# Prognostic value of inflammation- and nutrition-based biomarkers in patients with recurrent or metastatic oral squamous cell carcinoma treated with immune checkpoint inhibitors: A retrospective study

SACHIKO YAMASAKI[1], NANAKO ITO[1], ATSUKO HAMADA[1], FUMITAKA OBAYASHI[1], MIRAI HIGAKI[1], TAKAYUKI NAKAGAWA[2], SHIGEHIRO ONO[2], KOICHI KOIZUMI[1], TOMONAO AIKAWA[2] and SOUICHI YANAMOTO[1]

[1]Department of Oral Oncology, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Hiroshima 734-8553, Japan; [2]Department of Oral and Maxillofacial Surgery, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Hiroshima 734-8553, Japan

Received May 12, 2025; Accepted June 18, 2025

DOI: 10.3892/ol.2025.15249

**Abstract.** The prognostic value of inflammation- and nutrition-based biomarkers in oral squamous cell carcinoma (OSCC) remains unclear. The present study evaluated the prognostic significance of these biomarkers in patients with recurrent or metastatic OSCC (R/M-OSCC) undergoing immune checkpoint inhibitor (ICI) therapy. The retrospective study analyzed 45 patients with R/M-OSCC who were treated with ICIs at Hiroshima University Hospital (Hiroshima, Japan) between October 2017 and December 2024. Clinical and treatment data were collected alongside inflammation-based prognostic scores (IBPSs). These biomarkers were calculated prior to and 4-6 weeks after ICI initiation. The 1- and 2-year overall survival (OS) rates for patients were 40 and 22%, respectively, with a median OS of 8.1 months [95% confidence interval (CI): 5.2-14.2). The 1- and 2-year progression-free survival (PFS) rates for patients were 34 and 6.7%, respectively (median PFS, 5.3 months; 95% CI: 2.7-7.9). Post-treatment biomarkers demonstrated superior prognostic value compared with pre-treatment values. Male sex [hazard ratio (HR)=4.11, P=0.0059] and lower body mass index (HR=3.33, P=0.0188) were significantly associated with poorer OS. Post-treatment neutrophil-to-lymphocyte ratio (NLR) (HR=4.17, P=0.0337) and prognostic nutritional index (PNI) (HR=3.92, P=0.0073) were significantly associated with OS. Post-treatment NLR (HR=3.80, P=0.0339), lymphocyte-to-monocyte ratio (LMR) (HR=4.02, P=0.0304) and PNI (HR=2.96, P=0.0342) were significantly associated with PFS. Furthermore, post-treatment IBPS markers, including NLR (P=0.0006), LMR (P=0.0065), platelet-to-lymphocyte ratio (P=0.0396), C-reactive protein-to-albumin ratio (P=0.0062), PNI (P=0.0358) and lymphocyte counts (P=0.0321), were significantly associated with the disease control rate. In conclusion, post-treatment inflammation- and nutrition-based biomarkers could help clinicians identify early those patients most likely to benefit from ICIs and support the development of individualized treatment strategies.

*Correspondence to:* Dr Sachiko Yamasaki, Department of Oral Oncology, Graduate School of Biomedical and Health Sciences, Hiroshima University, 1-2-3 Kasumi, Minami, Hiroshima, Hiroshima 734-8553, Japan
E-mail: sayamasaki@hirosima-u.ac.jp

*Abbreviations:* 5-FU, 5-fluorouracil; AUC, area under the curve; BMI, body mass index; CAR, C-reactive protein-to-albumin ratio; CI, confidence interval; CPS, combined positive score; CR, complete response; CRP, C-reactive protein; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; IBPS, inflammation-based prognostic score; ICIs, immune checkpoint inhibitors; IFN-γ, interferon-γ; IL, interleukin; irAEs, immune-related adverse events; LMR, lymphocyte-to-monocyte ratio; mGPS, modified Glasgow Prognostic Score; NLR, neutrophil-to-lymphocyte ratio; ORR, objective response rate; OS, overall survival; OSCC, oral squamous cell carcinoma; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; PR, partial response; R/M-OSCC, recurrent or metastatic oral squamous cell carcinoma; ROC, receiver operating characteristic; SD, stable disease; TGF-β, transforming growth factor-β

*Key words:* OSCC, ICIs, IBPS, MLR, CAR, OS, PFS, DCR

## Introduction

Oral squamous cell carcinoma (OSCC) is the most common malignancy of the oral cavity and accounts for approximately 90% of all oral cancers (1-3). It represents a major subgroup of head and neck squamous cell carcinomas (HNSCCs), which are among the sixth most common cancers worldwide, with over 500,000 new cases annually (2). Despite advances in surgery, chemotherapy, and radiotherapy, the prognosis of patients with recurrent or metastatic OSCC (R/M-OSCC) remains poor.

Since the 1980s, platinum-based chemotherapy regimens have served as the standard treatment for advanced head and neck cancers. The EXTREME regimen, which combines 5-fluorouracil, cisplatin, and cetuximab, became a standard of care in 2012 (4). More recently, immune checkpoint inhibitors (ICIs), such as nivolumab and pembrolizumab, targeting the programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) pathway, have expanded the therapeutic landscape and shown promising efficacy in R/M-HNSCC, including OSCC (5,6). These agents are now widely used in clinical practice in Japan and globally. However, ICIs are not universally effective, and their clinical benefit is limited to a subset of patients (7). Therefore, there is a pressing need to identify reliable biomarkers to predict which patients are most likely to respond to ICI therapy. While previous studies have proposed PD-L1 expression, tumor mutational burden, and tumor-infiltrating lymphocytes (TILs) as candidate predictive biomarkers, none have demonstrated sufficient sensitivity or specificity for routine clinical use (8-10).

In recent years, inflammation- and nutrition-based biomarkers have emerged as potential prognostic indicators in various malignancies, including head and neck cancers (11-25). These include the neutrophil-to-lymphocyte ratio (NLR) (13-16,23,25-30), platelet-to-lymphocyte ratio (PLR) (14-18,23,24), lymphocyte-to-monocyte ratio (LMR) (25), C-reactive protein-to-albumin ratio (CAR) (12,20), prognostic nutritional index (PNI) (31,32), and modified Glasgow Prognostic Score (mGPS) (22,24). These markers are simple to calculate using routinely available laboratory data and reflect the complex interplay between systemic inflammation, nutritional status, and cancer progression. Although several reports have explored the prognostic significance of these markers in HNSCC, limited data exist regarding their role in predicting the response and outcomes of ICI treatment specifically in patients with OSCC. Moreover, it remains unclear whether the timing of biomarker evaluation, before or after ICI initiation, affects their prognostic utility.

Therefore, the aim of this retrospective study was to evaluate the clinical relevance of inflammation- and nutrition-based biomarkers as predictors of treatment response and prognosis in patients with R/M-OSCC receiving ICI therapy. We also investigated whether biomarker levels assessed after ICI administration offer superior prognostic value compared to those assessed prior to treatment.

## Materials and methods

*Study design and population*. We conducted a retrospective analysis of the clinical data of 45 patients with R/M-OSCC treated with ICIs between October 2017 and December 2024 at Hiroshima University Hospital (Hiroshima, Japan). Eligible patients were aged ≥18 years, had histologically confirmed OSCC arising exclusively from the oral cavity (excluding oropharyngeal subsites, such as the soft palate, base of the tongue, and tonsillar region; this definition aligns with previous clinical studies that focus solely on cancers of the oral cavity), received at least one cycle of ICI therapy, and had adequate clinical data including laboratory results and follow-up information. Patients were excluded if they had concurrent malignancies, active autoimmune diseases, or insufficient medical records. The observation period was defined as the interval from the initiation of ICI therapy to the date of death, last follow-up, or the data cutoff (February 1, 2025), whichever came first.

*Data collection and definitions*. We assessed the following parameters: Age, sex, Eastern Cooperative Oncology Group Performance Status (ECOG PS), primary tumor site, disease stage, presence of target lesions, treatment line, history of surgery, history of radiotherapy, combined positive score (CPS), chemotherapy regimen and dose, initial treatment, presence or absence of radiotherapy, observation period, number of treatment cycles, IBPSs before and after treatment, overall survival (OS), one-year and two-year survival rates, progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), best overall response, presence or absence of immune-related adverse events (irAEs), and details of irAEs. All patients were staged according to the eighth edition of the International Union Against Cancer (UICC) TNM staging system (33). In this study, OSCC was defined as squamous cell carcinoma that arises exclusively from the oral cavity, excluding oropharyngeal subsites, such as the soft palate, base of the tongue, and tonsillar region.

The IBPSs were calculated as follows: the NLR was determined by dividing the absolute neutrophil count (/mm$^3$) by the absolute lymphocyte count (/mm$^3$); LMR was calculated by dividing the absolute lymphocyte count (/mm$^3$) by the absolute monocyte count (/mm$^3$); PLR was determined by dividing the absolute platelet count (/mm$^3$) by the absolute lymphocyte count (/mm$^3$); CAR was calculated by dividing the C-reactive protein (CRP) concentration (mg/dl) by the serum albumin concentration (g/dL); and PNI was calculated as 10x serum albumin concentration (g/dl) + 0.005x total lymphocyte count (/mm$^3$). These values were obtained from the blood test results obtained within 1 week prior to the first day of ICI administration and 4-6 weeks after the initiation of ICI therapy.

In our department, the treatment strategy for R/M-OSCC is guided by platinum sensitivity. For platinum-resistant cases, nivolumab was administered intravenously at a dose of 3 mg/kg (between 2017 and September 2018) and at 240 mg every two weeks (from October 2018 to February 2025). For platinum-sensitive cases, pembrolizumab was used either as monotherapy or in combination therapy. In platinum-sensitive patients with adequate tolerance for combination therapy involving platinum agents and 5-fluorouracil (5-FU), treatment selection was based on the CPS. Specifically, PD-L1 expression was evaluated using immunohistochemistry with the Dako 22C3 pharmDx assay on formalin-fixed, paraffin-embedded tumor specimens. The CPS was calculated by dividing the number of PD-L1-positive cells (including tumor cells, lymphocytes, and macrophages) by the total number of viable tumor cells, then multiplying by 100. A CPS of ≥1 was considered positive, in accordance with established diagnostic criteria. All CPS evaluations were conducted by board-certified oral pathologists with expertise in head and neck malignancies. Pembrolizumab monotherapy was administered if CPS was ≥20%, while pembrolizumab was combined with cisplatin (80 mg/m$^2$) and 5-FU (800 mg/m$^2$) for CPS values of 1-19 and <1%, respectively. However, treatment decisions were made comprehensively, considering factors

such as age, comorbidities, tumor growth rate, and overall performance status. In cases where patients were unable to tolerate platinum-based agents or 5-FU, pembrolizumab monotherapy or the EXTREME regimen was considered as alternative treatment options. Following the discontinuation of ICIs, subsequent chemotherapy was administered at the physician's discretion.

Treatment efficacy was assessed using the Response Evaluation Criteria in Solid Tumors version 1.1 (34). Following the administration of ICIs, imaging studies, including computed tomography, magnetic resonance imaging, and F-fluorodeoxyglucose positron emission tomography, were performed every two to three months or as clinically indicated. The DCR was calculated as the sum of the complete response (CR), partial response (PR), and stable disease (SD) rates. OS was defined as the time from the first day of ICI administration to the date of death or the date of the final analysis (February 1, 2025), whichever was earlier. PFS was defined as the time from the first day of ICI administration to the date of disease progression or death.

*Statistical analysis*. To determine the cutoff values of biomarkers before and after treatment, receiver operating characteristic (ROC) curves were constructed for disease control (CR + PR + SD). OS and PFS were compared using the log-rank test and Kaplan-Meier survival curves. P-values were calculated using the log-rank test. Univariate and multivariate analyses were conducted to identify prognostic factors, with the multivariate analysis performed using the Cox proportional hazards model to determine predictors of OS and PFS. $P<0.05$ was considered to indicate a statistically significant difference. P-values were determined using chi-square tests to assess the association between categorical variables. In cases with small sample sizes or expected cell counts, Fisher's exact test was employed to ensure accurate statistical inference. All statistical analyses were performed using SPSS Statistics (version 30.0; IBM Corp., Armonk, NY, USA).

*Ethics statements*. This study was conducted in accordance with the principles of The Declaration of Helsinki and was approved by the Ethics Committee of Hiroshima University (approval no. E2024-0196). The requirement for informed consent was waived by the Ethics Committee owing to the retrospective design of the study.

## Results

*Patient characteristics and treatment outcomes*. A total of 45 patients were enrolled in the study (Table SI). The age of the patients ranged from 35 to 84 years, with a median of 67 years. The cohort consisted of 29 (64%) males and 16 (36%) females. Regarding ECOG PS, 34 patients had a PS of 0, six had a PS of 1, one had a PS of 2, and four had a PS of 3. The primary tumor site was predominantly the tongue, observed in 24 (53%) patients. Other primary sites included the maxillary gingiva in six (13%) patients, mandibular gingiva in five (11%) patients, and buccal mucosa and floor of the mouth in four (9%) patients each. At the initial diagnosis, four patients were classified as stage I, 13 as stage II, three as stage III, and 24 as stage IV. Nivolumab was administered to 23 (51%) patients, while pembrolizumab was used in 22 (49%) patients. Surgical resection was performed as the initial treatment in 42 (93%) patients, and radiotherapy was administered to 39 (87%) patients. Of the 42 patients who underwent surgery, 41 had neck dissections, and one had surgery on the primary tumor. In the one case, the patient discontinued outpatient follow-up after primary tumor resection. Upon re-presentation, disease progression was observed, and curative surgery was considered unfeasible due to local recurrence and cervical lymph node metastasis. Therefore, treatment with an ICI was initiated. Regarding target lesions, distant metastases were present in 21 (47%) patients, whereas 12 (27%) patients had local residual disease. CPS expression of ≥ 20% was observed in 29 (64%) patients. Regarding ICI administration, monotherapy was used in 33 (73%) patients, while 12 (27%) patients received combination therapy with chemotherapy.

The number of ICI administrations ranged from one to 68, with a median of five (Table SII). Treatment efficacy was evaluated according to the Response Evaluation Criteria in Solid Tumors criteria. CR was observed in four (9%) patients, PR in six (13%) patients, SD in five (11%) patients, and progressive disease in 30 (67%) patients. The ORR, calculated as the sum of CR and PR, was 22%, while the DCR, defined as the sum of CR, PR, and SD, was 33%. irAEs occurred in 13 (29%) patients. The most common irAE was thyroid dysfunction, observed in four (9%) patients, followed by interstitial pneumonia in three (7%) patients and colitis in two (4%) patients. Other reported adverse events included dermatologic disorders, interstitial nephritis, hypopituitarism, neurological impairment, atrial fibrillation, and acute kidney failure.

*Survival analysis for OS and PFS after ICI administration*. Figure 1 presents the results of OS analysis. In the overall cohort of ICI-treated patients, the 1-year survival rate was 40%, 2-year survival rate was 22%, and median OS was 8.1 months [95% confidence interval (CI): 5.2-14.2] (Fig. 1A). For patients receiving ICI monotherapy, the median OS was 7.5 months (95% CI: 016.2), whereas for those receiving ICI in combination with chemotherapy, the median OS was 9.7 months (95% CI: 7.1-12.2), with a log-rank test P-value of 0.788 (Fig. 1B).

For patients treated with nivolumab, the median OS was 7.5 months (95% CI: 0-17.3), whereas for those treated with pembrolizumab, the median OS was 9.7 months (95% CI: 5.2-14.2), with a P-value of 0.707 (Fig. 1C). Among patients treated with pembrolizumab, those receiving chemotherapy alone had a median OS of 6.6 months (95% CI: 0-14.5), whereas those receiving pembrolizumab in combination with chemotherapy had a median OS of 9.7 months (95% CI: 7.2-12.2) (Fig. 1D). Similar to the findings of the KEYNOTE-048 trial, a trend toward prolonged OS was observed with the addition of chemotherapy. The one-year and two-year PFS rates for all patients were 34 and 6.7%, respectively, with a median PFS of 5.3 months (Fig. 1E).

Figure 2 illustrates the OS according to CPS values. In patients with CPS <1, the median OS was 4.3 months (95% CI: 2.9-5.7), whereas for those with CPS between 1 and <20, the median OS was 9.8 months (95% CI: 6.4-13.2). For patients with CPS ≥20, the median OS was 9.7 months (95% CI: 0-19.4), with a P-value of 0.123 (Fig. 2A).

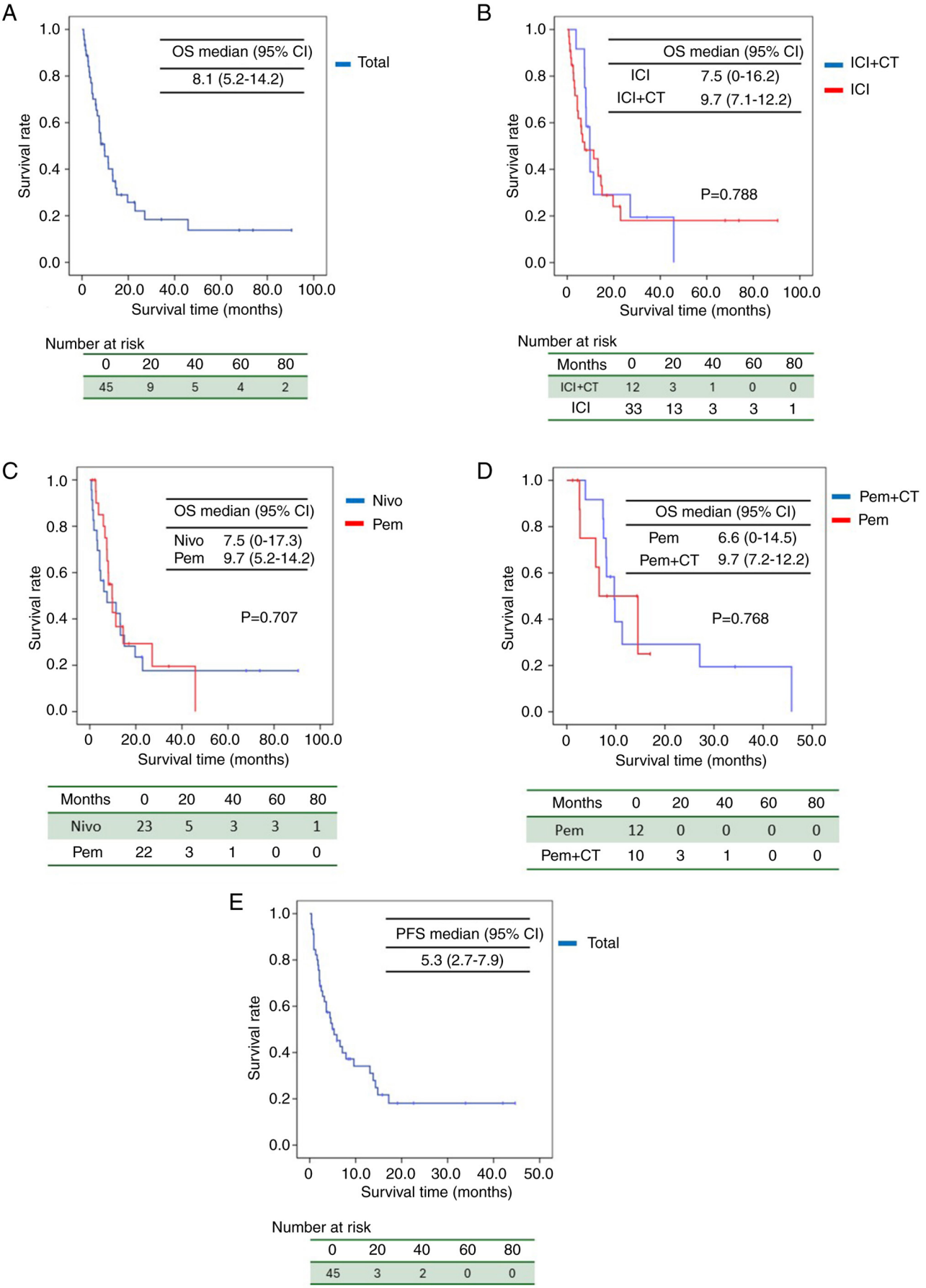
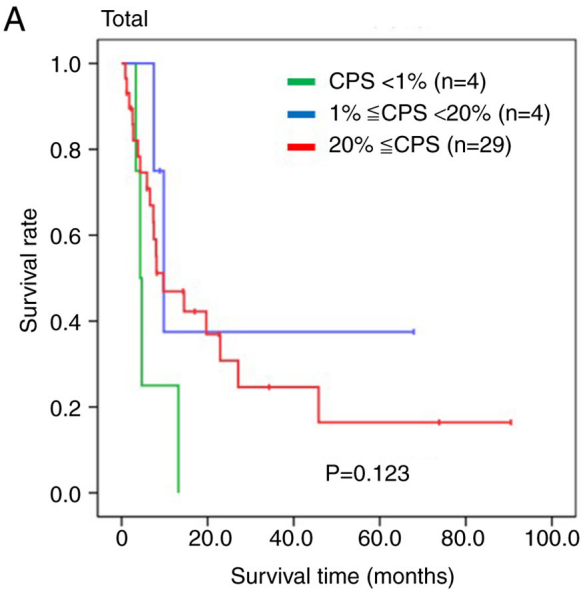
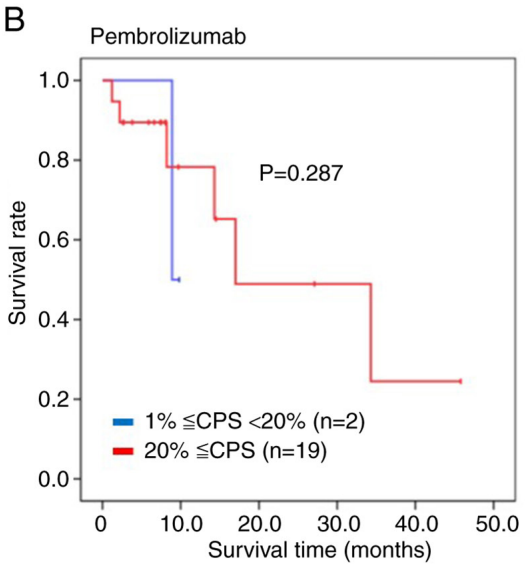



Figure 1. Kaplan-Meier curves for OS. (A) OS of the ICI-treated cohort, (B) OS of patients receiving ICI monotherapy or in combination with chemotherapy, (C) OS of patients treated with nivolumab or pembrolizumab, (D) OS of patients treated with pembrolizumab or in combination with chemotherapy, and (E) PFS of the ICI-treated cohort. ICI, immune checkpoint inhibitor; OS, overall survival; PFS, progression-free survival; CI, confidence interval; CT, chemotherapy; Nivo, nivolumab; Pem, pembrolizumab.

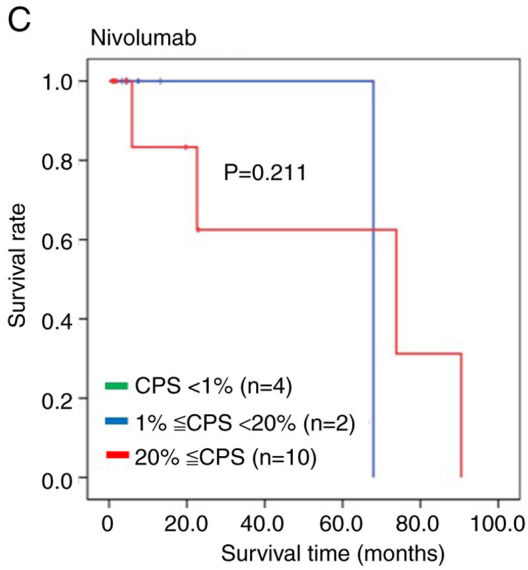



| | OS median (95% CI) |
|---|---|
| CPS <1% | 4.3 (2.9-5.7) |
| 1% ≦CPS <20% | 9.8 (6.4-13.2) |
| 20% ≦CPS | 9.7 (0-19.4) |

| Months | 0 | 20 | 40 | 60 | 80 |
|---|---|---|---|---|---|
| CPS <1% | 4 | 0 | 0 | 0 | 0 |
| 1% ≦CPS <20% | 4 | 1 | 1 | 1 | 0 |
| 20% ≦CPS | 29 | 7 | 3 | 2 | 1 |




| Months | 0 | 20 | 40 |
|---|---|---|---|
| 1% ≦CPS <20% | 2 | 0 | 0 |
| 20% ≦CPS | 19 | 3 | 1 |




| Months | 0 | 20 | 40 | 60 | 80 |
|---|---|---|---|---|---|
| CPS <1% | 4 | 0 | 0 | 0 | 0 |
| 1% ≦CPS <20% | 2 | 1 | 1 | 1 | 0 |
| 20% ≦CPS | 10 | 4 | 2 | 2 | 1 |

Figure 2. Comparison of OS by CPS values. (A) OS according to CPS values, (B) OS by CPS values in patients treated with pembrolizumab, and (C) OS by CPS values in patients treated with nivolumab. CPS, combined positive score; OS, overall survival.

Furthermore, in patients treated with pembrolizumab, those with CPS between 1 and <20 had a median OS of 8.9 months, whereas those with CPS ≥20 had a median OS of 17.0 months (95% CI: 0-34.6) (P=0.287) (Fig. 2B). Compared with patients with CPS <1, those with CPS ≥1 tended to have a prolonged median OS (Fig. 2A-C).

*Cutoff values for pre- and post-treatment markers according to ROC curve*. ROC curves were constructed to assess the discriminatory ability of biomarkers before and after treatment, and the area under the curve (AUC) was calculated (Fig. S1). The AUC values for pre-treatment markers were as follows: 0.53802 for pre-NLR, 0.4735 for pre-LMR, 0.59217

for pre-PNI, 0.50691 for pre-PLR, 0.39516 for pre-CAR, 0.55876 for pre-eosinophils, and 0.58641 for pre-lymphocytes. In contrast, the AUC values for post-treatment markers were 0.76959 for post-NLR, 0.68779 for post-LMR, 0.69585 for post-PNI, 0.64747 for post-PLR, 0.73618 for post-CAR, 0.51382 for post-eosinophils, and 0.69935 for post-lymphocytes. Among all markers evaluated before and after treatment, post-treatment NLR demonstrated the highest AUC of 0.76959, with a cutoff value of 7.17 (Table SIII).

*Univariate and multivariate analyses results of prognostic factors for OS and PFS*. We evaluated the impact of various factors on OS, including age, sex, ECOG PS, type of ICI, presence or absence of irAEs, ICI combination therapy, history of radiotherapy, body mass index (BMI) based on cutoff values calculated from the ROC curve, CPS value, DCR, and primary site (tongue vs. other), as shown in Table I. In univariate analysis, a higher ECOG PS was associated with poorer OS [hazard ratio (HR)=2.50; 95% CI=1.17-5.33; P=0.0185], and patients with PD as the efficacy of ICI had poorer OS (HR=4.30; 95% CI=1.79-10.33; P=0.0011). Conversely, in multivariate analysis, male sex was associated with poorer OS (HR=3.37; 95% CI=1.11-10.19; P=0.0316), and patients with PD as the efficacy of ICI demonstrated poorer OS (HR=6.96; 95% CI=1.80-27.03; P=0.0050).

In the univariate analysis of the same variables for PFS, ECOG PS, a history of radiotherapy, and DCR showed significant differences. Specifically, higher ECOG PS was associated with poorer PFS (HR=4.64; 95% CI=2.01-10.72; P=0.0003), while patients without prior radiotherapy exhibited poorer PFS (HR=2.57; 95% CI=1.03-6.44; P=0.043). Additionally, patients with PD as a response to ICI were associated with poor PFS (HR=5.54; 95% CI=2.15-14.27; P=0.0004). In the multivariate analysis, male sex was associated with poorer PFS (HR=3.86; 95% CI=1.32-11.31; P=0.0138). Furthermore, patients treated with nivolumab demonstrated poorer PFS (HR=11.75; 95% CI=2.68-51.49; P=0.0011), and those with PD as a response to ICI were also associated with poor PFS (HR=9.15; 95% CI=2.38-35.14; P=0.0013). Lastly, patients with primary tumors located in sites other than the tongue demonstrated significantly shorter PFS than those with tongue cancers (HR=4.87; 95% CI=1.51-15.72; P=0.0081) (Table SIV).

*Univariate and multivariate analyses results of pre- and post-treatment factors for OS and PFS*. Univariate analysis was performed to evaluate the association between pre-treatment factors, including age, sex, ECOG PS, CPS value, ICI combination, prior radiotherapy, BMI, and IBPS markers, encompassing both pre-treatment and post-treatment values for NLR, LMR, PNI, PLR, CAR, eosinophils, lymphocytes, and mGPS, and post-treatment factors, including the presence of irAE and IBPS markers, with OS and PFS as endpoints (Tables II and SV). Regarding OS, only a higher ECOG PS was associated with poor OS (HR=2.50; 95% CI=1.17-5.33; P=0.0185), and no significant differences were observed in pre-IBPS markers in the univariate analysis. Multivariate analysis indicated that pre-IBPS markers were not associated with prognosis; only sex and BMI were significantly linked to poor OS (Table II). However, 4-6 weeks after ICI administration, significant differences were found in NLR, PNI, CAR, and mGPS in the univariate analysis. Specifically, higher NLR (HR=2.15; 95% CI=1.07-4.33; P=0.034), lower PNI (HR=4.02; 95% CI=1.98-8.18; P=0.0002), higher CAR (HR=2.98; 95% CI=1.46-6.06; P=0.0025), and a mGPS of 1 (HR=2.26; 95% CI=1.02-5.05; P=0.0341) were associated with poorer OS. Additionally, higher NLR (HR=4.17; 95% CI=1.12-15.57; P=0.0337) and lower PNI (HR=3.92; 95% CI=1.44-10.64; P=0.0073) were associated with poorer OS in multivariate analysis.

For PFS, no significant differences were observed prior to ICI administration. Moreover, in univariate analysis, pre-IBPS markers showed no association with prognosis, though significant differences were noted in ECOG PS and history of radiotherapy. In multivariate analysis, pre-IBPS markers were not associated with prognosis; only sex was significantly correlated with poorer PFS. However, four to six weeks after ICI administration, significant differences were observed in NLR, PNI, and CAR. Higher NLR (HR=2.21; 95% CI=1.14-4.29; P=0.014), lower PNI (HR=3.25; 95% CI=1.61-6.55; P=0.0015), and higher CAR (HR=2.93; 95% CI=1.44-5.96; P=0.0029) were associated with poorer PFS. Moreover, significant differences were observed in NLR, LMR, and PNI in multivariate analysis. Higher NLR (HR=3.80; 95% CI=1.11-13.02; P=0.00339), lower PNI (HR=2.96; 95% CI=1.08-8.06; P=0.0342), and higher LMR (HR=4.02; 95% CI=1.14-14.18; P=0.0304) were associated with poorer PFS (Table SV).

*Univariate analysis results for prognostic factors for the DCR*. A univariate analysis was conducted to evaluate factors influencing the DCR (Table SVI). Significant differences were observed in ECOG PS (P=0.0018), CPS (P=0.007), BMI (P=0.032), and history of radiotherapy (P=0.027). The relationship between each IBPS item immediately prior to ICI administration and DCR was analyzed, but no significant differences were observed for any of the items (Table SVI). In contrast, when the relationship between post-treatment IBPS items and DCR was analyzed four to six weeks after ICI administration, significant differences were found in post-NLR (P=0.0006), post-LMR (P=0.0065), post-PNI (P=0.0358), post-PLR (P=0.0396), post-CAR (P=0.0062), and post-lymphocytes (P=0.0321).

*Kaplan-Meier curves of overall survival according to each IBPS*. Using the cutoff values determined from the ROC curve for each IBPS marker before and after treatment, patients were divided into two groups: High and Low. Then, Kaplan-Meier survival curves were generated with OS as the endpoint. Significant differences in OS were observed for the following markers: pre-NLR (P=0.004), pre-LMR (P<0.001), pre-PLR (P=0.008), pre-CAR (P=0.001), pre-lymphocytes (P=0.022), post-NLR (P=0.042), post-LMR (P=0.036), and post-lymphocytes (P=0.007) (Fig. 3).

In the Pre-NLR group, a significant difference in OS was observed between the Low group (NLR <7.17) and the High group (NLR ≥7.17) (P=0.042) (Fig. 3A). Similarly, in the Pre-LMR group, the Low group (LMR <1.29) and the High group (LMR ≥1.29) showed a significant difference (P<0.001) (Fig. 3B). However, no significant difference was found in the Pre-PNI group between the Low group

Table I. Univariate and multivariate analysis of prognosis factors for OS.

| | | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|---|
| Variable | Number | HR | 95% CI | P-value | HR | 95% CI | P-value |
| Age, years | | | | | | | |
| <65 | 20 | Ref. | | | | | |
| ≥65 | 25 | 1.06 | 0.53-2.14 | 0.864 | | | |
| Sex | | | | | | | |
| Male | 29 | 1.46 | 0.70-3.04 | 0.298 | 3.37 | 1.11-10.19 | 0.0316[a] |
| Female | 16 | Ref. | | | | | |
| ECOG PS | | | | | | | |
| 0 | 34 | Ref. | | | | | |
| ≥1 | 11 | 2.50 | 1.17-5.33 | 0.0185[a] | | | |
| ICI | | | | | | | |
| Nivolumab | 23 | 1.14 | 0.57-2.28 | 0.707 | | | |
| Pembrolizumab | 22 | Ref. | | | | | |
| irAE | | | | | | | |
| Positive | 13 | Ref. | | | | | |
| Negative | 32 | 1.18 | 0.47-2.96 | 0.736 | | | |
| ICI combination | | | | | | | |
| Monotherapy | 33 | Ref. | | | | | |
| With chemotherapy | 12 | 1.09 | 0.41-2.86 | 0.865 | | | |
| Radiation | | | | | | | |
| Previously | 39 | Ref. | | | | | |
| No | 6 | 2.09 | 0.82-5.28 | 0.146 | | | |
| BMI, kg/m$^2$ | | | | | | | |
| <18.37 | 20 | 1.57 | 0.69-3.14 | 0.200 | | | |
| ≥18.37 | 25 | Ref. | | | | | |
| CPS | | | | | | | |
| <20 | 8 | 1.18 | 0.47-2.96 | 0.736 | | | |
| ≥20 | 29 | Ref. | | | | | |
| DCR | | | | | | | |
| CR/PR/SD | 15 | Ref. | | | | | |
| PD | 40 | 4.30 | 1.79-10.33 | 0.0011[a] | 6.96 | 1.80-27.03 | 0.0050[a] |
| Primary site | | | | | | | |
| Tongue | 24 | Ref. | | | | | |
| Otherwise | 21 | 1.34 | 0.67-2.67 | 0.403 | | | |

[a]Indicates a significant difference among groups with P<0.05. OS, overall survival; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ICI, immune checkpoint inhibitor; BMI, body mass index; CPS, Combined Positive Score; DCR, Disease Control Rate; CR, Complete Response; PR, partial response; SD, stable disease; PD, progressive disease; HR, hazard ratio; CI, confidence interval; Ref, Reference.

(PNI <43.75) and the High group (PNI ≥43.75) (P=0.218) (Fig. 3C). In the Pre-PLR group, OS differed significantly between the Low group (PLR <453.5) and the High group (PLR ≥453.5) (P=0.008) (Fig. 3D). In the Pre-CAR group, a significant difference was found between the Low group (CAR <6.35) and the High group (CAR ≥6.35) (P=0.001) (Fig. 3E). Conversely, in the Pre-eosinophil group, no significant difference in OS was observed between the Low group (eosinophils <120/$\mu$l) and the High group (eosinophils ≥120/$\mu$l) (P=0.381) (Fig. 3F). A significant difference was observed in the Pre-lymphocytes group between the Low group (lymphocytes <670/$\mu$l) and the High group (lymphocytes ≥670/$\mu$l) (P=0.022) (Fig. 3G).

Regarding post-treatment IBPS markers, in the Post-NLR group, a significant difference in OS was found between the Low group (NLR <4.7) and the High group (NLR ≥4.7) (P=0.042) (Fig. 3H). In the Post-LMR group, the Low group (LMR <1.23) and the High group (LMR ≥1.23) also showed a significant

Table II. Univariate and multivariate analysis of pre- and post-treatment factors for OS.

A, Pre-treatment factors

| | | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|---|
| Variable | Number | HR | 95% CI | P-value | HR | 95% CI | P-value |
| Age, years | | | | | | | |
| <65 | 20 | Ref. | | | | | |
| ≥65 | 25 | 1.06 | 0.53-2.14 | 0.864 | | | |
| Sex | | | | | | | |
| Male | 29 | 1.46 | 0.70-3.04 | 0.298 | 4.11 | 1.50-11.24 | 0.0059[a] |
| Female | 16 | Ref. | | | | | |
| ECOG PS | | | | | | | |
| 0 | 34 | Ref. | | | | | |
| ≥1 | 11 | 2.50 | 1.17-5.33 | 0.0185[a] | | | |
| CPS | | | | | | | |
| <20 | 8 | 1.18 | 0.47-2.96 | 0.736 | | | |
| ≥20 | 29 | Ref. | | | | | |
| ICI combination | | | | | | | |
| Mono | 33 | Ref. | | | | | |
| With chemotherapy | 12 | 1.09 | 0.41-2.86 | 0.865 | | | |
| Radiation | | | | | | | |
| Previously | 39 | Ref. | | | | | |
| No | 6 | 2.09 | 0.82-5.28 | 0.146 | | | |
| BMI, kg/m$^2$ | | | | | | | |
| <18.37 | 20 | 1.57 | 0.69-3.14 | 0.200 | 3.33 | 1.22-9.08 | 0.0188[a] |
| ≥18.37 | 25 | Ref. | | | | | |
| Pre-NLR | | | | | | | |
| <4.7 | 16 | Ref. | | | | | |
| ≥4.7 | 29 | 1.42 | 0.69-2.90 | 0.338 | | | |
| Pre-LMR | | | | | | | |
| <1.29 | 32 | 1.73 | 0.88-3.40 | 0.123 | | | |
| ≥1.29 | 13 | Ref. | | | | | |
| Pre-PNI | | | | | | | |
| <43.75 | 30 | 1.31 | 0.69-2.48 | 0.397 | | | |
| ≥43.75 | 15 | Ref. | | | | | |
| Pre-PLR | | | | | | | |
| <453.5 | 31 | Ref. | | | | | |
| ≥453.5 | 14 | 1.18 | 0.62-2.29 | 0.630 | | | |
| Pre-CAR | | | | | | | |
| <6.35 | 43 | Ref. | | | | | |
| ≥6.35 | 2 | 4.33 | 0.99-18.99 | 0.100 | | | |
| Pre-eosinophil | | | | | | | |
| <120 | 18 | Ref. | | | | | |
| ≥120 | 27 | 1.21 | 0.65-2.22 | 0.550 | | | |
| Pre-lymphocytes | | | | | | | |
| <670 | 29 | 1.09 | 0.52-2.31 | 0.822 | | | |
| ≥670 | 16 | Ref. | | | | | |

Table II. Continued.

B, Post-treatment factors

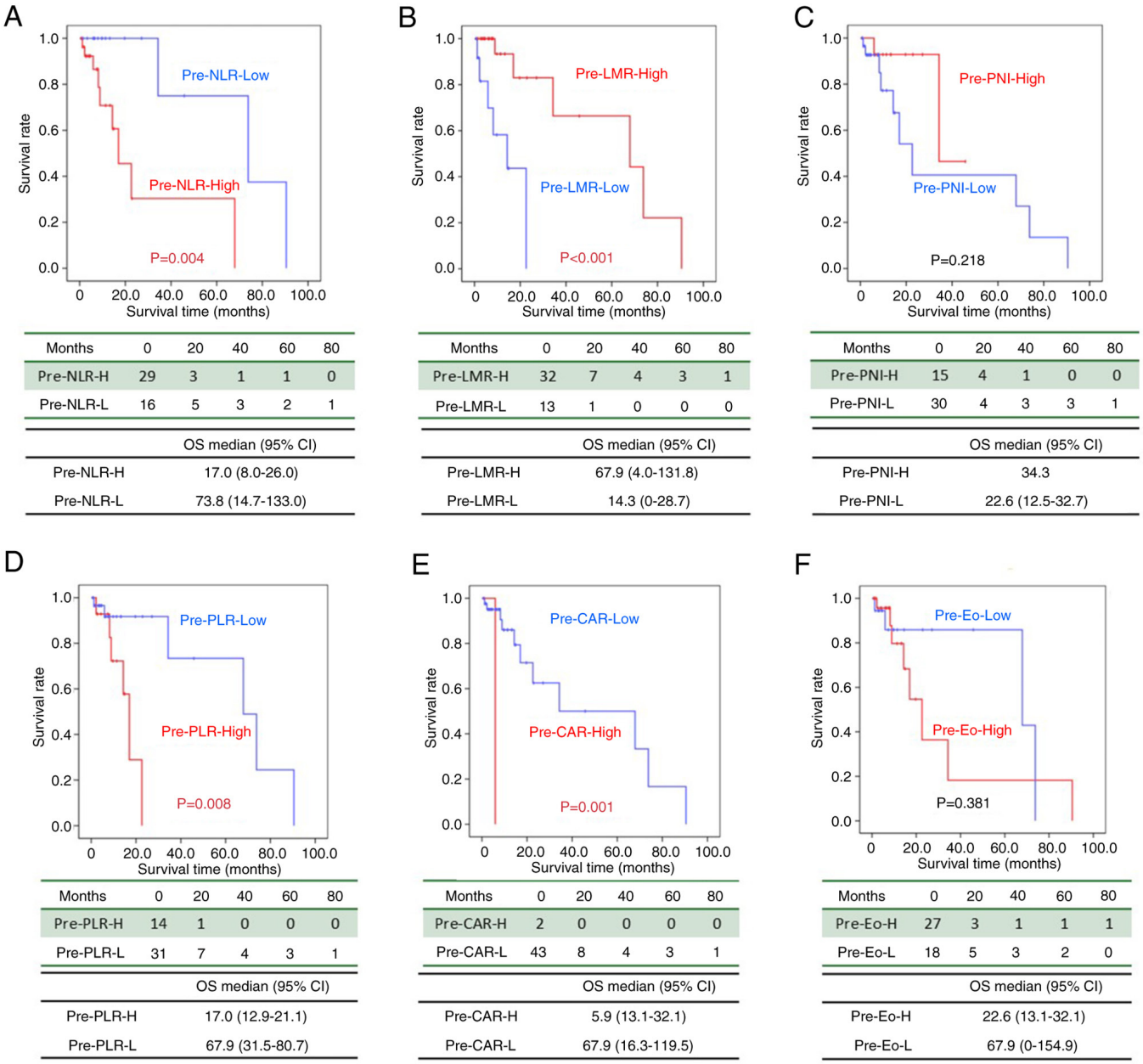
| Variable | Number | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|---|
| | | HR | 95% CI | P-value | HR | 95% CI | P-value |
| irAE | | | | | | | |
| Positive | 13 | Ref. | | | | | |
| Negative | 32 | 1.18 | 0.47-2.96 | 0.736 | | | |
| Post-NLR | | | | | | | |
| <7.17 | 22 | Ref. | | | | | |
| ≥7.17 | 23 | 2.15 | 1.07-4.33 | 0.034[a] | 4.17 | 1.12-15.57 | 0.0337 |
| Post-LMR | | | | | | | |
| <1.23 | 15 | 1.40 | 0.66-2.97 | 0.386 | | | |
| ≥1.23 | 30 | Ref. | | | | | |
| Post-PNI | | | | | | | |
| <36.6 | 16 | 4.02 | 1.98-8.18 | 0.0002[a] | 3.92 | 1.44-10.64 | 0.0073 |
| ≥36.6 | 29 | Ref. | | | | | |
| Post-PLR | | | | | | | |
| <221.1 | 13 | Ref. | | | | | |
| ≥221.1 | 32 | 1.34 | 0.62-2.91 | 0.442 | | | |
| Post-CAR | | | | | | | |
| <0.44 | 22 | Ref. | | | | | |
| ≥0.44 | 23 | 2.98 | 1.46-6.06 | 0.0025[a] | | | |
| Post-eosinophil | | | | | | | |
| <260 | 32 | 1.00 | 0.46-2.20 | 0.991 | | | |
| ≥260 | 13 | Ref. | | | | | |
| Post-lymphocytes | | | | | | | |
| <770 | 21 | 1.26 | 0.62-2.56 | 0.529 | | | |
| ≥770 | 25 | Ref. | | | | | |
| Post-mGPS | | | | | | | |
| 0 | 13 | Ref. | | | | | |
| 1 | 33 | 2.26 | 1.02-5.05 | 0.0341[a] | | | |

[a]Indicates a significant difference among groups with P<0.05. OS, overall survival; ECOG PS, Eastern Cooperative Oncology Group Performance Status; CPS, Combined Positive Score; ICI, Immune Checkpoint Inhibitor; BMI, body mass index; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PNI, prognostic nutritional index; PLR, platelet-to-lymphocyte ratio; CAR, C-reactive protein-to-albumin ratio; HR, hazard ratio; CI, confidence interval.

difference (P=0.036) (Fig. 3I). No significant difference was found in the Post-PNI group between the Low group (PNI <36.6) and the High group (PNI ≥36.6) (P=0.713) (Fig. 3J). Similarly, no significant difference was observed in the Post-PLR group (Low: PLR <221.1, High: PLR ≥221.1, P=0.493) (Fig. 3K), Post-CAR group (Low: CAR <0.44, High: CAR ≥0.44, P=0.309) (Fig. 3L), and the Post-eosinophil group (Low: eosinophils <260/$\mu$l, High: eosinophils ≥260/$\mu$l, P=0.147) (Fig. 3M). However, in the Post-lymphocytes group, a significant difference was observed between the Low group (lymphocytes <770/$\mu$l) and the High group (lymphocytes ≥770/$\mu$l) (P=0.007) (Fig. 3N). No significant difference was found between the Post-mGPS=0 group and the Post-mGPS=1 group (P=0.577) (Fig. 3O).

## Discussion

In this study, pre-treatment IBPS values did not show significant associations with OS or PFS. However, post-ICI treatment values for NLR, PNI, CAR, and mGPS were significantly correlated with OS. Similarly, post-treatment values for NLR, PNI, and CAR were significantly associated with PFS. While no significant association was observed between pre-treatment IBPS values and the DCR, post-treatment values of NLR, LMR, PNI, PLR, and CAR were significantly correlated with DCR. Survival analysis using Kaplan–Meier curves, with cutoff values derived from ROC analysis, revealed that high NLR, low LMR, high PLR, high CAR, and low lymphocyte




| Months | 0 | 20 | 40 | 60 | 80 |
|---|---|---|---|---|---|
| Pre-NLR-H | 29 | 3 | 1 | 1 | 0 |
| Pre-NLR-L | 16 | 5 | 3 | 2 | 1 |

| | OS median (95% CI) |
|---|---|
| Pre-NLR-H | 17.0 (8.0-26.0) |
| Pre-NLR-L | 73.8 (14.7-133.0) |

| Months | 0 | 20 | 40 | 60 | 80 |
|---|---|---|---|---|---|
| Pre-LMR-H | 32 | 7 | 4 | 3 | 1 |
| Pre-LMR-L | 13 | 1 | 0 | 0 | 0 |

| | OS median (95% CI) |
|---|---|
| Pre-LMR-H | 67.9 (4.0-131.8) |
| Pre-LMR-L | 14.3 (0-28.7) |

| Months | 0 | 20 | 40 | 60 | 80 |
|---|---|---|---|---|---|
| Pre-PNI-H | 15 | 4 | 1 | 0 | 0 |
| Pre-PNI-L | 30 | 4 | 3 | 3 | 1 |

| | OS median (95% CI) |
|---|---|
| Pre-PNI-H | 34.3 |
| Pre-PNI-L | 22.6 (12.5-32.7) |

| Months | 0 | 20 | 40 | 60 | 80 |
|---|---|---|---|---|---|
| Pre-PLR-H | 14 | 1 | 0 | 0 | 0 |
| Pre-PLR-L | 31 | 7 | 4 | 3 | 1 |

| | OS median (95% CI) |
|---|---|
| Pre-PLR-H | 17.0 (12.9-21.1) |
| Pre-PLR-L | 67.9 (31.5-80.7) |

| Months | 0 | 20 | 40 | 60 | 80 |
|---|---|---|---|---|---|
| Pre-CAR-H | 2 | 0 | 0 | 0 | 0 |
| Pre-CAR-L | 43 | 8 | 4 | 3 | 1 |

| | OS median (95% CI) |
|---|---|
| Pre-CAR-H | 5.9 (13.1-32.1) |
| Pre-CAR-L | 67.9 (16.3-119.5) |

| Months | 0 | 20 | 40 | 60 | 80 |
|---|---|---|---|---|---|
| Pre-Eo-H | 27 | 3 | 1 | 1 | 1 |
| Pre-Eo-L | 18 | 5 | 3 | 2 | 0 |

| | OS median (95% CI) |
|---|---|
| Pre-Eo-H | 22.6 (13.1-32.1) |
| Pre-Eo-L | 67.9 (0-154.9) |

Figure 3. Continued.

counts prior to ICI administration were associated with shorter OS. Furthermore, high NLR, low LMR, and low lymphocyte counts following ICI administration were significantly associated with shorter OS.

NLR is a marker of systemic inflammation and has been reported as a prognostic factor in various cancers, including R/M-OSCC (26-30). In our study, post-ICI NLR demonstrated the highest predictive accuracy (AUC=0.7696), with patients exhibiting NLR ≥7.17 having significantly shorter OS than those with NLR <7.17. An elevated NLR reflects an increase in neutrophils and a decrease in lymphocytes, suggesting tumor-associated inflammation and immune suppression (35). Several studies have reported that an increase in TILs is associated with a favorable prognosis (29,30). The mechanism underlying the association between elevated NLR and poor prognosis may be attributed to the inflammatory response, in which increased neutrophil production promotes tumor proliferation, invasion, and angiogenesis by inducing the secretion of chemokines and cytokines, further enhancing tumor-associated inflammation and suppressing anti-tumor immunity.

CAR is a marker that reflects systemic inflammation and nutritional status. In patients with a high CAR, elevated inflammatory cytokines stimulate CRP production while inhibiting albumin synthesis and accelerating its degradation, signaling the progression of cachexia (36-38). In head and neck squamous cell carcinoma, high interleukin-6 (IL-6) expression has been reported, and IL-6 signaling promotes immunosuppression and tumor progression (39,40). Local and systemic increases in IL-6 correlate with elevated CRP concentrations across various cancers (41,42). In our study, a high CAR was associated with a poor prognosis, highlighting its potential as an important prognostic marker for patients with squamous

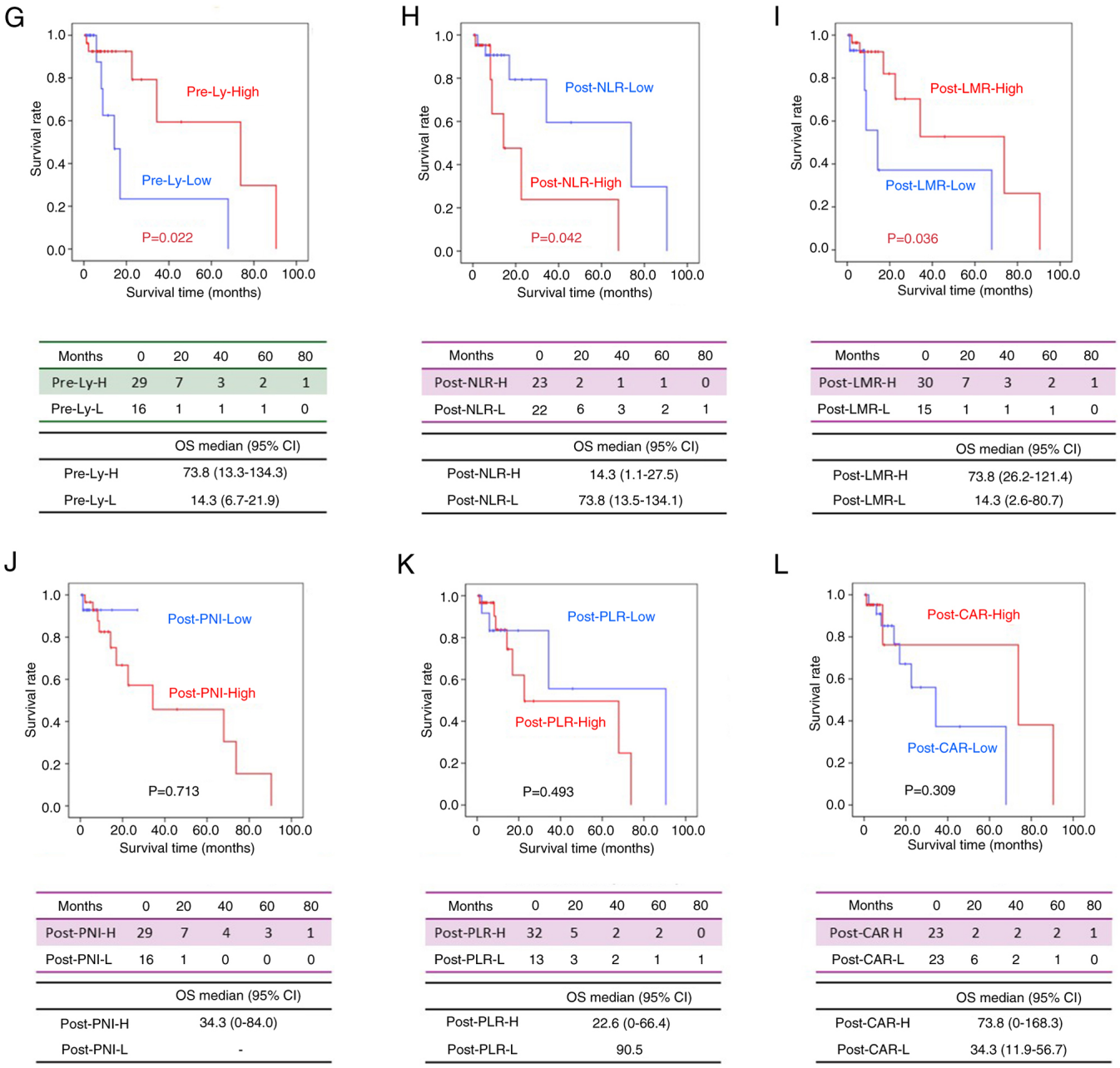



Figure 3. Continued.

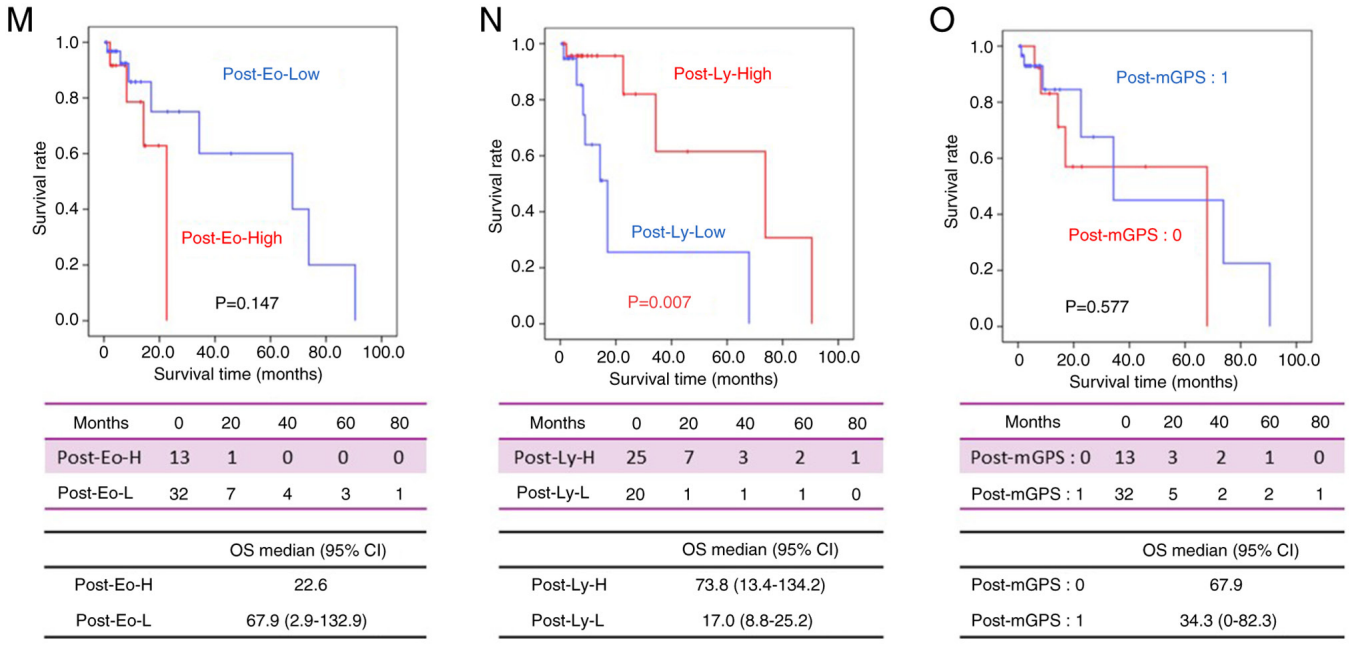
cell carcinoma undergoing chemoradiotherapy or cytotoxic chemotherapy.

Similarly, mGPS, calculated based on serum albumin and CRP levels (43), has been recognized as a prognostic factor for patients with recurrent or metastatic head and neck cancer (44-48). Consistent with these findings, our study also demonstrated a significant association between post-ICI mGPS values and OS.

PLR, another hematological inflammatory marker, is calculated from platelet and lymphocyte counts. Platelets, similar to neutrophils, play a key role in inflammation and are often elevated in patients with chronic inflammation associated with solid tumors (49,50). Elevated platelet counts have been linked to cancer progression, making PLR a promising predictive marker for tumor progression (31,32). Several studies have suggested that preoperative PLR values are valuable for prognosis prediction in gastrointestinal cancers, and more recent research has highlighted its potential for predicting the efficacy of systemic chemotherapy (14).

PNI, calculated using albumin levels and lymphocyte counts, reflects nutritional and immunological statuses (51). Previous studies have demonstrated that pre-ICI PNI is associated with the efficacy of ICIs in advanced or recurrent non-small cell lung cancer (52). Given the strong relationship between immune function and nutritional status, low PNI values are typically associated with poor prognosis. Our study further corroborates this, demonstrating that low PNI values are associated with reduced ICI efficacy and worse prognosis.

Notably, in our study, the AUC of nearly all hematological markers improved after treatment compared with pre-treatment values. This suggests that post-treatment values may serve as more reliable prognostic indicators in patients receiving ICI




| Months | 0 | 20 | 40 | 60 | 80 |
|---|---|---|---|---|---|
| Post-Eo-H | 13 | 1 | 0 | 0 | 0 |
| Post-Eo-L | 32 | 7 | 4 | 3 | 1 |

| | OS median (95% CI) |
|---|---|
| Post-Eo-H | 22.6 |
| Post-Eo-L | 67.9 (2.9-132.9) |

| Months | 0 | 20 | 40 | 60 | 80 |
|---|---|---|---|---|---|
| Post-Ly-H | 25 | 7 | 3 | 2 | 1 |
| Post-Ly-L | 20 | 1 | 1 | 1 | 0 |

| | OS median (95% CI) |
|---|---|
| Post-Ly-H | 73.8 (13.4-134.2) |
| Post-Ly-L | 17.0 (8.8-25.2) |

| Months | 0 | 20 | 40 | 60 | 80 |
|---|---|---|---|---|---|
| Post-mGPS : 0 | 13 | 3 | 2 | 1 | 0 |
| Post-mGPS : 1 | 32 | 5 | 2 | 2 | 1 |

| | OS median (95% CI) |
|---|---|
| Post-mGPS : 0 | 67.9 |
| Post-mGPS : 1 | 34.3 (0-82.3) |

Figure 3. Kaplan-Meier curves of OS according to each inflammation-based prognostic score. OS according to the (A) pre-NLR (A), (B) pre-LMR, (C) pre-PNI, (D) pre-PLR, (E) pre-CAR, (F) pre-Eo, (G) pre-Ly, (H) post-NLR, (I) post-LMR, (J) post-PNI, (K) post-PLR, (L) post-CAR, (M) post-Eo, (N) post-Ly and (O) post-mGPS. CAR, C-reactive protein-to-albumin ratio; Eo, eosinophils; LMR, lymphocyte-to-monocyte ratio; Ly, lymphocytes; mGPS, modified Glasgow Prognostic Score; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index.

therapy. Matsuo *et al* reported that pre-treatment IBPSs were insufficient for predicting prognosis in patients with R/M-head and neck squamous cell carcinoma, while post-nivolumab GPS, NLR, CAR, and eosinophil counts were significantly associated with survival outcomes (48). Similarly, Tachinami *et al* emphasized the importance of post-treatment IBPS, including NLR, CAR, and PLR, in predicting prognosis in R/M-OSCC (53). Our findings are consistent with those of these studies, suggesting that post-treatment data could be instrumental in predicting treatment response, enabling the early identification of patients with poor responses to ICI therapy and allowing for timely transition to alternative treatment strategies. In this study, the AUC values of biomarkers such as NLR, PNI, and CAR were below 0.8. While an AUC above 0.8 is considered to indicate high predictive accuracy, biomarkers with AUC values between 0.6 and 0.8 can still be clinically useful (54,55). Especially in patients with R/M-OSCC undergoing ICI therapy, the tumor immune microenvironment is complex, and it is challenging to predict prognosis with a single biomarker alone. In our analysis, even though the AUC values were moderate, NLR and PNI were found to be independent prognostic factors in multivariable analysis. Therefore, these markers may still have clinical value in supporting treatment decisions. Further improvements in predictive performance may be achieved by developing composite models that integrate multiple clinical and biological factors. Recent studies have identified several factors influencing the efficacy of ICIs, including irAEs, BMI, history of radiotherapy, ECOG PS, and CPS for PD-L1 expression (38,48,56-60). In our study, sex and BMI were significant predictors of OS, whereas sex, ICI type, presence of irAEs, and BMI were significant predictors of PFS. Additionally, ECOG PS, CPS values, BMI, and radiotherapy history were significantly associated with DCR.

In addition to hematological biomarkers such as IBPS, various other factors have been proposed as potential predictors of response to ICIs. Given the accessibility of peripheral blood samples, numerous studies have analyzed circulating cytokine levels, including tumor necrosis factor-alpha, interferon-γ (IFN-γ), IL-6, IL-8, and transforming growth factor-β (TGF-β) (61-63). Elevated IFN-γ levels have been associated with improved ICI efficacy and toxicity, while higher baseline levels of IL-8, IL-6, and TGF-β have been identified as negative predictive markers. However, the extent to which these circulating factors accurately reflect the tumor microenvironment remains debatable. Additionally, studies have indicated that a high neoantigen burden correlates with better treatment outcomes (64), whereas genetic mutations (e.g., epidermal growth factor receptor, *KRAS, PTEN, TP53*) and dysregulation of the Wnt signaling pathway may impact ICI response (65-69). Moreover, the use of corticosteroids, antibiotics, or proton pump inhibitors influences ICI efficacy, potentially through alterations in gut microbiota composition (70-72). Future research should aim to integrate these molecular, clinical, and therapeutic factors to optimize patient selection and enhance treatment strategies for ICI therapy.

One major limitation of this study is the small sample size, particularly after stratification into subgroups. This limitation is inherent to the retrospective design and the rarity of patients with R/M-OSCC treated with ICIs at a single institution. Although the limited cohort size reduced statistical power, we were still able to identify consistent trends in the performance of prognostic and predictive biomarkers, especially for NLR and PNI. These results aligned with those of previous reports (31,32,48,53) and suggest that inflammation- and nutrition-based biomarkers may provide meaningful clinical insights, even in smaller populations. In addition, potential selection biases related to treatment

history, clinical stage, and histological type were not fully controlled. Thus, further validation in prospective, multi-center studies with larger cohorts is essential to confirm our findings and develop robust predictive models. This study primarily aimed to identify pre-treatment biomarkers predictive of ICI efficacy in R/M-OSCC. While we also evaluated post-treatment biomarkers, their prognostic value seemed limited, likely due to their reflection of early treatment dynamics rather than baseline tumor biology. Nevertheless, post-treatment biomarkers assessed 4–6 weeks after ICI initiation showed potential for early prediction of treatment efficacy, which may help identify non-responders and guide timely treatment modifications. As our study did not include a control group receiving alternative treatments such as chemotherapy or targeted agents, the generalizability of our findings across different treatment modalities remains uncertain. Future prospective, multi-arm studies are warranted to evaluate the prognostic consistency of these biomarkers and to determine whether post-treatment markers retain predictive value independent of treatment type.

In conclusion, our study demonstrated that post-ICI values of NLR, PNI, CAR, and mGPS were significantly associated with survival outcomes in patients with R/M-OSCC. While pre-treatment IBPS values did not demonstrate significant associations with DCR, post-ICI values of NLR, LMR, PNI, PLR, and CAR exhibited significant correlations. These findings suggest that hematological biomarkers, including IBPS, may serve as valuable predictors of ICI treatment efficacy. Early prediction of ICI response and timely adjustments to treatment may lead to improved prognosis and the early identification of patients who could benefit from sequential treatment.

**Acknowledgements**

Not applicable.

**Funding**

This research was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture of Japan (grant no. 23K09398).

**Availability of data and materials**

The data generated in the present study may be requested from the corresponding author.

**Authors' contributions**

SaY and NI designed the study. SaY and AH organized the data collection and analyzed the data. SaY, NI, FO, TN, MH, SO, KK, TA and SoY participated in the treatment of patients with R/M-OSCC, and contributed to data analysis and interpretation. SaY and SoY were the main contributors to manuscript writing. SaY, NI and SoY confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

**Ethics approval and consent to participate**

This study was conducted in accordance with the principles of The Declaration of Helsinki and was approved by the Ethics Committee of Hiroshima University (approval no. E2024-0196). The requirement for informed consent was waived by the Ethics Committee owing to the retrospective design of the study.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

**References**

1. Werning JW: Oral cancer: Diagnosis, management, and rehabilitation. 1st Edition. Thieme Medical Publishing Group, New York, USA, pp 1, 2007.
2. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 74: 229-263, 2024.
3. Olson CM, Burda BU, Beil T and Whitlock EP: Screening for oral cancer: A targeted evidence update for the U.S. Preventive Services Task Force. Rockville, (MD), Agency for Healthcare Research and Quality (US), 2013.
4. Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, Erfan J, Zabolotnyy D, Kienzer HR, Cupissol D, *et al*: Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 359: 1116-1127, 2008.
5. Ferris RL, Blumenschein G Jr, Fayette J, Guigay J, Colevas AD, Licitra L, Harrington K, Kasper S, Vokes EE, Even C, *et al*: Nivolumab for recurrent Squamous-cell carcinoma of the head and neck. N Engl J Med 375: 1856-1867, 2016.
6. Cohen EEW, Soulières D, Le Tourneau C, Dinis J, Licitra L, Ahn MJ, Soria A, Machiels JP, Mach N, Mehra R, *et al*: Pembrolizumab versus standard therapy for recurrent or metastatic head and neck squamous cell carcinoma (KEYNOTE-048): A randomised, open-label, phase 3 study. Lancet 393: 156-167, 2019.
7. Hanna GJ, Schoenfeld JD and Ferris RL: Immunotherapy approaches in head and neck cancer: Current and emerging strategies. Front Immunol 13: 840904, 2022.
8. Zhang P, Su DM, Liang M and Fu J: Chemopreventive agents induce programmed death-1-ligand 1 (PD-L1) surface expression in breast cancer cells and promote PD-L1-mediated T cell apoptosis. Mol Immunol 45: 1470-1476, 2008.
9. Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA and Kinzler KW: Cancer genome landscapes. Science 339: 1546-1558, 2013.
10. Fridman WH, Pagès F, Sautès-Fridman C and Galon J: The immune contexture in human tumours: Impact on clinical outcome. Nat Rev Cancer 12: 298-306, 2012.
11. Forrest LM, McMillan DC, McArdle CS, Angerson WJ and Dunlop DJ: Evaluation of cumulative prognostic scores based on the systemic inflammatory response in patients with inoperable Non-small-cell lung cancer. Br J Cancer 89: 1028-1030, 2003.
12. Shibutani M, Maeda K, Nagahara H, Iseki Y, Hirakawa K and Ohira M: The significance of the C-reactive protein to albumin ratio as a marker for predicting survival and monitoring chemotherapeutic effectiveness in patients with unresectable metastatic colorectal cancer. Springerplus 5: 1798, 2016.
13. An X, Ding PR, Li YH, Wang FH, Shi YX, Wang ZQ, He YJ, Xu RH and Jiang WQ: Elevated neutrophil to lymphocyte ratio predicts survival in advanced pancreatic cancer. Biomarkers 15: 516-522, 2010.
14. Wu Y, Li C, Zhao J, Yang L, Liu F, Zheng H, Wang Z and Xu Y: Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios predict chemotherapy outcomes and prognosis in patients with colorectal cancer and synchronous liver metastasis. World J Surg Oncol 14: 289, 2016.
15. Yang L, Huang Y, Zhou L, Dai Y and Hu G: High pretreatment neutrophil-to-lymphocyte ratio as a predictor of poor survival prognosis in head and neck squamous cell carcinoma: Systematic review and meta-analysis. Head Neck 41: 1525-1535, 2019.
16. Rassouli A, Saliba J, Castano R, Hier M and Zeitouni AG: Systemic inflammatory markers as independent prognosticators of head and neck squamous cell carcinoma. Head Neck 37: 103-110, 2015.

17. Takenaka Y, Oya R, Kitamiura T, Ashida N, Shimizu K, Takemura K, Yamamoto Y and Uno A: Platelet count and platelet-lymphocyte ratio as prognostic markers for head and neck squamous cell carcinoma: Meta-analysis. Head Neck 40: 2714-2723, 2018.
18. Bardash Y, Olson C, Herman W, Khaymovich J, Costantino P and Tham T: Platelet-lymphocyte ratio as a predictor of prognosis in head and neck cancer: A systematic review and meta-analysis. Oncol Res Treat 42: 665-677, 2019.
19. Nishikawa D, Suzuki H, Koide Y, Beppu S, Kadowaki S, Sone M and Hanai N: Prognostic markers in head and neck cancer patients treated with nivolumab. Cancers (Basel) 10: 466, 2018.
20. Mohammed FF, Poon I, Zhang L, Elliott L, Hodson ID, Sagar SM and Wright J: Acute-phase response reactants as objective biomarkers of radiation-induced mucositis in head and neck cancer. Head Neck 34: 985-993, 2012.
21. Kano S, Homma A, Hatakeyama H, Mizumachi T, Sakashita T, Kakizaki T and Fukuda S: Pretreatment lymphocyte-to-monocyte ratio as an independent prognostic factor for head and neck cancer. Head Neck 39: 247-253, 2017.
22. Ikeguchi M: Glasgow prognostic score and neutrophil-lymphocyte ratio are good prognostic indicators after radical neck dissection for advanced squamous cell carcinoma in the hypopharynx. Langenbecks Arch Surg 401: 861-866, 2016.
23. Turri-Zanoni M, Salzano G, Lambertoni A, Giovannardi M, Karligkiotis A, Battaglia P and Castelnuovo P: Prognostic value of pretreatment peripheral blood markers in paranasal sinus cancer: Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratio. Head Neck 39: 730-736, 2017.
24. Mikoshiba T, Ozawa H, Saito S, Ikari Y, Nakahara N, Ito F, Watanabe Y, Sekimizu M, Imanishi Y and Ogawa K: Usefulness of hematological inflammatory markers in predicting severe side-effects from induction chemotherapy in head and neck cancer patients. Anticancer Res 39: 3059-3065, 2019.
25. Yasumatsu R, Wakasaki T, Hashimoto K, Nakashima K, Manako T, Taura M, Matsuo M and Nakagawa T: Monitoring the neutrophil-to-lymphocyte ratio may be useful for predicting the anticancer effect of nivolumab in recurrent or metastatic head and neck cancer. Head Neck 41: 2610-2618, 2019.
26. Ferrucci PF, Ascierto PA, Pigozzo J, Del Vecchio M, Maio M, Antonini Cappellini GC, Guidoboni M, Queirolo P, Savoia P, Mandalà M, *et al*: Baseline neutrophils and derived neutrophil-to-lymphocyte ratio: Prognostic relevance in metastatic melanoma patients receiving ipilimumab. Ann Oncol 27: 732-738, 2016.
27. Kiriu T, Yamamoto M, Nagano T, Hazama D, Sekiya R, Katsurada M, Tamura D, Tachihara M, Kobayashi K and Nishimura Y: The time-series behavior of neutrophil-to-lymphocyte ratio is useful as a predictive marker in non-small cell lung cancer. PLoS One 13: e0193018, 2018.
28. Sacdalan DB, Lucero JA and Sacdalan DL: Prognostic utility of baseline neutrophil-to-lymphocyte ratio in patients receiving immune checkpoint inhibitors: A review and meta-analysis. Onco Targets Ther 11: 955-965, 2018.
29. Diem S, Schmid S, Krapf M, Flatz L, Born D, Jochum W, Templeton AJ and Früh M: Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) as prognostic markers in patients with non-small cell lung cancer (NSCLC) treated with nivolumab. Lung Cancer 111: 176-181, 2017.
30. Bagley SJ, Kothari S, Aggarwal C, Bauml JM, Alley EW, Evans TL, Kosteva JA, Ciunci CA, Gabriel PE, Thompson JC, *et al*: Pretreatment neutrophil-to-lymphocyte ratio as a marker of outcomes in nivolumab-treated patients with advanced non-small-cell lung cancer. Lung Cancer 106: 1-7, 2017.
31. Jain S, Harris J and Ware J: Platelets: Linking hemostasis and cancer. Arterioscler Thromb Vasc Biol 30: 2362-2367, 2010.
32. Nieswandt B, Hafner M, Echtenacher B and Männel DN: Lysis of tumor cells by natural killer cells in mice is impeded by platelets. Cancer Res 59: 1295-1300, 1999.
33. Sobin LH, Gospodarowicz MK and Wittekind C: TNM classification of malignant tumours. 8th Edition. Wiley-Blackwell, Hoboken, NJ, 2016.
34. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, *et al*: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45: 228-247, 2009.
35. Granot Z and Jablonska J: Distinct functions of neutrophil in cancer and its regulation. Mediators Inflamm 2015: 701067, 2015.
36. Ferris RL: Immunology and immunotherapy of head and neck cancer. J Clin Oncol 33: 3293-3304, 2015.
37. Pettersen K, Andersen S, Degen S, Tadini V, Grosjean J, Hatakeyama S, Tesfahun AN, Moestue S, Kim J, Nonstad U, *et al*: Cancer cachexia associates with a systemic autophagy-inducing activity mimicked by cancer cell-derived IL-6 trans-signaling. Sci Rep 7: 2046, 2017.
38. Tanoue K, Tamura S, Kusaba H, Shinohara Y, Ito M, Tsuchihashi K, Shirakawa T, Otsuka T, Ohmura H, Isobe T, *et al*: Predictive impact of C-reactive protein to albumin ratio for recurrent or metastatic head and neck squamous cell carcinoma receiving nivolumab. Sci Rep 11: 2741, 2021.
39. Duffy SA, Taylor JM, Terrell JE, Islam M, Li Y, Fowler KE, Wolf GT and Teknos TN: Interleukin-6 predicts recurrence and survival among head and neck cancer patients. Cancer 113: 750-757, 2008.
40. Riedel F, Zaiss I, Herzog D, Götte K, Naim R and Hörmann K: Serum levels of interleukin-6 in patients with primary head and neck squamous cell carcinoma. Anticancer Res 25: 2761-2765, 2005.
41. Ravishankaran P and Karunanithi R: Clinical significance of preoperative serum interleukin-6 and C-reactive protein level in breast cancer patients. World J Surg Oncol 9: 18, 2011.
42. McKeown DJ, Brown DJ, Kelly A, Wallace AM and McMillan DC: The relationship between circulating concentrations of C-reactive protein, inflammatory cytokines and cytokine receptors in patients with non-small-cell lung cancer. Br J Cancer 91: 1993-1995, 2004.
43. Inoue Y, Iwata T, Okugawa Y, Kawamoto A, Hiro J, Toiyama Y, Tanaka K, Uchida K, Mohri Y, Miki C and Kusunoki M: Prognostic significance of a systemic inflammatory response in patients undergoing multimodality therapy for advanced colorectal cancer. Oncology 84: 100-107, 2013.
44. Matsuki T, Okamoto I, Fushimi C, Sawabe M, Kawakita D, Sato H, Tsukahara K, Kondo T, Okada T, Tada Y, *et al*: Hematological predictive markers for recurrent or metastatic squamous cell carcinomas of the head and neck treated with nivolumab: A multicenter study of 88 patients. Cancer Med 9: 5015-5024, 2020.
45. Ueki Y, Takahashi T, Ota H, Shodo R, Yamazaki K and Horii A: Predicting the treatment outcome of nivolumab in recurrent or metastatic head and neck squamous cell carcinoma: Prognostic value of combined performance status and modified Glasgow prognostic score. Eur Arch Otorhinolaryngol 277: 2341-2347, 2020.
46. Niwa K, Kawakita D, Nagao T, Takahashi H, Saotome T, Okazaki M, Yamazaki K, Okamoto I, Hirai H, Saigusa N, *et al*: Multicentre, retrospective study of the efficacy and safety of nivolumab for recurrent and metastatic salivary gland carcinoma. Sci Rep 10: 16988, 2020.
47. Minohara K, Matoba T, Kawakita D, Takano G, Oguri K, Murashima A, Nakai K, Iwaki S, Hojo W, Matsumura A, *et al*: Novel Prognostic Score for recurrent or metastatic head and neck cancer patients treated with Nivolumab. Sci Rep 11: 16992, 2021.
48. Matsuo M, Yasumatsu R, Masuda M, Toh S, Wakasaki T, Hashimoto K, Jiromaru R, Manako T and Nakagawa T: Inflammation-based prognostic score as a prognostic biomarker in patients with recurrent and/or metastatic head and neck squamous cell carcinoma treated with nivolumab therapy. In Vivo 36: 907-917, 2022.
49. Wagner DD: New links between inflammation and thrombosis. Arterioscler Thromb Vasc Biol 25: 1321-1324, 2005.
50. Stone RL, Nick AM, McNeish IA, Balkwill F, Han HD, Bottsford-Miller J, Rupairmoole R, Armaiz-Pena GN, Pecot CV, Coward J, *et al*: Paraneoplastic thrombocytosis in ovarian cancer. N Engl J Med 366: 610-618, 2012.
51. Zhang L, Ma W, Qiu Z, Kuang T, Wang K, Hu B and Wang W: Prognostic nutritional index as a prognostic biomarker for gastrointestinal cancer patients treated with immune checkpoint inhibitors. Front Immunol 14: 1219929, 2023.
52. Shoji F, Takeoka H, Kozuma Y, Toyokawa G, Yamazaki K, Ichiki M and Takeo S: Pretreatment prognostic nutritional index as a novel biomarker in non-small cell lung cancer patients treated with immune checkpoint inhibitors. Lung Cancer 136: 45-51, 2019.
53. Tachinami H, Tomihara K, Yamada SI, Ikeda A, Imaue S, Hirai H, Nakai H, Sonoda T, Kurohara K, Yoshioka Y, *et al*: Neutrophil-to-lymphocyte ratio as an early marker of outcomes in patients with recurrent oral squamous cell carcinoma treated with nivolumab. Br J Oral Maxillofac Surg 61: 320-326, 2023.

54. Zhou XH, Obuchowski NA and McClish DK: Statistical methods in diagnostic medicine. 2nd Edition. John Wiley & Sons, New Jersey, 2011.
55. Valero C, Lee M, Hoen D, Zehir A, Berger MF, Seshan VE, Chan TA and Morris LGT: Response rates to anti-PD-1 immunotherapy in microsatellite-stable solid tumors with 10 or more mutations per megabase. JAMA Oncol 7: 739-743, 2021.
56. Iwasa YI, Kitoh R, Yokota Y, Hori K, Kasuga M, Kobayashi T, Kanda S and Takumi Y: Post-treatment neutrophil/lymphocyte ratio is a prognostic factor in head and neck cancers treated with nivolumab. Cancer Diagn Progn 4: 182-188, 2024.
57. Shaverdian N, Lisberg AE, Bornazyan K, Veruttipong D, Goldman JW, Formenti SC, Garon EB and Lee P: Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: A secondary analysis of the KEYNOTE-001 phase 1 trial. Lancet Oncol 18: 895-903, 2017.
58. Öjlert ÅK, Nebdal D, Lund-Iversen M, Åstrøm Ellefsen R, Brustugun OT, Gran JM, Halvorsen AR and Helland Å: Immune checkpoint blockade in the treatment of advanced non-small cell lung cancer-predictors of response and impact of previous radiotherapy. Acta Oncol 60: 149-156, 2021.
59. Shankar B, Zhang J, Naqash AR, Forde PM, Feliciano JL, Marrone KA, Ettinger DS, Hann CL, Brahmer JR, Ricciuti B, *et al*: Multisystem immune-related adverse events associated with immune checkpoint inhibitors for treatment of non-small cell lung cancer. JAMA Oncol 6: 1952-1956, 2020.
60. Hsiehchen D, Naqash AR, Espinoza M, Von Itzstein MS, Cortellini A, Ricciuti B, Owen DH, Laharwal M, Toi Y, Burke M, *et al*: Association between immune-related adverse event timing and treatment outcomes. Oncoimmunology 11: 2017162, 2022.
61. Wang M, Zhai X, Li J, Guan J, Xu S, Li Y and Zhu H: The role of cytokines in predicting the response and adverse events related to immune checkpoint inhibitors. Front Immunol 12: 670391, 2021.
62. Fehrenbacher L, Spira A, Ballinger M, Kowanetz M, Vansteenkiste J, Mazieres J, Park K, Smith D, Artal-Cortes A, Lewanski C, *et al*: Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): A multicentre, open-label, phase 2 randomised controlled trial. Lancet 387: 1837-1846, 2016.
63. Sanmamed MF, Perez-Gracia JL, Schalper KA, Fusco JP, Gonzalez A, Rodriguez-Ruiz ME, Oñate C, Perez G, Alfaro C, Martín-Algarra S, *et al*: Changes in serum interleukin-8 (IL-8) levels reflect and predict response to anti-PD-1 treatment in melanoma and non-small-cell lung cancer patients. Ann Oncol 28: 1988-1995, 2017.
64. McGranahan N, Furness AJ, Rosenthal R, Ramskov S, Lyngaa R, Saini SK, Jamal-Hanjani M, Wilson GA, Birkbak NJ, Hiley CT, *et al*: Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. Science 351: 1463-1469, 2016.
65. Miao D, Margolis CA, Vokes NI, Liu D, Taylor-Weiner A, Wankowicz SM, Adeegbe D, Keliher D, Schilling B, Tracy A, *et al*: Genomic correlates of response to immune checkpoint blockade in microsatellite-stable solid tumors. Nat Genet 50: 1271-1281, 2018.
66. Giroux Leprieur E, Hélias-Rodzewicz Z, Takam Kamga P, Costantini A, Julie C, Corjon A, Dumenil C, Dumoulin J, Giraud V, Labrune S, *et al*: Sequential ctDNA whole-exome sequencing in advanced lung adenocarcinoma with initial durable tumor response on immune checkpoint inhibitor and late progression. J Immunother Cancer 8: e000527, 2020.
67. Guibert N, Jones G, Beeler JF, Plagnol V, Morris C, Mourlanette J, Delaunay M, Keller L, Rouquette I, Favre G, *et al*: Targeted sequencing of plasma cell-free DNA to predict response to PD1 inhibitors in advanced non-small cell lung cancer. Lung Cancer 137: 1-6, 2019.
68. Zhang W, Li Y, Lyu J, Shi F, Kong Y, Sheng C, Wang S and Wang Q: An aging-related signature predicts favorable outcome and immunogenicity in lung adenocarcinoma. Cancer Sci 113: 891-903, 2022.
69. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, Chow LQ, Vokes EE, Felip E, Holgado E, *et al*: Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 373: 1627-1639, 2015.
70. Arbour KC, Mezquita L, Long N, Rizvi H, Auclin E, Ni A, Martínez-Bernal G, Ferrara R, Lai WV, Hendriks LEL, *et al*: Impact of baseline steroids on efficacy of programmed cell death-1 and programmed death-ligand 1 blockade in patients with non-small-cell lung cancer. J Clin Oncol 36: 2872-2878, 2018.
71. Liu C, Guo H, Mao H, Tong J, Yang M and Yan X: An up-to-date investigation into the correlation between proton pump inhibitor use and the clinical efficacy of immune checkpoint inhibitors in advanced solid cancers: A systematic review and meta-analysis. Front Oncol 12: 753234, 2022.
72. Ochi N, Ichihara E, Takigawa N, Harada D, Inoue K, Shibayama T, Hosokawa S, Kishino D, Harita S, Oda N, *et al*: The effects of antibiotics on the efficacy of immune checkpoint inhibitors in patients with non-small-cell lung cancer differ based on PD-L1 expression. Eur J Cancer 149: 73-81, 2021.