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ORIGINAL ARTICLE

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Validation of the conventional Glasgow Prognostic Score and development of the improved Glasgow Prognostic Score in patients with stage 0-III colorectal cancer after curative resection

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Abstract

Aim: Many inflammation-nutrition scores, including the Glasgow Prognostic Score (GPS), have been reported as prognostic biomarkers in patients with colorectal cancer (CRC). We aimed to examine the predictive ability of the GPS and to improve the GPS.

Methods: We included a total of 438 patients with stage 0-III CRC who underwent curative surgery from 2010 to 2013. They were divided into a training set comprising 221 patients and a validation set comprising 227 patients, according to the date of surgery. In the training set, the GPS was verified using a Cox regression model, and cut-off values for C-reactive protein (CRP) and albumin for relapse-free survival (RFS) were calculated using receiver operating characteristics (ROC) curves. The improved GPS (iGPS) was developed with additional optimal cut-off values. We also compared the iGPS with the conventional GPS in the validation set.

Results: The high GPS (GPS: 1-2) was correlated with RFS and overall survival (OS) in the training set. Cut-off values of CRP and albumin for RFS were 1.6 and 3.9, and we modified the GPS accordingly, adding the cut-off values of 2 and 3.9 to CRP and albumin, respectively. In the validation set, a high iGPS was an independent prognostic factor for RFS (hazard ratio [HR]: 2.273; 95% confidence interval [CI]: 1.212-4.364; $P = .011$), although the conventional GPS was not.

Conclusion: The iGPS was a more accurate prognostic predictor for patients with stage 0-III CRC.

KEYWORDS

biomarkers, colorectal cancer, inflammation, nutrition, prognosis

1 | INTRODUCTION

Colorectal cancer (CRC) was the third most common malignancy and the fourth most frequent cause of cancer-related death worldwide in 2012.[1] Despite advances in therapeutic strategies, including surgical procedures, chemotherapy, and immunotherapy, the relapse and mortality rates of CRC remain high.[2] Therefore, it is crucial to predict the risk of recurrence in patients with CRC and to identify patients who will require additional therapeutic interventions even after curative resection. Currently, the tumor-node-metastasis (TNM) classification is widely used as a prognostic prediction system in various cancers, including CRC. However, TNM staging system reflects only tumor characteristics and does not convey patient status. In particular, the TNM staging system for CRC does not accurately apply to patients without metastasis.[3]

A growing body of studies has indicated that the inflammatory, nutritional, and immunological status of a patient has important functions in cancer progression and is associated with the prognosis of malignant tumors.[4-6] Increasingly, inflammatory scores such as the neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), prognostic nutritional index (PNI), Glasgow prognostic score (GPS), controlling nutritional status (CONUT), and systemic inflammation score (SIS) have been reported to be prognostic indicators.[7-12] All of these comprise some combination of blood cell counts, serum albumin level, total cholesterol concentration, and C-reactive protein (CRP) concentration. Among these, CRP is a critical factor in the prognosis of patients with CRC.[13]

The GPS consists of CRP and albumin and reflects both the inflammatory and nutritional status of the patient. The GPS was first reported as a prognostic indicator in patients with non-small-cell lung cancer in 2003.[14] Since then, many studies have shown the utility of the GPS in predicting prognoses for various cancers types.[10,15-17] Typically, these studies have utilized the common cut-off values for CRP and albumin, although some studies have used the modified GPS, which regards patients with only hypoalbuminemia as low risk. However, the optimal cut-off values for inflammatory scores should vary between cancers because the degree of inflammation and malnutrition depends on the types of cancer. For example, one study utilizing PNI in the investigation of T1-2N1 breast cancer used a cut-off value of 52.0, another study of unresectable advanced gastric cancer used 36.1, and a study of resectable CRC used 45.5.[18-20]

In the present study, we sought to investigate the predictive capacity of the GPS for the risk of relapse in patients with CRC undergoing curative resection without distant metastasis. To the best of our knowledge, this is the first report on the GPS that focused on relapse-free survival (RFS) in patients with stage 0-III CRC. Moreover, we developed the improved GPS (iGPS) with additional cut-off values for CRP and albumin. We validated the iGPS in a separate data set and compared it with the conventional GPS.

2 | METHODS

2.1 | Patients

In this retrospective study, we enrolled 531 patients with stage 0-III CRC who underwent curative resection at Osaka University Hospital between January 2010 and December 2013. We excluded 52 patients who underwent surgery after endoscopic resection, three with inflammatory bowel syndrome, and 38 for whom there was no available

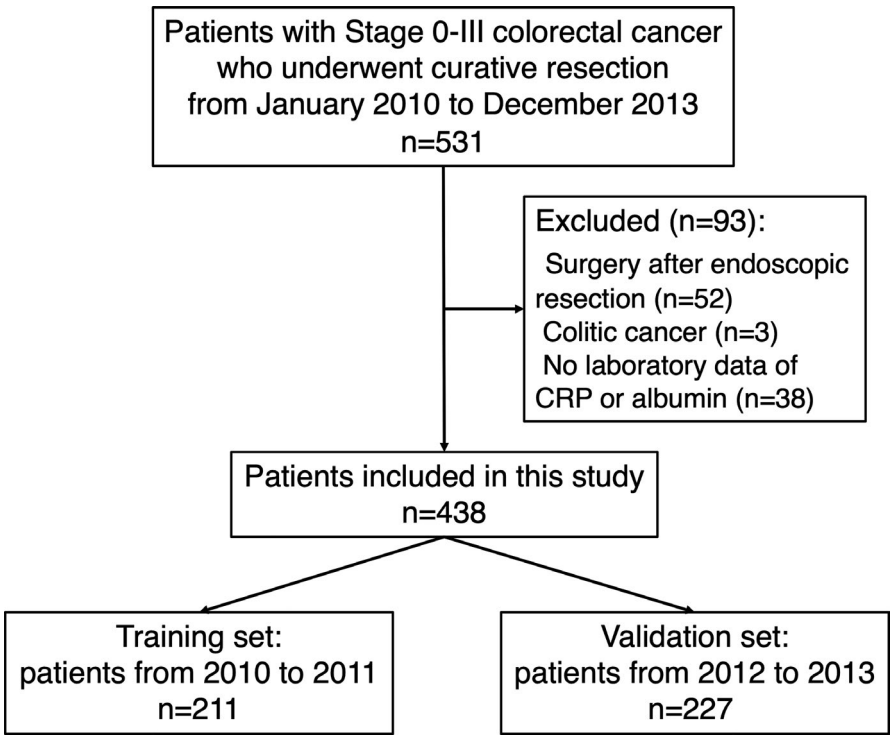

FIGURE 1 Flow diagram of the patients analyzed

laboratory data for CRP or albumin within the 30 days prior to surgery. The remaining 438 patients were divided into two groups: a training set, consisting of 211 patients who underwent surgery between 2010 and 2011, and a validation set, consisting of 227 patients who underwent surgery between 2012 and 2013 (Figure 1). We utilized the most recently obtained laboratory data within the 30 days prior to surgery, including CRP, albumin, and CEA. The clinicopathological findings were evaluated based on the eighth edition of the Unio Internationalis Contra Cancrum (UICC) TNM classification. The Institutional Review Boards of Osaka University granted ethical approval for this study.

2.2 | The GPS and the iGPS

The GPS was estimated using CRP and albumin, as described in previous reports.[10,14-16] Patients with both an elevated CRP (>10 mg/L) and hypoalbuminemia (<35 g/L) were given a GPS of 2, those with only one of these conditions were given a GPS of 1, and those with neither of these were given a GPS of 0. Receiver operating characteristics (ROC) curve analyses were used to determine the best cut-off values for CRP and albumin to predict relapse or death in the training set. We constructed the iGPS by adding the cut-off values to the conventional GPS.

2.3 | Survival data

After surgery, patients were followed up with a computed tomography (CT) scan and laboratory analysis of serum CEA and CA19-9 concentrations every 3-6 months, as well as a colonoscopy annually or biannually in accordance with Japanese national guidelines.[21] Data regarding patient survival and recurrence were collected from the medical records to calculate overall survival (OS), defined as the time in months from the date of surgery to the date of death from any cause, and relapse-free survival (RFS), defined as the time in months from the date of surgery to either the date of relapse or death.

2.4 | Statistical analysis

Patient characteristics are presented as mean ± standard deviation for continuous variables and the number of patients (as a percentage) for categorical variables. The difference between the two groups was analyzed using the chi-square test for categorical variables and the Mann-Whitney *U* test for continuous variables. Univariate and multivariate analyses were performed using a Cox proportional hazards model. Kaplan-Meier analyses were used to compare survival with the log-rank test. Receiver operating characteristics (ROC) curves for relapse or death were used to determine the CRP and albumin cut-off values in the training set. These statistical analyses were performed using JMP® software version 14 (SAS Institute Inc.). The predictive performance of GPS and iGPS was calculated using the concordance-index (c-index) with the R software program, v. 3. 1. 3 (CRAN; the R Foundation for Statistical Computing).

3 | RESULTS

3.1 | Patient characteristics

The characteristics of 211 patients in the training set and 227 patients in the validation set are summarized in Table S1. The training

TABLE 1 The relationship between GPS (0/1, 2) and patient characteristics in the training set

Variable	Number (%)	GPS		
		0 (%)	1-2 (%)	*P*-value
GPS		157 (74.4)	54 (25.6)	
Age[a] (years)		65.0 ± 11.1	70.4 ± 13.5	**.002**
Gender				
Male	128 (60.7)	96 (75.0)	32 (25.0)	.807
Female	83 (39.3)	61 (73.5)	22 (26.5)	
Primary tumor site				
Colon	155 (73.5)	115 (74.2)	40 (25.8)	.906
Rectum	56 (26.5)	42 (75.0)	14 (25.0)	
Histological grade				
Pap, Tub1 or Tub2	197 (93.4)	152 (77.2)	45 (22.8)	**.002**
Others[b]	14 (6.6)	5 (35.7)	9 (64.3)	
Tumor invasion				
Tis, T1 or T2	95 (45.0)	82 (86.3)	13 (13.7)	**<.001**
T3 or T4	116 (55.0)	75 (64.7)	41 (35.3)	
Lymph node metastasis[c]				
Absent	148 (70.5)	114 (77.0)	34 (23.0)	.166
Present	62 (29.5)	42 (67.7)	20 (32.3)	
Lymphatic invasion[d]				
Absent	63 (30.0)	54 (85.7)	9 (14.3)	**.010**
Present	147 (70.0)	102 (69.4)	45 (30.5)	
Venous invasion[e]				
Absent	145 (69.4)	116 (80.0)	29 (20.0)	**.005**
Present	64 (30.6)	39 (60.9)	25 (39.1)	
Preoperative CEA[f]				
CEA < 5	142 (78.4)	116 (81.7)	26 (18.3)	**<.001**
CEA ≥ 5	39 (21.6)	19 (48.7)	20 (51.3)	
TNM stage				
0, I	79 (37.4)	69 (87.3)	10 (12.7)	**<.001**
II, III	132 (62.6)	88 (66.7)	44 (33.3)	

Note: $P < .05$ indicated in bold.

Abbreviations: CEA, carcinoembryonic antigen; Pap, papillary adenocarcinoma; Tub1, well differentiated adenocarcinoma; Tub2, moderately differentiated adenocarcinoma.

[a]Continuous variable.

[b]Others: poorly differentiated adenocarcinoma, mucinous adenocarcinoma, or endocrine cell carcinoma.

[c]Unknown in one case.

[d]Unknown in one case.

[e]Unknown in two cases.

[f]Unknown in 30 cases.

TABLE 2 Univariate and multivariate analyses of relapse-free survival and overall survival by GPS in the training set

	Univariate			Multivariate		
Variable	HR	95% CI	*P*-value	HR	95% CI	*P*-value
A. Analyses of relapse-free survival						
Age (≥65/<65 years)	1.272	0.728-2.222	.397			
Gender (male/female)	1.255	0.710-2.218	.435			
Preoperative CEA (≥5/<5)	1.948	0.993-3.821	.052			
Primary tumor site (Rectum/Colon)	1.566	0.878-2.791	.129			
Histological grade (Others[a]/Pap, Tub1 or Tub2)	1.602	0.637-4.027	.316			
Tumor invasion (T3-4/Tis, T1-2)	2.615	1.419-4.819	**.002**	1.643	0.839-3.217	.148
Lymph node metastasis (present/absent)	1.959	1.129-3.399	**.017**	1.241	0.685-2.249	.477
Lymphatic invasion (present/absent)	1.673	0.879-3.183	.117			
Venous invasion (present/absent)	2.891	1.676-4.986	**<.001**	2.020	1.096-3.723	**.024**
GPS (1-2/0)	2.434	1.400-4.234	**.002**	1.877	1.052-3.349	**.033**
B. Analyses of overall survival						
Age (≥65/<65 years)	2.532	1.235-5.192	**.011**	2.574	1.205-5.502	**.015**
Gender (male/female)	2.009	0.981-4.111	.056			
Preoperative CEA (≥5/<5)	1.982	0.086-4.331	.086			
Primary tumor site (Rectum/Colon)	1.593	0.822-3.090	.168			
Histological grade (Others[a]/Pap, Tub1 or Tub2)	1.606	0.570-4.520	.370			
Tumor invasion (T3-4/Tis, T1-2)	2.575	1.258-5.269	**.010**	1.612	0.732-3.549	.236
Lymph node metastasis (present/absent)	1.811	0.961-3.410	.066			
Lymphatic invasion (present/absent)	1.562	0.743-3.282	.239			
Venous invasion (present/absent)	2.550	1.360-4.780	**.004**	1.975	0.994-3.923	.052
GPS (1-2/0)	3.042	1.628-5.684	**<.001**	2.107	1.077-4.123	**.030**

Note: $P < .05$ indicated in bold.

Abbreviations: CEA, carcinoembryonic antigen; CI, confidence interval; GPS, Glasgow prognostic score; HR, hazard ratio; Pap, papillary adenocarcinoma; Tub1, well differentiated adenocarcinoma; Tub2, moderately differentiated adenocarcinoma.

[a]Others: poorly differentiated adenocarcinoma, mucinous adenocarcinoma, or endocrine cell carcinoma

set consisted of 155 patients with colon cancer and 56 patients with rectal cancer, and the validation set consisted of 154 patients with colon cancer and 73 patients with rectal cancer. There were 157 patients with a GPS of 0, 43 patients with a GPS of 1, and 11 patients with a GPS of 2 in the training set, and the corresponding values were 169, 34, and 24, respectively, in the validation set.

3.2 | Clinicopathological factors and GPS

Clinicopathological factors in the training set were classified according to the GPS (low group: 0, high group: 1-2), as shown in Table 1. The high GPS group were older and had higher preoperative CEA levels than the low GPS group. Analysis of tumor factors revealed that the high GPS group had significantly deeper tumor invasion, more vascular invasion, and worse TNM stage than the low GPS group. Neoadjuvant and adjuvant chemotherapy regimens in the training set are shown in Table S2. Neoadjuvant chemotherapy was more frequently performed in the high GPS group than the low GPS group.

3.3 | Survival analyses according to GPS groups

Univariate and multivariate analyses for RFS and OS, according to the GPS groups in the training set, are shown in Table 2. RFS was significantly related to elevated CEA levels, deeper tumor invasion, presence of lymph node metastasis, presence of venous invasion, and a high GPS. Of these, a high GPS was the only independent prognostic factor for RFS in the multivariate analysis. OS was significantly related to age, deeper tumor invasion, presence of venous invasion, and a high GPS. Age and a high GPS were independent prognostic factors for OS. The high GPS group also had a worse prognosis than the low GPS group in Kaplan-Meier analyses for RFS and OS (Figure S1A,B). The difference in Kaplan-Meier curves for RFS between the GPS 0 and GPS 1-2 groups was more pronounced in stages II-III than in stages 0-I, as shown in Figure S2.

3.4 | Development of iGPS

The ROC curve analyses of CRP and albumin for relapse or death from any cause are shown in Figure S3A,B. The CRP and albumin values, which maximize the Youden indices (sensitivity + specificity-1), were calculated using these analyses. The cut-off values of CRP and albumin were 1.6 and 3.9, and the area under the curve (AUC) of the ROC curves was 0.659 and 0.608, respectively. We then modified the existing GPS, adding cut-off values of 2 (1.6 rounded up) to CRP and 3.9 to albumin, to improve the prognostic ability of GPS for recurrence (Table 3).

3.5 | Survival analyses according to iGPS groups in the training and validation sets

Table 4 displays the univariate and multivariate analyses for RFS and OS using the iGPS in the training set. A high iGPS was also an independent prognostic factor and was a more powerful predictor for RFS (hazard ratio [HR]: 2.393) and OS (HR: 2.903) than a high GPS (RFS HR: 1.982, OS HR: 2.269) in the multivariate analyses. We further examined the prognostic ability of iGPS for RFS in the validation set, as shown in Table 5. A high iGPS was a significant independent predictor for RFS (HR: 2.273; 95% CI: 1.212-4.264; $P = .011$), although conventional GPS was not an independent factor in the validation set (HR: 1.817; 95% CI: 0.962-3.432; $P = .066$). The Kaplan-Meier curves for RFS according to the GPS and the iGPS in the validation set are illustrated in Figure 2. Five-year RFS rates were 85.4% and 61.6% in the low iGPS group and the high iGPS group, respectively, compared to 83.1% and 64.8% in the low GPS group and the high GPS group, respectively. In addition, we compared the predictive accuracy between conventional GPS and iGPS using C-indices. The C-index of iGPS for RFS (0.644) was superior to that of GPS (0.621) in the validation set (Table 6). A high iGPS was also a significant independent predictor for OS (Table S3), and the iGPS had a higher C-index for OS (0.705) than the conventional GPS (0.677) in the validation sets (Table 6).

4 | DISCUSSION

Multiple studies have reported that the GPS is associated with prognosis in patients with various types of gastrointestinal cancers, including CRC.[22-27] The GPS divides patients into three groups based on their CRP and albumin levels: patients at high-risk, those at intermediate-risk, and those at low-risk. The conventional GPS utilizes only one cut-off value for each: 10 mg/L for CRP; and 35 g/L for albumin. However, this model can be too simple to precisely predict the prognosis in patients with differing types of cancers. In this study, roughly three-quarters of patients were classified as GPS 0, but some of these had a poor prognosis. Therefore, we added the cut-off values to the conventional GPS and developed the iGPS to predict RFS in patients with stage 0-III CRC with better accuracy. The resulting scores demonstrated an improved correlation with both RFS and OS compared to the conventional GPS. On the other hand, the modified GPS was not superior to the GPS as a prognostic indicator in these data sets, although some studies have shown that

TABLE 3 The GPS and the improved GPS based on CRP and albumin

		CRP (mg/L)		
GPS		**≤10**		**10<**
Albumin (g/L)	35≤	0		1
	<35	1		2
		CRP (mg/L)		
iGPS		**≤2**	**2<, ≤10**	**10<**
Albumin (g/L)	39≤	0	0	1
	35≤, <39	0	1	1
	<35	1	1	2

Abbreviations: CRP, C-reactive protein; GPS, Glasgow Prognostic Score; iGPS, improved Glasgow Prognostic Score.

TABLE 4 Univariate and multivariate analyses of relapse-free survival and overall survival by iGPS in the training set

	Univariate			Multivariate		
Variable	HR	95% CI	*P* value	HR	95% CI	*P* value
A. Analyses of relapse-free survival						
Age (≥65/<65 years)	1.272	0.728-2.222	.397			
Gender (male/female)	1.255	0.710-2.218	.435			
Preoperative CEA (≥5/<5)	1.948	0.993-3.821	.052			
Primary tumor site (Rectum/Colon)	1.566	0.878-2.791	.129			
Histological grade (Others[a]/Pap, Tub1 or Tub2)	1.602	0.637-4.027	.316			
Tumor invasion (T3-4/Tis, T1-2)	2.615	1.419-4.819	**.002**	1.556	0.795-3.043	.197
Lymph node metastasis (present/absent)	1.959	1.129-3.399	**.017**	1.257	0.692-2.284	.453
Lymphatic invasion (present/absent)	1.673	0.879-3.183	.117			
Venous invasion (present/absent)	2.891	1.676-4.986	**<.001**	2.079	1.129-3.829	**.019**
iGPS (1-2/0)	2.634	1.533-4.524	**<.001**	2.191	1.248-3.849	**.006**
B. Analyses of overall survival						
Age (≥65/<65 years)	2.532	1.235-5.192	**.011**	2.422	1.131-5.186	**.023**
Gender (male/female)	2.009	0.981-4.111	.056			
Preoperative CEA (≥5/<5)	1.982	0.086-4.331	.086			
Primary tumor site (Rectum/Colon)	1.593	0.822-3.090	.168			
Histological grade (Others[a]/Pap, Tub1 or Tub2)	1.606	0.570-4.520	.370			
Tumor invasion (T3-4/Tis, T1-2)	2.575	1.258-5.269	**.010**	1.523	0.695-3.340	.293
Lymph node metastasis (present/absent)	1.811	0.961-3.410	.066			
Lymphatic invasion (present/absent)	1.562	0.743-3.282	.239			
Venous invasion (present/absent)	2.550	1.360-4.780	**.004**	2.031	1.032-3.997	**.040**
iGPS (1-2/0)	4.080	2.138-7.785	**<.001**	2.683	1.376-5.229	**.004**

Note: $P < .05$ indicated in bold.

Abbreviations: CEA, carcinoembryonic antigen; CI, confidence interval; HR, hazard ratio; iGPS, improved Glasgow prognostic score; Pap, papillary adenocarcinoma; Tub1, well differentiated adenocarcinoma; Tub2, moderately differentiated adenocarcinoma.

[a]Others: poorly differentiated adenocarcinoma, mucinous adenocarcinoma, or endocrine cell carcinoma.

CRC patients with hypoalbuminemia alone and without elevated CRP levels had relatively better survival.[22]

Several studies have shown the relationship between systemic inflammation and cancer progression. Pro-inflammatory cytokines, such as tumor necrosis factor α, interleukin (IL)-6, and IL-8 are elevated during the course of inflammatory responses.[15] These cytokines, in particular IL-6, stimulate hepatocytes to increase the synthesis of acute-phase proteins including CRP and decrease the synthesis of albumin.[27] Thus, hypoalbuminemia is an indicator of not only nutrition and liver function but also systemic inflammation. In addition, CRP is involved in the function of infiltrating immune cells, including dendritic cells, natural killer cells, and T-lymphocytes.[28-30] The findings of this study indicate that even a mild increase in CRP level of <10 mg/L can reflect an inflammatory response.

This study has some limitations. It was a retrospective, single-center study, and the iGPS was validated in an internal cohort of different periods. Although the iGPS was examined in different independent patients, external cohorts are required to verify the validity of the iGPS further. Furthermore, we investigated only Japanese patients and the utility of the iGPS may differ according to race. However, a previous study showed that the GPS had a similar prognostic value between Asian and non-Asian patients, and this also appears to be the case with the iGPS.[16] Finally, we did not compare the iGPS with other inflammation scores. Although previous studies have claimed superiority for each prognostic score in patients with CRC,

TABLE 5 Univariate and multivariate analyses of relapse-free survival by GPS and iGPS in the validation set

	Univariate			Multivariate (GPS)			Multivariate (iGPS)		
Variable	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Analyses of relapse-free survival									
Age (≥65/<65)	1.930	1.051-3.547	**.034**	2.038	1.062-3.911	**.032**	1.956	1.015-3.767	**.045**
Gender (male/female)	1.437	0.798-2.589	.227						
CEA level (≥5/<5)	2.989	1.686-5.298	**<.001**	1.628	0.857-3.093	.136	1.540	0.803-2.954	.194
Primary tumor site (Rectum/Colon)	0.992	0.546-1.804	.992						
Histological grade (Others/Pap, Tub)	1.694	0.671-4.274	.264						
Tumor invasion (T3-4/Tis,T1-2)	3.217	1.677-6.172	**<.001**	1.460	0.663-3.216	.347	1.477	0.668-3.265	.335
Lymph node metastasis (N1-3/N0)	2.414	1.378-4.229	**.002**	1.414	0.716-2.793	.318	1.433	0.731-2.809	.295
Lymphatic invasion (Present/Absent)	2.937	1.498-5.761	**.002**	1.178	0.483-2.869	.719	1.144	0.470-2.784	.766
Venous invasion (Present/Absent)	3.307	1.865-5.866	**<.001**	2.140	1.091-4.198	**.027**	2.176	1.108-4.274	**.024**
GPS (1-2/0)	2.712	1.544-4.763	**<.001**	1.548	0.831-2.883	.168	—	—	—
iGPS (1-2/0)	3.166	1.805-5.551	**<.001**	—	—	—	1.879	1.020-3.461	**.043**

Note: $P < .05$ indicated in bold.

Abbreviations: CEA, carcinoembryonic antigen; CI, confidence interval; GPS, Glasgow prognostic score;HR, hazard ratio; iGPS, improved Glasgow prognostic score; Pap, papillary adenocarcinoma; Tub, Tubular adenocarcinoma.

[a]Others: poorly differentiated adenocarcinoma, mucinous adenocarcinoma, or endocrine cell carcinoma.

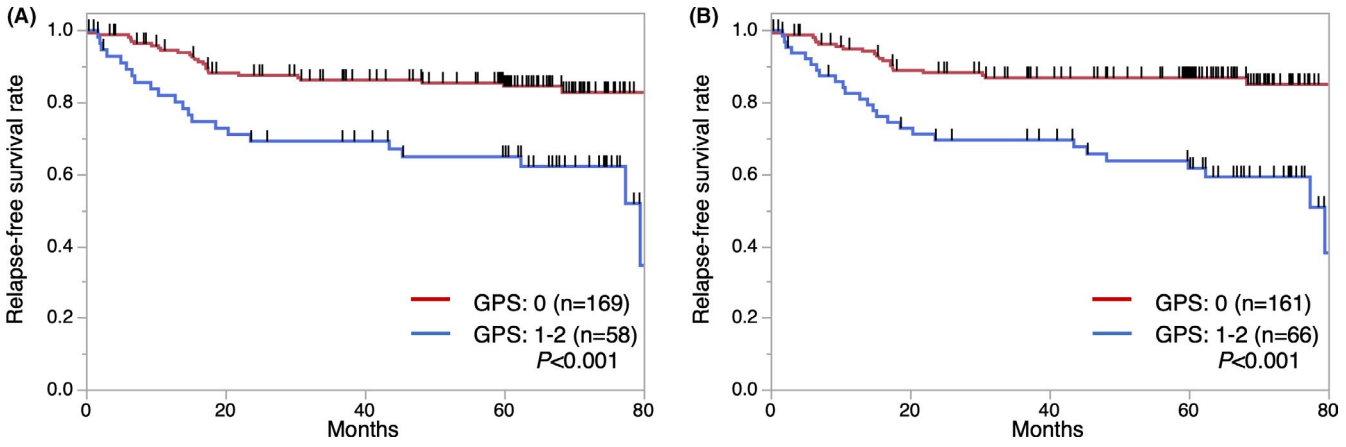

FIGURE 2 Kaplan-Meier curves for relapse-free survival (RFS) according to (A) the Glasgow Prognostic Score (GPS) and (B) the improved GPS (iGPS) in the validation set. (A) The RFS rate of the high GPS group (GPS: 1-2, n = 58) was significantly worse than that of the low GPS group (GPS: 0, n = 169) in the log-rank test ($P < .001$). (B) The RFS rate of the high iGPS group (iGPS: 1-2, n = 66) was significantly worse than that of the low iGPS group (GPS: 0, n = 161) in the log-rank test ($P < .001$)

including the NLR, LMR, PNI (albumin and total lymphocyte), Osaka Prognostic Score (the mGPS and total lymphocyte), SIS (albumin and LMR), CONUT (albumin, total cholesterol concentration, and total lymphocyte), and NPS (albumin, total cholesterol, the NLR, and the LMR), which of these scores is the optimal one remains controversial.[7-9,31-34]

A previous study showed that the prognostic performance of the NPS was better than that of the SIS, CONUT, and PNI and almost equal to that of the TNM staging system for determining OS.[34] It is notable that the iGPS was an independent prognostic factor for both RFS and OS, although the T factor and the N factor were not independent

TABLE 6 C-indices of the GPS and iGPS for RFS and OS in the training and validation sets

C-index		GPS	iGPS
RFS	Training set	0.596	0.613
	Validation set	0.621	0.644
OS	Training set	0.650	0.677
	Validation set	0.687	0.705

Abbreviations: GPS, Glasgow Prognostic Score; iGPS, improved Glasgow Prognostic Score; OS, overall survival; RFS, relapse-free survival.

prognostic factors in this study. The *P*-value of the iGPS for OS was less than that of TNM staging in multivariate analysis both in the training and validation sets (data not shown). Moreover, given that the iGPS is derived from only two serum laboratory measures, it is more straightforward than the SIS, CONUT, and NPS.

In conclusion, this study demonstrated that the iGPS correlated with recurrence and mortality in patients with stage 0-III CRC. The iGPS may be useful to identify patients who need careful follow-up and adjuvant chemotherapy even after curative surgery.

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DISCLOSURE

Conflicts of Interest: Authors declare no conflicts of interest for this article.

Author Contribution: All authors are in agreement with the content of the manuscript.

Ethical Approval: The protocol for this research project has been approved by a suitably constituted Ethics Committee of the institution and it conforms to the provisions of the Declaration of Helsinki. The Ethics Committee of Osaka University Hospital, Approval No. 08226. All informed consent was obtained from the subject(s) and/or guardian(s).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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