Impacts of Inflammation-Based Prognostic Scores on Survival in Patients With Hypopharyngeal Squamous Cell Carcinoma

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Abstract

Objective. To investigate the predictive accuracies of the modified Glasgow Prognostic Score (mGPS), neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR) as prognostic factors for patients with hypopharyngeal squamous cell carcinoma (HSCC).

Study Design. Retrospective study.

Setting. University hospital.

Methods. The records of 106 patients who were histologically diagnosed with HSCC between January 2007 and December 2017 were reviewed. mGPS, NLR, and PLR were analyzed; univariate and multivariate analyses were performed to evaluate the prognosis of overall survival (OS).

Results. The overall 5-year survival rates of patients with mGPS0, mGPS1, and mGPS2 were 82.0%, 41.9%, and 13.5%, respectively. The overall 5-year survival rates of patients with low and high NLRs and with low and high PLRs were 83.8%, 46.2%, 57.0%, and 59.1%, respectively. mGPS ($P < .001$) and NLR ($P < .05$) were independently associated with OS, whereas PLR was not. For stage IV HSCC, only mGPS was independently associated with OS ($P = .004$).

Conclusion. mGPS is an excellent prognostic factor for patients with HSCC.

Keywords

hypopharyngeal squamous cell carcinoma, modified Glasgow Prognostic Score, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio

Despite recent advances in early detection, surgical techniques, and chemoradiation therapies, the prognosis of hypopharyngeal cancer remains poor worldwide. Surgery is the mainstay treatment for the disease, but patients with advanced stage disease develop recurrence even after curative resection. The TNM staging system is used to differentiate between patients with early stage disease and those with advanced stages; it also provides reliable information on prognosis. However, the system is less accurate for predicting the prognosis of patients with an intermediate extent of tumor invasion.[1] Therefore, a more accurate method for predicting prognosis is warranted to improve patient survival and provide appropriate preoperative counseling. It was recently reported that cancer-associated systemic inflammatory responses significantly influence disease-related outcomes for various sites.[2]

Several inflammation-based prognostic scoring systems have been devised and have been shown to be strongly correlated with prognosis for patients with a variety of neoplasms, including the Glasgow Prognostic Score (GPS),[3] which incorporates increased circulating C-reactive protein (CRP) levels and hypoalbuminemia. In addition, a combination of neutrophil and lymphocyte counts in the form of the neutrophil-lymphocyte ratio (NLR)[4] and a combination of platelet and lymphocyte counts in the form of the platelet-lymphocyte ratio (PLR)[5] both reflect the full blood count derangements induced by acute phase reactions.

The GPS, which is an inflammation-based prognostic score that assesses serum levels of CRP and albumin, is one of the most useful scoring systems for the prognostication of patients with various advanced cancers.[6] The NLR has been shown to predict poor survival in patients with breast cancer.[7] A high PLR has also been shown to be associated

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with advanced disease stages.[5] However, few studies have reported the usefulness of these scoring systems on head and neck cancers. In addition, there are many reports on the entire head and neck cancer region, and the treatment method and prognosis for each primary lesion are different.

In the present study, we evaluated the clinical value of several inflammation-based prognostic scoring systems, including the GPS, NLR, and PLR, in predicting the prognosis of hypopharyngeal squamous cell cancer (HSCC).

Materials and Methods
Patients

Our study included 106 patients who were diagnosed with HSCC in our hospital and who underwent total laryngopharyngoesophagetomy or concurrent chemoradiotherapy (CCRT) as their initial treatment between January 2007 and December 2017. The exclusion criteria were as follows: (1) duplicated cancer cases, (2) recurrent cases, and (3) distant metastasis. The median follow-up period for survivors was 61 months (range, 1-127 months). All deaths were due to the primary disease. In the advanced stage, it is judged whether or not the primary lesion and cervical lymph node can be technically resected, and then surgery or chemotherapy is selected. Induction chemotherapy is basically followed by CCRT. Surgery is selected if the tumor grows after induction chemotherapy.

Docetaxel (60 mg/m^2, day 1) + cisplatin (60 mg/m^2, day 1) + fluorouracil (600 mg/m^2, days 1-4) (TPF) was administered as the induction chemotherapy before 2013. CCRT regimens, which included 80 mg carboplatin every week or 100 mg/m^2 cisplatin every 3 weeks, were also administered. All patients underwent computed tomography–based radiotherapy (RT) planning with either 3-dimensional conformal RT or intensity-modulated RT. The patients' clinical characteristics, laboratory data, and treatment schedule were obtained from a retrospective review of their records. The pathological classification of the primary tumor, the degree of lymph node involvement, and the presence of organ metastasis were determined according to the TNM classification system (*TNM Classification of Malignant Tumors*, eighth edition).[8]

This retrospective study was approved by the Institutional Review Board of Kagoshima University (180238).

Inflammation-Based Prognostic Scores

Laboratory measurements, including the serum levels of CRP and albumin, white blood cell count, neutrophil count, and lymphocyte count, were performed on the day of the first visit. The GPS, NLR, and PLR were calculated based on these clinical data, and the modified GPS (mGPS) was constructed as previously described.[9] mGPS2, mGPS1, and mGPS0 corresponded to patients exhibiting an elevated CRP level (0.5 mg/dL) and hypoalbuminemia (3.5 g/dL), those with only one of these biochemical abnormalities, and those with neither of these abnormalities, respectively. The NLR was defined as the absolute neutrophil count divided

by the absolute lymphocyte count, and the PLR was defined as the platelet count divided by the absolute lymphocyte count. The NLR and PLR were used to calculate the cutoff values from the receiver operating characteristic curves. The areas under the curve for the NLR and PLR were 0.627 and 0.571, respectively. For analytical purposes, the following values were assigned: NLR $\geq$1.8, high NLR; NLR <1.8, low NLR; PLR $\geq$207.7, high PLR; and PLR <207.7, low PLR.

Statistical Analysis

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing). More precisely, it is a modified version of the R commander designed to add statistical functions that are frequently used in biostatistics. A receiver operating characteristic (ROC) curve for overall survival (OS) 5 years after the start of treatment was plotted to verify the optimal cutoff values of continuous NLRs and PLRs. The relationships between the mGPS, NLR, and PLR and between other clinicopathological factors were analyzed with the Pearson χ^2 test or Kruskal-Wallis test. The Kaplan-Meier method was employed to analyze survival, and the log-rank test was applied to examine the differences in survival between study groups. All *P* values were two-sided, and *P* < .05 was considered statistically significant.

Results
Demographic Characteristics of the Patients

Table 1 shows the baseline characteristics of the 106 included patients. The age at diagnosis ranged from 48 to 88 years (median, 68.2 years), and the dominant sex was male (97.1%). Forty (37.7%), 41 (38.7%), and 25 (23.6%) patients were diagnosed as stage II, III, and IV, respectively. Other patient characteristics are shown in **Table 1**.

Associations of the mGPS, NLR, and PLR With Clinicopathological Characteristics

Table 2 shows the baseline patient and disease-related characteristics for the mGPS, NLR, and PLR groups and the comparisons between groups. Fifty-five (51.9%), 38 (35.8%), and 13 (12.3%) patients were allocated to the mGPS0, mGPS1, and mGPS2 groups, respectively. No significant correlations were observed between the mGPS and any clinical factors. Thirty-five patients (33.0%) had a low NLR, and the remainder had a high NLR. Furthermore, 89 patients (83.9%) had a low PLR and the remainder had a high PLR. No significant correlations were observed between either NLR or PLR and any clinical factors.

Association of T and N Classification and Stage With OS

Figure 1A shows the Kaplan-Meier curves of OS for the total cohort according to T classification of HSCC. The overall 5-year survival rates were 74.5%, 55.6%, and 40.8%

Table 1. Baseline Patient Characteristics (N = 106).[a]

Variable	Value
Age, median, y	68.2
Sex	
Male	103
Female	3
ECOG PS	
0	54
1	51
2	1
Tumor depth	
T2	40
T3	41
T4	25
Lymph node metastasis	
N0	36
N1	13
N2	55
N3	2
TNM stage	
II	21
III	18
IV	67
Location of tumor	
PS	84
PC	16
PW	6
Treatments	
NAC	53
CCRT	78
Ope	46

Abbreviations: CCRT, concurrent chemoradiotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; NAC, neoadjuvant chemotherapy; Ope, total laryngopharyngoesophagetomy; PC, postcricoid; PS, pyriform sinus; PW, posterior wall.
[a]Values are presented as numbers unless otherwise indicated.

for patients classified as T2, T3, and T4, respectively. Significant differences were observed in the OS between patients classified as T2, T3, and T4 ($P = .0022$). **Figure 1B** shows the Kaplan-Meier curves of OS for the total cohort drawn according to N classification of HSCC. The overall 5-year survival rates were 76.0%, 62.3%, and 49.6% for patients classified as N0, N1, and N2, respectively. Significant differences were observed in the OS between patients classified as N0, N1, and N2 ($P = .04$). **Figure 1C** shows the Kaplan-Meier curves of OS for the total cohort drawn according to stage. The overall 5-year survival rates were 86.8%, 45.8%, and 52.6% for patients classified as stage II, III, and IV of HSCC, respectively. Significant differences existed in the OS between patients classified as stage II, III, and IV ($P = .0139$); however, there was no significant difference in OS between stage III and IV patients.

Associations of the mGPS, NLR, and PLR With OS

Figure 2A shows the Kaplan-Meier curves of OS for the total cohort according to the mGPS. The overall 5-year survival rates were 82.0%, 41.9%, and 13.5% for patients classified as mGPS0, mGPS1, and mGPS2, respectively. Significant differences existed in the OS between patients classified as mGPS0, mGPS1, and mGPS2 ($P < .0001$). **Figure 2B** shows the Kaplan-Meier curves of OS for the total cohort according to the NLR. The overall 5-year survival rates were 83.8% and 46.2% for patients with low and high NLRs, respectively. Significant differences existed in the OS between patients with low and high NLRs ($P = .024$). **Figure 2C** shows the Kaplan-Meier curves of OS for the total cohort according to PLR. The overall 5-year survival rates were 57.0% and 59.1%, respectively. Significant differences in OS were not observed between patients with low and high PLRs ($P = .89$). As shown in **Table 3**, a multivariate analysis including the aforementioned parameters revealed that the mGPS and NLR were independent predictors of OS ($P < .05$). The radiation dose and total chemotherapy dose in patients undergoing CCRT were investigated, and there were no statistically significant differences between the GPS, NLR, and PLR groups (data not shown).

Associations of the mGPS, NLR, and PLR With OS in Stage IV Patients

Figure 3A illustrates the Kaplan-Meier curves of OS for stage IV patients of mGPS. The overall 5-year survival rates were 70.0%, 46.6%, and 33.3% for patients classified as mGPS0, mGPS1, and mGPS2, respectively. Significant differences existed in the OS between patients classified as mGPS0, mGPS1, and mGPS2 ($P < .0001$).

Figure 3B shows the Kaplan-Meier curves of OS for stage IV patients of NLR. The overall 5-year survival rates were 76.6% and 34.0% for patients with low and high NLRs, respectively. Significant differences were observed in the OS between patients with low and high NLRs ($P = .0006$). **Figure 3C** shows the Kaplan-Meier curves of OS for stage IV patients of PLR. The overall 5-year survival rates were 63.8% and 0% for patients with low and high PLRs, respectively. Significant differences existed in the OS between patients with low and high PLRs ($P < .0001$). As shown in **Table 4**, a multivariate analysis including the aforementioned parameters revealed that the mGPS was an independent predictor of OS ($P < .05$).

Discussion

The TNM staging system is a commonly used guideline for treatment decisions and the prognostic prediction of patients with HSCC.[10] Even when the primary tumor is in the early stages of advanced HSCC, it is sometimes diagnosed as stage IV because of lymph node metastasis.[11] Hence, TNM staging is useful in determining whether patients are in the early or advanced stages; however, prognostic evaluation using this system is not always sufficient for advanced

Table 2. Relationships Between mGPS, NLR, and PLR and Clinicopathological Features of All Patients.

Variables	mGPS0 (n = 55)	mGPS1 (n = 38)	mGPS2 (n = 13)	P value	Low NLR (n = 35)	High NLR (n = 71)	P value	Low PLR (n = 89)	High PLR (n = 17)	P value
Age, y, mean ± SD	71.42 ± 0.98	67.81 ± 1.44	73.23 ± 2.75	.0872[a]	68.11 ± 1.15	68.21 ± 1.12	.1271[a]	68.69 ± 0.89	65.53 ± 2.36	.9035[a]
Sex (male), No. (%)	53 (96)	37 (97)	13 (100)	.3712[a]	35 (100)	68 (96)	.3086[a]	86 (97)	17 (100)	.3546
Tumor location, No.				.8821[b]			.7181[b]			.8142[b]
PS	43	32	9		29	55		72	12	
PC	8	5	3		3	13		12	4	
PW	4	1	1		3	3		5	1	
Tumor depth, No.				.1538[b]			.8519[b]			.1320[b]
T2	27	10	3		15	25		35	5	
T3	21	14	6		13	28		34	7	
T4	7	14	4		7	18		20	5	
Lymph node metastasis, No.				.5786[b]			.3020[b]			.4638[b]
N0	22	10	4		13	23		31	5	
N1	7	2	4		4	9		9	4	
N2	26	25	4		18	37		47	8	
N3	0	1	1		0	2		2	0	
TNM stage, No.				.6654[b]			.1384[b]			.2329[b]
II	16	5	0		8	13		17	4	
III	9	3	6		5	13		14	4	
IV	30	30	7		22	45		58	9	
Treatments, No.				.3214[b]			.9932[b]			.1277[b]
NAC	15	15	5		11	24		31	4	
CCRT	14	19	1		11	23		26	8	
Ope	14	11	5		9	20		29	1	

Abbreviations: CCRT, concurrent chemoradiotherapy; mGPS, modified Glasgow Prognostic Score; NAC, neoadjuvant chemotherapy; NLR, neutrophil/lymphocyte ratio; Ope, total laryngopharyngoesophagetomy; PC, postcricoid; PLR, platelet/lymphocyte ratio; PS, pyriform sinus; PW, posterior wall.
[a]Pearson χ^2 test.
[b]Kruskal-Wallis test.
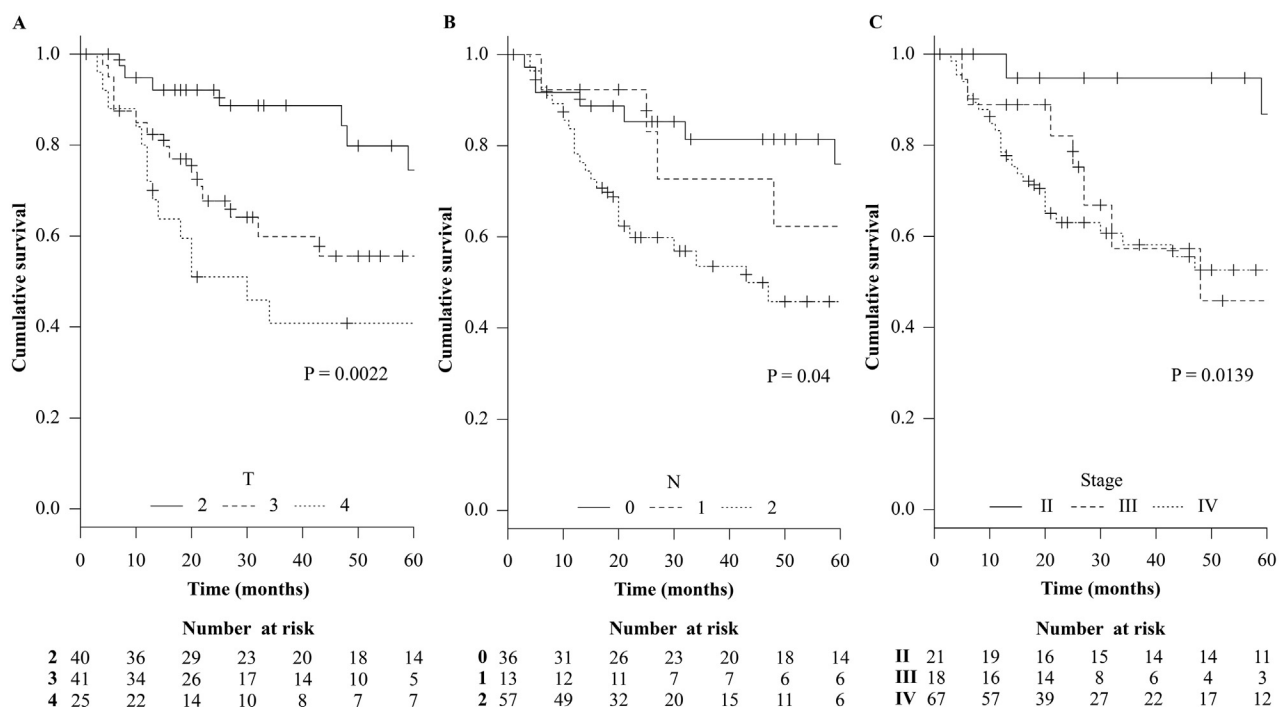
Figure 1. Overall survival of patients according to T and N classification and TNM staging. (A) T classification. (B) N classification. (C) Stage.

Table 3. Univariate and Multivariate Analyses to Assess Prognostic Factors for All Patients.

| Variable	Univariate analysis		Multivariate analysis	
	P value	HR (95% CI)	P value	HR (95% CI)
Age	.96	1.00 (0.96-1.05)		
Sex	.927	0.892 (0.0782-10.2)		
T	.00032	2.90 (1.62-5.16)	.056	1.74 (0.99-3.05)
N	.023	1.72 (1.08-2.75)	.13	1.72 (0.86-3.42)
Stage	.011	2.18 (1.20-3.99)	.91	0.94 (0.31-2.82)
mGPS (0/1/2)	.000021	4.42 (2.23-8.78)	.000014	3.03 (1.84-5.00)
NLR (low/high)	.0096	3.73 (1.38-10.10)	.034	2.66 (1.08-6.54)
PLR (low/high)	.61	0.80 (0.34-1.87)		

Abbreviations: HR, hazard ratio; mGPS, modified Glasgow Prognostic Score; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio.

stages. The present study showed that the T and N classifications each correlate with the prognosis of patients with HSCC, but TNM staging did not show any statistically significant differences in prognosis between stages III and IV. These results might be explained by the fact that stage IV occupies more than half of all the classifications. Therefore, to improve the prognostic efficacy for patients with HSCC, further studies should be conducted to identify markers of poor prognosis other than TNM staging.

Systemic inflammatory response markers are known to be prognostic factors in patients with advanced cancer.[12] The GPS is a technique that uses blood protein components, whereas the NLR and PLR are nutritional evaluation methods that use blood cell components. The results of this study

showed that the mGPS, NLR, and PLR were not correlated with T and N classifications or with TNM staging and treatments; therefore, mGPS, NLR, and PLR are prognostic factors independent of TNM staging and therapeutic methods. The GPS is determined by the dynamics of the acute phase protein produced by interleukin 6 acting on hepatocytes.[13] Moreover, the total number of lymphocytes is a classical nutritional evaluation index and can act as a tumor suppressor.[14] Conversely, neutrophils and platelets are factors that closely link inflammation with cancer progression.[15,16] These findings might explain why the mGPS, NLR, and PLR are independent of TNM staging.

The GPS has been reported as a useful prognostic factor for various solid cancers.[17-19] The GPS, which incorporates
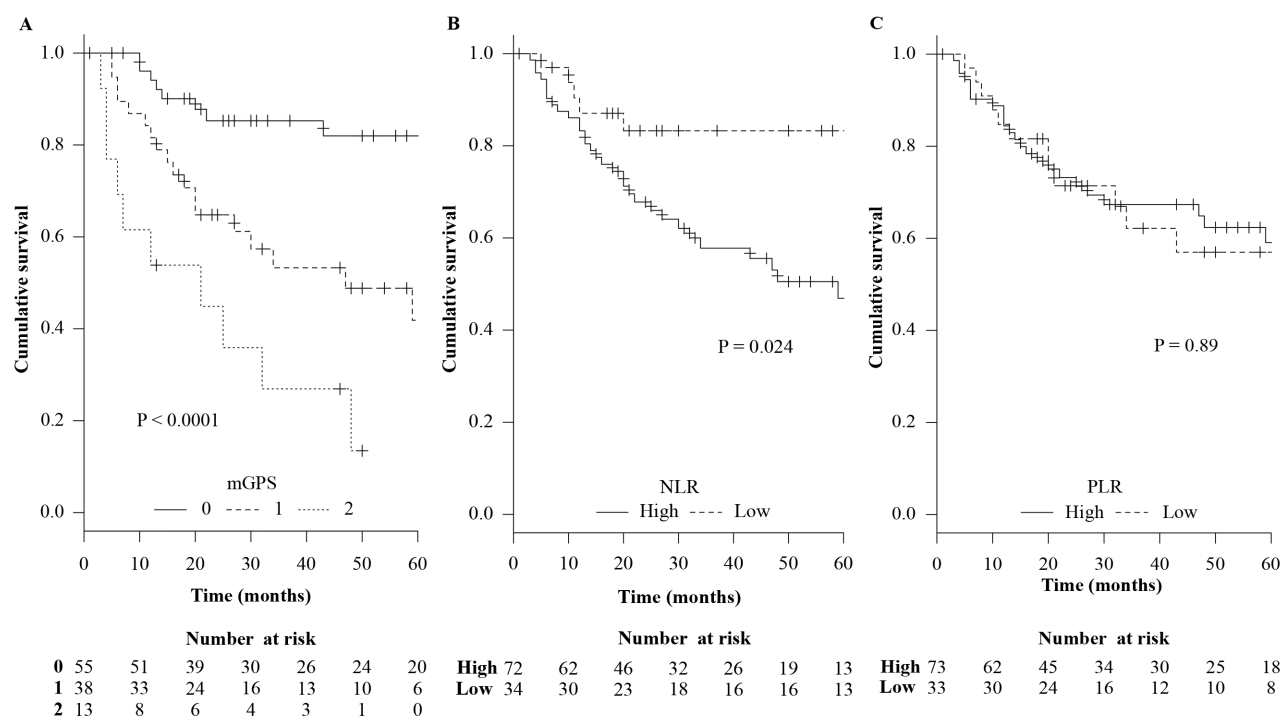
Figure 2. Overall survival of patients according to inflammation-based prognostic score. (A) Modified Glasgow Prognostic Score (mGPS). (B) Neutrophil/lymphocyte ratio (NLR). (C) Platelet/lymphocyte ratio (PLR).
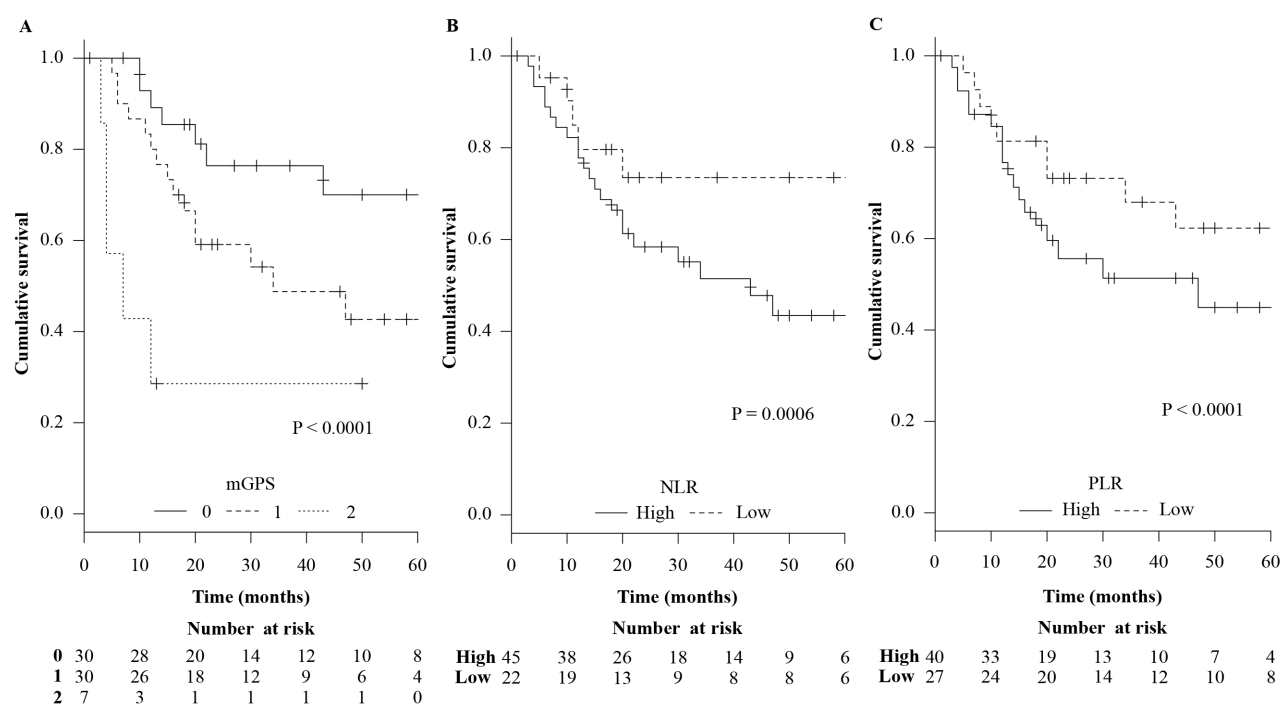
Figure 3. Overall survival of patients according to the inflammation-based prognostic score for stage IV cancer. (A) Modified Glasgow Prognostic Score (mGPS). (B) Neutrophil/lymphocyte ratio (NLR). (C) Platelet/lymphocyte ratio (PLR).

CRP and serum albumin levels, reflects the presence of nutritional depletion and functional decline, which result in poor survival outcomes.[19] Inoue et al[20] reported that the cutoff value of CRP as a prognostic marker in Japanese patients was 0.5 mg/dL. In this study, a similar cutoff value was used, and the OS was shown to decrease with increasing mGPS levels. Moreover, the multivariate analysis revealed that the GPS was an independent predictor of OS.

Table 4. Univariate and Multivariate Analyses to Assess Prognostic Factors for Patients With Stage IV Cancer.

Variable	Univariate analysis		Multivariate analysis	
	P value	HR (95% CI)	P value	HR (95% CI)
Age	.59	0.98 (0.93-1.04)		
Sex	.39	0.81(0.49-1.31)		
T	.0068	2.74 (1.32-5.67)	.16	1.48 (0.85-2.58)
N	.51	1.32 (0.57-3.06)		
mGPS (0/1/2)	.013	2.81 (1.25-6.34)	.0043	2.43 (1.32-4.48)
NLR (low/high)	.069	0.36 (0.12-1.08)		
PLR (low/high)	.4	0.65 (0.24-1.76)		

Abbreviations: HR, hazard ratio; mGPS, modified Glasgow Prognostic Score; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio.

These findings suggest that the mGPS is useful as a prognostic marker in patients with HSCC.

The NLR and PLR are reported to be important prognostic factors for patients with a variety of solid cancers.[20,21] In this study, we defined the cutoff values of NLR and PLR as 1.8 and 203, respectively, according to the best predictive values calculated by the ROC analysis. These values are higher than those reported in other studies.[21,22] In head and neck cancers, chronic inflammation due to tobacco usage or chronic infection with human papillomavirus or Epstein-Barr virus is known to induce carcinogenesis; therefore, inflammatory cells might be more strongly associated with tumor development in the head and neck region than in other sites.[23] By determining the cutoff values according to these results, a significant difference in OS was confirmed with the NLR but not the PLR. Moreover, the multivariate analysis revealed that the NLR was an independent predictor of OS. The combination of mGPS and NLR may provide a clearer prognostic score.

The present study showed that the mGPS, NLR, and PLR were useful prognostic factors in patients with stage IV HSCC. This result suggests that more detailed prognostic predictions are possible using the mGPS, NLR, and PLR among stage IV cases, but only the mGPS was found to be an independent prognostic factor, indicating that a more accurate prognostic prediction might be obtained by referring to the mGPS in stage IV patients. Most studies reporting a significant difference in the survival rate used a cutoff value that was calculated from either the median or the ROC curve based on actual data.[12,24] However, these retrospectively calculated cutoff values cannot be used in a prospective study and are unsuitable for future clinical applications in predicting treatment outcomes. Further investigations with a larger sample size are warranted to make more accurate prognoses.

Hanai et al[25] reported that high-sensitivity mGPS (HS-mGPS) is effective in head and neck cancer areas. We plan to further investigate the prognostic factors of hypopharyngeal cancer by comparing mGPS with HS-mGPS in future studies. In addition, since this evaluation was performed in stage IV, we plan to consider stage III cases in future.

This study has certain limitations. The sample size was relatively small, and this study was a retrospective, single-center study, which implies a certain bias in recruiting participants.

Conclusion

In this study, the mGPS and NLR were correlated with the prognosis of patients with HSCC. Furthermore, the mGPS displayed similar results in stage IV patients. These findings suggest that more accurate prognostic predictions can be obtained by combining the mGPS with conventional TNM staging.

Author Contributions

Hiroyuki Iuchi, acquired and organized retrospective data, drafted initial rough draft of work and revised based on corresponding author comments, approved final version; **Takayuki Kyutoku,** acquired and organized retrospective data, drafted initial rough draft of work and revised based on corresponding author comments, interpreted data; **Kotoko Ito**, analyzed retrospective data, revised work; **Hayato Matsumoto**, interpreted data, revised multiple drafts; **Junichiro Ohori**, analyzed retrospective data, revised multiple drafts, approved final version; **Masaru Yamashita**, formulated research question, collected retrospective data, drafted and revised manuscript, approved final version.

Disclosures

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