

Comparison of systemic inflammatory and nutritional scores in colorectal cancer patients who underwent potentially curative resection

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Abstract

Background Various systemic inflammatory and nutritional scores have been reported to predict postoperative outcomes. This study aimed to investigate the best systemic inflammatory and nutritional scores in colorectal cancer (CRC) patients who underwent potentially curative resection.

Method We evaluated 468 consecutive CRC patients in this study. Comparisons of systemic inflammatory and nutritional scores, including the neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), prognostic index (PI), prognostic nutritional index (PNI), and modified Glasgow prognostic score (mGPS), were performed using univariate/multivariate analyses for patient survival.

Results The PNI and mGPS, but not the NLR, PLR, and PI, were significantly associated with overall and relapse-free survival. The mGPS, but not the PNI, was strongly correlated with TNM stage ($P < 0.001$). Cox multivariate analysis showed that both the PNI and mGPS were exclusive independent prognostic factors for both overall and relapse-free survival ($P < 0.001$). Furthermore, the PNI status predicted patient survival more clearly than the mGPS in combination with TNM stage.

Conclusions This study suggests that the PNI and mGPS are useful predictive scores in CRC patients who undergo

potentially curative resection, especially the PNI in combination with TNM stage. Routine evaluation of the host status using the scores may be useful in CRC treatment.

Keywords Colorectal cancer · Modified Glasgow prognostic score · Prognostic nutritional index · Systemic inflammatory and nutritional scores · Treatment

Abbreviations

CRC	Colorectal cancer
mGPS	Modified Glasgow prognostic score
CRP	C-reactive protein
NLR	Neutrophil to lymphocyte ratio
PLR	Platelet to lymphocyte ratio
PI	Prognostic index
PNI	Prognostic nutritional index
BMI	Body mass index
CEA	Carcinoembryonic antigen
HR	Hazard ratio
CI	Confidence interval
OS	Overall survival
DFS	Disease-free survival

Introduction

Cancer patients are often in an accelerated metabolic state, and inflammation status is reportedly related to the degree of cancer progression [1]. In gastrointestinal cancer patients, difficulty in nutrient intake sometimes appears in the perioperative period, leading to poor postoperative outcomes [2]. Nutritional management is indispensable for successful gastrointestinal surgery. Therefore, various systemic inflammatory and nutritional scores have been reported to predict postoperative complications [3–5],

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recurrence, or prognosis [6]. However, in cancer patients, the type of cancer, location, histopathological type, and stage are not the same. Consequently, which is the best predictive score depending on the case needs to be considered.

In colorectal cancer (CRC) patients who underwent potentially curative resection, Park et al. recently reported that the combination of TNM stage and modified Glasgow prognostic score (mGPS) stratified postoperative outcomes [7]. However, how this finding might be used for Japanese patients and whether the mGPS is the best systemic inflammatory and nutritional score are still unclear because of different body types or dietary habits. As curative resection is the best treatment protocol in CRC, preoperative prediction of postoperative recurrence and prognosis is helpful in clinical use.

Therefore, in the present study, we aimed to determine the prognostic impact of systemic inflammatory and nutritional scores using a database of 468 CRC patients who underwent potentially curative resection. Our data may indicate the characteristics and usefulness of each score for CRC.

Methods

Patients

A total of 591 consecutive patients with primary CRC underwent colectomy at Kumamoto University Hospital in Kumamoto, Japan, from March 2005 to August 2014. Of these, 472 patients underwent potentially curative resection. Survival data were available in all cases. Among them, we excluded four patients for whom necessary preoperative data for calculating systemic inflammatory and nutritional scores were unavailable. Finally, a total of 468 patients were enrolled in this study (277 (59.2%) men and 191 (40.8%) women), with a mean age of 68 years (range 19–93 years).

Study design

Treatment data were obtained retrospectively from the patient records. Patients were observed until their death or until July 31, 2016, whichever came first. The mean follow-up time was 48.5 months (range 2–124 months). Surgical procedures, including the extent of colectomy and lymph node dissection, were based on the Japanese CRC treatment guidelines [8–10]. Disease staging was performed according to the 7th edition of Union for International Cancer Control classification [11]. Follow-up of all patients was carried out in our hospital or affiliated hospitals. Tumor markers were checked every 3 months and diagnostic imaging was performed at least every 6 months,

based on surveillance suggested in the guidelines. In cases of suspected recurrence, ethoxybenzyl-magnetic resonance imaging or positron emission tomography-computed tomography was added to the diagnostic imaging. Use of the clinical data was approved by the human ethics review committee of the Graduate School of Medicine, Kumamoto University.

Systemic inflammatory and nutritional scores and other markers

Serum samples were collected and measured within 2 weeks prior to potentially curative resection. Laboratory measurements included C-reactive protein (CRP) levels, albumin levels, and white blood cell, neutrophil, lymphocyte, and platelet counts. We determined the following systemic inflammatory and nutritional scores—neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), prognostic index (PI), prognostic nutritional index (PNI), and mGPS, which were calculated as described in Supplementary Table 1. Cut-off values were determined according to previous reports. Briefly, the NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. An NLR ≥ 5 was considered elevated [12]. The same calculation was applied to derive the PLR. A PLR ≥ 300 was considered elevated [13]. For PI scoring, patients with an elevated CRP serum level (>10 mg/L) and elevated white cell count ($>11 \times 10^9$ /L) were classified as PI 2; those with either abnormality were classified as PI 1, and those with neither abnormality were classified as PI 0 [14]. The PNI was calculated as follows—albumin value (g/L) $+0.005 \times$ total lymphocyte count. A PNI <45 was considered decreased [15]. In mGPS scoring, patients with an elevated CRP serum level (>10 mg/L) and hypoalbuminemia (<35 g/L) were classified as mGPS 2; those with either abnormality were classified as mGPS 1, and those with neither abnormality were classified as mGPS 0 [7].

Patient body mass index (BMI) was calculated from preoperative height and weight, which were measured by our clinical staff on the date of admission. BMI was divided into three groups— <18.5 , 18.5–24.9, and ≥ 25 . The cut-off values for serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels were set at 5.0 ng/ml [16] and 37 U/ml [17], respectively.

Statistical analysis

All statistical analyses were performed using JMP statistical software package version 10 (SAS Institute Inc., Cary, NC, USA) and Excel 2010 (Microsoft, Redmond, WA, USA). All analyses were performed in patients for whom

all systemic inflammatory and nutritional scores were available ($n = 468$).

Univariate analyses were performed to investigate clinicopathological factors and systemic inflammatory and nutritional scores. The chi-squared test was used for categorical data and Student's t test was used for age. The P value for significance was adjusted for multiple hypothesis testing by Bonferroni correction to $P = 0.0045$ ($=0.05/11$). The Kaplan–Meier method and log-rank test were used for survival analysis according to systemic inflammatory and nutritional score status. Cox proportional hazards regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). Backward elimination was

performed with a threshold of $P = 0.05$ to avoid overfitting. A P value of <0.05 was considered statistically significant in all multivariate analyses.

Results

Associations of systemic inflammatory and nutritional score status with the patient survival

Preoperative systemic inflammatory and nutritional scores for the 468 patients were constructed as mentioned above. Figure 1 shows the associations of systemic inflammatory

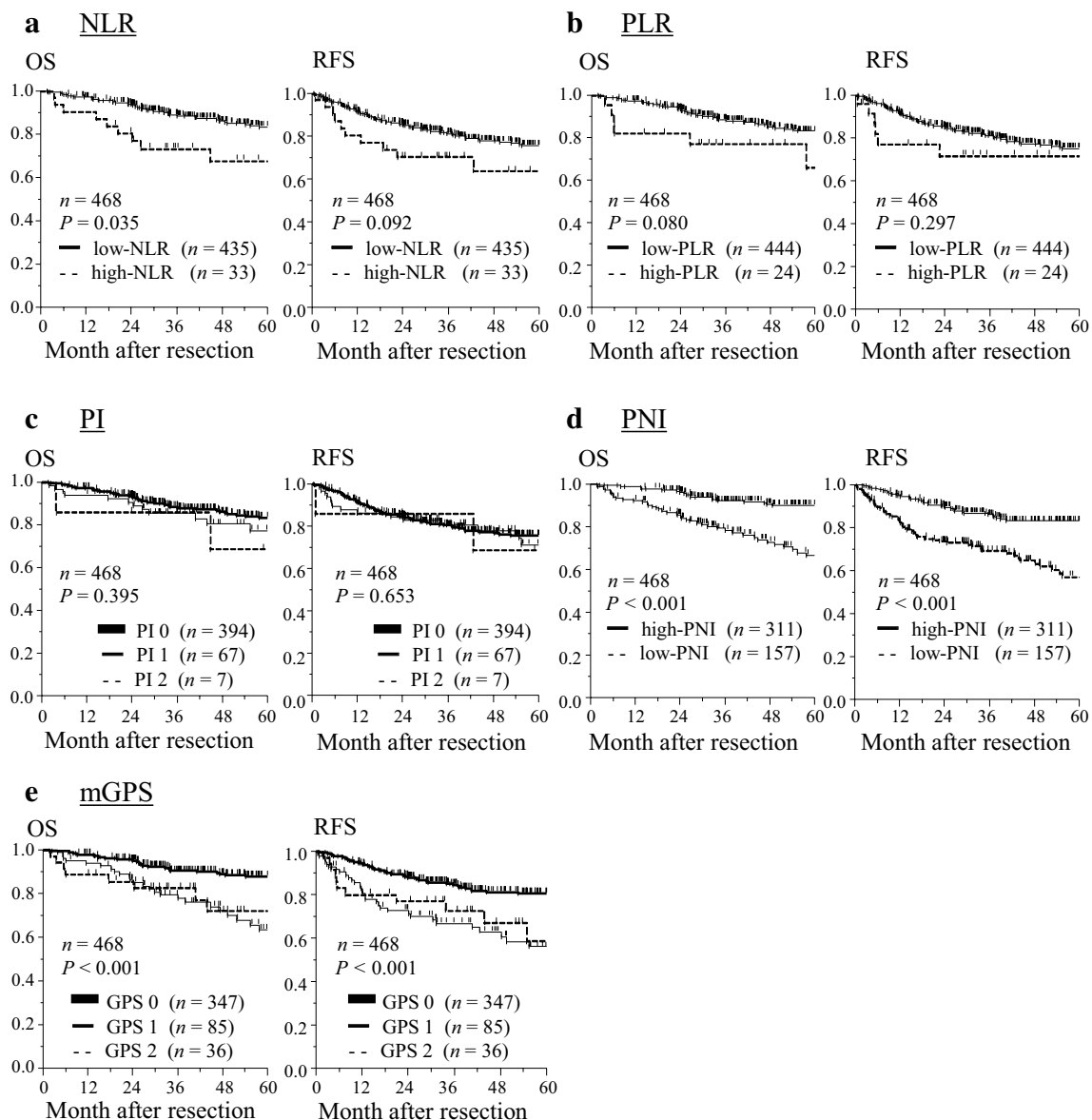


Fig. 1 Overall (OS) and relapse-free survival (RFS) curves according to five preoperative systemic inflammatory and nutritional scores. **a** NLR, **b** PLR, **c** PI, **d** PNI, **e** mGPS

and nutritional score status with overall survival (OS) and relapse-free survival (RFS). The PNI and mGPS, but not the NLR, PLR, PI, were significantly associated with both OS and RFS. The 5-year OS was 90.0 and 66.7% ($P < 0.001$), and the 5-year RFS was 83.2 and 57.2% ($P < 0.001$) with a high PNI and low PNI status, respectively. The 5-year OS was 88.0, 63.3, and 72.1% ($P < 0.001$), and the 5-year RFS was 80.8, 56.0, and 58.6% ($P < 0.001$) with mGPS 0, 1, and 2 status, respectively.

Associations of systemic inflammatory and nutritional score status with clinicopathological factors

We investigated the associations of PNI and mGPS status with clinicopathological factors because they had a strong correlation with patient survival. According to mGPS, we analysed them after integrating the mGPS 1 with the mGPS 2, because of similar survival data (Table 1). The mean age of low PNI status patients (71.3 ± 12.1 years) was significantly higher than that of high PNI status patients (65.9 ± 12.0 years, $P < 0.001$). However, the mGPS status did not show a significant correlation with age ($P = 0.101$). Both the PNI and the mGPS status showed a strong correlation with BMI, depth of tumor invasion, CEA levels, and CA19-9 levels. Interestingly, only the mGPS status showed a strong correlation with TNM stage ($P < 0.001$). All of these factors remained after Bonferroni correction ($P < 0.0045$; $=0.05/11$).

We also investigated the associations of NLR, PLR, and PI status with clinicopathological factors to identify the characteristic of each status (Supplementary Table 2). The NLR status did not have a strong correlation with clinicopathological factors, and the PLR status only had a strong correlation with BMI ($P < 0.001$). Additionally, the PI status showed a strong correlation with depth of tumor invasion ($P < 0.001$), TNM stage ($P < 0.001$), and histopathological type ($P < 0.001$).

Analysis for survival using systemic inflammatory and nutritional score status and clinicopathological factors

We next identified the factors that affected the survival of CRC patients who underwent potentially curative resection (Table 2). In our dataset ($n = 468$), postoperative recurrence occurred in 61 (13.0%) patients—eight (4.1%) in stage I, 20 (13.4%) in stage II, and 33 (27.0%) in stage III.

In univariate analysis, the PNI ($P < 0.001$) and mGPS ($P < 0.001$) were significantly associated with both OS and RFS. In addition, in multivariate analysis, we adjusted for clinicopathological factors that showed a significant difference for survival in univariate analysis to identify the usefulness of the PNI and mGPS (Table 2). Cox multivariate

analysis showed that both the PNI and the mGPS were exclusive independent prognostic factors for both OS ($P < 0.001$) and RFS ($P < 0.001$).

Associations of PNI or mGPS status with TNM stage in predicting patient survival

We re-analyzed the association of PNI or mGPS status with patient OS and RFS in each TNM stage (Table 3). Subgroup analysis showed that in stage I and III, there were significant associations of PNI or mGPS with both OS and RFS. However, in stage II, PNI but not mGPS, had significant associations with OS and RFS.

Furthermore, OS and RFS were significantly different among the combinations of PNI or mGPS and TNM stage status (Fig. 2). Of interest for both OS and RFS, stage II patients with a low PNI status had worse survival than stage III patients with a high PNI status. However, the combination of mGPS and TNM stage status did not show the difference.

Discussion

This study examined the associations of systemic inflammatory and nutritional scores, including the NLR, PLR, PI, PNI, and mGPS, with clinicopathological factors and survival of CRC patients who underwent potentially curative resection. We found that the PNI and mGPS could predict postoperative recurrence and prognosis. Additionally, in combination with TNM stage, the PNI predicted patient survival more clearly than the mGPS. This combination may be a useful strategy as a preoperative predictive method.

Systemic inflammatory and nutritional scores reportedly play an important role in various cancers in certain situations. Previous reports have shown that inflammation promotes tumor invasion and metastasis, through activation of interleukin-6 and recruitment of regulatory T lymphocytes [18]. In addition, malnutrition is a commonly encountered problem when treating CRC patients. Serum albumin levels are closely correlated with the degree of malnutrition and are also correlated with the prognosis in CRC patients [19]. Therefore, various systemic inflammatory and nutritional scores have been developed, which can reflect host status and predict cancer progression. However, there are few reports that have compared the five well-known scores of the NLR, PLR, PI, PNI, and mGPS [14, 20]. In patients with CRC who underwent potentially curative resection, Guthrie et al. demonstrated that the mGPS was an independent predictor of poor cancer-specific survival [21]. However, their study only compared the mGPS with the NLR.

Table 1 Associations of each inflammatory and nutritional score with clinicopathological factors ($n = 468$)

	PNI status		<i>P</i> value	mGPS status		<i>P</i> value
	High PNI	Low PNI		0	1–2	
Patients (%)	311 (66)	157 (34)		347 (74)	121 (26)	
Age (years)						
mean \pm SD	65.9 \pm 12.0	71.3 \pm 12.1	<0.001	67.2 \pm 12.5	69.3 \pm 11.7	0.101
Sex						
Male	193 (62)	84 (54)		209 (60)	68 (56)	
Female	118 (38)	73 (46)	0.076	138 (40)	53 (44)	0.438
BMI (kg/m ²)						
<18.5	27 (9)	34 (22)		33 (10)	28 (23)	
\geq 18.5, < 25.0	203 (65)	98 (62)		227 (65)	74 (61)	
\geq 25.0	81 (26)	25 (16)	<0.001	87 (25)	19 (16)	<0.001
Tumor location						
Proximal	93 (30)	59 (38)		106 (31)	46 (38)	
Distal	218 (70)	98 (62)	0.096	241 (69)	75 (62)	0.134
Preoperative chemotherapy						
Absent	301 (97)	145 (92)		335 (97)	112 (93)	
Present	9 (3)	12 (8)	0.023	12 (3)	9 (7)	0.084
Depth of tumor invasion						
T1	87 (27)	35 (23)		103 (29)	19 (16)	
T2	73 (24)	27 (17)		84 (24)	16 (13)	
T3	127 (41)	64 (41)		144 (41)	47 (39)	
T4	24 (8)	31 (20)	0.002	16 (6)	39 (32)	<0.001
Lymph node metastasis						
Negative	231 (74)	116 (74)		264 (76)	83 (69)	
Positive	80 (26)	41 (26)	0.927	83 (24)	38 (31)	0.110
Stage						
I	140 (45)	57 (36)		165 (48)	32 (27)	
II	91 (29)	58 (37)		99 (28)	50 (41)	
III	80 (26)	42 (27)	0.145	83 (24)	39 (32)	<0.001
Histopathological types						
Well-moderate	297 (96)	145 (92)		334 (96)	108 (89)	
Poorly	14 (4)	12 (8)	0.171	13 (4)	13 (11)	0.007
CEA (ng/ml) ^a						
Negative	257 (83)	109 (69)		288 (84)	78 (64)	
Positive	51 (17)	48 (31)	<0.001	56 (16)	43 (36)	<0.001
CA19-9 (U/ml) ^b						
Negative	283 (93)	124 (80)		315 (93)	92 (77)	
Positive	21 (7)	31 (20)	<0.001	24 (7)	28 (23)	<0.001

The *P* value for significance was adjusted for multiple hypothesis testing to $P = 0.05/11 = 0.0045$

BMI body mass index, *CA19-9* carbohydrate antigen 19-9, *CEA* carcinoembryonic antigen, *mGPS* modified Glasgow prognostic score, *PNI* prognostic nutritional index, *SD* standard deviation

^a Three patients were excluded because of data loss

^b Nine patients were excluded because of data loss

Our study showed that the PNI and mGPS were selectively effective scores for CRC patients who underwent potentially curative resection. Interestingly, mGPS status, but not PNI status, had a strong correlation with TNM stage. In addition, subgroup analysis showed that PNI

status predicted survival of stage II patients more clearly. Our data support previous reports showing that the PNI and mGPS are effective prognostic scores for cancer patients [7, 15]. However, although the NLR, PLR, and PI have been reported as predictive scores for cancer patients, they

Table 3 Subgroup analysis for survival ($n = 468$)

	No. patients (%)	PNI			mGPS		
		HR (log)	HR	<i>P</i> value	HR (log)	HR	<i>P</i> value
Overall survival							
All cases	468		3.23	<0.001		2.75	<0.001
Stage I	197 (42)		2.45	0.029		3.53	0.004
Stage II	149 (32)		4.66	<0.001		2.15	0.060
Stage III	122 (26)		3.25	0.003		2.51	0.020
Relapse free survival							
All cases	468		2.73	<0.001		2.56	<0.001
Stage I	197 (42)		2.45	0.022		3.95	<0.001
Stage II	149 (32)		2.99	0.001		1.67	0.136
Stage III	122 (26)		2.78	0.001		2.19	0.016

Horizontal lines represent 95% CIs. Each square represents the HR point estimate. The square situated at the vertical line is at the null value, and that situated at the right of the vertical line represents a higher risk

HR hazard ratio, mGPS modified Glasgow prognostic score, PNI prognostic nutritional index

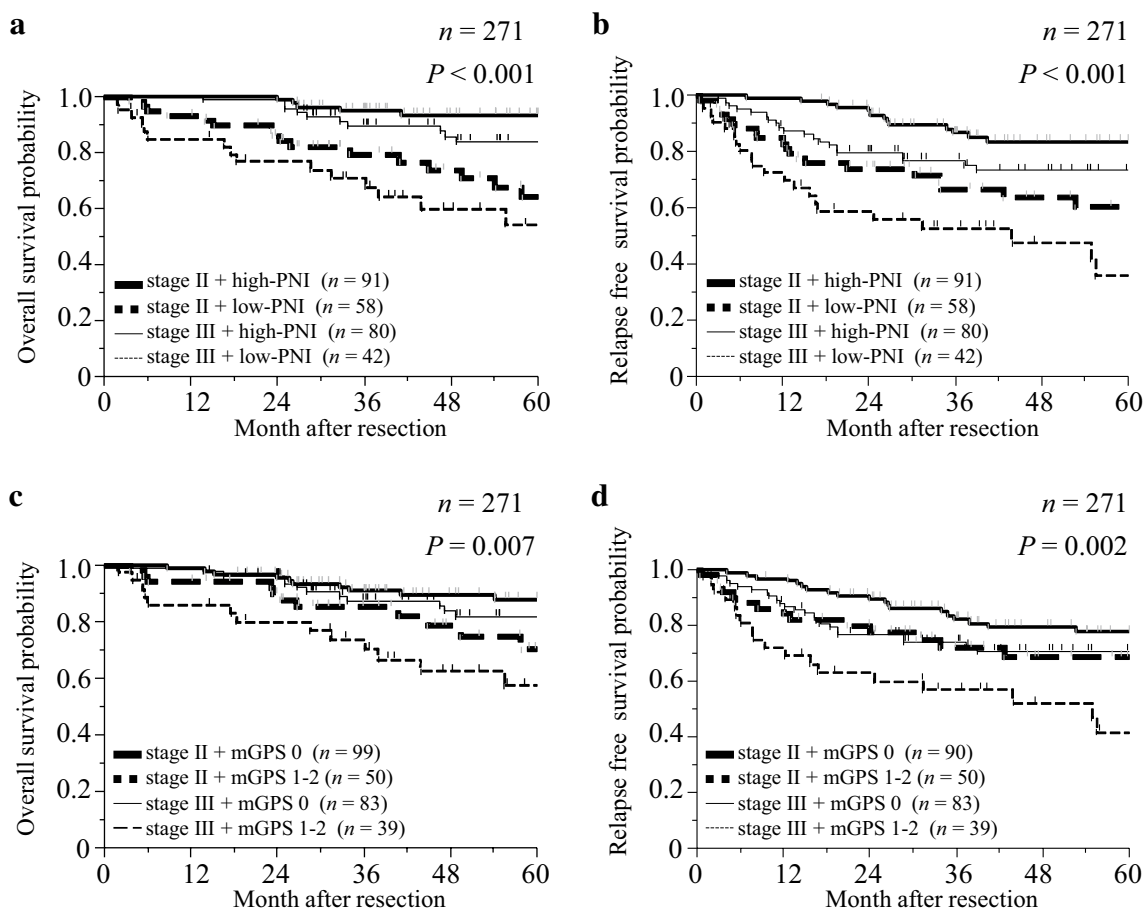


Fig. 2 Overall (OS) and relapse-free survival (RFS) curves according to the combination of TNM stage and preoperative PNI or mGPS status. **a, b** OS (**a**) and RFS (**b**) curves according to the combination

of TNM stage and preoperative PNI. **c, d** OS (**c**) and RFS (**d**) curves according to the combination of TNM stage and preoperative mGPS

subtypes [27]. The malignancy potential or stage of cancer progression itself predicts patient outcomes. However, success in treatment, especially in surgery, also requires a stable host status. Therefore, systemic inflammatory and nutritional scores indicating the host status using commonly used serum data may be useful for routine medical care.

There are some limitations in this study. First, our dataset did not include data of visceral fat or sarcopenia, which is reportedly related to cancer progression [28, 29]. However, prognostic scores should be easy to use and simple. Second, nutritional disorders in cancer patients occur not only by cancer pathology itself, but also by preoperative chemotherapy or radiotherapy. In our study, the PNI and mGPS did not show a significant correlation with preoperative chemotherapy because of the small number of cases. Third, this study was retrospective and was performed at a single institution. Nevertheless, this is the first study to compare the significance of five systemic inflammatory and nutritional scores for CRC patients who underwent potentially curative resection, based on a dataset of 468 patients. Large-scale prospective studies accounting for these scores are needed to confirm our findings.

In conclusion, this study shows that the PNI and mGPS may be a useful predictive score in CRC patients who undergo potentially curative resection, especially the PNI in combination with TNM stage. Additionally, large-scale studies are warranted to assess the clinical utility of systemic inflammatory and nutritional scores.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to declare.

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