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Preoperative inflammatory response as prognostic factor of patients with colon cancer

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Abstract

Purpose This study aimed to investigate the abilities of the modified Glasgow prognostic score (mGPS) and other inflammatory scores to predict recurrence-free survival (RFS) among patients with colon cancer (CC). In addition, we evaluated the abilities of the mGPS to predict recurrence of stage II disease and the efficacy of adjuvant chemotherapy (AC) for stage III disease.

Methods This retrospective study evaluated 477 patients with stage I–III CC who underwent curative surgery. These patients were categorized as having a low mGPS (mGPS 0) or a high mGPS (mGPS 1–2).

Results Patients in the high mGPS group had significantly poorer RFS than patients in the low mGPS group ($p < 0.01$). Multivariate analysis revealed that a high mGPS independently predicted poor RFS ($p < 0.01$). Among patients with stage II CC, multivariate analysis revealed that the independent predictors of poor RFS were pT4 status ($p < 0.01$) and a high mGPS ($p = 0.04$). Among patients with stage III CC, AC was not significantly associated with the 5-year RFS for patients with a low mGPS ($p = 0.38$), although AC significantly improved the 5-year RFS for patients with a high mGPS ($p < 0.01$).

Conclusion The preoperative mGPS significantly predicted recurrence among patients with CC, even among patients with stage II CC. In addition, mGPS may provide valuable information regarding subgroups of patients with stage III CC who might benefit from AC.

Keywords Colon cancer · Recurrence · Preoperative inflammatory response · mGPS · Adjuvant chemotherapy

Introduction

Colorectal cancer (CRC) is the third most common cancer in men and the second most common cancer in women (nearly 1.4 million new cases were diagnosed in 2012), as well as the fourth leading cause of cancer-related deaths [1, 2]. Despite recent advances in surgical procedures and chemotherapy, a considerable number of patients still experience relapse after curative resection, which is associated with a high mortality rate. The pathological staging of the resected tumor, based on the TNM criteria, is widely used to predict outcomes, although the prognosis is variable among patients with the same disease stage, which highlights the inability of the TNM stage to clearly identify patients with a high risk of recurrence and mortality, especially among patients with lymph node-negative disease [3]. Among patients with lymph node-positive disease, adjuvant chemotherapy (AC) after curative surgery is the standard treatment, although it is difficult to predict each patient's response because there are no widely utilized biomarkers or classification systems for predicting AC efficacy in stage III CRC. Therefore, ongoing efforts aim to identify factors, such as distribution of lymph node metastasis, that can predict survival after potentially curative surgery for CRC and the efficacy of AC in this setting [4].

Several systemic inflammation-based prognostic scores have been used to predict prognosis for various malignancies, such as the Glasgow prognostic score (GPS) or the modified GPS (mGPS), which are based on serum C-reactive protein

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(CRP) and albumin; the neutrophil-to-lymphocyte ratio (NLR); the platelet-to-lymphocyte ratio (PLR); and the prognostic nutritional index (PNI), which is based on albumin and lymphocyte counts [5, 6]. Among these scoring systems, the mGPS is simple to measure and has a clearly defined cut-off value, which has led to it being recognized as one of the most useful systems for predicting long-term outcomes among patients with various cancers [7–10]. However, only a few reports have described the ability of the mGPS to predict recurrence among patients with CRC, especially among patients with stage II disease, or to predict AC efficacy among patients with stage III disease. The present study aimed to investigate the abilities of the mGPS and other inflammation-based scores to predict recurrence-free survival (RFS) among patients with colon cancer (CC) after curative resection, as well as to determine whether these scores could predict recurrence in patients with stage II disease and AC efficacy among patients with stage III disease.

Methods

Patients

This study retrospectively evaluated records from 707 consecutive patients with pathological stage I–III CRC who underwent curative surgery in our institution between 2008 and 2015. However, we excluded 65 patients with synchronous or metachronous malignancies (within 5 years), 2 patients who died during their hospital stay, and 4 patients with missing data. Moreover, due to the differences in anatomical-, prognostic-, and treatment-related factors and the unproven benefit of adjuvant chemotherapy in rectal cancer, we also excluded 159 patients with rectal cancer. The remaining 477 CC patients were included in this study. The patients' characteristics, pathological and surgical findings, and postoperative clinical course were evaluated using their medical records and our institution's databases. The preoperative diagnosis of colorectal adenocarcinoma was confirmed using endoscopy and biopsy. Colectomy and lymph node dissection were performed according to the guidelines of the Japanese Society for Cancer of the Colon and Rectum (JSCCR) [11]. Tumor staging was determined based on the 7th edition of the International Union Against Cancer tumor, node, metastasis (TNM) classification system [12]. Macroscopic and histological types and lymphatic or venous invasions were classified according to the 8th edition of the Japanese classification of colorectal carcinoma [13]. The presence and severity of postoperative complications were evaluated using the Clavien-Dindo scale, with complications considered present at grade II or higher [14, 15]. Intra-abdominal complications were defined as anastomotic leakage, intra-abdominal abscess, pancreatic fistula, or ileus.

Patients with favorable performance status and stage III or high-risk stage II disease could receive AC after surgery according to the JSCCR guidelines [11]. The AC was started within 4–8 weeks after surgery. Monotherapy was provided using 5-fluorouracil, TS-1, or capecitabine, while the combination regimens included oxaliplatin, 5-fluorouracil, plus folinic acid (FOLFOX), capecitabine plus oxaliplatin (CapOX), or UFT plus leucovorin. The patients were subsequently followed-up every 3–6 months for the first 2 years after surgery, and follow-up continued for at least 5 years. The follow-up evaluations consisted of physical examinations, blood testing (including for tumor markers, such as carcinoembryonic antigen [CEA]), computed tomography (CT), and colonoscopy. The presence of recurrence was confirmed via imaging, which generally involved CT. Recurrence was confirmed histologically if possible via surgical biopsy, needle biopsy, or appropriate fluid cytology.

GPS scoring and other systemic inflammatory scores

Preoperative peripheral blood samples were routinely collected from the patients within 30 days before the potentially curative surgery. The laboratory data included serum CRP and albumin levels, as well as counts of neutrophils, lymphocytes, and platelets. The systemic inflammatory and nutritional scores (GPS, NLR, PLR, and PNI) were calculated based on the test results, and the scores' cut-off values were defined according to previous reports. The GPS was calculated as a score of 2 (elevated CRP [> 10 mg/L] plus hypoalbuminemia [< 35 g/L]), a score of 1 (elevated CRP or hypoalbuminemia), or a score of 0 (no elevated CRP and no hypoalbuminemia) [16]. In contrast, the mGPS was calculated as a score of 2 (elevated CRP plus hypoalbuminemia), a score of 1 (elevated CRP but no hypoalbuminemia), or a score of 0 (no elevated CRP, regardless of whether hypoalbuminemia was present) [17]. The NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count and a high NLR was defined as a ratio ≥ 5 [18]. The PLR was calculated as the absolute platelet count divided by the absolute lymphocyte count and a high PLR was defined as ≥ 300 [19]. The PNI was calculated as [albumin (g/L) + 0.005 × total lymphocyte count], and a PNI of < 45 was considered low [20].

Statistical analysis

Continuous variables were reported as median (range). Categorical variables were compared using the chi-square test. The primary endpoint of this study was RFS. Time to recurrence was measured from the date of resection to the date of confirmation of recurrence. The RFS curves were compared using the Kaplan-Meier method and log-rank test. Cox proportional hazards regression models were used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) for

each variable. Multivariate survival analysis was performed using Cox's proportional hazard regression model to identify factors that independently predicted RFS. All statistical analyses were performed using the JMP software for Macintosh (version 10.0; SAS Institute, Cary, NC, USA).

Results

Associations between preoperative mGPS and prognosis

Figure 1 shows the associations of the mGPS with RFS and OS in colon cancer patients. The 5-year RFS rates were significantly different for an mGPS of 0, 1, and 2 (87.3 vs. 61.1 vs. 44.7%, respectively; $p < 0.01$). The 5-year OS rates were also significantly different for an mGPS of 0, 1, and 2 (88.2 vs. 71.3 vs. 34.9%, respectively; $p < 0.01$). Besides, a high mGPS was significantly associated with worse RFS and OS among colon cancer patients (87.3 vs. 57.9%, $p < 0.01$; HR: 4.51, 95% CI 2.72–7.23/88.2 vs. 68.2%, $p < 0.01$; HR 3.83, 95% CI 2.04–6.87). Moreover, Supplemental Fig. 1 showed that a

poor RFS was also significantly associated with a high GPS (87.4 vs. 64.9%, $p < 0.01$; HR 3.67, 95% CI 2.24–5.92), a high PLR (84.2 vs. 71.0%, $p = 0.01$; HR 2.42, 95% CI 1.06–4.76), a high NLR (85.1 vs. 62.7%, $p < 0.01$; HR 3.22, 95% CI 1.80–5.40), and a low PNI (86.7 vs. 71.6%, $p < 0.01$; HR 2.58, 95% CI 1.57–4.17). These results suggested that mGPS was more strongly associated with RFS in colon cancer patients among these inflammatory scores.

Correlation between mGPS and clinicopathological factors

Table 1 shows the correlations of the mGPS with the patients' clinicopathological factors. A high mGPS (1–2) was significantly associated with a BMI of < 22 kg/m^2 ($p = 0.01$), right-sided colon tumors ($p = 0.01$), a tumor size of ≥ 35 mm ($p < 0.01$), a type 2–4 macroscopic appearance ($p < 0.01$), deeper invasion of the primary tumor (pT3–4; $p < 0.01$), advanced stage ($p < 0.01$), the presence of venous invasion ($p = 0.01$), a CEA level of ≥ 5 ng/mL ($p < 0.01$), and open surgery ($p = 0.01$). Thus, mGPS might be associated with more advanced cancer.
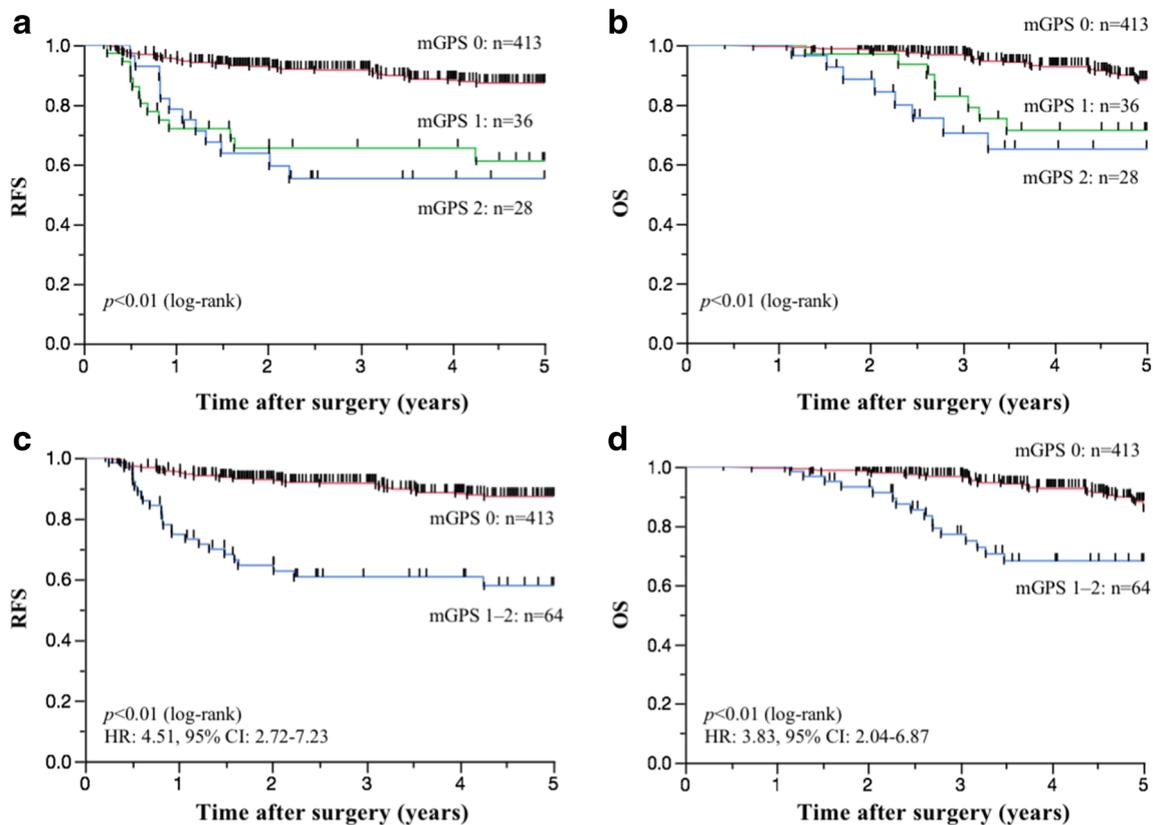
Fig. 1 Comparing the abilities of preoperative inflammatory scores to predict recurrence. Recurrence-free survival (RFS) curves were created using the Kaplan-Meier method according to the modified Glasgow prognostic score (mGPS: **a, b**), Glasgow prognostic score (GPS: **c**), platelet-to-lymphocyte ratio (PLR: **d**), neutrophil-to-lymphocyte ratio (NLR: **e**), and prognostic nutritional index (PNI: **f**). *HR* hazard ratio, *CI* confidence interval

Table 1 Comparison of clinicopathological factors

Variables		n = 477	mGPS				p value [c]
			0 (n = 413)		1–2 (n = 64)		
Age, years	≥ 70	222	189	(46%)	33	(52%)	0.38
	< 70	255	224	(54%)	31	(48%)	
Sex	Female	218	184	(45%)	34	(53%)	0.20
	Male	259	229	(55%)	30	(47%)	
BMI, kg/m^2	≥ 22	259	233	(56%)	26	(41%)	0.01
	< 22	218	180	(44%)	38	(59%)	
Location	Right	175	143	(35%)	32	(50%)	0.01
	Left	302	270	(65%)	32	(50%)	
Tumor size, mm	≥ 35	256	197	(48%)	59	(92%)	< 0.01
	< 35	221	216	(52%)	5	(8%)	
Histopathological type[a]	por/sig/muc	39	31	(8%)	8	(13%)	0.17
	tub/pap	438	382	(92%)	56	(87%)	
Macroscopic type[a]	2–4	328	269	(65%)	59	(92%)	< 0.01
	0–1	149	144	(35%)	5	(8%)	
pT stage[b]	T3–4	292	234	(57%)	58	(90%)	< 0.01
	T1–2	185	179	(43%)	6	(10%)	
pN stage[b]	N1–2	152	128	(31%)	24	(38%)	0.29
	N0	325	285	(69%)	40	(62%)	
Stage[b]	3	152	128	(31%)	24	(38%)	< 0.01
	2	168	133	(32%)	35	(55%)	
	1	157	152	(37%)	5	(7%)	
Lymphatic invasion[a]	Present	226	194	(47%)	32	(50%)	0.65
	Absent	251	219	(53%)	32	(50%)	
Venous invasion[a]	Present	216	178	(43%)	38	(60%)	0.01
	Absent	261	235	(57%)	26	(40%)	
Operative blood loss, g	≥ 100	63	52	(13%)	11	(17%)	0.31
	< 100	414	361	(87%)	53	(83%)	
Operative time, min	≥ 220	204	173	(42%)	31	(48%)	0.32
	< 220	273	240	(58%)	33	(52%)	
No. of nodes examined	< 12	116	106	(26%)	10	(16%)	0.08
	≥ 12	361	307	(74%)	54	(84%)	
CEA, ng/mL	≥ 5	143	112	(27%)	31	(48%)	< 0.01
	< 5	334	301	(73%)	33	(52%)	
Intra-abdominal complication	Present	32	27	(7%)	5	(8%)	0.70
	Absent	445	386	(93%)	59	(92%)	
Approach	Open	54	41	(10%)	13	(20%)	0.01
	Laparoscopic	423	372	(90%)	51	(80%)	

[a] According to the 8th edition of the Japanese classification of colorectal carcinoma

[b] According to the 7th edition of the UICC/TNM staging system

[c] p values were calculated using the chi-squared test

mGPS modified Glasgow prognostic score, *BMI* body mass index, tub: tubular adenocarcinoma, *pap* papillary adenocarcinoma, *por* poorly differentiated adenocarcinoma, *sig* signet-ring cell carcinoma, *muc* mucinous adenocarcinoma, *CEA* carcinoembryonic antigen

Table 2 Univariate and multivariate analyses of recurrence-free survival

Variables		n = 477	Univariate		Multivariate		
			5-year RFS (%)	p value[c]	HR	95% CI	p value[d]
Age, years	≥ 70	222	81.3	0.42			
	< 70	255	85.1				
Sex	Male	218	86.3	0.20			
	Female	259	81.1				
BMI, kg/m^2	≥ 22	259	82.7	0.84			
	< 22	218	84.3				
Location	Right	175	83.9	0.74			
	Left	302	83.1				
Tumor size, mm	≥ 35	256	74.0	< 0.01	1.58	0.78–3.50	0.20
	< 35	221	94.2				
Histopathological type[a]	por/sig/muc	39	65.9	< 0.01	1.17	0.58–2.17	0.63
	tub/pap	438	84.9				
Macroscopic type[a]	2–4	328	77.6	< 0.01	1.60	0.43–4.78	0.44
	0–1	149	96.1				
T stage[b]	T3–4	292	74.1	< 0.01	3.95	1.12–17.3	0.03
	T1–2	185	97.7				
N stage[b]	N1–2	152	63.6	< 0.01	3.73	2.20–6.54	< 0.01
	N0	325	92.6				
Lymphatic invasion[a]	Present	226	77.0	< 0.01	1.23	0.73–2.12	0.42
	Absent	251	89.0				
Venous invasion[a]	Present	216	74.9	< 0.01	1.96	1.16–3.43	0.01
	Absent	261	90.3				
Operative blood loss, g	≥ 100	63	74.2	0.03	1.63	0.87–2.86	0.11
	< 100	414	84.8				
Operative time, min	≥ 220	204	80.7	0.41			
	< 220	273	85.0				
No. of nodes examined	< 12	116	82.9	0.91			
	≥ 12	361	83.7				
CEA, ng/mL	≥ 5	143	67.0	< 0.01	2.43	1.48–4.02	< 0.01
	< 5	334	90.0				
Intra-abdominal complication	Present	32	68.2	0.05			
	Absent	445	84.4				
mGPS	1–2	64	57.9	< 0.01	2.91	1.70–4.91	< 0.01
	0	477	87.3				

[a] According to the 8th edition of the Japanese classification of colorectal carcinoma

[b] According to the 7th edition of the UICC/TNM staging system

[c] p values were calculated using the log-rank test

[d] p values were calculated using Cox's proportional hazard model

RFS recurrence-free survival, *HR* hazard ratio, *CI* confidence interval, *mGPS* modified Glasgow prognostic score, *BMI* body mass index, *tub* tubular adenocarcinoma, *pap* papillary adenocarcinoma, *por* poorly differentiated adenocarcinoma, *sig* signet-ring cell carcinoma, *muc* mucinous adenocarcinoma, *CEA* carcinoembryonic antigen

Predicting RFS using preoperative inflammatory and clinicopathological scores

Table 2 shows the correlations of RFS with the 477 patients' clinicopathological factors. In the univariate analysis, a high mGPS was significantly associated with poor RFS ($p < 0.01$). The multivariate analysis, which was adjusted for the clinicopathological factors and mGPS, revealed that poor RFS was independently associated with a high mGPS (HR 2.91, 95% CI 1.70–4.91, $p < 0.01$), as well as deeper tumor invasion, the presence of lymph node metastasis, the presence of venous invasion, and higher CEA.

The RFS and OS curves stratified based on pathological stage were compared according to mGPS (Fig. 2), which revealed no significant difference for stage I disease (Fig. 2a, b). However, a high mGPS was associated

with significantly poorer RFS and OS than a low mGPS among patients with stage II disease (Fig. 2c 67.1 vs. 91.5%, $p < 0.01$, Fig. 2d 73.2 vs. 90.5%, $p < 0.01$) and among patients with stage III disease (Fig. 2e 35.6 vs. 68.7%, $p < 0.01$, Fig. 2f 55.2 vs. 79.1%, $p < 0.01$).

Risk factors for recurrence of stage II CC

The mGPS was strongly associated with RFS, even among patients with stage II CC, which prompted us to compare its predictive ability to that of the known risk factors for recurrence of stage II CC. These risk factors are pT4 status, the presence of preoperative obstruction or perforation, a poorly differentiated histological type, the presence of venous or lymphatic invasion, and suboptimal lymph node dissection (< 12 lymph nodes), based on the major Western guidelines

Fig. 2 Survival analysis of patients with pathological stage III CC according to adjuvant chemotherapy status and stratified based on mGPS. Survival analysis among all patients (**a,** $n = 200$) and among patients with a mGPS of 0 (**b,** $n = 175$) or a mGPS of 1–2 (**b,** $n = 25$). mGPS modified Glasgow prognostic score, RFS recurrence-free survival, HR hazard ratio, CI confidence interval
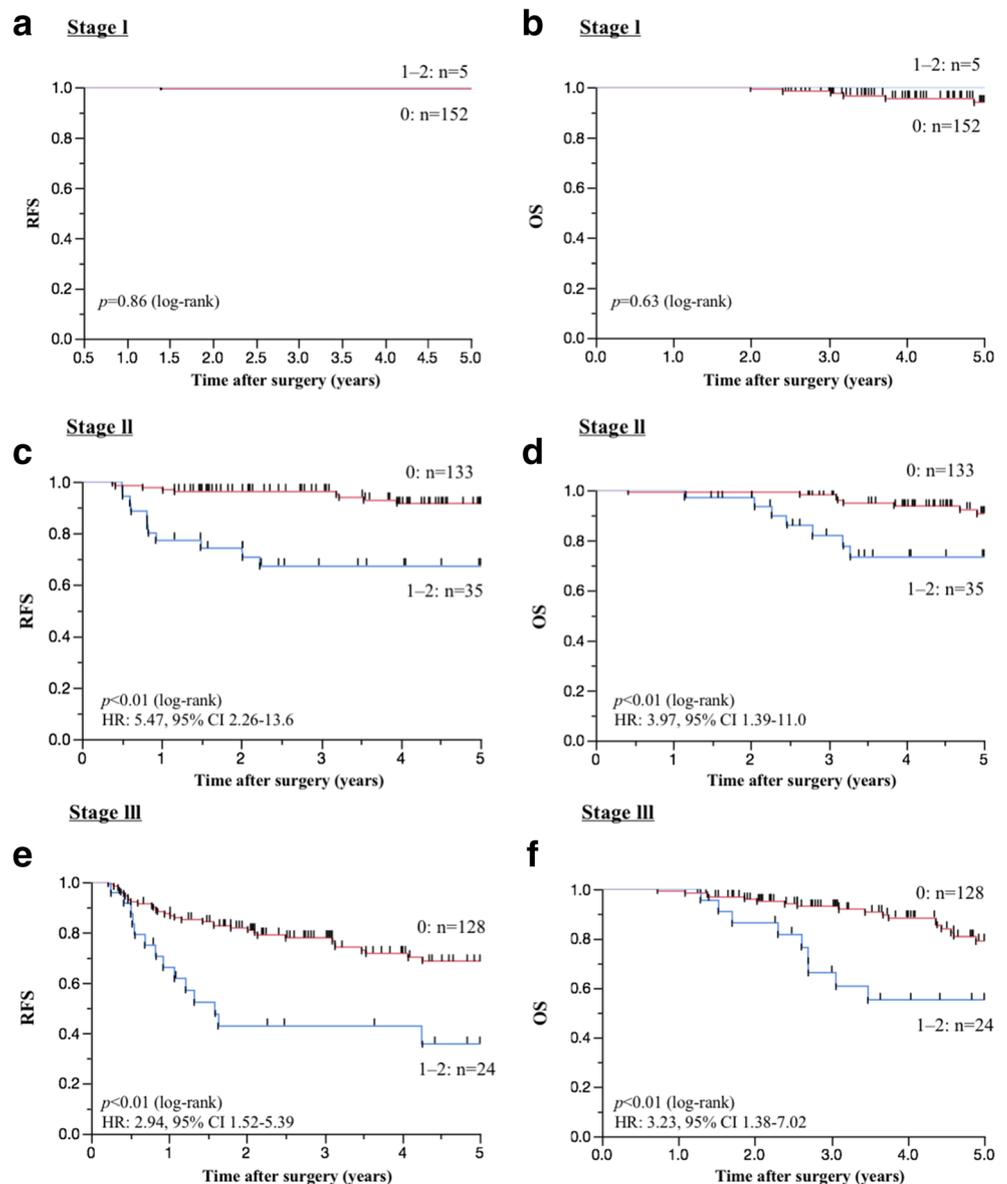
[21–23]. Among patients with stage II CC, a significant difference was detected in the 5-year RFS rates, which were 91.0% for a mGPS of 0, 75.0% for a mGPS of 1, and 59.8% for a mGPS of 2 ($p < 0.01$) and in the 5-year OS rates, which were 90.5% for a mGPS of 0, 90.9% for a mGPS of 1, and 57.0% for a mGPS of 2 ($p < 0.01$). Table 3 shows the correlations of RFS with the clinicopathological factors of the 168 patients with stage II CC. In the univariate analysis, poor RFS was significantly associated with the pT4 status ($p < 0.01$), the presence of venous invasion ($p = 0.04$), higher CEA levels ($p = 0.04$), and a high mGPS ($p < 0.01$). Multivariate analysis revealed that poor RFS was independently associated with T4 status (HR 4.78, 95% CI 1.78–13.7, $p < 0.01$) and a high mGPS (HR 2.71, 95% CI 1.02–7.39, $p = 0.04$).

Clinical significance of mGPS in stage III patients

We also performed the survival analysis using patients with stage III CC (Table 4). Among these patients, poor RFS was

Table 3 Univariate and multivariate analyses of recurrence-free survival in stage II

Variables		$n = 168$	Univariate		Multivariate		
			5-years RFS (%)	p value[c]	HR	95% CI	p value[d]
Age, years	≥ 70	95	86.8	0.60			
	< 70	73	85.3				
Sex	Female	84	88.6	0.34			
	Male	84	83.8				
BMI, kg/m²	≥ 22	85	85.7	0.69			
	< 22	83	86.5				
Location	Right	69	84.8	0.34			
	Left	99	87.0				
Tumor size, mm	≥ 35	131	86.2	0.79			
	< 35	37	86.5				
Preoperative obstruction or perforation	Presence	30	82.4	0.32			
	Absence	138	87.1				
Histopathological type[a]	por, sig, muc	17	73.2	0.12			
	pap, tub1, tub2	151	87.7				
Macroscopic type[a]	2–4	156	86.9	0.53			
	0–1	12	68.7				
T stage[b]	T4	33	58.3	< 0.01	4.78	1.78–13.7	< 0.01
	T3–1	135	94.2				
Lymphatic invasion[a]	Presence	96	91.1	0.08			
	Absence	72	79.6				
Venous invasion[a]	Presence	83	80.8	0.04	1.82	0.71–5.25	0.21
	Absence	85	91.3				
Operative blood loss, ml	≥ 100	26	79.3	0.28			
	< 100	142	87.8				
Operative time, min	≥ 220	79	82.2	0.46			
	< 220	89	89.4				
No. of nodes examined	< 12	31	78.9	0.39			
	≥ 12	137	87.9				
Adjuvant chemotherapy	Presence	28	76.3	0.11			
	Absence	140	88.4				
Intra-abdominal complication	Presence	13	84.6	0.55			
	Absence	155	86.5				
CEA, ng/ml	≥ 5	63	78.5	0.04	1.41	0.56–3.63	0.45
	< 5	105	90.3				
mGPS	1, 2	133	91.5	< 0.01	2.71	1.02–7.39	0.04
	0	35	67.1				

[a] According to the 8th edition of the Japanese classification of colorectal carcinoma

[b] According to the 7th edition of the UICC/TNM staging system

[c] p values were calculated using the log-rank test

[d] p values were calculated using Cox's proportional hazard model

RFS recurrence-free survival, HR hazard ratio, CI confidence interval, mGPS modified Glasgow prognostic score, BMI body mass index, tub tubular adenocarcinoma, pap papillary adenocarcinoma, por poorly differentiated adenocarcinoma, sig signet-ring cell carcinoma, muc mucinous adenocarcinoma, CEA carcinoembryonic antigen

independently predicted by the mGPS (HR 3.26, 95% CI 1.67–6.07, $p < 0.01$), as well as T stage, N stage, and serum CEA level. According to the JSCCR guidelines, stage III colon cancer patients can receive AC, so we analyzed the association between mGPS and AC in stage III patients. No significant difference was observed regarding tumor status when the patients were also classified according to their AC status (Supplemental Table 1). Among stage III patients,

prognosis in patients with AC tended to be better than that in patients without AC (Supplemental Fig. 2a: $p = 0.14$). Furthermore, subgroup analysis based on mGPS revealed that having received AC did not significantly affect the 5-year RFS among patients with a low mGPS (Supplemental Fig. 2b: $p = 0.71$) while AC significantly improved the 5-year RFS among patients with a high mGPS (Supplemental Fig. 2c: $p < 0.01$).

Table 4 Univariate and multivariate analyses of recurrence-free survival in stage III

Variables		$n = 152$	Univariate		Multivariate		
			5-year RFS (%)	p value[c]	HR	95% CI	p value[d]
Age, years	≥ 70	69	59.5	0.47			
	$<7 0$	83	67.1				
Sex	Male	87	59.7	0.50			
	Female	65	69.0				
BMI, kg/m^2	≥ 22	81	59.0	0.60			
	<22	71	69.1				
Location	Right	52	67.0	0.72			
	Left	100	61.9				
Tumor size, mm	≥ 35	106	86.2	0.79			
	<35	46	86.5				
Preoperative obstruction or perforation	Presence	18	60.1	0.32			
	Absence	134	64.4				
Histopathological type[a]	por, sig, muc	18	58.3	0.31			
	pap, tub1, tub2	134	64.5				
Macroscopic type[a]	2–4	135	60.4	0.07			
	0–1	17	88.2				
T stage[b]	T4	40	34.8	<0.01	2.42	1.31–4.42	<0.01
	T1–3	112	74.1				
N stage[b]	N2	42	39.8	<0.01	1.89	1.03–3.43	0.03
	N1	110	73.2				
Lymphatic invasion[a]	Present	97	62.5	0.94			
	Absent	55	65.5				
Venous invasion[a]	Present	91	59.2	0.06			
	Absent	61	70.6				
Operative blood loss, g	≥ 100	20	52.3	0.18			
	<100	132	65.2				
Operative time, min	≥ 220	70	65.9	0.62			
	<220	82	61.9				
No. of lymph nodes examined	<12	32	60.0	0.86			
	≥ 12	120	64.9				
Adjuvant chemotherapy	Present	119	65.9	0.14			
	Absent	33	54.9				
Intra-abdominal complication	Present	13	78.2	0.19			
	Absent	139	66.2				
CEA, ng/mL	≥ 5	61	46.5	<0.01	2.43	1.35–4.50	<0.01
	<5	91	75.2				
mGPS	1–2	24	35.6	<0.01	3.26	1.67–6.07	<0.01
	0	128	68.7				

[a] According to the 8th edition of the Japanese classification of colorectal carcinoma

[b] According to the 7th edition of the UICC/TNM staging system

[c] p values were calculated using the log-rank test

[d] p values were calculated using Cox's proportional hazard model

RFS recurrence-free survival, *HR* hazard ratio, *CI* confidence interval, *mGPS* modified Glasgow prognostic score, *BMI* body mass index, *tub* tubular adenocarcinoma, *pap* papillary adenocarcinoma, *por* poorly differentiated adenocarcinoma, *sig* signet-ring cell carcinoma, *muc* mucinous adenocarcinoma, *CEA* carcinoembryonic antigen

Discussion

Various reports have described the prognostic significance of the systemic inflammatory response among patients with CRC, which can be evaluated using the NLR, PLR, PNI, GPS, and mGPS. For example, Park et al. [24] and Tokunaga et al. [25] reported that the mGPS was associated with cancer-specific survival and RFS among patients with stage I–III CRC. Furthermore, Lin et al. [26] reported that the GPS independently predicted overall survival among patients with stage II CRC. Moreover, Toiyama et al. [27] reported that postoperative AC may be recommended for patients with stage II CRC and a high mGPS, while Zou et al. [28] reported that AC was most effective for all stages of CRC among patients with a high NLR or PLR. However, few studies have examined the associations of GPS or mGPS with RFS among patients with CRC, especially among patients with stage II CRC, as well as these scores' abilities to predict the efficacy of AC in patients with stage III CRC. The present study revealed that preoperative markers of a systemic inflammatory response were significantly associated with poor RFS after curative surgery for CC, with an especially strong association between the preoperative mGPS and RFS. This association was also observed among patients with stage II CC, and the efficacy of AC was also associated with mGPS. The cancer's malignant potential or stage also has prognostic value, and a stable patient status is needed to successfully perform curative surgery for CRC. Therefore, systemic inflammatory scores may be useful in this setting, as they reflect the patient's status and are based on commonly used blood test data.

There is no clear evidence regarding the efficacy of AC and risk factors for recurrence of stage II CRC. Nevertheless, the JSCCR guidelines state that AC should be considered for patients with stage II colon cancer and a "high risk of recurrence" after they have received adequate education, based on the Western guidelines [21–23]. In this context, the risk of recurrence or efficacy of AC for stage II CRC is thought to be associated with T4 lesions, < 12 lymph nodes being dissected, perforation or obstruction, lymphovascular involvement, poorly differentiated histopathology, perineural invasion, and high CEA levels based on the guidelines from the National Comprehensive Cancer Network [21], the American Society of Clinical Oncology [22], and the European Society for Medical Oncology [23]. The present study confirmed that, in addition to the mGPS, poor RFS among patients with stage II CC was associated with preoperative obstruction or perforation, pT4 status, and a high CEA level. Moreover, the multivariate analysis revealed that pT4 status and a high mGPS were independent risk factors for poor RFS.

The JSCCR guidelines also recommend postoperative AC for stage III CRC based on the results of several phase III randomized trials [29–32]. However, no biomarkers or classification systems can accurately predict the efficacy of AC in this setting, or clearly identify high-risk patients who should receive more intensive AC. The present study revealed that AC was beneficial

among patients with stage III CC and a high mGPS. Moreover, other inflammatory markers such as GPS, PLR, NLR, and PNI, also predicted the efficacy of AC for stage III CC patients, whereas the difference in prognosis between patients with AC and without AC was not significant when patients were stratified by tumor-related factor (data not shown). These findings may provide valuable information regarding subgroups of patients who might benefit from AC for stage III CC rather than subgroups of patients who might not need the close follow-up or AC. Moreover, the molecular markers such as K-RAS mutations, the BRAF V600E mutation, and microsatellite instability recently have been reported to be useful for the prediction of prognosis or the efficacy of chemotherapy in advanced CRC [33–35]. However, in Japan, these molecular analyses are not routinely performed for resectable stage III CRC due to high associated costs. On the other hand, mGPS is simply and easily obtained from routine preoperative examination for CRC patients at relatively low cost. Thus, we consider mGPS as a useful and convenient marker even in stage III disease. Nevertheless, the basis of a relationship between the systemic inflammatory response and the efficacy of AC remains unclear in this setting. Interestingly, previous reports have demonstrated that tumor sidedness or molecular status affected the efficacy of AC in patients with stage III colon cancer [33–36]. The present study revealed that mGPS was strongly associated with tumor sidedness, which may explain the ability of mGPS to predict the efficacy of AC among patients with stage III CC.

The present study has several limitations. The first is the retrospective single-center design. The second is that patients with stage III CC had received various types of AC after surgery. Third, no data on molecular characteristics of the tumor, such as BRAF and KRAS mutation or microsatellite instability, was available, although we hypothesized that the significant association between AC efficacy and mGPS might be related to these characteristics. Finally, the small sample of patients with stage III CC and a high mGPS limited our analysis of whether the mGPS could predict AC efficacy in this setting. Therefore, large prospective studies that include patients who receive single-agent AC for stage III CC are needed to validate our findings.

Conclusion

Our findings indicate that preoperative inflammatory scores can help predict recurrence after curative surgery for CC. In particular, a high mGPS independently predicted a high risk of recurrence among patients with stage II CC. Furthermore, the preoperative inflammatory scores may provide valuable information regarding subgroups of patients who might benefit from AC for stage III CC. These scores may be used in combination with traditional risk factors to create personalized treatment and follow-up strategies for patients with CC.

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