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ORIGINAL RESEARCH

Correlation of Prognostic Nutritional Index and Systemic Immune-Inflammation Index with the Recurrence and Prognosis in Oral Squamous Cell Carcinoma with the Stage of III/IV

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Introduction: This study aimed to explore the correlation of systemic immune-inflammation index (SII) and prognostic nutritional index (PNI) with the recurrence and prognosis in patients with advanced oral squamous cell carcinoma (OSCC).

Methods: A total of 298 OSCC patients with the stage of III/IV were finally included in the study. SII = neutrophil count (10^9/L) × platelet count (10^9/L)/lymphocyte count (10^9/L). PNI = serum albumin (g/L) + 5 × total lymphocyte count (10^9/L).

Results: High preoperative SII and low preoperative PNI were independent risk factors for tumor recurrence in OSCC patients of the stage of III/IV. The area under the curves (AUC) for SII was 0.69 (0.63 to 0.76), for PNI was 0.72 (0.67 to 0.78), and for joint model was 0.81 (0.76 to 0.85). Patients with low level of joint model had significantly higher overall survival rate for 5 years follow-up than those with high level.

Discussion: Both preoperative SII and PNI are valuable independent tumor recurrence prediction index in patients with advanced OSCC. Meanwhile, the combination of preoperative SII and PNI is also valuable on OSCC recurrence and prognosis prediction.

Keywords: oral squamous cell carcinoma, prognostic nutritional index, systemic immune-inflammation index, recurrence, prognosis

Introduction

Oral squamous cell carcinoma (OSCC) is aggressive. Studies have shown that the incidence and mortality of OSCC in rural and urban China are on the rise.[1] The prognosis of patients with OSCC is affected by many factors. Although the level of diagnosis and treatment of oral cancer has been improved worldwide, the prognosis of OSCC patients has not been significantly improved. Tumor recurrence is still the main cause of death in patients. Patients with recurrence have lower 5-year overall survival rate than patients without recurrence.[2] How to accurately implement individualized treatment and scientifically evaluate the prognosis of patients with advanced OSCC has important clinical significance.

The impact of malnutrition on disease prognosis is manifested in multiple ways.[3] First, the occurrence of malnutrition leads to the decline of the function of various organs of the body and the imbalance of components leads to the decline of the functions of various systems. Second, malnutrition can lead to a compromised immune system. Prognostic nutritional index (PNI) is a widely used index based on total lymphocyte counts and serum albumin (ALB) levels.[4]

Preoperative systemic inflammatory response participates in tumor development and consequently to overall survival.[5] Systemic immune-inflammation index (SII) is a powerful prognostic indicator in several malignancies.[6]

The purpose of this work is to explore the correlation between PNI and SII and OSCC recurrence and prognosis, and the value of PNI and SII and their combined detection on OSCC recurrence and prognosis prediction.

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Methods

Patients

The data of 380 OSCC patients was collected. Inclusion criteria: (1) Patients with primary oral tumor and diagnosed as squamous cell carcinoma by pathological examination; (2) Patients with age over 18 years old; (3) Patients received systematic treatment in our hospital; (4) Patients with complete clinical, pathological, and follow-up data; (5) Patients with clinical stage III~IV. Exclusion criteria: (1) Patients with serious underlying diseases; (2) Patients with a history of other malignant tumors; (3) Patients with active infection or inflammatory disease within 4 weeks before surgery; (4) Patients lost to follow-up. 298 patients were finally included in this study. The study was approved by XXX, and all the participants signed the informed written consent.

Recurrence is defined as in situ (local) recurrence of malignancy of the same histological origin in the in situ or neck or in situ + neck or distant area at least 4 weeks after the first standard surgical treatment. Recurrence was diagnosed through physical examination, magnetic resonance imaging (MRI), computed tomography (CT), and pathological examination. Distant metastases were diagnosed through medical history, clinical signs, positron emission tomography (PET), and CT.

TNM staging criteria for OSCC patients: based on the 2017 AJCC/UICC oral cancer TNM staging criteria combined with previous clinical and pathological data.

Treatment and Follow-Up

According to the Oral Cancer Diagnosis and Treatment Guidelines and our treatment experience, OSCC patients received surgery treatment, preoperative induction chemotherapy + surgery, surgery + postoperative radiotherapy and chemotherapy, and preoperative induction chemotherapy + surgery + postoperative radiotherapy and chemotherapy. The basis for the patient to receive preoperative induction chemotherapy are: (1) The tumor grows rapidly; (2) The pain is obvious; (3) Invasion of multiple anatomical structures makes resection more difficult. Patients treated with TP (cisplatin + docetaxel) regimen will be transferred to the radiotherapy department of our hospital to receive concurrent chemoradiotherapy. Surgical options include extended local excision of the primary tumor, extended primary tumor excision + neck lymphadenectomy, extended primary tumor excision + neck lymphadenectomy + free flap reconstruction.

The follow-up time of this study began on the first day after the operation of the patients. The follow-up methods were telephone and online appointments, and the patients were followed up in outpatient clinics, and the results of physical examination and auxiliary examination were recorded. The follow-up was continued for at least 5 years.

Nutritional Assessment

Prognostic nutritional index (PNI) was calculated by the following equation: serum albumin (g/L) + 5 × total lymphocyte count (10^9/L).

Immune Inflammation Assessment

Systemic immune inflammation index (SII) was calculated by the following equation: neutrophil count (10^9/L) × platelet count (10^9/L)/lymphocyte count (10^9/L)

Statistical Analyses

Analysis was performed by the SPSS software. The plot was made using GraphPad Prism 8.3.0. The data were shown as mean ± standard deviation (SD) or n (percentage). The comparisons of data between the two groups were done by unpaired *t* test with Welch's correction, Fisher's exact test, or Chi-square test. The correlation between PNI and SII was analyzed by the Pearson correlation analysis. Receiver operating characteristic (ROC) curves were plotted to evaluate the specificity, sensitivity, and differences by assessing area under the curves (AUC) of PNI and SII. The optimal cutoff value was calculated with the Youden index. Logit (Joint model) = 0.006 * SII - 0.067 * PNI. p values <0.05 were considered statistically significant.

Results

Clinicopathological Factors for Tumor Recurrence

There were 126 patients with tumor recurrence and 172 patients without recurrence. The overall recurrence rate was 42.3%, including 77 patients (61.1%) with primary tumor recurrence, 23 (18.3%) with cervical lymph node metastasis, 14 (11.1%) with both primary tumor recurrence and cervical lymph node metastasis, and 12 (9.5%) with distant metastasis.

The baseline characteristics of patients with tumor recurrence and with non-tumor recurrence were shown in Table 1. Age, gender, M classification, invasion depth, preoperative chemotherapy, postoperative radio-chemotherapy, and tumor location showed no significant difference between the two groups. The proportion of advanced T-stages ($p = 0.009$) and N-stages ($p = 0.001$) in patients with tumor recurrence were significantly higher than in those with non-tumor recurrence. Patients with tumor recurrence had significantly higher preoperative SII than those with non-tumor recurrence ($p < 0.001$), while the preoperative PNI was significantly lower ($p < 0.001$).

Table 1 Univariate Analysis of Clinicopathological Factors for Tumor Recurrence in Patients with Oral Squamous Cell Carcinoma of the Stage of III/IV

Factors	NTR (n=172)	TR (n=126)	p value
Age (years)			
≤ 60	97 (56.4%)	59 (46.8%)	0.127
> 60	75 (43.6%)	67 (53.2%)	
Gender			
Male	89 (51.7%)	71 (56.3%)	0.481
Female	83 (48.3%)	55 (43.7%)	
cT classification			
cT2	3 (1.7%)	2 (1.6%)	0.009
cT3	118 (68.6%)	65 (51.6%)	
cT4	51 (29.7%)	59 (46.8%)	
cN classification			
cN0	127 (73.8%)	65 (51.6%)	0.001
cN1	15 (8.8%)	19 (15.1%)	
cN2	21 (12.2%)	27 (21.4%)	
cN3	9 (5.2%)	15 (11.9%)	
M classification			
M0	165 (95.9%)	116 (92.1%)	0.206
M1	7 (4.1%)	10 (7.9%)	
Depth of invasion			
≤ 5 mm	17 (9.9%)	6 (4.8%)	0.057
5–10 mm	51 (29.7%)	28 (22.2%)	
> 10 mm	104 (60.4%)	92 (73.0%)	

(*Continued*)

Table 1 (Continued).

Factors	NTR (n=172)	TR (n=126)	p value
Preoperative chemotherapy			
Yes	27 (15.7%)	29 (23.0%)	0.133
No	145 (84.3%)	97 (77.0%)	
Postoperative radio-chemotherapy			
Yes	91 (52.9%)	59 (46.8%)	0.348
No	81 (47.1%)	67 (53.2%)	
Tumor location			
Oral tongue	54 (31.4%)	52 (41.3%)	0.162
Lip	27 (15.7%)	10 (7.9%)	
Buccal mucosa	42 (24.4%)	26 (20.6%)	
Gum	34 (19.8%)	21 (16.7%)	
Floor of mouth	8 (4.6%)	9 (7.2%)	
Hard palate	7 (4.1%)	8 (6.3%)	
Preoperative SII index	309.32 ± 116.61	410.14 ± 150.97	<0.001
Preoperative PNI	49.42 ± 14.49	38.28 ± 10.82	<0.001

Notes: The data were shown as mean ± SD or n (percentage). The comparisons of data between the two groups were done by Unpaired *t* test with Welch's correction, Fisher's exact test or Chi-square test.
Abbreviations: TNM, Tumor Node Metastasis; SII, systemic immune-inflammation; PNI, prognostic nutritional index; TR, tumor recurrence; NTR, Non-tumor recurrence.

Risk Factors for Tumor Recurrence

In 126 patients with tumor recurrence, the preoperative SII were significantly higher than in 172 patients without recurrence ($p < 0.001$) (Figure 1A). The preoperative PNI in patients with tumor recurrence were significantly lower than in patients without recurrence ($p < 0.001$) (Figure 1B).

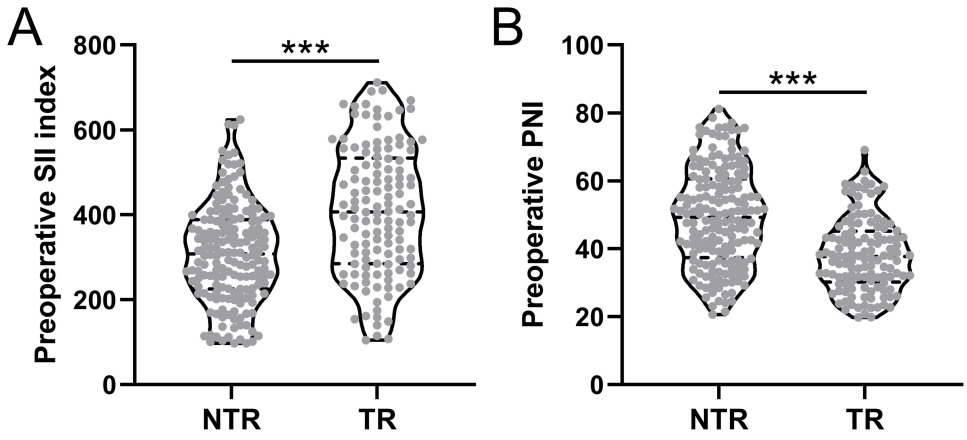

Figure 1 Comparisons of preoperative systemic immune-inflammation (SII) index (**A**) and prognostic nutritional index (PNI, **B**) between tumor recurrence (TR, n = 126) and non-tumor recurrence (NTR, n = 172) in patients with oral squamous cell carcinoma of the stage of III/IV.
Notes: The plot was made using GraphPad Prism 8.3.0. ***p < 0.001 from Unpaired *t* test with Welch's correction.

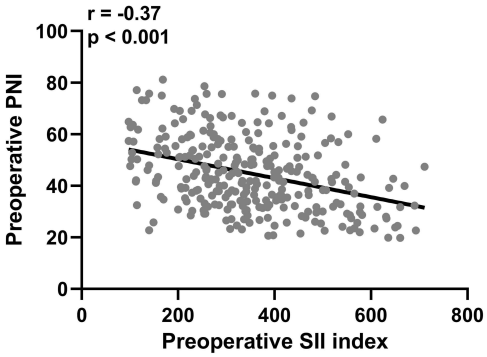

Figure 2 Pearson correlation analysis of preoperative systemic immune-inflammation (SII) index and prognostic nutritional index (PNI) in patients with oral squamous cell carcinoma of the stage of III/IV (n = 298).
Notes: The plot was made using GraphPad Prism 8.3.0.

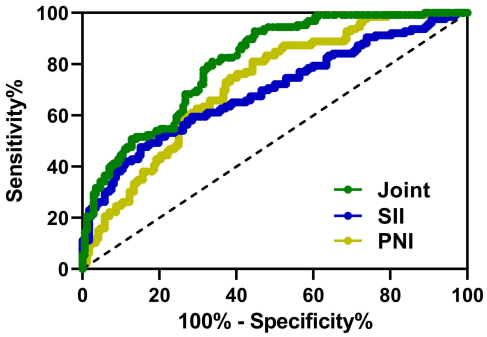

Figure 3 ROC analysis of predictive values of preoperative systemic immune-inflammation (SII) index, prognostic nutritional index (PNI) and their joint test model for tumor recurrence in patients with oral squamous cell carcinoma of the stage of III/IV.
Note: The plot was made using GraphPad Prism 8.3.0.

Predictive Performance of PNI and SII for Tumor Recurrence

Pearson correlation analysis showed that PNI had a negative correlation with SII in patients with OSCC of the stage of III/IV (Figure 2).

The ROC and AUC were used to compare the predictive abilities of PNI, SII, and their joint for tumor recurrence (Figure 3 and Table 2). The AUC for SII was 0.69 (0.63 to 0.76), for PNI was 0.72 (0.67 to 0.78), and for joint model was 0.81 (0.76 to 0.85). The joint test model had higher AUC than single detection.

Predictive Performance of the Combination of PNI and SII for Overall Survival

Overall survival curves for 5 years follow-up was shown in Figure 4. Patients with low level of joint model had significantly higher overall survival rate for 5 years follow-up than those with high level (p = 0.006).

Table 2 Predictive Values in ROC Analysis

	Cut-off value	AUC (95% Confidence Interval)	p	Sensitivity (%)	Specificity (%)	Youden Index
Preoperative SII index	418.4	0.69 (0.63 to 0.76)	< 0.001	47.62	84.88	0.33
Preoperative PNI	47.6	0.72 (0.67 to 0.78)	< 0.001	80.95	55.81	0.37
Joint model	−0.94	0.81 (0.76 to 0.85)	< 0.001	80.95	66.28	0.47

Note: Logit (Joint model) = 0.006 * SII - 0.067 * PNI.
Abbreviations: SII, systemic immune-inflammation; PNI, prognostic nutritional index.

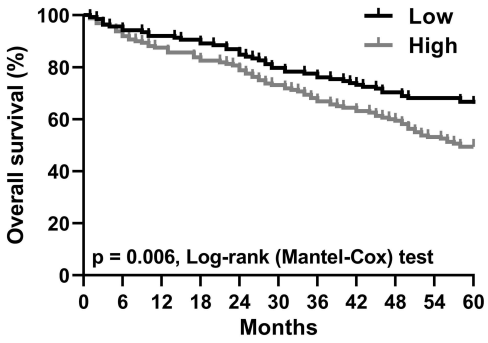

Figure 4 According to the cut off in ROC analysis of the joint test model of preoperative SII and PNI, 298 cases of patients with oral squamous cell carcinoma of the stage of III/IV were divided into high (> −0.94, n = 160) and low (< −0.94, n = 138) level.
Notes: Overall survival curves during 5 years follow-up were plot. The plot was made using GraphPad Prism 8.3.0.

Discussion

The clinical outcome of OSCC patients after surgery can be predicted by TNM staging; however, there are significant differences in prognosis among patients at the same TNM stage. Therefore, TNM staging is far from the best indicator in clinical prognosis evaluation.[7]

Host immune dysregulation, systemic or local excessive inflammation can promote tumor growth, metastasis, and treatment resistance.[8] The number and function of tumor-infiltrating lymphocytes are significantly correlated with tumor onset and progression and clinical response to immunotherapy. Previous studies have shown that immune cells can exhibit both tumor-promoting and anti-tumor abilities according to their differentiation status.[9] Tumor-infiltrating lymphocytes is composed of two complementary cellular components with different immune mechanisms, among which neutrophils can secrete a variety of cytokines and participate in non-specific inflammatory reactions, while lymphocytes respond to immune regulation, and the ratio of the two can stably reflect the inflammatory state of the body.[10] Hematological indicators such as SII are considered as independent factors in the prognostic of many malignant tumors.[11–14] High SII values have association with less favorable disease-free survival (DFS) and overall survival (OS) after curative resection in OSCC patients.[15] In univariate analysis, high SII were significantly associated with worse disease-specific survival (DSS), and progression-free survival (PFS) of patients with OSCC.[16] Another study demonstrated that SII is significantly associated with a poorer OS in univariate analysis but not a significant independent predictor in the multivariate analysis.[17]

Patients with OSCC of the stage of III/IV were analyzed. In patients with tumor recurrence, the preoperative SII index were significantly higher than in those with no tumor recurrence. This result indicated that the inflammation levels were higher preoperatively in patients with recurrence. The ROC curve was used to determine the predictive value of preoperative SII in OSCC recurrence, using the recurrence or non-recurrence of patients as the dependent variable during the observation period, and the SII value at the highest Youden index as the cut-off value. In this study, the preoperative SII cut-off value was 418.4.

PNI can reflect the immune and nutritional status of cancer patients.[18] PNI is an effective prognostic factor in patients with various tumors.[19–21] It was used to evaluate the preoperative surgical risk and postoperative complications of patients with tumors.

In advanced OSCC, the risk of malnutrition is increased by dysphagia and odynophagia.[22] During the therapy, the changes in PNI are caused by influenced nutritional status and inflammation response. The clinical significance of PNI for OSCC has been elucidated.[23] Compared with other inflammation-based biomarkers, PNI is not susceptible to infection, medication, and comorbidity, and is more reproducible and available.[24] Thus, PNI is a reliable biomarker to reflect the condition of host antitumor immunity. A low PNI was noted to exhibit a significant association with shorter OS and DFS in patients with OSCC.[25] Multivariate analysis identified PNI as an independent prognostic factor for OSCC patients and PNI offered an independent prognostic biomarker in OSCC patients undergoing radical surgery.[26]

In patients with OSCC of the stage of III/IV, the preoperative PNI were also analyzed. The preoperative PNI was significantly lower in those with tumor recurrence than in those with no tumor recurrence. This result indicated that the nutritional status was worse preoperatively in patients with recurrence. Multivariate analysis between patients with recurrence and patients without recurrence showed that low preoperative PNI was an independent risk factor for postoperative recurrence in OSCC patients. The ROC curve was employed to determine the predictive value of preoperative PNI in OSCC recurrence and the preoperative PNI cut-off value was 47.6.

In this study, we also analyzed the correlation between preoperative PNI and preoperative SII in 298 patients with OSCC of the stage of III/IV. The significant negative correlation between the two indexes suggested that high levels of inflammation are associated with poor nutritional status in stage III–IV OSCC patients. We built a SII and PNI joint model for the prediction of tumor recurrence in OSCC patients. Logit (Joint model) = 0.006 * SII - 0.067 * PNI. ROC analysis of predictive values of the joint test model indicated that this joint model significantly improves the sensitivity or specificity and area under the curve of a single index.

According to the cut off in ROC analysis of the joint test model of preoperative SII and PNI, 298 cases of patients with OSCC of the stage of III/IV were divided into high (> −0.94, n = 160) and low (< −0.94, n = 138) level. Patients with low level of joint model had significantly higher overall survival rate for 5 years follow-up than those with high level. The combined detection of preoperative SII and PNI also had significant value for the long-term prognosis of OSCC patients.

Patients' immune system exerts a profound impact on the tumor microenvironment of human cancers, whereas the comprehensive investigation of cytokine profiles in tumor-infiltrating T-cells remains lacking. However, in specific tumor contexts (such as Kaposi's sarcoma, Hodgkin's disease, bronchial carcinoma, and cervical carcinoma), these T-cells predominantly express interleukins (ILs) 4 and 5, while exhibiting minimal interferon production. Notably, IL-4 and IL-5 are cytokines typically associated with T-helper type 2 (Th2) immune responses, whereas interferon is primarily linked to Th1 responses.[27] Our current study therefore provides such an instance where high inflammation is associated with poor nutritional status in late stage OSCC patients. Moreover, the comprehensive analysis of cytokine and chemokine expression profiles within the tumor microenvironment holds greater relevance than focusing solely on the specific immune cell composition,[28] hence it will be interesting to explore in the future the association of cytokine profiles, and perhaps the number of leukocytes, with the development of OSCC among different stages of patients.

This study also comes with limitations. First, the patients included were all of Chinese ethnicity, and a more diversified sample pool should be included to further validate the results. Second, this was a single-centered study, therefore to expand the scope and validity of the current data, a multi-centered study should be considered in the future.

Conclusions

In conclusion, both preoperative SII and PNI are valuable independent tumor recurrence prediction index in patients with advanced OSCC. Meanwhile, the combination of preoperative SII and PNI is also valuable on OSCC recurrence and prognosis prediction.

Data Sharing Statement

Data will be made available on request from the corresponding author Manjun Ye.

Statement of Ethics

The study was approved by the ethics committee of Daqing General Hospital, the study was performed in strict accordance with the Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects.

Informed Consent

All participants signed appropriate consent for participating this study.

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Disclosure

The authors declare that they have no conflicts of interest.

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