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Inflammation-based score (Glasgow prognostic score) as an independent prognostic factor in colorectal cancer patients

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Purpose: This study was conducted to evaluate the systemic inflammatory response in colorectal cancer patients, and to estimate the usefulness of the Glasgow prognostic score (GPS) as a prognostic factor.
Methods: Patients with biopsy-proven colorectal adenocarcinoma who were operated between April 2005 and December 2008 were enrolled in this study. The GPS was estimated based on the measurement of CRP and serum albumin level. The GPS was compared with other clinicopathological factors. Univariate and multivariate analyses were performed to evaluate the factors affecting cancer-specific survival.
Results: GPS was significantly higher in patients with anemia, thrombocytosis, a high neutrophil to lymphocyte ratio, tumor of the colon, and large tumor. Patient age, gender, serum CEA level, tumor gross appearance, TNM stage, and tumor differentiation were not related with the GPS. In univariate analysis, hemoglobin, CEA, gross appearance of tumor, TNM stage, tumor differentiation, and GPS were associated with cancer-specific survival. In multivariate analysis, TNM stage (III or IV : I or II; hazard ratio [HR], 12.322; P = 0.015), tumor differentiation (poorly differentiated : well or moderately differentiated; HR, 3.112; P = 0.021), and GPS (GPS 2 : GPS 0 or 1; HR, 5.168; P = 0.003) were identified as independent prognostic factors in colorectal cancer.
Conclusion: Our study showed that the GPS was an independent variable from tumor stage and a good and convenient prognostic factor in colorectal cancer patients.
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Key Words: Colorectal neoplasms, Inflammation, Prognosis

INTRODUCTION

Malignant disease and inflammation have a close relationship with each other. Cancer can develop in several inflammatory conditions such as chronic hepatitis, chronic gastritis, inflammatory bowel diseases, and chronic pancreatitis [1]. Conversely, cancer can induce local or systemic inflammation, which is mediated by activation of transcription factors and production of major inflammatory cytokines [2]. Cancer-related inflammation can influence cell proliferation, cell survival, angiogenesis, tumor cell migration, invasion, metastasis, and inhibition of adaptive immunity [2].

Colorectal cancer (CRC) also has a close relationship with inflammation. Ulcerative colitis and Crohn disease, the most common inflammatory bowel diseases, are known as the premalignant conditions for CRC [3]. Cyclooxygenase-2 inhibitors and nonsteroidal anti-inflammatory drugs (NSAIDs) were found to decrease the incidence of colorectal adenoma,

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and NSAIDs were also found to reduce the incidence of CRC [4]. Elevated C-reactive protein (CRP), which is a marker of systemic inflammation was reported as the risk factor for CRC [5].

Glasgow prognostic score (GPS), an inflammation-based prognostic score, which is assessed by simply using the serum CRP and albumin level, has been found to be a useful prognostic factor in several types of cancer [6]. Therefore, we hypothesized that systemic inflammation in CRC patients would be an important prognostic factor. This study was conducted to evaluate the systemic inflammatory response in CRC patients, and to estimate the usefulness of the GPS as a prognostic factor.

Table 1. Glasgow prognostic score (GPS) of colorectal cancer patients based on the serum levels of C-reactive protein (CRP) and albumin

	CRP ≤ 1.0 ng/dL		CRP > 1.0 ng/dL	
	No. of patients	GPS	No. of patients	GPS
Albumin (g/dL)				
≥3.5	69	0	16	1
<3.5	7	1	13	2

METHODS

Patients with biopsy-proven colorectal adenocarcinoma who were operated between April 2005 and December 2008 were enrolled in this study. Among these patients, data of serum CRP and albumin levels were available in 116 cases. Two cases of hospital mortality, 7 cases with TNM stage 0, one case of inaccurate staging, and one case of cancer perforation were excluded. None of the cases had other accompanying systemic inflammatory diseases. Finally, 105 patients were evaluated in this study.

Patients' data recorded in our CRC database were analyzed. The following clinicopathological factors were selected and evaluated: age, gender, hemoglobin, thrombocytosis, neutrophil to lymphocyte ratio (NLR, NLR was defined as the absolute

Table 2. The relationship between Glasgow prognostic score (GPS) and other clinicopathological characteristics

Characteristic	GPS 0	GPS 1	GPS 2	P-value
Age (yr)				0.322
<70	53	14	9	
≥70	16	9	4	
Gender				0.586
Male	39	15	9	
Female	30	8	4	
Hemoglobin (g/dL)				<0.001
<12	19	16	12	
≥12	50	7	1	
Thrombocytosis (/mm^3)				<0.001
<400,000	66	16	8	
≥400,000	2	7	5	
Neutrophil-to-lymphocyte ratio				<0.001
≤3	61	13	4	
>3	7	10	9	
Carcinoembryonic antigen (ng/mL)				0.276
<5.0	45	13	5	
≥5.0	24	10	7	
Location of the tumor				0.032
Colon	40	19	11	
Rectum	19	4	2	
Tumor size (cm)				0.001
<5.0	40	5	1	
≥5.0	27	16	9	
Tumor appearance				0.182
Fungating	49	15	4	
Infiltrating	17	7	5	
TNM stage				0.173
I or II	29	10	2	
III or IV	40	13	11	
Tumor differentiation				0.374
Well or moderately differentiated	43	12	4	
Poorly differentiated	26	10	6	

neutrophil count divided by the absolute lymphocyte count), CEA, location of tumor (colon or rectum), tumor size, gross appearance of tumor, TNM stage (American Joint Committee on Cancer 7th ed.), and tumor differentiation. The GPS was estimated as described previously [7]. Briefly, patient with both an elevated level of CRP (>1.0 mg/dL) and hypoalbuminemia (<3.5 g/dL) were allocated a score of 2. Patients with only one of the above two abnormalities were allocated a score of 1. Patients with neither of the above two abnormalities were allocated a score of 0. Cancer-specific survival (CSS) was measured from the date of surgery to the date of death from CRC; the observations were censored at death from causes other than CRC.

Categorical variables were analyzed by χ^2 test. Kaplan-Meier method was used to calculate the cumulative survival rate and to plot the survival curves. The long-rank test was used to compare the curves. Cox proportional hazards regression was performed to confirm the independent relationship with survival. $P < 0.05$ was considered to be statistically significant.

RESULTS

The patient's median age was 63 years (range, 32–86 years). The number of male and female patients are 63 and 42. The number of colon cancer cases was 70, and the number of rectal cancer cases was 35. Twelve cases were in the stage I, and 29, 40, and 24 cases were in the stages II, III, and IV, respectively. The mean follow-up was 44 months (range, 2–81 months).

Median serum level of albumin was 3.8 g/dL, and the range was 2.5–4.6 g/dL. Median CRP level was 0.2 ng/dL (range, 0–14.6 ng/dL). The GPS was 0 in 69 cases (65.7%), 1 in 23 cases (21.9%) and 2 in 13 cases (12.4%) (Table 1).

The relationship between the GPS and other clinicopathological characteristics was analyzed and is shown in Table 2. The GPS was significantly higher in patients with anemia, thrombocytosis, a high NLR, tumor of the colon, and a large tumor. Patient age, gender, serum CEA level, tumor gross appearance, TNM stage, and tumor differentiation were not related with the GPS.

CSS was evaluated according to the GPS. There was a significant difference in the survival rate according to the GPS (Fig. 1) ($P < 0.001$). But, the survival curve of the patients with a GPS of 0 was not different from that of the patients with a GPS of 1 ($P = 0.6027$). In univariate analysis of the other clinicopathological variables, hemoglobin, CEA, gross appearance of tumor, TNM stage, and tumor differentiation were associated with CSS. In multivariate analysis, TNM stage (III or IV : I or II; hazard ratio [HR] 12.322; $P = 0.015$), tumor differentiation (poorly differentiated : well or moderately differentiated; HR, 3.112; P =

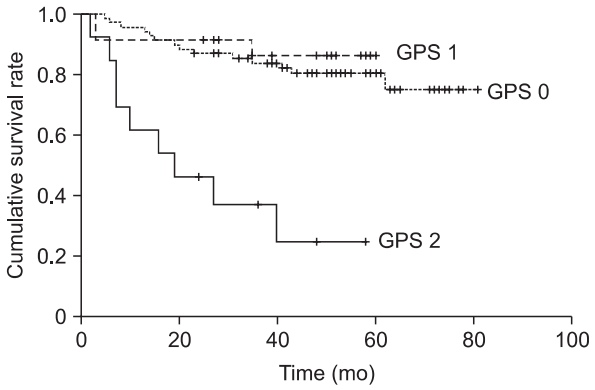

Fig. 1. Cancer-specific survival curve according to the Glasgow prognostic score (GPS). There was a significant difference in the survival rate according to the GPS ($P < 0.001$). Survival curve of the patients with a GPS of 0 was not different from that of the patients with a GPS of 1 ($P = 0.6027$).

Table 3. Univariate and multivariate analyses for cancer-specific survival

Variable	Univariate			Multivariate		
	HR	95% CI	P-value	HR	95% CI	P-value
Age (yr), ≥70	1.623	0.722–3.649	0.241			
Female gender	1.063	0.488–2.315	0.878			
Hemoglobin (g/dL), <12	3.389	1.466–7.835	0.004			0.205
Thrombocytosis (/mm^3), ≥400,000	1.266	0.434–3.689	0.666			
NLR, >3	1.910	0.847–4.309	0.119			
CEA (ng/mL), ≥5	2.874	1.302–6.341	0.009			0.224
Location of the tumor, rectum	1.519	0.636–3.632	0.347			
Tumor size (cm), ≥5	2.556	0.960–6.805	0.060			
Gross appearance, infiltrating	2.735	1.137–6.583	0.025			0.214
TNM stage, III or IV	20.126	2.723–148.741	0.003	12.322	1.627–93.296	0.015
Differentiation, poorly differentiated	2.754	1.155–6.568	0.022	3.112	1.186–8.165	0.021
GPS, 2	6.491	2.825–14.916	<0.001	5.168	1.760–15.175	0.003

HR, hazard ratio; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; GPS, Glasgow prognostic score.

0.021), and GPS (GPS 2 : GPS 0 or 1; HR, 5.168; P = 0.003) were identified as independent prognostic factors in CRC (Table 3).

DISCUSSION

Chronic inflammation affects all phases of carcinogenesis. Inflammation can induce the initial genetic mutation and epigenetic changes for cancer initiation. Inflammation can modify the tissue microenvironment that permits cancer cells to progress and metastasize. Inflammation can also suppress the immune response to tumor cells [1].

Conversely, cancer cells induce an inflammatory response which can be observed in the early phase of carcinogenesis. A recent experimental study showed that oncogenes could activate several inflammatory factors: colony stimulating factors (CSFs) which could recruit leukocytes and extend the survival; interleukin 1β, one of the main inflammatory cytokines; chemokines (CCL2, CCL20, IL-8) which activate monocyte recruitment and angiogenesis; chemokines and chemokine receptors (CXCL12, CXCR4) which activate tumor cell migration, proliferation, survival, and metastasis; proteases (matrix metalloproteinase [MMP]7, MMP9, MMP10, and urokinase-type plasminogen activator and its receptor) which are related with tumor cell invasion and dissemination [2,8]. Cancer producing proinflammatory cytokines induce the acute phase protein, which is a key marker of systemic inflammation. Systemic inflammation has been found to be positively associated with weight loss, hypermetabolism, anorexia, and poor prognosis in cancer patients [9].

In CRC, inflammation has an important role in the initiation and progression [3]. In colitis-associated colon cancer, chronic inflammation causes oxidative damage to DNA, leading to p53 mutations in tumor cells, and the inflamed epithelium and the inflammatory microenvironment at the tumor border can influence several key stages of invasion and metastasis [10]. McMillan et al. [11] reported that the prognostic score based on the serum CRP and albumin levels had an independent prognostic value after resection of CRC. Both CRP and albumin are acute phase proteins. Acute phase proteins are produced in the liver in response to inflammatory cytokines, mainly IL-6 and IL-1β. CRP level can be elevated to as much as 1,000-fold after an inflammatory stimulus [12]. But, the albumin level is decreased in response to inflammation. The albumin level is known to be decreased in cancer patients due to malnutrition and systemic inflammation [13].

Forrest et al. [7] designed the GPS, an inflammation-based prognostic score, which was assessed by simply using the serum CRP and serum albumin levels. The GPS has been proved to be an independent prognostic factor in many studies which have been performed in unselected cohorts, operable cancer patients, and chemo-radiotherapy and inoperable cancer patients [14].

In our study, we retrospectively evaluated the GPS of CRC patients without considering the TNM stages. A large number of patients were not enrolled in this study because we did not routinely check the CRP level in cancer patients until 2005.

In comparison with the other clinicopathological factors, the GPS was significantly higher in patients with anemia, thrombocytosis, a high NLR, tumor of the colon, and large tumor. Anemia and thrombocytosis are considered to be the common manifestations induced by inflammatory cytokines in cancer patients [12]. NLR is another well-known indicator of systemic inflammatory response and a prognostic factor in CRC patients [15]. In comparison with rectal cancer, colon cancer and larger tumors had a close relationship with a high GPS in this study. In another study also, colon cancer was associated with a higher GPS [11]. CRP level was reported to be higher in patients with colon cancer and larger tumors [16]. In our study, patient age, gender, serum CEA level, tumor gross appearance, TNM stage, and tumor differentiation were not related with the GPS. TNM stage and serum CEA level are very good indicators of tumor progression. This finding indicates that the GPS may not be a dependent variable reflecting tumor progression. McMillan et al. [11] showed that the GPS was not related with Dukes' stage of the tumor. But, other authors reported that the GPS was positively correlated with advanced TNM stage and high level of CEA [17].

Many studies confirmed that the GPS was a good indicator of prognosis in several kinds of cancers including lung cancer [7], CRC [11], gastric cancer [18], and hepatocellular carcinoma [19]. In this study of CRC patients, patients with a GPS of 0 and a GPS of 1 had a similar prognosis, but patients with a GPS of 2 had worse prognosis compared with that in patients with a GPS of 0 or 1 in the multivariate analysis. The GPS was proved to be a valuable independent prognostic factor in this study. Our results suggest that anti-inflammatory agents with other therapeutic modalities may prolong the survival of CRC patients [20].

In conclusion, our study showed that the GPS was an independent variable from tumor stage and a good and convenient prognostic factor in CRC patients.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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