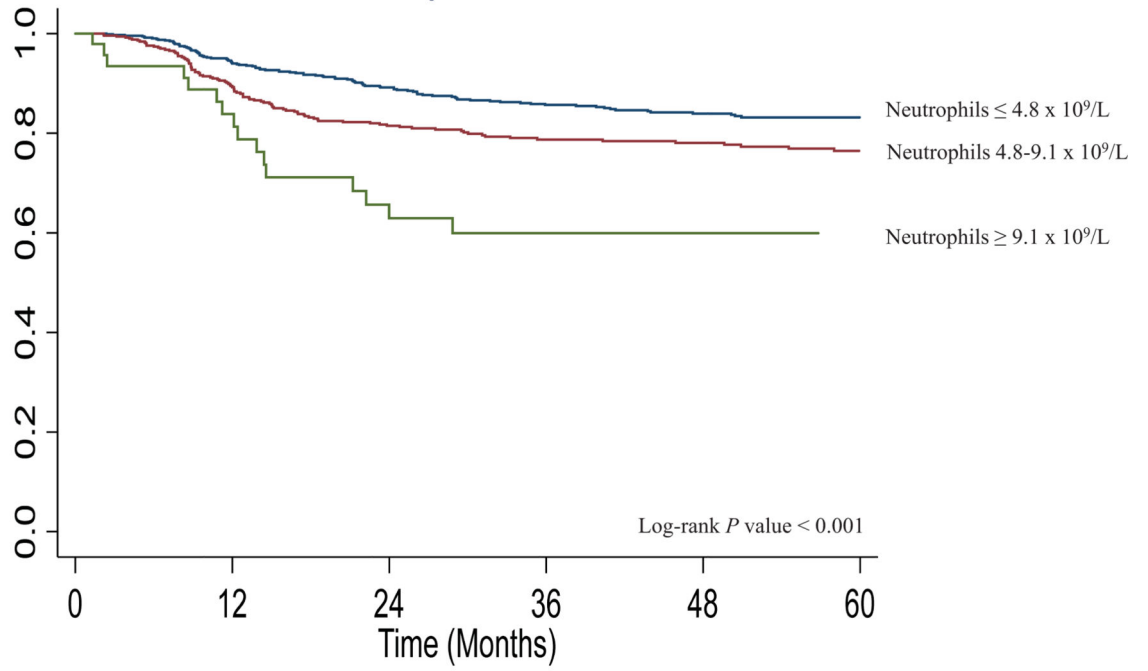
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B

Disease-Specific Survival

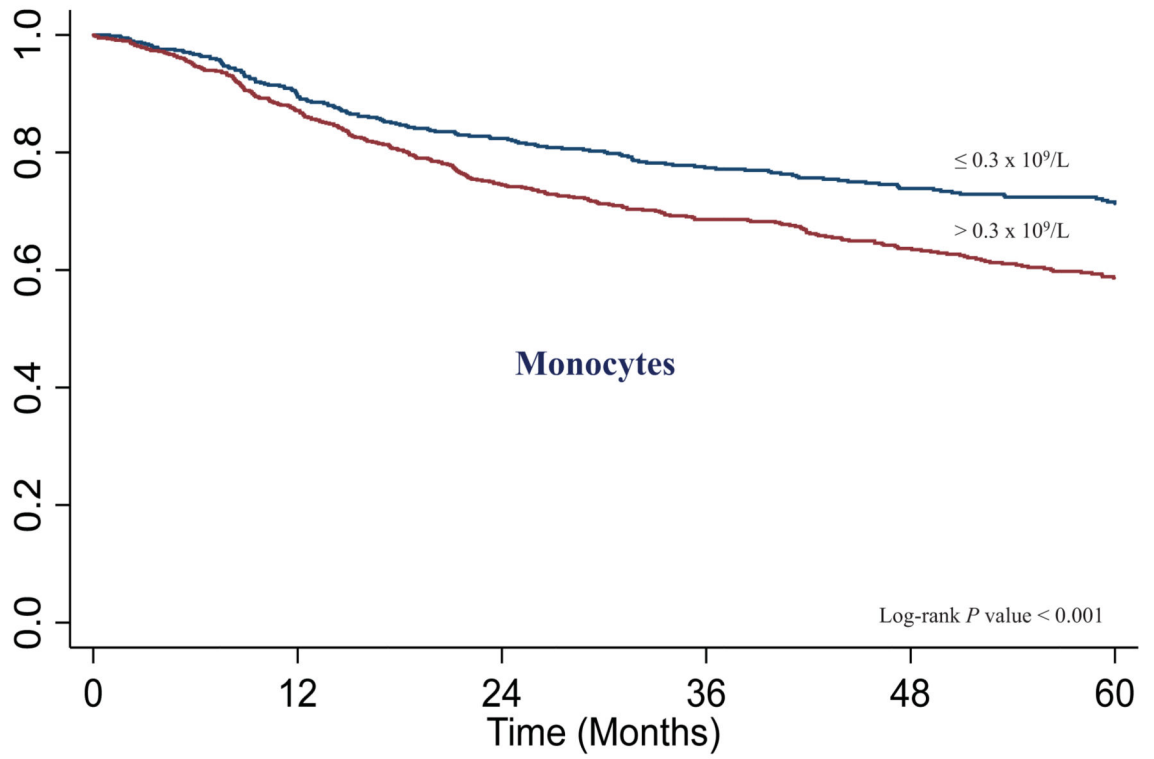


	Number at risk					
	0	12	24	36	48	60
Neutrophils $\leq 4.8 \times 10^9/L$	770	639	538	442	349	271
Neutrophils $4.8-9.1 \times 10^9/L$	549	407	328	261	218	159
Neutrophils $\geq 9.1 \times 10^9/L$	50	34	23	15	9	6

Figure 1. (a) Overall survival, and (b) disease-specific survival in Group A according to neutrophil count categories defined by the new oral cavity cutoffs

A

Overall Survival



Number at risk

Monocytes $\leq 0.3 \times 10^9/L$	577	489	428	371	316	258
Monocytes $> 0.3 \times 10^9/L$	792	657	531	426	336	243

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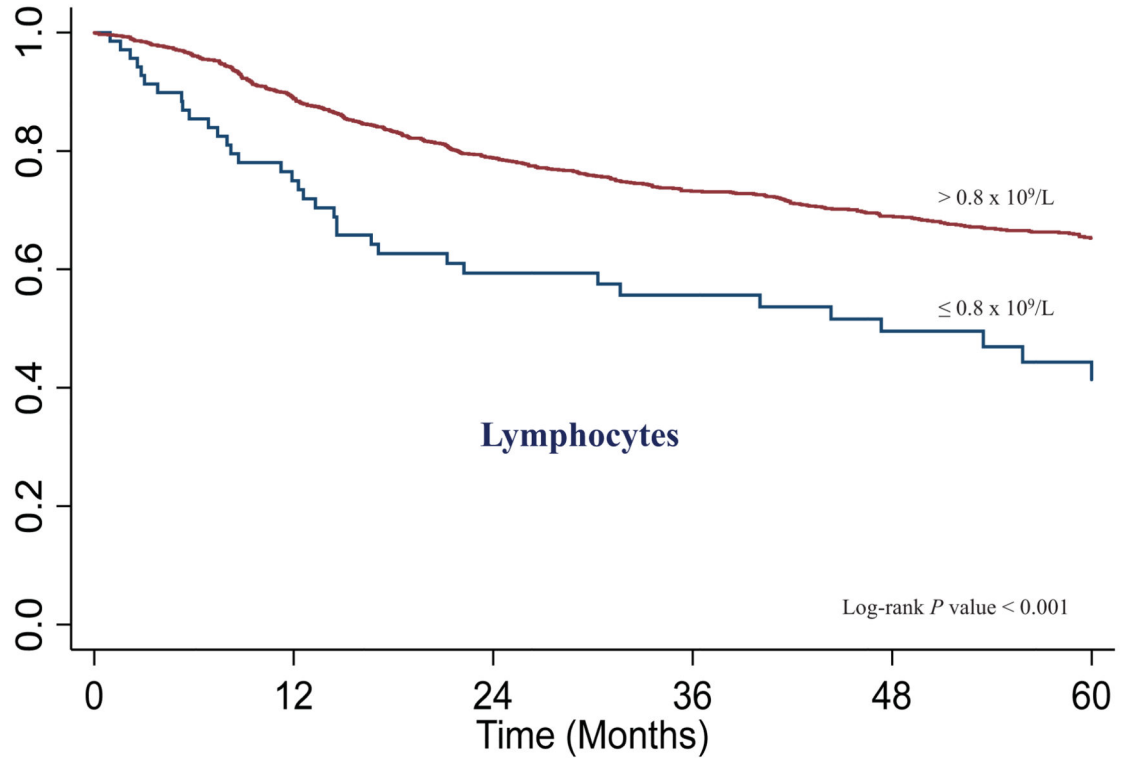
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B

Overall Survival



Number at risk		0	12	24	36	48	60
Lymphocytes $\leq 0.8 \times 10^9/L$	69	49	36	28	23	14	
Lymphocytes $> 0.8 \times 10^9/L$	1300	1097	923	769	629	487	

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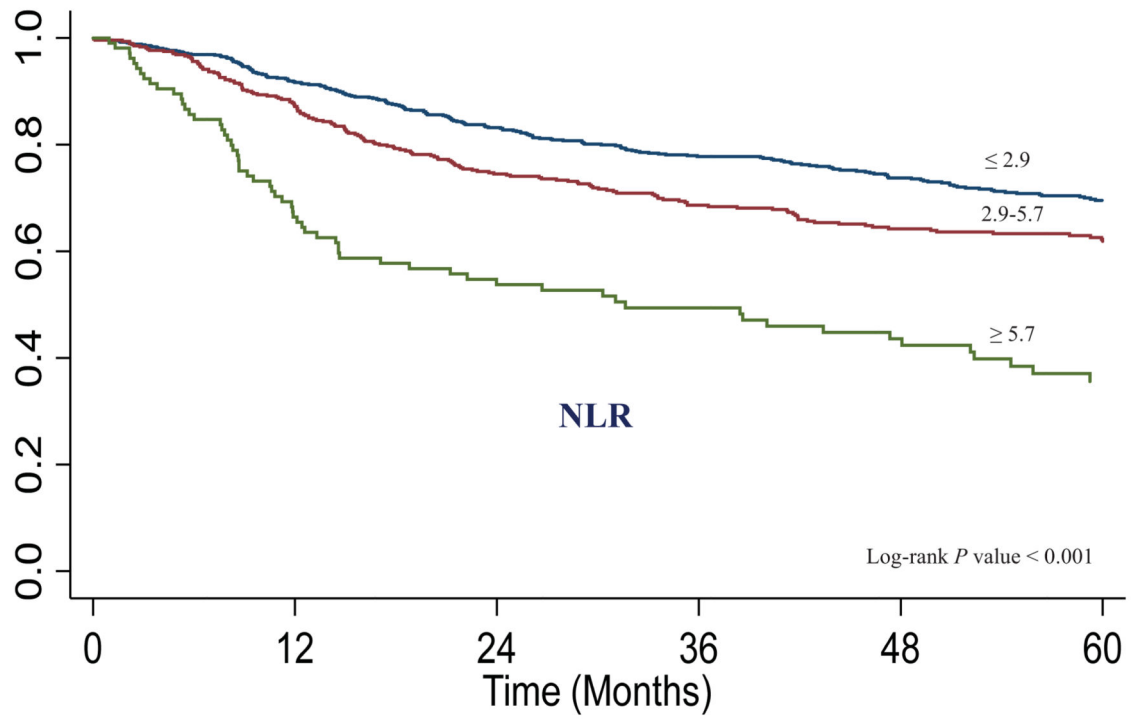
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C

Overall Survival

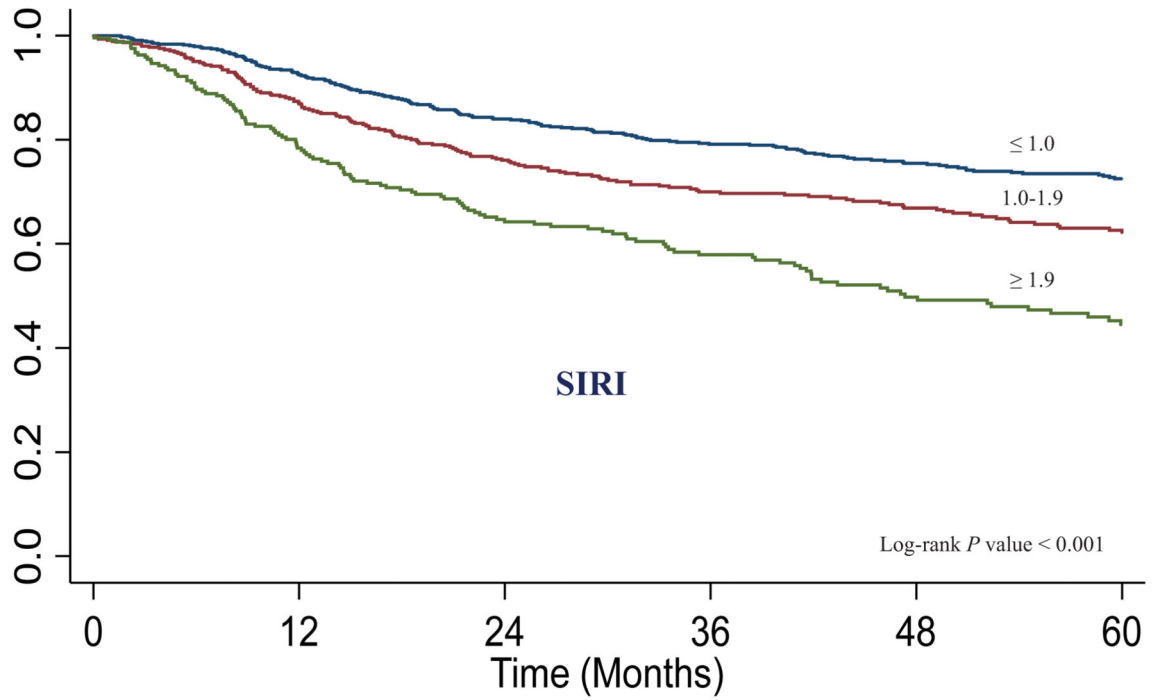


Number at risk

	0	12	24	36	48	60
NLR ≤ 2.9	783	678	581	488	399	307
NLR 2.9-5.7	481	399	326	266	217	170
NLR ≥ 5.7	105	69	52	43	36	24

D

Overall Survival



Number at risk

SIRI ≤ 1.0	676	588	511	439	361	287
SIRI 1.0-1.9	449	371	304	246	207	153
SIRI ≥ 1.9	244	187	144	112	84	61

Figure 2. Overall survival in Group A according to (a) Monocytes, (b) Lymphocytes, (c) Neutrophil-to-Lymphocyte Ratio (NLR), and (d) Systemic Inflammation Response Index (SIRI) categories defined by the new oral cavity cutoffs

Table 1.

Clinicopathologic characteristics of the test set (Group A) and validation set (Group B)

Characteristics	MSK ^a OSCC ^b GROUP A (n = 1369)		HSCSP ^c OSCC GROUP B (n = 119)		P value
	n	%	n	%	
Age Mean (SD ^d , range) years	61.9 (14.4, 18.3–100.4)		66.2 (12.9, 31.1–91.7)		0.002
Sex					0.032
Female	599	43.8%	40	33.6%	
Male	770	56.2%	79	66.4%	
Tobacco					0.301
Never	514	37.5%	39	32.8%	
Ever	855	62.5%	80	67.2%	
Alcohol					0.096
Never	417	30.5%	45	37.8%	
Ever	952	69.5%	74	62.2%	
WUHNCI^e					0.013
0	977	71.4%	72	60.5%	
1	392	28.6%	47	39.5%	
Subsite					< 0.001
Oral tongue	734	53.6%	49	41.2%	
Lower gum	181	13.2%	7	5.9%	
Floor of mouth	162	11.8%	28	23.5%	
Buccal mucosa	105	7.7%	14	11.8%	
Upper gum	93	6.8%	3	2.5%	
Retromolar trigone	68	5.0%	12	10.1%	
Hard palate	26	1.9%	6	5.0%	
pT^f stage (AJCC^g 8th edition)					0.003
pT1	446	32.6%	32	26.9%	
pT2	342	25.0%	35	29.4%	
pT3	258	18.8%	18	15.1%	
pT4	256	18.7%	34	28.6%	
Not recorded	67	4.9%	0	0.0%	
pN^h stage (AJCC 8th edition)					0.014
pN0	936	68.4%	70	58.8%	
pN1	124	9.1%	17	14.3%	
pN2	132	9.6%	21	17.6%	
pN3	158	11.5%	11	9.2%	

Characteristics	MSK ^a OSCC ^b GROUP A (n = 1369)		HSCSP ^c OSCC GROUP B (n = 119)		P value
	n	%	n	%	
Not recorded	19	1.4%	0	0.0%	
Overall stage (AJCC 8th edition)					0.013
Stage I	406	29.7%	28	23.5%	
Stage II	241	17.6%	22	18.5%	
Stage III	210	15.3%	21	17.6%	
Stage IV	441	32.2%	48	40.3%	
Not recorded	71	5.2%	0	0.0%	
Grade					< 0.001
Well differentiated	231	16.9%	30	25.2%	
Moderately differentiated	870	63.6%	85	75.4%	
Poorly differentiated	204	14.9%	4	3.4%	
Not recorded	64	4.7%	0	0.0%	
Treatment					< 0.001
Surgery	851	62.2%	53	44.5%	
Surgery + radiotherapy	394	28.8%	23	19.4%	
Surgery + chemoradiotherapy	124	9.1%	6	5.0%	
Radiotherapy/chemoradiotherapy	0	0.0%	30	25.2%	
Palliative	0	0.0%	7	5.9%	

^a-MSK: Memorial Sloan Kettering;

^b-OSCC: oral cavity squamous cell carcinoma;

^c-HSCSP: Hospital de la Santa Creu i Sant Pau;

^d-SD: standard deviation;

^e-WUHNCI: Washington University Head and Neck Comorbidity Index;

^f-pT: pathological tumor;

^g-AJCC: American Joint Committee on Cancer;

^h-pN: pathological nodal

Table 2.Survival outcomes in Group A patients according to leukocyte counts using the new specific OSCC^a cutoffs

	Number of patients (n=1369)	5-year OS ^b %	HR ^c (95% CI ^d)	P value	5-year DSS ^e %	HR (95% CI)	P value
Neutrophils^f							
4.8	770	69.7	1	< 0.001	83.2	1	< 0.001
4.8–9.1	549	59.4	1.536 (1.295–1.822)		76.4	1.539 (1.185–1.999)	
9.1	50	31.5	3.076 (2.170–4.360)		59.9	3.069 (1.816–5.186)	
Monocytes^f							
0.3	577	71.3	1	< 0.001	83.3	1	0.014
> 0.3	792	58.6	1.473 (1.240–1.749)		76.9	1.387 (1.068–1.802)	
Lymphocytes^f							
0.8	69	41.4	1	< 0.001	75.6	1	0.246
> 0.8	1300	65.3	0.427 (0.314–0.579)		80.0	0.709 (0.396–1.267)	
NLR^f							
2.9	783	69.5	1	< 0.001	83.1	1	< 0.001
2.9–5.7	481	61.9	1.376 (1.151–1.646)		77.8	1.462 (1.114–1.919)	
5.7	105	35.6	3.083 (2.396–3.967)		61.6	2.941 (1.976–4.377)	
SIRI^g							
1.0	675	72.5	1	< 0.001	84.0	1	< 0.001
1.0–1.9	450	62.2	1.543 (1.273–1.871)		79.0	1.404 (1.046–1.885)	
1.9	244	44.5	2.485 (2.017–3.061)		67.9	2.261 (1.644–3.111)	

^a-OSCC: oral cavity squamous cell carcinoma;^b-OS: overall survival;^c-HR: hazard ratio;^d-CI: confidence interval;^e-DSS: disease-specific survival;^f-NLR: neutrophil-to-lymphocyte ratio;^g-SIRI: Systemic Inflammation Response Index.^f: Units × 10⁹/L

Table 3.Multivariable analysis in Group A including SIRI^d as independent variable for predicting overall survival

Variable	Univariable analysis			Multivariable analysis		
	HR ^b	95% CI ^c	P value	HR	95% CI	P value
Age			< 0.001			< 0.001
60 years	1			1		
> 60 years	2.017	1.688–2.410		1.904	1.569–2.311	
Sex			0.490			
Female	1					
Male	0.943	0.800–1.113				
Tobacco use			0.004			0.841
Never	1			1		
Ever	1.297	1.089–1.545		1.020	0.841–1.237	
Alcohol use			0.269			
Never	1					
Ever	0.906	0.759–1.080				
WUHNCI^d			< 0.001			0.078
0	1			1		
1	1.614	1.359–1.917		1.187	0.981–1.436	
Vascular invasion			< 0.001			0.080
Absent	1			1		
Present	2.119	1.713–2.621		1.242	0.975–1.583	
Perineural invasion			< 0.001			0.013
Absent	1			1		
Present	2.143	1.806–2.543		1.310	1.060–1.620	
Margin status			< 0.001			0.001
Negative	1			1		
Close	1.531	1.252–1.871		1.282	1.025–1.603	
Positive	2.962	2.287–3.836		1.794	1.317–2.445	
Histologic grade			< 0.001			0.613
Well differentiated	1			1		
Moderately differentiated	1.542	1.207–1.970		1.149	0.863–1.531	
Poorly differentiated	2.203	1.647–2.946		1.174	0.826–1.670	
pT^e status (AJCC^f 8th Edition)	1		< 0.001	1		< 0.001
pT1	1.632	1.266–2.104		1.323	1.001–1.749	
pT2	2.582	2.008–3.320		1.543		

Variable	Univariable analysis			Multivariable analysis		
	HR ^b	95% CI ^c	P value	HR	95% CI	P value
pT3	4.076	3.212–5.173		2.183	1.129–2.111	
pT4					1.588–3.001	
pN^g status (AJCC 8th Edition)			< 0.001			< 0.001
pN0	1			1		
pN1	1.527	1.148–2.031		1.622	1.179–2.232	
pN2	2.206	1.710–2.846		2.138		
pN3	5.461	4.409–6.765		3.628	1.578–2.896 2.708–4.860	
Adjuvant treatment			< 0.001			< 0.001
None	1			1		
Radiotherapy	1.412	1.181–1.689		0.576	0.456–0.727	
Chemoradiotherapy	2.208	1.686–2.892		0.523	0.374–0.733	
SIRI			< 0.001			< 0.001
1.0	1			1		
1.0–1.9	1.543	1.273–1.871		1.323	1.074–1.630	
1.9	2.485	2.017–3.061		1.685	1.329–2.135	

^a- SIRI: Systemic Inflammation Response Index;

^b- HR: hazard ratio;

^c- CI: confidence interval;

^d- WUHNCI: Washington University Head and Neck Comorbidity Index;

^e- pT: pathological tumor;

^f- AJCC: American Joint Committee on Cancer;

^g- pN: pathological nodal.

Table 4.Validation of the cutoffs developed in Group A in the subset of OSCC^a from the previous cohort (Group B)

	Number of patients (n = 119)	5-year OS ^b %	Log-rank P value	HR ^c (95% CI ^d)	P value
Neutrophils^I					
4.8	70	60.8	< 0.001	1	0.002
4.8–9.1	47	37.7		1.578 (0.984–2.531)	
9.1	2	0.0		11.387 (2.622–49.448)	
Monocytes^I					
0.3	8	62.5	0.314	1	0.321
> 0.3	111	49.8		1.797 (0.565–5.712)	
Lymphocytes^I					
0.8	1	0.0	0.250	1	0.275
> 0.8	118	51.1		0.330 (0.045–2.413)	
NLR^e					
2.9	76	65.3	< 0.001	1	< 0.001
2.9–5.7	39	27.2		2.382 (1.465–3.871)	
5.7	4	0.0		7.815 (2.644–23.098)	
SIRI^f					
1.0	33	69.7	< 0.001	1	< 0.001
1.0–1.9	46	59.8		1.292 (0.677–2.464)	
1.9	40	24.0		3.069 (1.655–5.691)	

^a- OSCC: oral cavity squamous cell carcinoma;^b- OS: overall survival;^c- HR: hazard ratio;^d- CI: confidence interval;^e- NLR: neutrophil-to-lymphocyte ratio;^f- SIRI: Systemic Inflammation Response Index.^I: Units × 10⁹/L