

Post-treatment Neutrophil/Lymphocyte Ratio Is a Prognostic Factor in Head and Neck Cancers Treated With Nivolumab

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Abstract. *Background/Aim:* Inflammation and nutrition-based biomarkers, such as the neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), lymphocyte/monocyte ratio (LMR), C-reactive protein/albumin ratio (CAR), prognostic nutritional index (PNI), systemic immune inflammation index (SII), and systemic inflammation response index (SIRI), have prognostic value for several types of malignancies. Markers that precisely reflect the prognosis of patients with head and neck cancers (HNCs) treated with immune-checkpoint inhibitors remain unclear. This retrospective study aimed to investigate the prognostic value of hematological markers before and after treatment with nivolumab in patients with recurrent or metastatic HNC (RM-HNC). *Patients and Methods:* We evaluated the clinical data of 44 patients with recurrent/metastatic head and neck squamous cell carcinoma treated with nivolumab between April 2017 and April 2023 at Shinshu University Hospital. Values of hematological biomarkers (NLR, LMR, PLR, CAR, PNI, SII, and SIRI) were calculated before and 4-6 weeks after nivolumab initiation. Receiver operating characteristic curves were constructed to determine the cutoff values of pre- and post-treatment markers for overall survival (OS) and progression-free

survival (PFS). *Results:* Among all pre- and post-treatment markers, post-treatment NLR showed the highest area under the curve (AUC=0.702). A high post-treatment NLR (cutoff value, 4.01) was associated with a poor OS ($p=0.027$) and a tendency for shorter PFS ($p=0.117$). Multivariate analysis showed that a high post-treatment NLR was significantly associated with poor OS ($p=0.026$). *Conclusion:* A high post-treatment NLR was associated with poor response to nivolumab in head and neck cancers.

Head and neck cancer (HNC) is the 6th most common malignancy worldwide (1), and its major histological type is squamous cell carcinoma, which accounts for >90% of the cases. Nivolumab is a humanized monoclonal antibody against human programmed death-ligand 1 (PD-L1) that was approved in March 2017 in Japan for treating recurrent or metastatic HNC (RM-HNC) after platinum-based drug administration. Approval was based on the randomized phase III CheckMate 141 study (2), in which the median overall survival (OS) was significantly better in the nivolumab group than in the investigator's choice group (cetuximab, docetaxel, and methotrexate) (median OS 7.5 vs. 5.1 months, $p=0.01$). Based on clinical trial results, nivolumab has become the standard second-line treatment for platinum-refractory HNC.

Although nivolumab has improved the prognosis of RM-HNCs, its efficacy and clinical courses of treated patients are diverse. Therefore, robust biomarkers for predicting treatment outcomes are desirable. Inflammation and nutrition-based biomarkers, such as the neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), lymphocyte/monocyte ratio (LMR), C-reactive protein/albumin ratio (CAR), prognostic nutritional index (PNI), systemic immune inflammation index (SII), and systemic inflammation response index (SIRI), have prognostic value for several types of malignancies, including HNC (3-11). Furthermore, recent studies have shown that these biomarkers are predictors of immune-checkpoint

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inhibitor (ICI) efficacy (12-14). However, little is known about the prognostic value of these markers in patients with HNC treated with ICIs. Thus, the markers that precisely reflect the prognosis and the timing of evaluation of these markers remain unclear.

Therefore, this study aimed to investigate the prognostic value of NLR, LMR, PLR, CAR, PNI, SII, and SIRI before and after treatment with nivolumab in patients with RM-HNC.

Patients and Methods

Study population and data collection. We evaluated the clinical data of 44 patients with recurrent or metastatic head and neck squamous cell carcinoma (RM-HNSCC) treated with nivolumab between April 2017 and April 2023 at Shinshu University Hospital. The clinicopathological data of the patients, including age, sex, and performance status, were evaluated using the Eastern Cooperative Oncology Group (ECOG PS). Primary tumor site, clinical stage at diagnosis (according to the 8th edition of the TNM classification), p16 status, PD-L1 status, and hematological data were obtained from the medical records. Baseline data were defined as the status within 1 week before the first administration of nivolumab.

NLR, LMR, PLR, CAR, PNI, SII, and SIRI values were calculated as follows: total neutrophil count ($/\text{mm}^3$) divided by total lymphocyte count ($/\text{mm}^3$), total lymphocyte count ($/\text{mm}^3$) divided by total monocyte count ($/\text{mm}^3$), platelet count ($/\text{mm}^3$) divided by total lymphocyte count ($/\text{mm}^3$), serum C-reactive protein (mg/dl) divided by serum albumin (g/dl), $10 \times$ serum albumin (g/dl) + 0.005 \times total lymphocyte count ($/\text{mm}^3$), platelet count ($/\text{mm}^3$) \times neutrophil count ($/\text{mm}^3$) divided by total lymphocyte count ($/\text{mm}^3$), and monocyte count ($/\text{mm}^3$) \times neutrophil count ($/\text{mm}^3$) divided by total lymphocyte count ($/\text{mm}^3$), respectively. These values were calculated based on blood test results obtained within 1 week before the first day of nivolumab administration (pre-treatment markers) and 4-6 weeks after the initiation of nivolumab (post-treatment markers). The prefixes pre- and post- were used to indicate the pre- and post-treatment values, respectively.

Treatment efficacy was assessed using the Response Evaluation Criteria in Solid Tumors, version 1.1 (15). After initiating nivolumab, imaging studies, such as computed tomography, magnetic resonance imaging, or F-fluorodeoxyglucose positron emission tomography, were performed every 2-3 months or when clinically necessary. The objective response rate (ORR) was the sum of the complete response (CR) and partial response (PR) rates. The disease control rate (DCR) was the sum of the CR, PR, and stable disease (SD) rates.

Treatment. Nivolumab was administered intravenously at 3 mg/kg (from April 2017 to September 2018), 240 mg/body every two weeks (from October 2018 to April 2023), and 480 mg/body every four weeks when the disease condition and patients' general condition were stable. After nivolumab discontinuation, subsequent chemotherapy was administered at the physician's discretion.

Ethics. This study was approved by the Ethics Committee of the Shinshu University School of Medicine (approval number: 5296). Informed consent was obtained from all participants using an opt-out form. This study was conducted according to the principles outlined in the Declaration of Helsinki.

Statistical analysis. A receiver operating characteristic (ROC) curve for disease control (CR+PR+SD) was generated to determine the cutoff values of the pre- and post-treatment markers. OS was defined as the time from the first nivolumab administration to the date of all-cause death. Progression-free survival (PFS) was defined as the period from the start of nivolumab treatment until death or first disease progression. OS and PFS were compared using the log-rank test and Kaplan-Meier survival curves. Univariate and multivariate analyses were performed to identify the prognostic factors. Cox proportional hazard models were used to perform multivariate analysis using a backward stepwise selection method to determine the predictive factors for OS. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using IBM SPSS Statistics (version 29.0; IBM Corp., Armonk, NY, USA).

Results

Patient characteristics. The baseline demographic and clinicopathological characteristics of the 44 patients are shown in Table I. The median age was 68 years (range=42-89 years), with 38 men (82.6%) and six women (17.4%). Eleven (25.0%) patients had an ECOG PS score of 2. The primary tumor sites were the oral cavity (n=5, 11.4%), nasopharynx (n=9, 20.5%), oropharynx (n=6, 13.6%), hypopharynx (n=15, 34.1%), larynx (n=4, 9.1%), nasal cavity/maxillary sinus (n=3, 6.8%), and salivary glands (n=2, 4.5%). Nivolumab was administered as the second-, third-, and fourth-line or later treatment in 26 (59.1%), 13 (29.5%), and 5 (11.4%) patients, respectively. Thirty-eight patients (82.6%) were platinum-refractory (defined as relapse within six months), and six patients (17.4%) were platinum-sensitive (defined as relapse after 6 months).

Treatment outcomes. The median follow-up duration was 14.3 months (1.4-52.3 months). The median number of nivolumab cycles was nine (1-74). The best overall responses are shown in Table II. CR and PR were observed in two (4.5%) and seven (15.9%) patients, respectively. Furthermore, SD and progressive disease were observed in eight (18.2%) and 24 (54.5%) patients, respectively, resulting in an ORR of 20.5% and a DCR of 38.6%.

ROC curve analysis for pre- and post-treatment markers. ROC curves were constructed, and the area under the curve (AUC) was calculated to assess the discriminating ability of the pre- and post-treatment markers (Figure 1). AUCs for pre-NLR, pre-LMR, pre-PLR, pre-CAR, pre-PNI, pre-SII, and pre-SIRI were 0.613, 0.514, 0.590, 0.500, 0.507, 0.593, and 0.527, respectively. In contrast, AUCs for post-NLR, post-LMR, post-PLR, post-CAR, post-PNI, post-SII, and post-SIRI were 0.702, 0.538, 0.593, 0.563, 0.546, 0.685, and 0.647, respectively. Among all pre- and post-treatment markers, post-treatment NLR showed the highest AUC (0.702) with a cutoff value of 4.01.

Table I. Baseline demographic and clinicopathological characteristics of the study participants.

		n (%)
Age, years	Median (range)	68 (42-89)
Sex	Male	38 (82.6)
	Female	6 (17.4)
ECOG PS	0	9 (20.5)
	1	24 (54.5)
	2	11 (25.0)
Primary site	Oral cavity	5 (11.4)
	Nasopharynx	9 (20.5)
	Oropharynx	6 (13.6)
	Hypopharynx	15 (34.1)
	Larynx	4 (9.1)
	Nasal cavity/Maxillary sinus	3 (6.8)
	Salivary gland	2 (4.5)
Prior treatments	1	26 (59.1)
	2	13 (29.5)
	≥3	5 (11.4)
Stage at diagnosis	I	2 (4.3)
	II	6 (6.5)
	III	5 (17.4)
	IV	31 (71.7)
Distant metastasis	Yes	18 (40.9)
	No	26 (59.1)
p16 status	Positive	4 (9.1)
	Negative/Unknown	40 (90.9)
PD-L1 status	≥1%	8 (18.2)
	Not tested	36 (81.8)
Platinum refractory	Yes	38 (86.4)
	No	6 (13.6)

ECOG: Eastern Cooperative Oncology Group; PS: performance status; PD-L1: programmed death-ligand 1.

Survival analysis and prognostic factors for OS after nivolumab. Figure 2 shows the Kaplan–Meier curves for PFS and OS according to post-NLR. Patients in the high post-NLR (post-NLR ≥ 4.01) group had a significantly poorer OS [hazard ratio (HR)=2.541; 95% confidence interval (CI)=1.080-5.978; $p=0.027$] and tended to have shorter PFS (HR=1.730; 95%CI=0.860-3.481; $p=0.117$).

Univariate analysis showed that poor ECOG PS ($p<0.001$) and high post-NLR ($p=0.033$) were associated with inferior OS (Table III). Multivariate analysis also showed that a worse ECOG PS ($p=0.001$) and high post-NLR ($p=0.026$) were significantly associated with poor OS.

Discussion

ICIs have unprecedentedly impacted the systemic therapy of various cancers and have provided long-term survival even in patients with advanced-stage cancer. In Japan, the anti-PD-L1 antibodies nivolumab and pembrolizumab were approved for treating RM-HNCs in 2017 and 2019,

Table II. Best overall response, overall response rate and disease control rate.

		n (%)
Best overall response	CR	2 (4.5)
	PR	7 (15.9)
	SD	8 (18.2)
	PD	24 (54.5)
	NE	3 (6.8)
Overall response rate		9 (20.5)
Disease control rate		17 (38.6)

CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease; NE: not evaluable.

respectively, and their efficacy and safety have been validated in real-world settings (16-18). However, the treatment responses to ICI and clinical courses of treated patients are diverse. Although high expression of PD-L1 could be a predictor of favorable outcomes of anti-PD-L1 therapy (19), the PD-L1 level alone cannot explain the variation in clinical outcomes; some PD-L1-negative patients show a good response and long-term efficacy is observed in a limited number of PD-L1-positive patients. The precise mechanisms underlying the diverse responses to ICI have yet to be fully understood, and reliable predictive biomarkers are desirable in the clinical setting. In this study, we investigated the prognostic value of multiple hematological biomarkers (NLR, LMR, PLR, CAR, PNI, SII, and SIRI) in nivolumab-treated RM-HNCs. Notably, we investigated not only baseline but also post-treatment values. In this study, post-NLR had the best prognostic value among all pre- and post-treatment hematological biomarkers and was an independent prognostic factor in the multivariate analysis.

NLR is an easily available hematological biomarker reflecting systemic inflammation, and its elevation indicates increased neutrophil and decreased lymphocyte counts. Neutrophils play a pivotal role in inflammation-driven tumorigenesis, with tumor-associated neutrophils influencing tumor growth through various mechanisms, including extracellular matrix remodeling, promotion of tumor cell invasion and metastasis, angiogenesis, lymphangiogenesis, and immune suppression (20). Lymphocytes play a major role in antitumor activity in the tumor microenvironment and the inhibition of tumor proliferation (21). Thus, an elevated NLR indicates tumor-induced inflammation and low antitumor immunity and could be associated with poor outcomes. Previous studies have shown that a high NLR is associated with a poor prognosis in several types of malignancies treated with ICIs, including RM-HNSCC (12, 14, 22, 23). Hwang *et al.* performed serial RNA sequencing of baseline and post-ICI non-small cell lung carcinoma (NSCLC) and reported

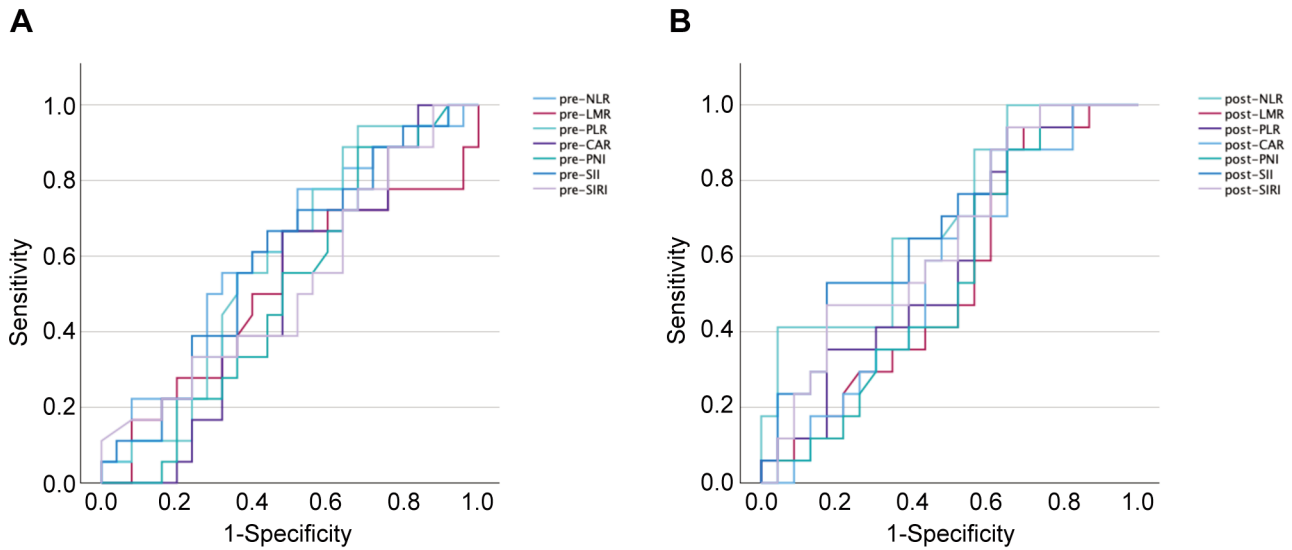


Figure 1. Receiver operating characteristic (ROC) curves for the hematological markers before (A) and after (B) treatment.

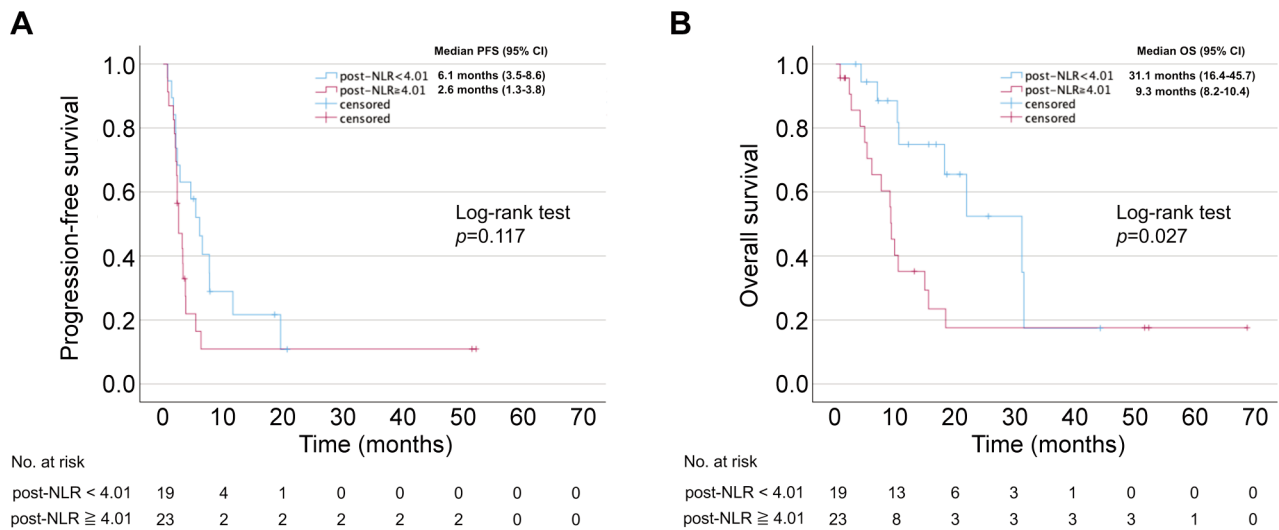


Figure 2. Kaplan-Meier curves for progression-free survival (A) and overall survival (B) according to the post-treatment neutrophil to lymphocyte ration (NLR).

upregulation of the antitumor adaptive immune response in patients with decreased NLR, suggesting that early NLR dynamics reflect changes in the tumor microenvironment and capture the antitumor immune response (24). Interestingly, our results showed that AUCs of all hematological markers increased after treatment compared to those before treatment, suggesting that post-treatment values could be more reliable prognostic markers in patients receiving ICIs. Our results are similar to those of Matsuo *et al.*, who reported the importance

of post-treatment inflammation-based prognostic scores (IBPS), such as NLR, CAR, and PLR, and concluded that pre-treatment IBPS are not adequately prognostic in patients with RM-HNSCC treated with nivolumab (25). Indeed, our results did not show a significant difference in OS between patients with a high and low pre-NLR ($p=0.081$) (data not shown). Recent studies have focused on post-treatment markers or dynamic changes in these hematological markers, and similar results regarding the NLR have been reported in

Table III. Univariate and multivariate analysis of overall survival.

	Overall survival			
	Univariate analysis		Multivariate analysis	
	Hazard ratio (95%CI)	<i>p</i> -Value	Hazard ratio (95%CI)	<i>p</i> -Value
Age				
<75	1			
≥75	0.978 (0.328-2.916)	0.968		
Sex				
Female	1			
Male	0.783 (0.226-2.712)	0.783		
ECOG PS				
0, 1	1		1	
2	5.355 (2.117-13.546)	<0.001*	5.019 (1.882-13.384)	0.001*
Distant metastasis				
No	1			
Yes	1.048 (0.479-2.297)	0.906		
p16 status				
Positive	1			
Negative/unknown	0.711 (0.167-3.023)	0.644		
Prior treatments				
1	1			
≥2	1.685 (0.748-3.795)	0.208		
Platinum refractory				
No	1			
Yes	0.558 (0.208-1.495)	0.246		
irAE				
No	1			
Yes	0.624 (0.261-1.493)	0.289		
post-NLR				
<4.01	1		1	
≥4.01	2.541 (1.080-5.978)	0.033*	2.666 (1.123-6.328)	0.026*

**p*<0.05.

other types of cancers, such as NSCLC (26), melanoma (14), gastric cancer (27), and renal cell carcinoma (28, 29). Post-treatment markers or dynamic changes in these markers may reflect differences in tumor immunity in the tumor microenvironment due to ICI administration and could be more accurate prognostic biomarkers.

This study has several limitations. First, this was a single-center retrospective analysis with potential selection bias. Second, the PD-L1 status must still be fully evaluated; only 18.2% of the patients were tested for PD-L1 expression. Finally, the sample size was small. Further prospective studies with large cohorts are warranted to verify our results.

Conclusion

In conclusion, post-treatment NLR could be a useful clinical prognostic marker in patients receiving nivolumab for RM-HNSCC.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Conceptualization: Yoh-ichiro Iwasa; Methodology: Yoh-ichiro Iwasa; Format analysis and investigation: Yoh-ichiro Iwasa; Writing: Yoh-ichiro Iwasa; Resources: Yoh-ichiro Iwasa, Ryosuke Kitoh, Yoh Yokota, Kentaro Hori, Mariko Kasuga, Takashi Kobayashi, Shintaro Kanda; Supervision: Yutaka Takumi.

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