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Investigating the Clinical and Prognostic Significance of Pan-Immune-Inflammation Values in Oral Cavity Squamous Cell Carcinoma

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Abstract

The pan-immune-inflammation value (PIV), a newly proposed marker, had not yet been assessed in oral cavity squamous cell carcinoma (OSCC). In this investigation, PIV was computed using the formula (neutrophil count × platelet count × monocyte count) / lymphocyte count, derived from automated hematology analyzer results, among 853 OSCC patients treated from 2005 to 2017. The optimal preoperative cutoff for PIV was determined to be 268 via ROC curve analysis. Statistically significant differences (all $P < 0.05$) were noted between high- and low-PIV groups regarding alcohol use, smoking status, pT stage, pN stage, overall pathological stage, extranodal extension, histological differentiation, depth of invasion, and perineural invasion. Kaplan-Meier estimates and univariate Cox regression demonstrated that higher PIV was significantly associated with inferior overall survival, disease-free survival, locoregional recurrence-free survival, and distant metastasis-free survival (all $P < 0.001$). In multivariate models accounting for various clinical variables, PIV remained an independent prognostic indicator for overall survival ($P = 0.027$, HR: 1.281) and distant metastasis-free survival ($P = 0.031$, HR: 1.274). These findings indicate that elevated PIV correlates with unfavorable clinicopathological characteristics in OSCC and can help forecast poorer post-treatment outcomes, especially overall survival and freedom from distant metastases.

Keywords: Oral cavity, Squamous cell carcinoma, Oan-immune-inflammation value, OSCC, Head and neck

Introduction

Head and neck cancer represents an aggressive malignancy that can be fatal without proper intervention. It ranks as the seventh most prevalent cancer globally, with roughly 700,000 new cases and approximately 350,000 deaths reported in 2018 [1, 2]. The oral cavity is the most common subsite in the head and neck region, and squamous cell carcinoma is the primary histological subtype. For decades, the tumor-node-metastasis (TNM) staging system has provided standard guidance for treatment decisions and outcome assessment in head and neck cancers. Contemporary management of oral cavity squamous cell carcinoma (OSCC) typically centers on upfront surgical resection followed by adjuvant radiotherapy or chemoradiotherapy for individuals displaying high-risk features. Nevertheless, accurate risk stratification remains difficult for certain patients. The five-year relative survival rate for OSCC is only 49%, and many individuals develop locoregional recurrence or distant metastasis [2, 3].

Mounting research has linked cancer progression to systemic inflammatory processes [4-8]. Previous

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investigations, including our own, have demonstrated that composite inflammation-based scores and related indices are tied to multiple adverse prognostic factors and reduced disease-free survival following OSCC therapy [9-11]. In 2020, Fuca *et al*. [12] proposed the pan-immune-inflammation value (PIV) as a novel biomarker. It has demonstrated superior predictive ability compared with other inflammation markers, such as the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio, in metastatic colorectal cancer. Subsequent studies have further confirmed PIV as a robust prognostic tool in various solid tumors [12-17].

Despite its evaluation in multiple cancer types, the relationship between PIV and clinicopathological features, as well as its prognostic significance in head and neck malignancies, has not been clarified. Accordingly, the present study sought to examine associations between PIV and clinicopathological variables in OSCC patients and to assess the utility of PIV in predicting post-treatment survival outcomes through univariate and multivariate analyses.

Materials and Methods

Patients

This retrospective study analyzed clinicopathological information from OSCC patients treated between 2005 and 2017. Consecutive individuals presenting to the otolaryngology department for management of OSCC were included. Exclusion criteria encompassed prior history of any cancer, known distant metastases or second primary tumors identified before therapy, or receipt of neoadjuvant radiotherapy or chemotherapy. The Institutional Review Board of Chang Gung Memorial Hospital approved (Approval number: 201305685A3), and informed consent was secured from participants. Patients were classified as betel nut chewers if they consumed two or more betel nuts daily for at least one year, as smokers if they smoked daily for at least one year, and as alcohol drinkers if they consumed alcohol at least once weekly for six months or longer. PIV was derived from the equation (neutrophil count [10^3/mL] × platelet count [10^3/mL] × monocyte count [10^3/mL])/lymphocyte count [10^3/mL], using data from automated hematology analyzers [12].

All participants were treatment-naïve at enrollment and underwent primary surgical resection. Preoperative evaluation included detailed medical history, physical examination, laboratory tests, chest X-rays, cross-sectional imaging (CT or MRI), liver ultrasound, and positron emission tomography or bone scintigraphy as indicated. Individuals aged 65 years or older were categorized as elderly [10, 11]. Tumor excision was performed with clear margins verified by intraoperative frozen sections, either transorally or via a lip-split approach, accompanied by neck dissection (levels I–III for cN0 or I–V for cN+ disease). Immediate reconstruction was performed using primary closure or flaps, depending on the defect size. Pathological staging was performed according to the 8th edition of the American Joint Committee on Cancer criteria [18, 19]. A multidisciplinary tumor board made adjuvant radiation or chemoradiation decisions, largely aligned with National Comprehensive Cancer Network recommendations. Postoperative radiotherapy (typically 60–75 Gy at 2 Gy per fraction) was recommended for close margins (< 5 mm), perineural invasion, bone involvement, or T3–T4 disease. Chemoradiotherapy was advised for positive margins, extranodal extension (ENE), or multiple pathologically positive nodes. Follow-up occurred every 2–3 months in the first year, every 3–4 months in years 2 and 3, and every 6 months thereafter.

Statistical analysis

Statistical computations were conducted with SAS software (version 9.4; SAS Institute, Cary, NC, USA). Differences in clinicopathological variables between high- and low-PIV groups were assessed using chi-square and Wilcoxon tests. The optimal PIV cutoff was determined using ROC curve analysis, with Youden's J statistic selecting the threshold that maximized the index value. Survival probabilities were visualized via Kaplan–Meier curves and compared with the log-rank test. Univariate and multivariate Cox proportional hazards models were used to evaluate associations between variables and survival. Follow-up extended until August 2021 or patient death. All tests were two-tailed, with $P < 0.05$ considered statistically significant.

Results and Discussion

Patient characteristics and clinicopathological data

The study cohort comprised 853 OSCC patients diagnosed between 2005 and 2017. The average age was 53.5 years, with 780 (91.4%) males. Smoking prevalence was 83.9%, alcohol consumption 68.3%, and betel nut chewing 81.9%. The interval from blood sampling to surgery averaged 4.9 ± 2.8 days. Detailed

clinicopathological features of the OSCC patients are presented in **Table 1**.

Table 1. Baseline clinicopathological characteristics of patients with oral cavity squamous cell carcinoma (n = 853).

Variable	Characteristics
Age (years)	
< 65	713 (83.6%)
≥ 65	140 (16.4%)
Gender	
Male	780 (91.4%)
Female	73 (8.6%)
Personal Habits	
Alcohol consumption	583 (68.3%)
Betel nut chewing	699 (81.9%)
Cigarettes smoking	716 (83.9%)
Tumor site	
Buccal mucosa	323 (37.9%)
Tongue	310 (36.3%)
Others	220 (25.8%)
Overall stage	
I	164 (19.2%)
II	189 (22.2%)
III	129 (15.1%)
IV	371 (43.5%)
pT classification	
T1	194 (22.7%)
T2	286 (33.5%)
T3	91 (10.7%)
T4	282 (33.1%)
pN classification	
N0	547 (64.1%)
N1	116 (13.6%)
N2	188 (22.0%)
N3	2 (0.3%)
PNI	303 (35.6%)
ENE	171 (20.1%)
LVI	64 (7.5%)
DOI ≥ 10 mm	427 (50.1%)
Surgical margin	
< 5 mm	260 (30.5%)
≥ 5 mm	593 (69.5%)
Adjuvant therapy	
Absent	366 (42.9%)
Radiotherapy	164 (19.2%)
Chemoradiotherapy	323 (37.9%)
Neutrophil ($\times 10^3$ μL^{-1}) §	5.5 ± 16.5
Platelets ($\times 10^3$ μL^{-1}) §	258.6 ± 92.0

Monocyte ($\times 10^3$ μL^{-1}) §	0.5 ± 0.2
Lymphocyte ($\times 10^3$ μL^{-1}) §	2.0 ± 0.8
PIV §	410.9 ± 1048.9

Abbreviations: PNI = perineural invasion; ENE = extranodal extension; LVI = lymphovascular invasion; DOI = depth of invasion; PIV = pan-immune-inflammation value. § Mean ± SD.

Correlation of PIV stratification with clinicopathological variables in OSCC patients

Receiver operating characteristic (ROC) analysis was performed, as illustrated in **Figure 1**. Youden's J statistic enabled the division of OSCC patients into high-PIV and low-PIV subgroups. The optimal PIV threshold, corresponding to the highest Youden's index, was determined to be 268, and relevant clinicopathological characteristics were contrasted in **Table 2**. Statistically significant variations emerged in gender, alcohol intake, betel nut use, smoking status, pT category, pN category, overall pathological stage, extranodal extension, histological differentiation, lymphovascular involvement, depth of invasion, and perineural infiltration between patients exhibiting PIV levels ≥ 268 and those with levels < 268 (P-values < 0.001, 0.005, < 0.001, 0.005, < 0.001, < 0.001, < 0.001, < 0.001, 0.006, 0.024, < 0.001, and <0.001, respectively).

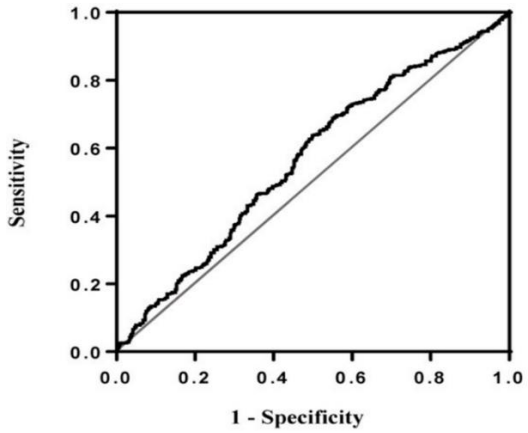


Figure 1. The ROC curve illustrating the prognostic performance of PIV for predicting overall survival, distinguishing between patients with higher (≥ 268) and lower (< 268) PIV values. The area under the curve (AUC) for PIV was 0.566.

Table 2. Baseline clinicopathological characteristics according to the PIV.

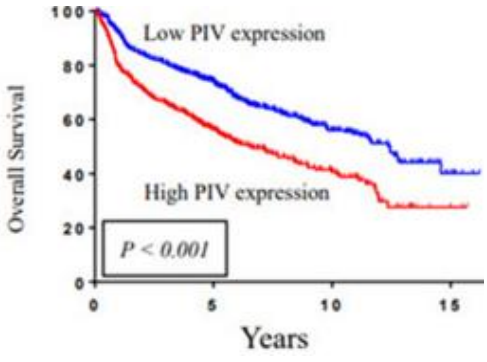
	PIV		
Variable	**≥ 268 (n = 366)**	**< 268 (n = 487)**	**P-value**
Age (years)			
< 65	313 (85.5%)	400 (82.1%)	0.186
≥ 65	53 (14.5%)	87 (17.9%)	
Gender			
Male	350 (95.6%)	430 (88.3%)	< 0.001 *
Female	16 (4.4%)	57 (11.7%)	
Alcohol consumption			
No	97 (26.6%)	173 (35.6%)	0.005 *
Yes	268 (73.4%)	313 (64.4%)	
Betel nut chewing			
No	47 (12.9%)	107 (22.0%)	< 0.001 *
Yes	318 (87.1%)	379 (78.0%)	
Cigarettes smoking			
(−)	44 (12.1%)	93 (19.1%)	0.005 *
(+)	321 (87.9%)	393 (80.9%)	
pT classification			
T1–T2	131 (35.8%)	349 (71.7%)	< 0.001 *
T3–T4	235 (64.2%)	138 (28.3%)	
pN classification			

N0	202 (55.2%)	345 (70.8%)	< 0.001 *
N1–N3	164 (44.8%)	142 (29.2%)	
Overall Stage			
I–II	85 (23.2%)	268 (55.0%)	< 0.001 *
III–IV	281 (76.8%)	219 (45.0%)	
ENE			
Absent	261 (71.3%)	421 (86.5%)	< 0.001 *
Present	105 (28.7%)	66 (13.5%)	
Cell differentiation			
W-D/M-D	311 (85.0%)	443 (91.0%)	0.006 *
P-D	55 (15.0%)	44 (9.0%)	
LVI			
Absent	330 (90.2%)	459 (94.3%)	0.024 *
Present	36 (9.8%)	28 (5.7%)	
PNI			
Absent	198 (54.3%)	351 (72.1%)	< 0.001 *
Present	167 (45.7%)	136 (27.9%)	
DOI			
< 10 mm	114 (31.2%)	312 (64.1%)	< 0.001 *
≥ 10 mm	252 (68.8%)	175 (35.9%)	

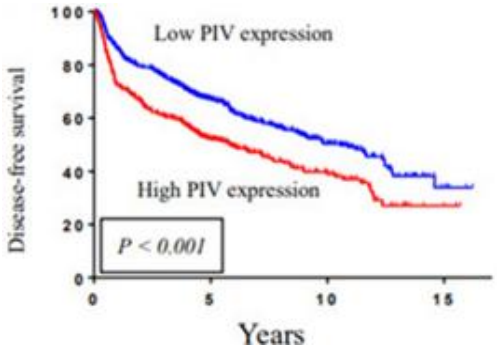
Abbreviations: PNI = perineural invasion; ENE = extranodal extension; LVI = lymphovascular invasion; DOI = depth of invasion; PIV = pan-immune-inflammation value; W-D = well-differentiated, M-D = moderately differentiated, and P-D = poorly differentiated; * statistically significant.

Impact of PIV grouping on survival outcomes among OSCC patients

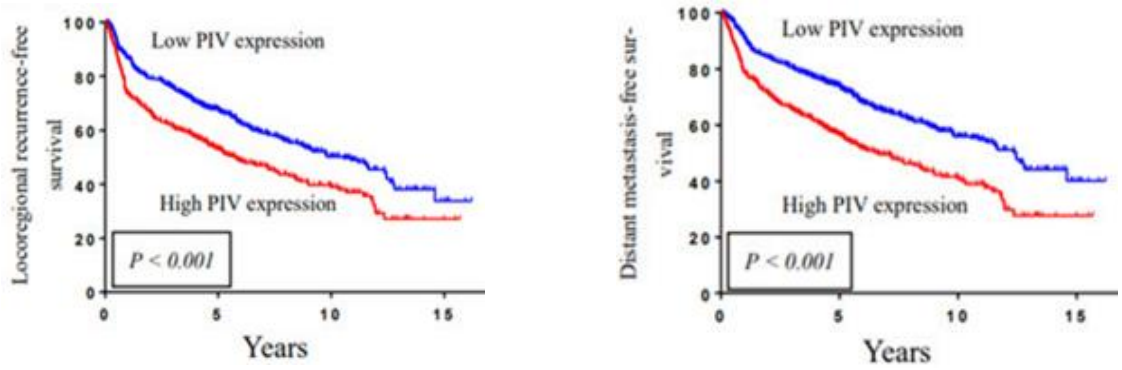
Survival differences between high- and low-PIV cohorts were visualized using Kaplan–Meier curves in **Figure 2**. At a threshold of 268, individuals in the higher PIV group exhibited substantially inferior overall, disease-free, locoregional recurrence-free, and distant metastasis-free survival. According to these Kaplan-Meier plots, the 5-year survival rates for the subgroups separated by this PIV cutoff were as follows: overall survival 74.1% versus 56.4%, disease-free survival 67.1% versus 52.3%, locoregional recurrence-free survival 67.6% versus 53.1%, and distant metastasis-free survival 73.9% versus 56.5% (P < 0.001, < 0.001, < 0.001, and < 0.001, respectively); **(Figure 2)**. The log-rank test determined all p-values.



a)



b)



c) d)

Figure 2. Kaplan-Meier curves reveal the 5-year (a) overall survival, (b) disease-free survival, (c) locoregional recurrence-free survival, and (d) distant metastasis-free survival rates among patient subgroups categorized by PIV using a cutoff of 268 as 74.1% versus 56.4%, 67.1% versus 52.3%, 67.6% versus 53.1%, and 73.9% versus 56.5%, respectively (P < 0.001 for each comparison). The p-values were derived from log-rank testing.

In the univariate Cox proportional hazards analysis, several variables—including age, advanced overall pathological stage (III–IV compared with I–II), narrow surgical margin (< 5 mm versus ≥ 5 mm), presence of extranodal extension, poor cell differentiation (versus good or moderate), positive perineural invasion, greater depth of invasion (≥ 10 mm versus < 10 mm), lymphovascular invasion, lack of adjuvant therapy (versus receipt of radiotherapy or chemoradiotherapy), and high PIV—showed significant associations with overall survival, disease-free survival, locoregional recurrence-free survival, and distant metastasis-free survival **(Table 3)**.

Table 3. Univariate analysis of poor prognostic factors for OS, DFS, LRFS, and DMFS in OSCC patients.

	OS		DFS		LRFS		DMFS	
Variable	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
Age (years)								
< 65	Reference		Reference		Reference		Reference	
≥ 65	1.622	< 0.001 *	1.454	0.001 *	1.459	0.001 *	1.597	< 0.001 *
	(1.275–2.064)		(1.149–1.839)		(1.154–1.846)		(1.254–2.035)	
Gender								
Female	Reference		Reference		Reference		Reference	
Male	0.833	0.275	0.773	0.102	0.773	0.102	0.832	0.269
	(0.601–1.156)		(0.567–1.053)		(0.567–1.053)		(0.599–1.154)	
Overall Stage								
I–II	Reference		Reference		Reference		Reference	
III–IV	2.614	< 0.001 *	2.287	< 0.001 *	2.282	< 0.001 *	2.610	< 0.001 *
	(2.084–3.279)		(1.852–2.824)		(1.848–2.818)		(2.080–3.274)	
Surgical margin								
< 5 mm	Reference		Reference		Reference		Reference	
≥ 5 mm	1.352	0.005 *	1.282	0.016 *	1.279	0.017 *	1.353	0.004 *
	(1.096–1.668)		(1.047–1.571)		(1.045–1.567)		(1.096–1.670)	
ENE								
Absent	Reference		Reference		Reference		Reference	
Present	3.072	< 0.001 *	2.865	< 0.001 *	2.853	< 0.001 *	3.096	< 0.001 *
	(2.471–3.819)		(2.318–3.540)		(2.309–3.526)		(2.490–3.850)	
Cell differentiation								

W-D/M-D	Reference		Reference		Reference		Reference	
P-D	1.746	< 0.001 *	1.745	< 0.001 *	1.751	< 0.001 *	1.758	< 0.001 *
	(1.323–2.305)		(1.337–2.277)		(1.341–2.285)		(1.331–2.320)	
LVI								
Absent	Reference		Reference		Reference		Reference	
Present	1.721	0.001 *	1.631	0.003 *	1.608	0.004 *	1.731	0.001 *
	(1.231–2.406)		(1.177–2.260)		(1.161–2.228)		(1.238–2.420)	
PNI								
Absent	Reference		Reference		Reference		Reference	
Present	1.871	< 0.001 *	1.718	< 0.001 *	1.716	< 0.001 *	1.860	< 0.001 *
	(1.530–2.289)		(1.415–2.084)		(1.414–2.082)		(1.520–2.275)	
DOI								
< 10 mm	Reference		Reference		Reference		Reference	
≥ 10 mm	2.309	< 0.001 *	2.047	< 0.001 *	2.041	< 0.001 *	2.303	< 0.001 *
	(1.877–2.841)		(1.682–2.490)		(1.678–2.484)		(1.871–2.834)	
Adjuvant Tx								
Without	Reference		Reference		Reference		Reference	
With	2.326	< 0.001 *	2.199	< 0.001 *	2.195	< 0.001 *	2.321	< 0.001 *
	(1.868–2.896)		(1.787–2.706)		(1.784–2.701)		(1.864–2.890)	
PIV								
< 268	Reference		Reference		Reference		Reference	
≥ 268	1.723	< 0.001 *	1.531	< 0.001 *	1.521	< 0.001 *	1.717	< 0.001 *
	(1.410–2.105)		(1.264–1.854)		(1.255–1.842)		(1.405–2.099)	

Abbreviations: OS = overall survival; DFS = disease-free survival; LRFS = locoregional recurrence-free survival; DMFS = distance metastasis-free survival; HR = hazard ratio; CI = confidence interval; ENE = extranodal extension; W-D = well-differentiated, M-D = moderately differentiated, and P-D = poorly differentiated; LVI = lymphovascular invasion; PNI = perineural invasion; DOI = depth of invasion; Adjuvant tx = radiotherapy or chemoradiotherapy; PIV = pan-immune-inflammation value; * Statistically significant.

Multivariable analysis, which accounted for age, sex, pathological stage, extranodal extension, perineural invasion, lymphovascular invasion status (positive vs. negative), surgical margins, tumor differentiation, invasion depth, and receipt of adjuvant radiotherapy or chemoradiotherapy, identified PIV as an independent predictor of overall survival as well as distant metastasis-free survival (P = 0.027 and 0.031, respectively); **(Table 4)**.

Table 4. Multivariate analysis of poor prognostic factors for OS, DFS, LRFS, and DMFS in OSCC patients.

	OS		**DFS**		**LRFS**		**DMFS**	
Variable	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
Age (years)								
< 65	Reference		Reference		Reference		Reference	
≥ 65	1.023	< 0.001 *	1.018	< 0.001 *	1.018	< 0.001 *	1.022	< 0.001 *
	(1.014–1.032)		(1.009–1.027)		(1.010–1.027)		(1.013–1.031)	
Gender								
Female	Reference		Reference		Reference		Reference	
Male	0.823	0.257	0.780	0.126	0.783	0.132	0.824	0.260
	(0.588–1.153)		(0.567–1.073)		(0.569–1.077)		(0.589–1.154)	
Overall Stage								
I–II	Reference		Reference		Reference		Reference	
III–IV	1.460	0.025 *	1.292	0.111	1.290	0.114	1.459	0.026 *
	(1.047–2.036)		(0.943–1.770)		(0.941–1.769)		(1.046–2.034)	

ENE								
Absent	Reference		Reference		Reference		Reference	
Present	2.004	< 0.001 *	1.961	< 0.001 *	1.963	< 0.001 *	2.024	<0.001 *
	(1.551–2.589)		(1.530–2.514)		(1.531–2.516)		(1.565–2.617)	
Surgical margin								
< 5 mm	Reference		Reference		Reference		Reference	
≥ 5 mm	1.013$$%(0.816–1.256)	0.910	0.997$$%(0.810–1.227)	0.975	0.994$$%(0.807–1.224)	0.953	1.013$$%(0.816–1.257)	0.904
DOI								
< 10 mm	Reference		Reference		Reference		Reference	
≥ 10 mm	1.468	0.004 *	1.359	0.017 *	1.370	0.014 *	1.467	0.004 *
	(1.126–1.915)		(1.055–1.750)		(1.064–1.764)		(1.124–1.913)	
Cell Differentiation								
W-D/M-D	Reference		Reference		Reference		Reference	
P-D	1.117	0.456	1.169	0.275	1.184	0.237	1.126	0.426
	(0.834–1.497)		(0.883–1.546)		(0.895–1.566)		(0.841–1.509)	
PNI								
Absent	Reference		Reference		Reference		Reference	
Present	1.160	0.221	1.092	0.452	1.088	0.468	1.144	0.268
	(0.914–1.472)		(0.868–1.373)		(0.865–1.369)		(0.901–1.453)	
LVI								
Absent	Reference		Reference		Reference		Reference	
Present	0.873	0.458	0.893	0.525	0.881	0.477	0.880	0.485
	(0.609–1.251)		(0.630–1.266)		(0.622–1.249)		(0.614–1.261)	
Adjuvant tx								
Without	Reference		Reference		Reference		Reference	
With	1.055	0.751	1.174	0.326	1.170	0.337	1.056	0.749
	(0.757–1.472)		(0.852–1.617)		(0.849–1.613)		(0.757–1.472)	
PIV								
< 268	Reference		Reference		Reference		Reference	
≥ 268	1.281	0.027 *	1.165	0.157	1.159	0.170	1.274	0.031 *
	(1.027–1.596)		(0.943–1.438)		(0.939–1.432)		(1.022–1.588)	

Abbreviations: OS = overall survival; DFS = disease-free survival; LRFS = locoregional recurrence-free survival; DMFS = distance metastasis-free survival; HR = hazard ratio; CI = confidence interval; ENE = extranodal extension; DOI = depth of invasion; W-D = well-differentiated, M-D = moderately differentiated, and P-D = poorly differentiated; PNI = perineural invasion; LVI = lymphovascular invasion; Adjuvant tx = radiotherapy or chemoradiotherapy; PIV = pan-immune-inflammation value; * Statistically significant.

A growing body of research suggests that systemic inflammatory responses play a key role in cancer development and progression. Routine blood tests can reveal this inflammation through various markers, including neutrophils, lymphocytes, platelets, and monocytes [4-8]. Ratios derived from these parameters have been widely used to forecast patient prognosis, and earlier investigations have explored combinations of these biomarkers to enhance predictive accuracy, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic inflammation score [11]. Elevated neutrophil counts or reduced lymphocyte counts can inhibit lymphokine-activated killer cell activity, while lymphocytopenia often signals broader immune suppression that negatively impacts survival [20, 21]. Consequently, elevated pretreatment NLR values may create an environment conducive to tumor proliferation, invasiveness, and relapse [22]. Platelets have also been shown to impair natural killer cell function, thereby modulating immune responses

[21]. Similarly, higher PLR levels exert effects comparable to NLR on clinical outcomes, with some evidence suggesting that PLR may outperform NLR in predicting disease-free and overall survival, positioning it as an independent prognostic marker in oral squamous cell carcinoma (OSCC) [21-23].

Beyond NLR and PLR, Chang *et al*. [24] developed the systemic inflammation score for prognostic assessment in clear-cell renal cell carcinoma by integrating serum albumin and the lymphocyte-to-monocyte ratio. In our clinical observations, elevated systemic inflammation scores correlated strongly with adverse clinicopathological features and served as independent predictors of disease-free and overall survival in OSCC patients [11].

The pan-immune-inflammation value (PIV), which incorporates circulating platelets, monocytes, neutrophils, and lymphocytes, represents a novel indicator of systemic immune-inflammatory status. It has demonstrated strong predictive capability for clinical outcomes in colorectal, breast, small-cell lung, prostate, and malignant melanoma cases [10, 12, 13, 15, 17, 25-30]. For example, elevated PIV has been linked to poorer prognosis in small-cell lung cancer [14], whereas lower PIV levels signaled favorable outcomes in metastatic colorectal cancer [12]. Overall, higher PIV values were consistently associated with increased risks of mortality and disease advancement compared to lower levels. This aligns with expectations, given PIV's positive correlation with both NLR and PLR. More recently, Ligorio *et al*. [13] found that PIV correlated more strongly with survival than NLR or PLR in patients with HER2-positive advanced breast cancer, suggesting it may offer a more robust and comprehensive biomarker for post-treatment prognosis.

Despite these advances, the prognostic significance of pretreatment PIV in OSCC remains largely unexplored. To address this gap, we conducted a retrospective analysis of 853 OSCC patients to examine their clinicopathological features, therapeutic responses, and long-term outcomes. To our knowledge, this represents the first study to assess PIV in OSCC or, more broadly, in head and neck malignancies.

We evaluated associations between PIV levels and clinicopathological variables through univariate and multivariate survival analyses. Optimal stratification of PIV was achieved via receiver operating characteristic curve analysis, with the best cutoff determined using Youden's J statistic (yielding the maximum Youden's index). This approach established objective thresholds to categorize patients into high (≥ 268) and low PIV groups. In this cohort, elevated PIV was linked to alcohol use, smoking, and betel nut chewing—findings consistent with prior research showing that these agents act as carcinogens capable of triggering chronic inflammation and promoting tumor progression or second primary tumors [8, 31-33]. Higher PIV levels also correlated with more advanced pathological characteristics, including pT stage, pN stage, overall pathological stage, extranodal extension, histological differentiation, depth of invasion, and perineural invasion. These features collectively indicate greater tumor aggressiveness. Biologically, elevated PIV reflects increased neutrophils, platelets, and monocytes alongside relatively decreased lymphocytes. Neutrophils promote angiogenesis and invasion by releasing factors such as vascular endothelial growth factor, interleukin-8, and matrix metalloproteinase-9, while platelets enhance tumor vascular permeability [22]. Monocytes and platelets further facilitate metastasis via extracellular matrix remodeling and adhesion mechanisms [21-23]. Conversely, relative lymphocytopenia points to impaired immune surveillance, limiting the host's ability to control tumor growth and spread [20, 21]. Collectively, these mechanisms explain why higher PIV levels associate with increased nodal involvement, extranodal extension, perineural invasion, and advanced pT stage in the present analysis.

Our findings demonstrate that PIV is a practical, straightforward index readily applicable in routine clinical practice. As complete blood counts are standard pretreatment evaluations, the components required for PIV calculation are immediately available without additional steps. Crucially, PIV offers valuable insights into patients' systemic condition, supporting improved preoperative risk assessment and personalized treatment planning.

Conclusion

This study highlights a practical biomarker that reflects patients' immune status throughout OSCC management. Higher PIV levels were significantly associated with multiple unfavorable clinicopathological features, including advanced pT status, pN status, overall pathological stage, extranodal extension, poorer cell differentiation, greater depth of invasion, and perineural invasion. In univariate analyses, patients with elevated

PIV experienced significantly worse overall survival, disease-free survival, locoregional recurrence-free survival, and distant metastasis-free survival. After multivariate adjustment for various clinicopathological variables, PIV emerged as an independent prognostic factor for overall survival and distant metastasis-free survival, suggesting its potential utility for pretreatment risk stratification and outcome prediction.

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