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Original

Inflammation-Based Prognostic Scores as Prognostic Factors in Patients with Oral Squamous Cell Carcinoma after Primary Surgery: A Single-Center Retrospective Cohort Study

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Summary

Introduction: Inflammation-based prognostic scores (IBPSs) is suggested to be associated with prognosis in many carcinomas including oral squamous cell carcinoma (OSCC), but we are skeptical that each IBPS alone is a strong prognostic factor. We examined whether IBPSs are valid prognostic predictors in a retrospective cohort study of patients undergoing primary surgery for OSCC.

Methods: The study was performed in 287 patients with OSCC primarily treated by surgery from 2007 to 2019 at our center. The IBPSs examined were the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), prognostic index (PI), and modified Glasgow prognostic score (mGPS), evaluated by blood tests at the first visit and at the end of primary treatment.

Results: There was no significant difference in OS and DFS between the two groups based on the cutoffs for NLR, PLR and LMR at first visit. Similarly, a comparison in OS and DFS for cases with mGPS and PI scores of 0 and 1 + 2 at the first visit showed no significant difference. The relative (at the end of primary treatment/the first visit) NLR, PLR and LMR had no effect on death or events. Whereas, worsening of mGPS and of PI at the end of primary treatment were both significantly correlated with poor prognosis for death and events (both $p < 0.001$).

Conclusions: This study found that IBPSs were not effective as presurgical prognostic factors for patient with OSCC in our center. Further investigation and validation of indices and assessment methods are required to improve the impact of IBPS biomarkers on prognosis prediction and treatment choice in patients with OSCC.

Key Words: inflammation-based prognostic scores, oral squamous cell carcinoma, prognostic factor

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Introduction

Oral squamous cell carcinoma (OSCC) is mainly treated with surgery in combination with chemotherapy (including molecular-targeted drugs), immune checkpoint inhibitors, and radiotherapy. These treatments have improved overall survival (OS) in patients with OSCC, but local recurrence, cervical lymph node metastasis, and distant metastasis may still occur after initial clinical complete resection. Therefore, a number of prognostic predictors have been investigated in OSCC.

Cancer-related inflammation is associated with regulation of the tumor microenvironment[1], and systemic inflammatory responses play an important role in carcinogenesis and metastasis of tumors[2,3]. Thus, various biomarkers reflecting the inflammatory conditions of patients with cancer have been reported as prognostic predictors for several carcinomas[4-18]. These biomarkers are collectively referred to as inflammation-based prognostic scores (IBPSs), and include the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and lymphocyte-monocyte ratio (LMR), which are expressed as ratios of hemocyte composition; the prognostic index (PI), and the modified Glasgow prognostic score (mGPS), which are based on C-reactive protein (CRP) and/or albumin (ALB) levels[4-18].

IBPSs is suggested to be associated with recurrence and prognosis in oral cancer[12-18], but we are skeptical that each IBPS alone is a strong prognostic factor. IBPSs are easy to obtain from blood test data, but on the other hand, it is easily affected by multiple factors. In this study, we examined whether IBPSs are valid prognostic predictors in a retrospective cohort study of patients undergoing primary surgery for OSCC.

Patients and Methods

Patients and data sources

The subjects were 287 patients with OSCC who underwent primary surgery at the Department of Oral and Maxillofacial Surgery, Dokkyo Medical University Hospital between 2007 and 2019 and had data for IBPS estimation. The retrospective cohort study design was approved by the Medical Ethical Research Committee of Dokkyo Medical University Hospital (approval ID R-22-12J). Inclusion into the study was voluntary and no patients chose to opt out. Baseline demographic and clinical data, including age, sex, and performance status (PS), were collected at the first visit. Primary surgery was performed within one month of this visit based on the preoperative diagnosis. In cases with a resected tumor close to the surgical margin (within 5 mm) or a tumor on the surgical margin, additional resection was performed within 1 week after recognition of the status of the surgical margin. Therefore, complete resection of the visible tumor with a safety margin was confirmed in all patients. Cancer staging was performed using the UICC TNM Classification of Malignant Tumours, 8th edition[19].

Values of IBPSs

The IBPSs examined were the NLR, PLR, LMR, PI, and mGPS. Blood tests necessary for IBPS evaluation were performed at the first visit and at the end of primary treatment. We used the following definition of "the end of primary treatment" in this study. For patients with only surgical therapy, we used blood results taken immediately after discharge (within 1 month). For patients with postoperative treatment (radiotherapy or intravenous chemotherapy), we used blood samples taken immediately after discharge (within 1 month, for inpatient treatment) or at the next visit on the day of completion of postoperative treatment (within 1 month, for outpatient treatment), depending on histopathologic risk assessment. Postoperative S-1 or UFT administration as adjuvant therapy was not included in the primary treatment.

mGPS was scored based on the levels of CRP and serum ALB, as 2 points (CRP > 1 mg/dL, ALB < 3.5 g/dL), 1 point (CRP > 1 mg/dL, ALB ≥ 3.5 g/dL), and 0 points (CRP ≤ 1 mg/dL). PI was scored using the CRP level and white blood cell (WBC) count, as 0 points (CRP ≤ 1.0 mg/dL, WBC ≤ 11,000/μL), 1 point (CRP > 1.0 mg/dL, WBC ≤ 11,000/μL; or CRP > 1.0 mg/dL, WBC ≤ 11,000/μL), and 2 points (CRP > 1.0 mg/dL, WBC > 11,000/μL). Some IBPSs were not calculated for cases in which the required data were not available.

Statistical analysis

Postoperative events were defined as local recurrence, cervical lymph node metastasis, distal metasta-

Table 1 Clinical background data

Item	Number	% or SD	Item	Number	% or SD
Sex, n (%)			Primary treatment, n (%)		
Male	165	57.5	Surgery only	221	77.0
Female	122	42.5	+ Postoperative chemotherapy	22	7.7
Age, mean (SD) (years)	66.39	14.0	+ Postoperative radiotherapy	12	4.2
Age, median (years)	68		+ Postoperative chemoradiotherapy	32	11.1
Performance status, n (%)			Adjuvant chemotherapy, n (%)	105	36.6
0	258	89.9	Clinical T category, n (%)		
1	19	6.6	Tis	11	3.8
2	7	2.4	T1	45	15.7
3	1	0.4	T2	73	25.4
4	2	0.7	T3	53	18.5
NLR, mean (SD)	2.67	1.8	T4a	103	35.9
NLR, median	2.15		T4b	2	0.7
PLR, mean (SD)	159.6	151.7	Clinical N category, n (%)		
PLR, median	159.6		N0	165	57.5
LMR, mean (SD)	5.27	2.5	N1	60	20.9
LMR, median	4.94		N2b	48	16.7
mGPS, n (%)			N2c	11	3.8
0	216	90.4	N3b	3	1.0
1	17	7.1	Clinical stage, n (%)		
2	6	2.5	Stage 0	11	3.8
PI, n (%)			Stage 1	44	15.3
0	233	90.3	Stage 2	50	17.4
1	23	8.9	Stage 3	62	21.6
2	2	0.8	Stage 4a	114	39.7
Primary site, n (%)			Stage 4b	6	2.1
Tongue	137	47.7	Prognoses		
Lower gingiva	64	22.3	Death in 5-year period, n (%)	46	16.0
Upper gingiva	37	12.9	Events in 5-year period, n (%)	55	19.2
Buccal mucosa	23	8.0			
Oral floor	18	6.3			
Lip	5	1.7			
Palate	3	1.0			

sis, and secondary cancer. The period to death or a postoperative event was calculated based on the date of surgery, regardless of implementation of postoperative treatment. The postoperative observation period was until March 2020. Five-year OS and disease-free survival (DFS) rates were evaluated in each clinical cancer stage and for each IBPS using Kaplan-Meier analysis, with significance determined by Log-rank test. Cutoffs for NLR, PLR and LMR were evaluated using receiver operating characteristic (ROC) curves. The prognostic effects of relative NLR, PLR, and LMR (value at the end of primary treatment/value at the first visit) are shown using box-and-whisker plots. Means for survival vs. non-survival and event-free vs. event-occurrence cases were compared by Student t test. PI and mGPS scores were divided into groups (no change + improved vs. worsened) for evaluation of survival and event occurrence, using a chi-square test for significance. A two-tailed $p < 0.05$ was considered to be significant in all analyses. IBM SPSS ver. 24.0 (IBM SPSS, Inc., Tokyo, Japan) was used for all calculations.

Results

Characteristics and treatment of patients with OSCC

The characteristics of the 287 patients with OSCC are shown in Table 1. The patients included 165 males (57.5%) and the median age was 68 years. PS was 0, 1 and 2-4 in 258 (89.9%), 19 (6.6%), and 10 (3.5%) subjects, respectively. The median NLR, PLR and LMR were 2.15, 159.6, and 4.94; mGPS scores were 0, 1 and 2 in

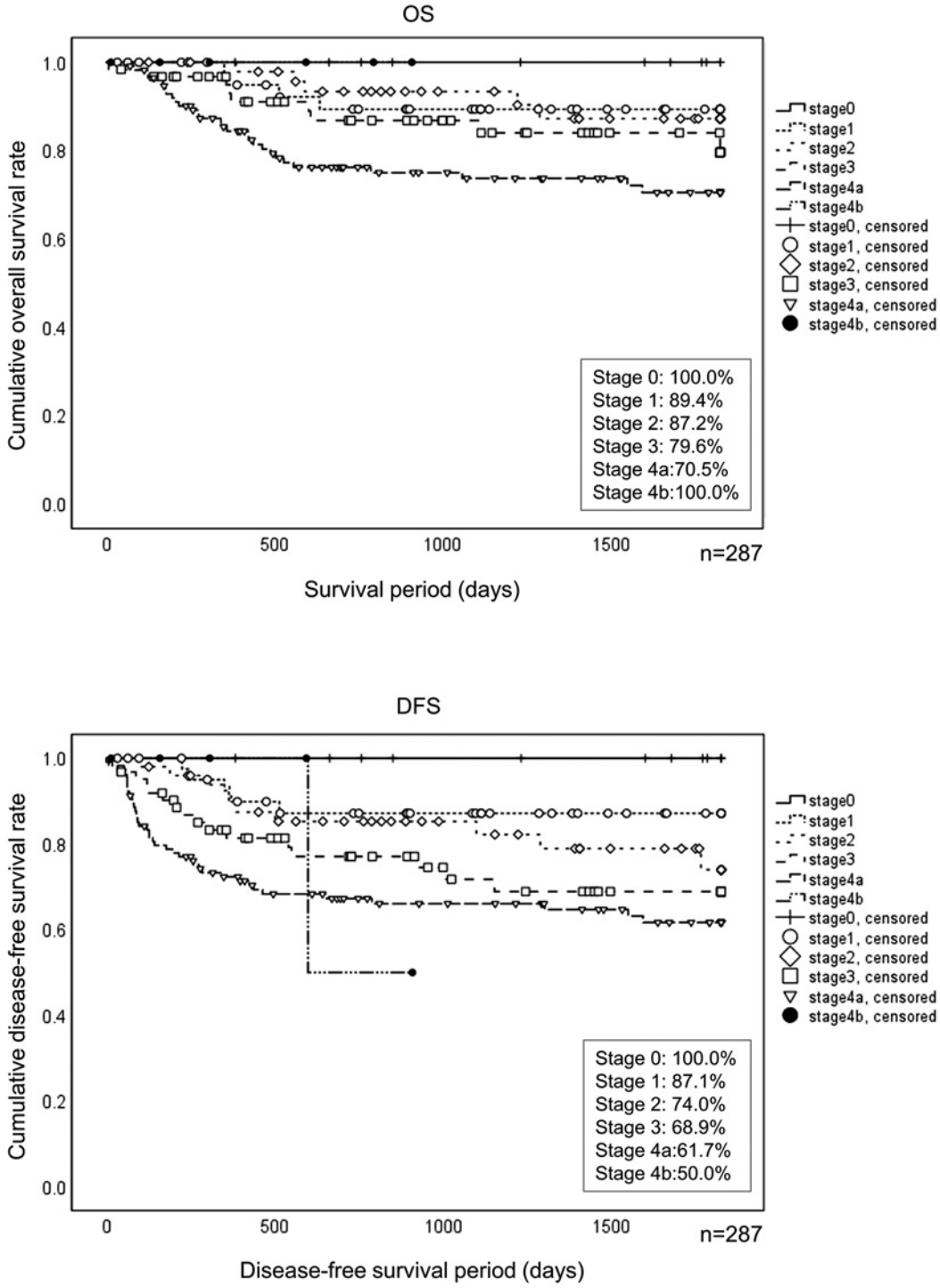

Figure 1 Overall survival (OS) and Disease-free survival (DFS) in patients with OSCC. The cumulative 5-year OS rates in each clinical cancer stage were 100%, 89.4%, 87.2%, 79.6%, 70.5%, and 100%, and DFS rates were 100%, 87.1%, 74.0%, 68.9%, 61.7%, and 50.0% for stages 0, 1, 2, 3, 4a and 4b, respectively.

216 (90.4%), 17 (7.1%), and 6 (2.5%) subjects; and PI scores were 0, 1 and 2 in 233 (90.3%), 23 (8.9%), and 2 (0.8%) subjects, respectively. The most common primary site was the tongue (n = 137, 47.7%), followed by the lower gingiva (n = 64, 22.3%). In staging, cases of cT4a (n = 103, 35.8%), cN0 (n = 165, 57.4%) and cN1 (n = 60, 20.9%), and cStage 4a (n = 114, 39.7%) and cStage 3 (n = 62, 21.6%) were frequently observed. Surgery alone was used in 221 subjects (77.0%), combined surgery and postoperative treatment in 66 (23.0%), postop-

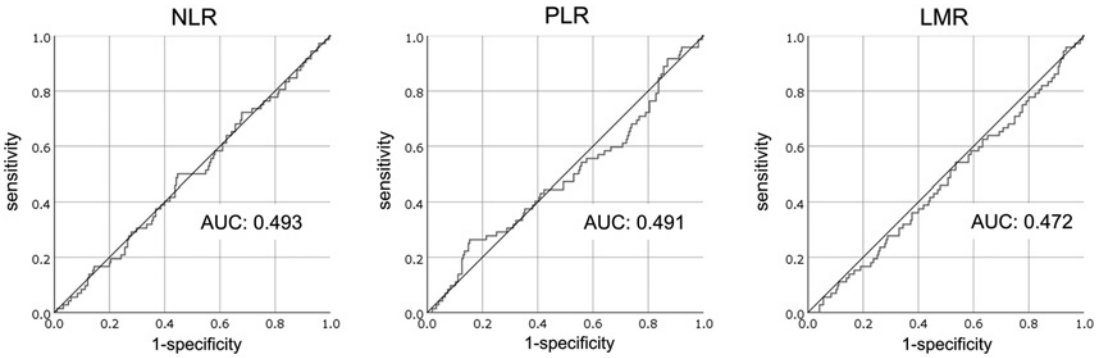

Figure 2 Cutoff setting for neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and lymphocyte-monocyte ratio (LMR) using receiver operating characteristic (ROC) curves. The areas under the curve (AUCs) were below 0.5: 0.493 for NLR, 0.491 for PLR, and 0.472 for LMR.

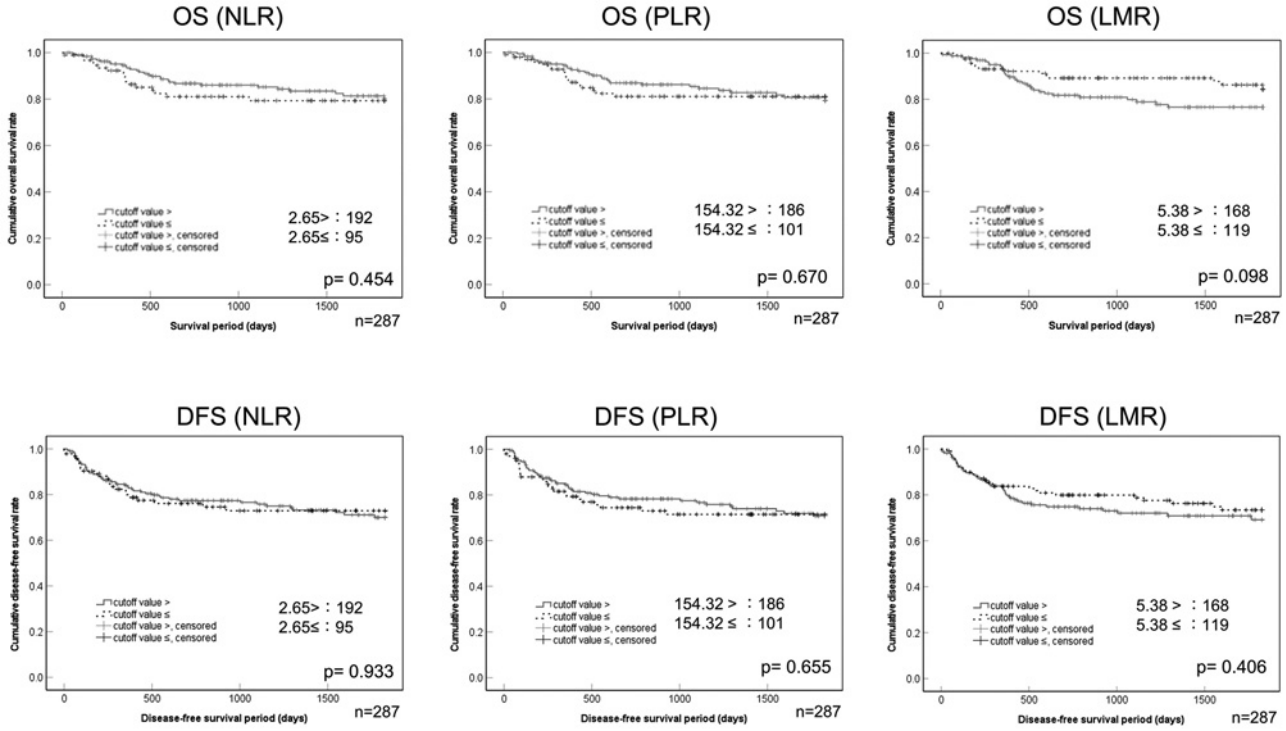

Figure 3 Cumulative OS and DFS rate classified by NLR, PLR and LMR at the first visit. There was no significant difference in OS and DFS between groups with NLR, PLR and LMR above and below cutoffs for each parameter: NLR (OS: p = 0.454, DFS: p = 0.933), PLR (OS: p = 0.670, DFS: p = 0.655), LMR (OS: p = 0.098, DFS: p = 0.406).

erative chemotherapy in 22, postoperative radiotherapy in 12, and postoperative chemoradiotherapy in 32 subjects. Adjuvant therapy was administered in 105 subjects (36.6%). There were 46 all-cause (disease nonspecific) deaths (16.0%) within 5 years after surgery, and postoperative events occurred in 55 subjects (19.2%). The cumulative 5-year OS rates in each clinical cancer stage were 100%, 89.4%, 87.2%, 79.6%, 70.5%, and 100%, and DFS rates were 100%, 87.1%, 74.0%, 68.9%, 61.7%, and 50.0% for stages 0, 1, 2, 3, 4a and 4b, respectively (Fig. 1, $p < 0.001$).

Prognosis based on IBPSs at the first visit

To establish cutoffs for NLR, PLR and LMR, ROC curves were drawn for these IBPSs and events or death (Fig. 2). However, the areas under the curve (AUCs) were all below 0.5: 0.493 for NLR, 0.491 for PLR, and 0.472 for LMR, and thus, cutoffs could not be

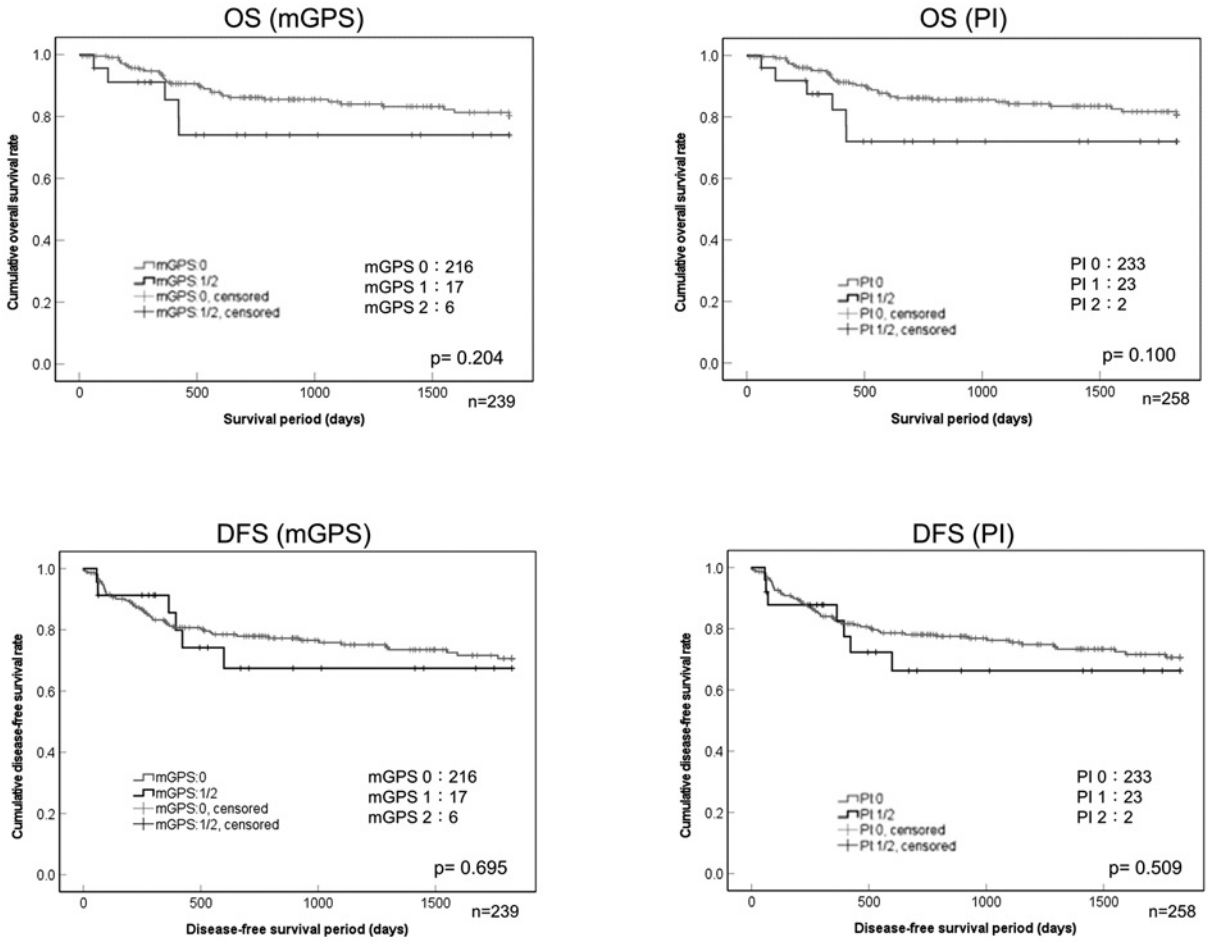

Figure 4 Cumulative OS and DFS rate classified by prognostic index (PI) and modified Glasgow prognostic score (mGPS) at the first visit. There was no significant difference in OS and DFS between groups with PI or mGPS scores of 0 and 1 + 2: mGPS (OS: p = 0.204, DFS: p = 0.695), PI (OS: p = 0.100, DFS: p = 0.509).

determined using ROC curves. Therefore, cutoff values (NLR: 2.65, PLR: 154.32, LMR: 5.38) were defined based on a previous study of Japanese patients with OSCC[16]. The cumulative 5-year OS and DFS rates for NLR, PLR and LMR at the first visit for groups of subjects divided using these cutoffs are shown in Fig. 3. There was no significant difference in OS and DFS between the two groups based on the cutoffs for NLR (OS: p = 0.454, DFS: p = 0.933), PLR (OS: p = 0.670, DFS: p = 0.655) and LMR (OS: p = 0.098, DFS: p = 0.406). Similarly, a comparison of 5-year OS and DFS rates for cases with mGPS and PI scores of 0 and 1 + 2 at the first visit (Fig. 4) showed no significant difference for mGPS (OS: p = 0.204, DFS: p = 0.695) and PI (OS: p = 0.100, DFS: p = 0.509).

Prognosis based on changes of IBPSs from pre- to post-treatment

Changes in IBPSs from the first visit to the end of primary treatment were calculated to investigate possible relationships with prognosis. Comparisons of relative NLRs (value at the end of primary treatment/value at the first visit) for survival vs. non-survival and event-free vs. event-occurrence cases in the 5 years after surgery are shown in Fig. 5. The median relative NLRs (i.e., quartile 2/4 (Q2) and quartile 3/4 (Q3)) were higher in non-survival and event-occurrence cases, but without a significant difference in either comparison; thus, the relative NLR had no effect on death (p = 0.802) or event occurrence (p = 0.320). In similar comparisons, the relative PLR (Fig. 6) and relative LMR (Fig. 7) had no significant effects on death (PLR: p = 0.573, LMR: p = 0.709) or event occurrence (PLR: p = 0.460, LMR: p = 0.714). A comparison of survival vs.

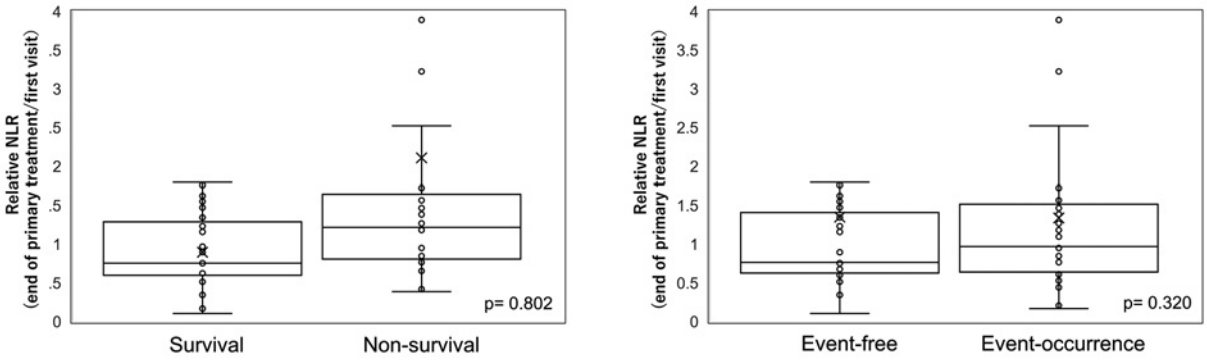

Figure 5 Comparison of survival vs. non-survival and event-free vs. event occurrence in 5 years after surgery based on the relative NLR (NLR at end of primary treatment/NLR at first visit). Relative NLR had no effect on death (p = 0.802) or event occurrence (p = 0.320).

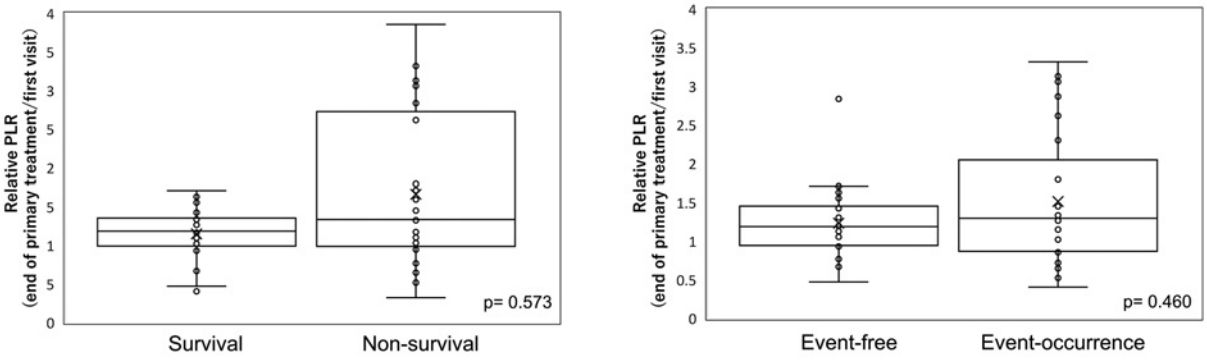

Figure 6 Comparison of survival vs. non-survival and event-free vs. event occurrence in 5 years after surgery based on the relative PLR (PLR at end of primary treatment/PLR at first visit). Relative PLR had no effect on death (p = 0.573) or event occurrence (p = 0.460).

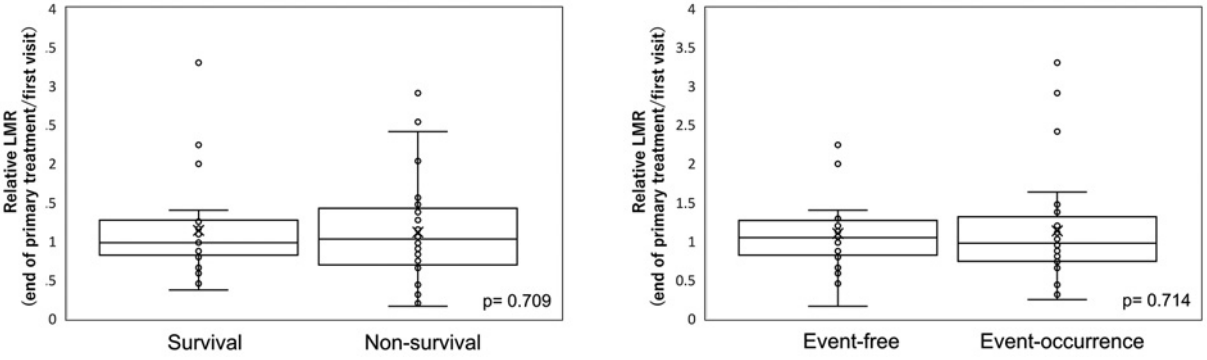

Figure 7 Comparison of survival vs. non-survival and event-free vs. event occurrence in 5 years after surgery based on the relative LMR (LMR at end of primary treatment/LMR at first visit). Relative LMR had no effect on death (p = 0.709) or event occurrence (p = 0.714).

non-survival and event-free vs. event-occurrence cases in the 5 years after surgery between cases with change/improvement vs. worsening of mGPS and PI from the first visit to the end of primary treatment is shown in Table 2. Worsening of mGPS and of PI were both significantly correlated with poor prognosis for death and event occurrence (both $p < 0.001$).

Table 2 Prognostic prediction based on changes in mGPS and PI from the first visit to the end of primary treatment

Change of mGPS or PI	Survival	Non-survival	P value	Event-free	Event occurrence	P value
No change / improvement of mGPS	188	23		174	37	
Worsening of mGPS	14	15	$p < 0.001$	19	10	$p < 0.001$
No change / improvement of PI	207	29		194	42	
Worsening of PI	10	12	$p < 0.001$	14	8	$p < 0.001$

Discussion

In this study, we investigated the usefulness of IBPSs as prognostic predictors in patients undergoing primary surgery for OSCC. The results showed that NLR, PLR, LMR, mGPS, and PI at the first visit were not significantly correlated with prognosis. Similarly, changes in NLR, PLR, LMR at the end of primary treatment relative to the value at the first visit also had no significant correlation with prognosis. However, in contrast, worsening of mGPS and PI at the end of primary treatment were significantly correlated with poor prognosis.

IBPSs have been suggested to be useful prognostic predictors after treatment of many carcinomas[4-18]. In oral cancer, IBPSs have been examined for prediction of postoperative OS and prognosis in early stage cancer or after primary treatment with neck dissection[12-18]. Templeton et al. found that NLR is useful in predicting prognosis[5] and Wei et al. suggested that PLR may play an important role in cancer onset and progression due to platelet-leukocyte interactions[18]. LMR was suggested to reflect both host immune status and extent of tumor progression by Furukawa et al.[14], and Iuchi et al. discussed that a poor mGPS, which incorporates CRP and ALB levels, reflects nutritional depletion and physical function deterioration, resulting in decreased survival[9].

In contrast to previous studies, IBPSs were not found to be useful as prognostic predictors in the current study. There are several possible explanations for these findings. Data dispersion (mean (SD) NLR: 2.67 (1.8); PLR: 159.6 (151.7); LMR: 5.27 (2.5)) occurred due to calculation of absolute ratios of values obtained from blood tests. Firstly, data were based on blood tests at a specific point before the start of treatment, resulting in systemic bias. the causes of poor IBPSs include the possession of chronic inflammatory and autoimmune diseases, oral intake difficulties and low nutrition, but also simply transient infection and inflammation at the time of blood collection. In previous reports, a study excluded patients with acute and chronic inflammatory disease and those treated with steroids as subjects[16]. Secondly, it was also difficult to establish effective cutoff values. Furthermore, our center had superior outcomes for patients in all cancer stages compared to previous reports from other center. Then, the differences in outcomes between patients with early-stage and advanced cancers were less pronounced. If the prognosis is good at all stages, the involvement of each IBPSs is unlikely to lead to statistically significant differences[23,25-27]. On contrast, the differences of mGPS and PI between the first visit and the end of primary treatment were correlated with prognosis. mGPS and PI can be clearly classified and there is no need to establish cutoff values. However, mGPS and PI did not have any advantage as pretreatment prognostic factors.

Several recent studies have examined use of new IBPSs[28-33]. The systemic inflammation response index (SIRI) is calculated from neutrophil count × monocyte count/lymphocyte count[28], multiple IBPSs and blood test results have been combined to give new biomarkers[29-33], and sarcopenia and IBPSs have also been used in combination[32,33]. However, it is difficult to relate combinations of blood test values alone with prognosis prediction. IBPSs as prognostic predictors are also currently being examined in retrospective cohorts, and there have been no RCTs with OSCC patients of selection of primary or postoperative treatment based on each factor. Thus, large-scale multicenter studies and big data analyses are required for improved identification of more effective IBPSs.

In conclusion, this study found that NLR, PLR, LMR, PI, and mGPS were not effective as presurgical prognostic factors for patient with OSCC in our center. Further investigation and validation of indices and as-

sessment methods are required to improve the impact of IBPS biomarkers on prognosis prediction and treatment choice in patients with OSCC.

Funding

Not applicable.

Ethics approval

The study design was approved by the Medical Ethical Research Committee of Dokkyo Medical University Hospital (approval ID R-22-12J).

Authors' contributions

CF, RS and HK contributed to the study conception and design. Data collection and analysis was performed by CF and RS. The first draft of the manuscript was written by CF and HK. All authors commented on versions of the manuscript. All authors read and approved the final version of the manuscript.

Conflict of Interest

The authors declare no conflicts of interest.

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