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ORIGINAL RESEARCH

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Prognostic values of systemic inflammation and nutrition-based prognostic indices in oropharyngeal carcinoma

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Abstract

Objective: Pretreatment systemic inflammation and nutrition-based prognostic indices (SINBPI) have demonstrated significance. This study investigated the prognostic value of pretreatment SINBPI for patients with oropharyngeal cancer and identified unfavorable prognostic markers.

Methods: We retrospectively reviewed the data of 124 patients with oropharyngeal squamous cell carcinoma (OPSCC) who received definitive treatment between January 2010 and December 2018. The prognostic utility of the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), prognostic nutritional index, and high-sensitivity modified Glasgow prognostic score (HS-mGPS) was assessed for disease-free survival (DFS), disease-specific survival (DSS), and overall survival (OS) using univariate and multivariate analyses.

Results: Multivariate analyses revealed that human papillomavirus (HPV) status and HS-mGPS were significantly associated with DFS, DSS, and OS. Patients with a HS-mGPS of 2 had a significantly higher rate of treatment-related deaths than those with a HS-mGPS of 0 or 1. The combination of the HS-mGPS and PLR had more accurate predictive ability in DFS and OS compared with the HS-mGPS alone, and the combination of the HS-mGPS and LMR had more accurate predictive ability in DSS and OS.

Conclusion: Our results indicated that the HS-mGPS was a useful prognostic marker for patients with OPSCC, and combined markers consisting of the HS-mGPS and PLR or LMR may provide more accurate prognostic predictions.

Level of Evidence: 3.

KEYWORDS
high-sensitivity modified Glasgow prognostic score, lymphocyte-to-monocyte ratio, neutrophil-to-lymphocyte ratio, oropharyngeal cancer, platelet-to-lymphocyte ratio

1 | INTRODUCTION

Oropharyngeal cancer (OPC) accounts for approximately 0.5% of all cancer cases.[1] In developed countries, the consumption of alcohol and smoking is declining and cancer prevalence is consequently decreasing[2]; however, the incidence of human papillomavirus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC) is increasing.[3] Although tumor-node-metastasis (TNM) classification and HPV status are well known to indicate prognosis based on tumor stage or characteristics,[4] they cannot reflect systemic conditions or treatment tolerability of patients. Malnutrition and higher inflammatory status have an impact on treatment tolerability and survival after treatment for patients with head and neck cancers.[5–7] Definitive treatments, such as surgery, radiation therapy (RT), and chemoradiation therapy (CRT), are generally selected for patients with OPC.[8] However, some patients do not have tolerability to definitive treatments because of malnutrition and higher inflammation conditions. Therefore, proper assessment and intervention strategies to improve nutritional and inflammatory conditions before treatment are needed from head and neck oncologists.

Previous studies have shown the significance of pretreatment systemic inflammation and nutrition-based prognostic indices (SINBPI), such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), prognostic nutritional index (PNI), and Glasgow prognostic score (GPS) for head and neck cancers (HNSs).[9–13] GPS is a useful systemic inflammatory index that presents the status of cancer cachexia, and the modified GPS (mGPS) is a more sensitive systemic inflammatory index than GPS for head and neck cancers.[14] Furthermore, recent studies have shown that high-sensitivity mGPS (HS-mGPS) is more sensitive than mGPS for prognostic utility in head and neck cancers.[15,16] However, limited information is available concerning SINBPI for OPC. Regarding the prognostic role of pretreatment SINBPI in OPC, a few studies have shown that NLR is an independent and prognostic predictor.[17,18] Additionally, Kreinbrink et al.[19] reported that the absolute lymphocyte count is a predictor of improved survival in HPV-related OPSCC.

Furthermore, a multivariate analysis by Iuchi et al.[20] demonstrated that the HS-mGPS is an independent prognostic factor for patients with HPV-positive or HPV-negative OPC. However, these studies only investigated one type of SINBPI (only NLR, absolute lymphocyte count, or HS-mGPS).[17–20] This study aimed to evaluate the prognostic value of pretreatment SINBPI for patients with OPSCC receiving definitive treatment, and determine which SINBPI independently and precisely have prognostic utility for patients with OPSCC receiving definitive treatment.

2 | MATERIALS AND METHODS

2.1 | Patients

We retrospectively screened 160 patients diagnosed with OPSCC at Kurume University Hospital between January 2010 and December 2018. Patients with unknown HPV status, distant metastasis at initial diagnosis, and/or best supportive care were excluded. Based on these criteria, 124 patients with OPSCC were included in the study (Figure 1). The tumors were staged according to the system adopted by the American Joint Committee on Cancer Staging Manual, 8th edition.[21] HPV status was assessed by hybrid-capture HPV DNA detection or p16 immunohistochemistry. All patients underwent surgery, RT, cisplatin-based RT for CRT, or cetuximab-RT (Cet-RT) for definitive treatment.

This study (reference number: 17203) followed the provisions outlined in the Declaration of Helsinki and was approved by the Institutional Review Board of Kurume University. Informed consent was obtained from all patients for this study.

2.2 | Clinical data collection and investigation of SINBPI

Blood laboratory data were examined within 7 days before the initial treatment. Demographic characteristics were obtained from medical records, including age, sex, performance status (PS), smoking status, alcohol consumption, tumor subsite, HPV status, TNM classification, clinical stage, and treatment.

2.3 | Treatment

Treatment was determined based on TNM stage, clinical laboratory data, and patients' PS. Although patients with a clinical stage III or IV

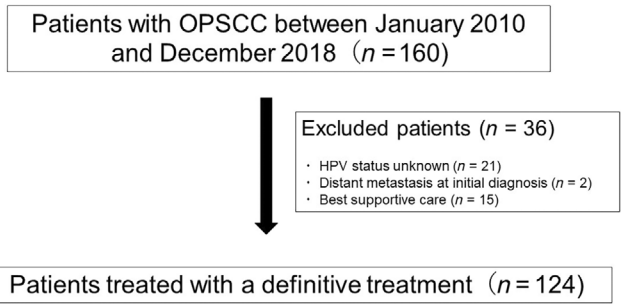

FIGURE 1 Flowchart of patient selection.

TABLE 1 Patient characteristics.

Characteristics	All patients ($n = 124$)	HPV-positive ($n = 71$)	HPV-negative ($n = 53$)	*p*-value
Age				.001
Median	63	60	67	
Range	34–83	34–81	39–83	
Sex				.468
Male	103 (83)	57 (80)	46 (87)	
Female	21 (17)	14 (20)	7 (13)	
Performance status				.008
0	82 (66)	53 (75)	29 (55)	
1	34 (27)	12 (17)	22 (41)	
2	8 (6)	6 (8)	2 (4)	
Smoking				.072
(Brinkman Index)	61 (49)	40 (56)	21 (40)	
<465	63 (51)	31 (44)	32 (60)	
≧465				
Alcohol consumption				
Never	32 (26)	24 (34)	8 (15)	.003
Moderate	12 (10)	10 (14)	2 (4)	
Heavy	80 (64)	37 (52)	43 (81)	
Subsite				.005
Lateral wall	75 (60)	50 (70)	25 (47)	
Anterior wall	34 (27)	18 (25)	16 (30)	
Posterior wall	11 (9)	3 (4)	8 (15)	
Superior wall	4 (3)	0	4 (8)	
T classification				.927
T1	13 (10)	7 (10)	6 (11)	
T2	57 (46)	32 (45)	25 (47)	
T3	37 (30)	21 (30)	16 (30)	
T4	17 (14)	11 (15)	6 (11)	
N classification				<.001
N0	38 (31)	8 (11)	30 (57)	
N1	55 (13)	49 (69)	6 (11)	
N2	39 (54)	12 (17)	17 (32)	
N3	2 (2)	2 (3)	0	
Clinical stage				<.001
I	39 (31)	34 (48)	5 (9)	
II	38 (31)	23 (32)	15 (28)	
III	28 (23)	14 (20)	14 (26)	
IV	19 (15)	0	19 (36)	
NAC				.004
TPF	86 (69)	57 (80)	29 (55)	
PF	1 (1)	0	1 (2)	
None	37 (30)	14 (20)	23 (43)	
Definitive treatment				
Surgery	33 (27)	12 (17)	21 (40)	.013
Surgery + (C) RT	14 (11)	7 (10)	7 (13)	
Cisplatin based-RT	70 (56)	48 (67)	22 (41)	
Cetuximab-RT	6 (5)	4 (6)	2 (4)	
RT	1 (1)	0	1 (2)	

Abbreviations: (C)RT, (chemo) radiation therapy; NAC, neoadjuvant chemotherapy; RT, radiation therapy.

TABLE 2 Correlations between patient characteristics and SINBPI.

Characteristics	No. of patients (%)	NLR		*p* value	PLR		*p* value	LMR		*p* value	PNI		*p* value	HS-mGPS			*p* value
		Low <1.65	High ≧1.65		Low <153.1	High ≧153.1		Low < 3.2	High ≧ 3.2		Low < 41	High ≧ 41		0	1	2	
	124	19	105		71	53		26	98		46	78		85	32	7	
Age (years)				1.000			.029			.270			.353				.739
<64	62	10 (53)	52 (49)		29 (41)	33 (62)		16 (62)	46 (47)		20 (43)	42 (54)		44 (52)	14 (44)	4 (57)	
≧64	62	9 (47)	53 (51)		42 (59)	20 (38)		10 (38)	52 (53)		26 (57)	36 (46)		41 (48)	18 (56)	3 (43)	
Sex				1.000			1.000			.073			.218				.709
Male	103	16 (84)	87 (83)		59 (83)	44 (83)		25 (96)	78 (80)		41 (89)	62 (79)		70 (82)	26 (81)	7 (100)	
Female	21	3 (16)	18 (17)		12 (17)	9 (17)		1(4)	20 (20)		5 (11)	16 (21)		15 (18)	6 (19)	0 (0)	
PS				.796			.179			.643			.120				.009
0	82	12 (63)	70 (67)		43 (61)	39 (74)		16 (62)	66 (67)		26 (56)	56 (72)		61 (72)	20 (63)	1 (14)	
1 or 2	42	7 (37)	35 (33)		28 (39)	14 (26)		10 (38)	32 (33)		20 (44)	22 (28)		24 (28)	12 (37)	6 (86)	
Smoking				.320			.364			.123			.042				.013
BI <465	61	7 (37)	54 (51) 51		32 (45)	29 (55)		9 (35)	52 (53)		17 (37)	44 (56)		49(58)	11 (34)	1 (14)	
BI ≧465	63	12 (63)	(49)		39 (55)	24 (45)		17 (65)	46 (47)		29 (63)	34 (44)		36 (42)	21 (66)	6 (86)	
Alcohol				.423			1.000			1.000			.233				.796
Never or moderate	38	4 (21)	34 (32)		22 (31)	16 (30)		8 (31)	30 (31)		11 (24)	27 (35)		27 (32)	10 (31)	1 (14)	
Heavy	86	15 (79)	71 (68)		49 (69)	37 (70)		18 (69)	68 (69)		35 (76)	51 (65)		58 (68)	22 (69)	6 (86)	
Subsite				.611			.578			.823			.451				.435
Lateral	75	13 (68)	62 (59)		41 (58)	34 (64)		15 (58)	60 (61)		30 (65)	45 (58)		50 (59)	19 (59)	6 (86)	
Others	49	6 (32)	43 (41)		30 (42)	19 (36)		11 (42)	38 (39)		16 (35)	33 (42)		35 (41)	13 (41)	1 (14)	
T classification				.619			.360			.122			.091				.016
T1–T2	70	12 (63)	58 (55)		43 (61)	27 (51)		11 (42)	59 (60)		21 (46)	49 (63)		54 (64)	15 (47)	1 (14)	
T3–T4	54	7 (37)	47 (45)		28 (39)	26 (49)		15 (58)	39 (40)		25 (54)	29 (38)		31 (36)	17 (53)	6 (86)	
N classification				1.000			.170			.638			.428				.288
N 0	38	6 (32)	32 (30)		18 (25)	20 (38)		9 (35)	29 (30)		12 (26)	26 (33)		30 (35)	7 (22)	1 (14)	
N1-3	86	13 (68)	73 (70)		53 (75)	33 (62)		17 (65)	69 (70)		34 (74)	52 (67)		55 (64)	25 (78)	6 (86)	
HPV status				.802			.714			.504			.133				.743
Negative	53	9 (47)	44 (42)		29 (41)	24 (45)		13 (50)	40 (41)		24 (52)	29 (37)		36 (42)	13 (41)	4 (57)	
Positive	71	10 (53)	61 (58)		42 (59)	29 (55)		13 (50)	58 (59)		22 (48)	49 (63)		49 (58)	19 (59	3 (43)	

TABLE 2 (Continued)

Characteristics	No. of patients (%)	NLR			PLR			LMR			PNI			HS-mGPS			
		Low <1.65	High ≧1.65	*p* value	Low <153.1	High ≧153.1	*p* value	Low < 3.2	High ≧ 3.2	*p* value	Low < 41	High ≧ 41	*p* value	0	1	2	*p* value
NAC				1.000			.554			.232			1.000				.489
TPF or PF	87	13 (68)	74 (70)		48 (68)	39 (74)		21 (81)	66 (67)		34 (69)	53 (71)		57 (67)	25 (78)	5 (71)	
None	37	6 (32)	31 (30)		23 (32)	14 (26)		5 (19)	32 (33)		15 (31)	22 (29)		28 (33)	7 (22)	2 (29)	
Definitive treatment				.615			.852			.368			1.000				.018
Non surgery	77	13 (68)	64 (61)		45 (63)	32 (60)		14 (54)	63 (64)		29 (63)	48 (63)		43 (51)	24 (75)	6 (86)	
Surgery ± (C) RT	47	6 (32)	41 (39)		26 (37)	21 (40)		12 (46)	35 (36)		17 (37)	30 (37)		42 (49)	8 (25)	1 (14)	

Note: Others (anterior, posterior, and superior wall); non surgery (cisplatin based-RT, Cetuximab-RT, and RT).

Abbreviations: (C)RT, (chemo) radiation therapy; BI, Brinkman Index; HS-mGPS, high-sensitivity modified Glasgow prognostic score; LMR, lymphocyte to monocyte ratio; NAC, neoadjuvant chemotherapy; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; PNI, prognostic nutritional index; PS, performance status; RT, radiation therapy.

disease received TPF (docetaxel, cisplatin, and 5-fluorouracil) or PF (cisplatin and 5-fluorouracil) therapy as neoadjuvant chemotherapy (NAC) in principle, some patients with PS 1 or 2 did not receive NAC. Definitive radiation therapy included single daily irradiation administered at 2 Gy per fraction (total, 60–70 Gy), and cisplatin or cetuximab was concomitantly administered with RT. Postoperative CRT containing cisplatin or RT was performed with daily irradiation administered at 2 Gy per fraction (total, 60–62 Gy).

2.4 | Systemic inflammation and nutrition-based prognostic indices

As previously reported, NLR and LMR were calculated from the neutrophil and lymphocyte counts and lymphocyte and monocyte counts, respectively.[9–11,17,18] PLR was calculated using the platelet and lymphocyte counts.[10] PNI was calculated using the following formula: 10 × albumin (g/dL) + 0.005 × lymphocyte (/mm^3); HS-mGPS was calculated as 0 (C-reactive protein [CRP] ≤0.3 mg/dL), 1 (CRP >0.3 mg/dL and albumin ≥3.5 g/dL), or 2 (CRP >0.3 mg/dL and albumin <3.5 g/dL).[12–15] The cutoff values of the NLR, LMR, PLR, and PNI were determined using operating characteristic curves optimized for overall survival (OS). The each value of area under the curve, sensitivity, and specificity are shown in Table S1.

2.5 | Statistical analyses

Disease-free survival (DFS) was calculated from the date of treatment initiation to tumor relapse (locoregional recurrence, distant metastasis, or both) or death from any cause. Disease-specific survival (DSS) was calculated from the date of treatment initiation to death due to OPC. OS was calculated from the date of treatment initiation to death. Kaplan–Meier analysis was performed to assess patient survival and the log-rank test was performed to evaluate significant differences between and among two or three groups, respectively. The relationships between the SINBPI and clinical factors and between the causes of death and HS-mGPS were assessed using Fisher's exact test. Univariate and multivariate analyses to identify prognostic factors were performed using a Cox proportional hazards model. Clinical variables associated with a *p*-value <.1 in the univariate analysis were subjected to a multivariate analysis. Furthermore, Harrell's C-index was calculated to assess the prognostic utility of each combined markers. Statistical significance was set at a *p*-value of <.05. Statistical analyses were conducted using JMP version 16.2.0 (SAS Institute, Inc., Cary, NC) and R version 4.0.0 (R Foundation, Vienna, Austria).

3 | RESULTS

3.1 | Patient characteristics

The clinical characteristics in HPV-positive and negative patients in this study are summarized in Table 1. The median age of the patients

TABLE 3 Univariate and multivariate analyses for prognostic factor.

	DFS		DSS		OS	
	Univariate *p* value[a] HR (95% CI)	Multivariate *p* value[a] HR (95% CI)	Univariate *p* value[a] HR (95% CI)	Multivariate *p* value[a] HR (95% CI)	Univariate *p* value[a] HR (95% CI)	Multivariate *p* value[a] HR (95% CI)
Age	0.120		0.462		0.256	
≧64 vs. <64	1.54 (0.89–2.64)		1.38 (0.58–3.28)		1.49 (0.75–2.94)	
Sex	0.188		0.277		0.105	
Male vs. female	1.77 (0.75–4.13)		2.25 (0.52–9.65)		2.66 (0.81–8.72)	
PS	0.017	0.063	0.030	0.211	0.002	0.038
1–2 vs. 0	1.92 (1.12–3.29)	1.72 (0.97–3.14)	2.59 (1.10–6.12)	1.84 (0.71–4.83)	2.90 (1.49–5.67)	2.22 (1.05–4.73)
Smoking (Brinkman Index)	0.301		0.194		0.028	0.244
≧465 vs. <465	1.33 (0.78–2.28)		1.79 (0.74–4.33)		2.19 (1.09–4.40)	1.53 (0.74–3.13)
Alcohol consumption	0.008	0.073	0.182		0.047	0.304
Heavy vs. moderate or never	2.64 (1.17–5.94)	2.00 (0.94–4.27)	2.10 (0.71–6.25)		2.43 (1.01–5.88)	1.68 (0.62–4.55)
Subsite	0.317		0.416		0.202	
Lateral wall vs. others	0.76 (0.44–1.30)		0.71 (0.30–1.65)		0.65 (0.33–1.26)	
T classification	0.694		0.098	0.637	0.202	
T3–T4 vs. T1–T2	1.11 (0.65–1.90)		2.10 (0.87–5.07)	1.27 (0.47–3.49)	1.54 (0.79–2.99)	
N classification	0.757		0.887		0.392	
N1-3 vs. N0	1.09 (0.62–1.93)		1.07 (0.41–2.76)		0.74 (0.37–1.47)	
HPV status	0.003	0.040	0.016	0.011	< 0.001	0.008
Negative vs. positive	2.31 (1.34–3.97)	1.86 (1.02–3.37)	3.06 (1.23–7.57)	3.48 (1.33–9.07)	3.44 (1.68–7.05)	3.05 (1.33–7.00)
NLR	0.433		0.156		0.068	0.092
≧1.65 vs. <1.65	1.38 (0.62–3.05)		4.28 (0.58–32.0)		3.78 (0.90–15.80)	3.62 (0.81–16.21)
PLR	0.043	0.292	0.002	0.091	0.001	0.232
≧153.1 vs. <153.1	1.74 (1.02–2.97)	1.42 (0.74–2.74)	4.84 (1.77–13.22)	2.86 (0.84–9.71)	2.53 (1.27–5.03)	1.70 (0.71–4.05)
LMR	0.008	0.094	< 0.001	0.171	< 0.001	0.248
≧ 3.2 vs. <3.2	0.45 (0.25–0.81)	0.55 (0.27–1.11)	0.18 (0.08–0.43)	0.44 (0.13–1.42)	0.29 (0.15–0.58)	0.58 (0.23–1.46)
PNI	0.300		0.013	0.894	0.007	0.459
≧41 vs. <41	0.75 (0.44–1.29)		0.32 (0.13–0.79)	0.93 (0.30–2.85)	0.40 (0.20–0.78)	0.73 (0.33–1.65)
HS-mGPS	0.002	0.032	< 0.001	0.013	< 0.001	0.006
2 vs. 0–1	3.77 (1.60–8.87)	2.78 (1.09–7.08)	10.31 (3.73–28.47)	7.73 (2.06–28.9)	6.74 (2.76–16.41)	4.97 (1.58–15.68)

Note: Others (anterior, posterior, and superior wall).

Abbreviations: DFS, disease free survival; DSS, disease specific survival; HS-mGPS, high-sensitivity modified Glasgow prognostic score; LMR, lymphocyte to monocyte ratio; NLR, neutrophil to lymphocyte ratio; OS, overall survival; PLR, platelet to lymphocyte ratio; PNI, prognostic nutritional index; PS, performance status.

[a]Cox proportional hazards model.

at diagnosis was 63 (range, 34–83) years. Of the 124 patients, 103 (83%) and 21 (17%) were male and female, respectively. The Brinkman Index (BI) was used to assess smoking status; of the 124 patients, 61 and 63 had BI values of <465 and ≥465, respectively. Examination for HPV status by p16 immunohistochemistry staining or by hybrid-capture HPV DNA detection method was performed in 85 and 39 patients, respectively. Seventy-one patients had a positive HPV status, and the remaining patients had a negative HPV status. Eighty-seven patients underwent NAC. Forty-seven patients underwent surgery, 14 of whom underwent (C)RT for postoperative adjuvant therapy. Seventy-seven patients received non-surgical treatment, of whom 70, six, and one received cisplatin-based RT, Cet-RT, and RT, respectively. The significant differences HPV-positive and negative patients were observed in age

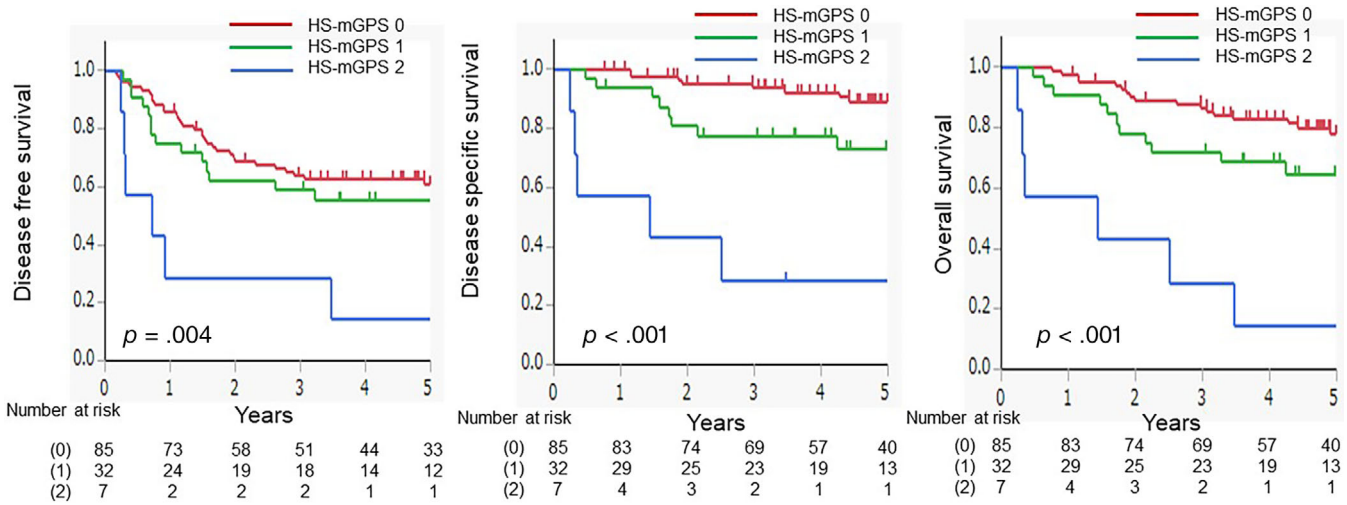

FIGURE 2 Kaplan–Meier analysis for disease-free survival, disease-specific survival, and overall survival based on the HS-mGPS of patients with OPSCC. Significant differences were evaluated using the log-rank test. HS-mGPS, high-sensitivity modified Glasgow prognostic score; OPSCC, oropharyngeal squamous cell carcinoma.

TABLE 4 Cause of death.

		HS-mGPS			
	n	0	1	2	*p*-value
All death	35	18 (21)	11(34)	6 (86)	.001
Cancer death	29	15 (18)	11 (34)	3 (43)	.060
Treatment-related death	4	1 (1)	0	3 (43)	<.001

Abbreviation: HS-mGPS, high-sensitivity modified Glasgow prognostic score.

($p = .001$), PS ($p = .008$), alcohol consumption ($p = .003$), subsite ($p = .005$), N classification ($p < .001$), clinical stage ($p < .001$), NAC ($p = .004$), and definitive treatment ($p = .013$). The median follow-up period was 5.3 (range, 1.1–10.5) years.

3.2 | Correlations between patient characteristics and SINBPI

The relationships between patient demographics and SINBPI are presented in Table 2. We detected significant correlations between PLR and age ($p = .029$) and between PNI and smoking ($p = .042$). Additionally, significant correlations were observed between HS-mGPS and PS ($p = .009$), smoking ($p = .013$), T classification ($p = .016$), and definitive treatment ($p = .018$). Six of the seven patients with a HS-mGPS of 2 received non-surgical treatment.

3.3 | Univariate and multivariate analyses for prognostic factor

The univariate and multivariate analysis results are presented in Table 3. The univariate analysis showed that PS ($p = .017$), alcohol consumption ($p = .008$), HPV status ($p = .003$), PLR ($p = .043$), LMR ($p = .008$), and HS-mGPS ($p = .002$) were significant predictive factors for DFS, and the multivariate analysis demonstrated that HPV status (hazard ratio [HR], 1.86; 95% confidence interval [CI], 1.02–3.37; $p = .040$) and HS-mGPS (HR, 2.78; 95% CI, 1.09–7.08; $p = .032$) were significant and independent predictive factors for DFS. Additionally, the univariate analysis showed that PS ($p = .030$), HPV status ($p = .016$), PLR ($p = .002$), LMR ($p < .001$), PNI ($p = .013$), and HS-mGPS ($p < .001$) were significant predictive factors for DSS, and the multivariate analysis demonstrated that HPV status (HR, 3.48; 95% CI, 1.33–9.07; $p = .011$) and HS-mGPS (HR 7.73; 95% CI 2.06–28.90; $p = .013$) were significant and independent predictive factors for DSS. Furthermore, the univariate analysis showed that PS ($p = .002$), smoking ($p = .028$), alcohol consumption ($p = .047$), HPV status ($p < .001$), PLR ($p = .001$), LMR ($p < .001$), PNI ($p = .007$), and HS-mGPS ($p < .001$) were significant predictive factors for OS. The multivariate analysis demonstrated that PS (HR, 2.22; 95% CI, 1.05–4.73; $p = .038$), HPV status (HR, 3.05; 95% CI, 1.33–7.00; $p = .008$), and HS-mGPS (HR, 4.97; 95% CI, 1.58–15.68; $p = .006$) were significant and independent predictive factors for OS.

3.4 | Survival analysis

In the multivariate analyses of SINBPI, a high HS-mGPS was an unfavorable prognostic factor for DFS, DSS, and OS. The Kaplan–Meier curves for DFS, DSS, and OS according to HS-mGPS are shown in

TABLE 5 Comparison of model according to C-index.

Model	C-index		
	DFS	DSS	OS
HS-mGPS	0.547	0.618	0.581
HS-mGPS + NLR	0.525	0.651	0.561
HS-mGPS + PLR	0.596	0.696	0.622
HS-mGPS + LMR	0.595	0.699	0.622

Abbreviations: DFS, disease free survival; DSS, disease specific survival; HS-mGPS, high-sensitivity modified Glasgow prognostic score; LMR, lymphocyte to monocyte ratio; NLR, neutrophil to lymphocyte ratio; OS, overall survival; PLR, platelet to lymphocyte ratio.

Figure 2. The 5-year DFS and DSS rates of patients with a HS-mGPS of 0, 1, and 2 were 61.1%, 55.4%, and 14.3% ($p = .004$) and 88.8%, 73.0%, and 28.6% ($p < .001$), respectively. Additionally, the 5-year OS rates of the patients with a HS-mGPS of 0, 1, and 2 were 77.9%, 64.6%, and 14.3% ($p < .001$), respectively.

3.5 | Death patterns according to the HS-mGPS

We examined the association between the cause of death and HS-mGPS (Table 4). Death due to OPSCC or other cancers occurred in 15, 11, and three patients with a HS-mGPS of 0, 1, and 2, respectively. Treatment-related deaths were observed in one and three patients with a HS-mGPS of 1 and 2, respectively. The rate of death was significantly higher in patients with a HS-mGPS of 2 ($p < .001$). Among three patients with a HS-mGPS of 2, one died from septic shock and two from pneumonia.

3.6 | Prognostic efficacy of combined marker with the HS-mGPS

We investigated whether the prognostic effect increased by the combination of biochemical (HS-mGPS) and hematological induces (NLR, PLR, or LMR) (Table 5). In this analysis, we excluded PNI for combined makers with the HS-mGPS because calculation of the PNI and HS-mGPS were defined by the CRP level. The results revealed that the combination of the HS-mGPS and PLR (C-index, 0.596) and the HS-mGPS and LMR (C-index, 0.699) had the highest prognostic accuracy (higher C-index) for DFS and DSS, respectively. Additionally, the combination of the HS-mGPS and PLR or LMR (C-index, 0.622) had the highest prognostic accuracy for OS.

4 | DISCUSSION

In the present study, we investigated the association between SINBPI and prognosis in patients with OPSCC receiving a definitive treatment. We demonstrated that the HS-mGPS had a statistically significant prognostic impact on DFS, DSS, and OS among the SINBPI examined in this study.

Several studies, including a meta-analysis, have reported the prognostic utility of the NLR, LMR, PLR, PNI, and HS-mGPS in head and neck cancers.[9–20,22–29] Regarding previous reports on a systematic review and meta-analysis, Yang et al.[22] investigated a total of 25 studies and demonstrated that higher pretreatment NLR was associated with poorer prognosis. Takenaka et al.[23] reviewed 19 studies of head and neck cancer and showed that an elevated pretreatment NLR had a predictive value of poorer OS and DSS. Tham et al.[24] investigated 4260 patients with head and neck cancer in seven cohorts and demonstrated that elevated LMR is significantly associated with improved OS and DFS. Kumarasamy et al.[10] investigated 49 studies on head and neck cancer and demonstrated that the PLR, NLR, and monocyte-lymphocyte ratio could be powerful prognostic markers. Shi et al.[25] investigated 10 studies and demonstrated that pretreatment PNI was a significant prognostic marker in patients with head and neck neoplasms treated with RT. However, to the best of our knowledge, no meta-analysis limited to OPC is currently available.

Regarding studies of OPC, in a study by Ng et al.[17] including a cohort of 848 patients with OPC treated with RT, the NLR (cutoff value, 3) before RT was an independent prognostic factor. Fanetti et al.[26] reported that a high NLR (cutoff value, 3) was a negative prognostic factor in a cohort of 125 patients with locally advanced OPC treated with CRT. Staniewska et al.[27] investigated the prognostic utility of red cell distribution width, NLR, and PLR using the receiver operating characteristic (ROC) method in patients with OPC receiving RT and showed that the NLR (cutoff value, 2.099) was an independent predictor of OS in their multivariate analysis. In this study, the NLR cutoff value (1.65) determined by the ROC optimized for OS was not associated with DFS, DSS, or OS in the univariate and multivariate analyses. Tsai et al.[28] investigated the prognostic utility of PNI and LMR in patients with HPV-negative OPC using the ROC method optimized for OS and demonstrated that both PNI (cutoff value, 50.5) and LMR (cutoff value, 4.45) were independent prognostic indicators for 5-year OS in their multivariate analysis. Takahashi et al.[29] investigated the prognostic utility of LMR, NLR, and PLR by optimal cutoff values using the ROC and demonstrated that LMR (cutoff value, 4.97) was an independent prognostic factor in their multivariate analysis. The present study showed that higher LMR (cutoff value, 3.2) or lower PLR (cutoff value, 153.1) was significantly associated with favorable DFS, DSS, and OS in our univariate analysis, although these were not significant in our multivariate analysis. Additionally, although our univariate analysis showed that higher PNI (cutoff value, 41) was significantly associated with favorable DSS and OS, it was not significant in our multivariate analysis.

Although meta-analyses of the prognostic value of pretreatment GPS or mGPS in several cancer types have been reported,[30–34] no meta-analysis has been reported for head and neck cancers. Furthermore, no meta-analysis on the HS-mGPS is available. Peng et al.[32] performed a meta-analysis to evaluate the prognostic value of NLR, LMR, PLR, and GPS in a cohort of patients with osteosarcoma and demonstrated that higher NLR and GPS were significantly associated with

poorer OS in patients with osteosarcoma, although there were no significant associations between PLR or LMR and OS or DFS. In a systematic review and meta-analysis including 72 studies, Jiang et al.[30] investigated the association of the NLR, PLR, LMR, CRP to albumin ratio (CAR), systemic inflammation index, GPS, and mGPS with prognostic value in esophageal cancer and demonstrated that the pretreatment CAR and mGPS had an excellently prognostic value relative to any other markers.

In this study, we determined the cutoff values of NLR, LMR, PLR, and PNI using the ROC optimized for OS and demonstrated that the HS-mGPS was the most significant and independent prognostic factor among the SINBPI examined. Additionally, although we conducted a prognostic analysis using the median cutoff values of NLR, LMR, PLR, and PNI, the HS-mGPS was the most significant and independent prognostic factor among these SINBPI (Table S2).

HS-mGPS, consisting of the serum levels of CRP and albumin, is easily and inexpensively available from clinical data. CRP is a sensitive marker of systemic inflammation, and an elevated serum CRP level is associated with tumor growth, lymph node metastasis, and tumor recurrence.[35–37] Additionally, albumin is widely used as an indicator of nutritional status, and patients with head and neck cancers have often been reported to have chronic malnutrition at diagnosis due to poor nutritional habits, and alcohol or tobacco abuse in addition to tumor-related symptoms, such as mechanical obstruction, dysphagia, and anorexia.[29,38,39] Therefore, patients with head and neck cancers tend to have hypoalbuminemia. Malnutrition induced by hypoalbuminemia is attributed to difficulty completing treatment or exacerbation of adverse effects. In this study, the rate of treatment-related death in patients with a HS-mGPS of 2 was higher than that for those with a HS-mGPS of 0 or 1, and these patients who had received CRT had treatment-related death. CRT causes several toxic effects, such as nausea, vomiting, xerostomia, mucositis, fatigue, and taste deficiency, and further deterioration of nutritional status is induced by these toxicities. Mikosiba et al.[40] reported that a high CAR and mGPS were independent predictors of the incidence of severe side effects. Therefore, the future of patients with OPSCC with an elevated HS-mGPS who may receive CRT is so serious that multimodal and nutritional treatment should be offered, which may delay or prevent the onset of cachexia and/or treatment-related deaths. Furthermore, HS-mGPS may assist in the rational selection of patients for pretreatment interventions, including increasing dietary and palliative care.

We identified the prognostic value of HS-mGPS in present study and demonstrated that combining HS-mGPS and PLR (C-index, 0.596) or LMR (C-index, 0.699) had a more accurate predictive ability for DFS and DSS compared with HS-mGPS alone (C-index, 0.547 and 0.618), respectively. We also demonstrated that combining HS-mGPS and PLR (C-index, 0.622) or LMR (C-index, 0.622) had a more accurate predictive ability for OS. Previous studies have demonstrated a C-index of 0.610–0.750 for a combination of inflammatory and nutritional markers for head and neck cancers. Moreover, Wei et al.,[41] in a study on a prognostic model in patients with locoregional recurrent nasopharyngeal carcinoma, investigated the predictive ability for OS through five combined factors–age, Alb, recurrent T stage, NLR, and systematic immune-inflammation index–and yielded a C-index of 0.636 and 0.610 in the test and validation cohorts, respectively. Tsai et al.[42] investigated the prognostic value of preoperative HS-mGPS, NLR, and PLR for patients with oral cavity cancer and showed that HS-mGPS combined with NLR (C-index, 0.71) had a more accurate predictive ability for survival than HS-mGPS alone (C-index, 0.66). Additionally, Zhuang et al.[43] investigated the prognostic value of albumin/globulin ratio (AGR), NLR, and PLR in patients with oral SCC and showed that AGR combined with the NLR score (C-index, 0.658) was a useful predictive marker for OS in patients with oral SCC. Furthermore, Kao et al.[44] reviewed 613 patients who underwent ablative surgery for oral SCC and showed that the albumin/NLR score (C-index, 0.750) had a more accurate predictive ability for OS compared to TNM staging (C-index, 0.688). Compared to the C-indexes in the aforementioned reports, the C-index of our prognostic model is not high, and the accuracy of our established predictive model might not be of high quality. Our study demonstrated that patients with a HS-mGPS of 2 had worse prognosis and higher treatment-related mortality than those with a lower HS-mGPS, meaning that this HS-mGPS might have the ability to isolate patients having a much worse prognosis from the remainder of the population, although though it has some limitations. Although we showed an improvement in the C-index by comparing the combined HS-mGPS and LMR or PLR to HS-mGPS alone, the clinical effectiveness of the combined markers might not be significant, owing to the low C-index. Therefore, it is necessary to develop a prognostic marker with a high C-index in the future.

This study has some limitations. First, it was a retrospective cohort study involving a small number of patients. Second, there was potential selection bias owing to the retrospective nature of this study. Third, treatment varied on a case-by-case basis. Finally, the HPV status assessment methods were not uniform. We would like to confirm the significance of our findings in future studies using external validation cohorts or a large prospective study.

5 | CONCLUSION

We investigated the prognostic utility of pretreatment SINBPI for patients with OPSCC and our findings revealed that the HS-mGPS was an independent prognostic factor. Patients with an elevated HS-mGPS had more unfavorable treatment-related outcomes, disease control, and survival rate. HS-mGPS may assist in the rational selection of patients for pretreatment interventions, which may contribute to favorable treatment outcomes. In the future, the development of a combination of HS-mGPS and hematological markers, including LMR or PLR, is warranted.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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