Clinical Significance of an Inflammation-based Prognostic System for Gastric Cancer Patients with a Preoperative Normal Serum Level of Carcinoembryonic Antigen

MITSURU ISHIZUKA, YUSUKE OYAMA, AKIHITO ABE, KAZUMA TAGO, GENKI TANAKA and KEIICHI KUBOTA

Department of Gastroenterological Surgery, Dokkyo Medical University, Tochigi, Japan

Abstract. *Aim: To investigate the significance of the Glasgow Prognostic Score (GPS) for predicting the postoperative survival of gastric cancer (GC) patients with a normal preoperative serum level of carcinoembryonic antigen (CEA). Because CEA is a useful marker for prognostication of several types of cancer, some patients with GC have a normal CEA level. On the other hand, the GPS has been established as a valuable inflammation-based prognostic system for cancer patients. Patients and Methods: Among 650 patients who had undergone elective surgery for GC, 425 with a normal preoperative serum CEA level (≤5.0 ng/ml) were enrolled. Uni- and multivariate analyses were performed to evaluate the relationship of the GPS to overall survival. The Kaplan-Meier analysis and log rank test were used to compare the survival curves among patients with GPS 0, 1 and 2. Results: Multivariate analysis using clinical characteristics selected from univariate analyses revealed that the GPS (0, 1/2) was associated with overall survival (hazard ratio=2.048; 95% C.I. (confidence interval)=1.002-4.185; p=0.049) along with age (≤70/>70) (years), sex, tumor type (3, 4, 5/0, 1, 2), lymph node metastasis (presence/absence) and platelet count (≤35/>35) (×10^4/mm^3). The Kaplan-Meier analysis and log rank test demonstrated that there were significant differences in overall survival among patients with GPS 0, 1 and 2 (p<0.001). Conclusion: Even if GC patients have a normal serum level of CEA, the GPS is able to predict their postoperative survival and classify such patients into three independent groups before surgery.*

Among several markers for gastrointestinal malignancy, it is well known that the carcinoembryonic antigen (CEA) is a valuable marker of both colorectal cancer (CRC) (1) and gastric cancer (GC) (2, 3) along with the carbohydrate antigen 19-9 (CA19-9) (4, 5). Because an increased serum level of CEA might reflect not only tumor growth but also progression, it is closely associated with postoperative survival (2) and recurrence after surgery (6). In fact, recent studies have revealed that high preoperative serum levels of CEA and CA19-9 were correlated with lymph node metastasis and liver or peritoneal metastasis in patients with advanced GC (7). However, it is not unusual for some patients with advanced GC to have a normal serum CEA level before surgery (8). Therefore, pre- or postoperative evaluation of CEA in such patients would have no benefit in terms of surveillance for tumor progression and recurrence.

On the other hand, there is increasing evidence that systemic inflammation-based prognostic systems can be useful in patients with several types of cancer (9). Among such systems, the Glasgow Prognostic Score (GPS), which reflects the systemic inflammatory response (SIR) based on tumor *versus* host interaction, has become established in view of its ability to classify and predict the outcome of various cancers (10). In fact, recent studies have revealed that both the GPS (11, 12) and its modified version, the modified GPS (mGPS), (13, 14) are useful for prognostication of patients with GC.

In addition, a recent study has shown that even if patients with CRC have a normal serum level of CEA before surgery, the GPS is able to predict their postoperative survival and classify them into three independent groups (15).

Abbreviations: CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CRC, colorectal cancer; CRP, C-reactive protein; GC, gastric cancer; GPS, Glasgow Prognostic Score; IL-6, interleukin-6; NLR, neutrophil to lymphocyte ratio; mGPS, modified Glasgow Prognostic Score; ROC, receiver operating characteristic; SIR, systemic inflammatory response.

Correspondence to: Mitsuru Ishizuka, MD, Department of Gastroenterological Surgery, Dokkyo Medical University, 880 Kitakobayashi, Mibu, Tochigi 321-0293, Japan. Tel: +81 282872158, Fax: +81 282866317, e-mail: mm-ishizuka@umin.ac.jp

Key Words: Carcinoembryonic antigen, gastric cancer, Glasgow Prognostic Score, inflammation-based prognostic system, systemic inflammatory response.

On the basis of this evidence, the present study was performed to test the hypothesis that even if patients with GC have a normal serum level of CEA before surgery, the GPS would be able to predict their postoperative survival and classify them into three independent groups, as is the case for patients with CRC.

Patients and Methods

Patients. A retrospective review was performed using a database of 650 patients who had undergone elective surgery for GC. All procedures had been performed by the same surgical team at the Department of Gastroenterological Surgery, Dokkyo Medical University Hospital, between May 2000 and September 2010. Among these patients, 425 with a preoperative normal serum level of CEA (≤5 ng/ml) were enrolled. Routine laboratory measurements including the serum levels of C-reactive protein (CRP), albumin and tumor markers, such as CEA (upper physiological value: 5 ng/ml) and CA19-9 (upper physiological value: 37 U/ml), were carried out on the day of admission in order to exclude any effects attributable to inflammation associated with sequential preoperative examinations. None of the patients had clinical evidence of infection or other inflammatory conditions including pyloric stenosis and none had received preoperative chemotherapy or irradiation.

The GPS was estimated as described previously (16). Briefly, patients with both an elevated CRP level (>1.0 mg/dl) and hypoalbuminemia (<3.5 g/dl) were allocated a score of 2. Patients in whom only one of these biochemical abnormalities was present were allocated a score of 1 and those in whom neither of these abnormalities was present were allocated a score of 0.

In order to classify the patients into two groups, the cut-off values of clinicolaboratory parameters were determined using receiver operating characteristic (ROC) curve analyses. The recommended cut-off values of such parameters were based on the most prominent point on the ROC curve for "sensitivity" and "1-specificity", respectively. Then, the ideal cut-off values were defined using the Youden index (maximum (sensitivity+specificity-1)) (17). The area under the ROC curve was also calculated.

Univariate analysis was performed to evaluate clinical characteristics including age (≤70/>70) (years), gender (men/women), operation time (≤235/>235) (min), intraoperative bleeding volume (≤315/>315) (ml), surgical procedures (total gastrectomy/others), tumor location (upper, middle/lower), tumor type (3, 4, 5/0, 1, 2), number of tumors (≥2/1), histology (pap and tub1, 2/others, see below for definitions), lymphatic invasion (absence/presence), venous invasion (absence/presence), lymph node metastasis (absence/presence), white blood cell (WBC) count ($\times 10^3/mm^3$) (≤6.0/>6.0) ($\times 10^3/mm^3$), neutrophil ratio (≤65/>65) (%), lymphocyte ratio (≤25/>25) (%), platelet count (≤35/>35) ($\times 10^4/mm^3$), neutrophil to lymphocyte ratio (NLR) (≤2.6/>2.6), serum levels of CRP (≤0.3/>0.3) (mg/dl), albumin (≤3.6/>3.6) (g/dl), CEA (≤2.0/>2.0) (ng/ml) and CA19-9 (≤15/>15) (U/ml), as well as GPS (0, 1/2) to select those that were useful for prediction of overall survival.

All these cut-off values were defined using ROC analyses, except for gender (men/women), surgical procedures (total gastrectomy/others), tumor location (upper, middle/lower), tumor type (3, 4, 5/0, 1, 2), number of tumors (≥2/1), histology (pap and tub1, 2/others), lymphatic invasion (absence/presence), venous invasion (absence/presence), lymph node metastasis (absence/presence) and GPS (0, 1/2).

Table I. *Relationships between clinical background characteristics and GPS*.

Variable	GPS 0 n=298)	GPS 1 (n=99)	GPS 2 (n=28)	*p*-Value
Age (years)				
≤70	190	44	17	
>70	108	55	11	0.003
Gender				
Men	208	73	20	
Women	90	26	8	0.755
Tumor site				
Upper	68	26	9	
Middle	115	29	6	
Lower	115	44	13	0.241
Tumor type				
0, 1, 2	234	64	14	
3, 4, 5	64	35	14	<0.001
Number of tumors				
1	279	89	25	
≥2	19	10	3	0.383
Procedures				
Total gastrectomy	96	51	11	
Others	202	48	17	0.003
Histology				
pap and tub1, 2	155	48	7	
Others	143	51	21	0.023
Lymphatic invasion				
Absence	129	21	4	
Presence	169	78	24	<0.001
Venous invasion				
Absence	176	30	5	
Presence	122	69	23	<0.001
Lymph node metastasis				
Absence	216	41	6	
Presence	82	58	22	<0.001
Stage				
I	217	39	6	
II	33	22	7	
III	33	17	5	
IV	15	21	10	<0.001

Chi-squared test; pap, papillary adenocarcinoma; tub1, well-differentiated adenocarcinoma; tub2, moderately differentiated adenocarcinoma.

In order to explore the clinical characteristics most closely associated with postoperative survival, multivariate analysis was performed using variables selected from the results of univariate analysis on the basis of a cut-off probability value of $p<0.05$.

The Kaplan-Meier analysis and log rank test were used to compare the overall survival curves for the three GPS groups.

Definition of macroscopic tumor types and pathological findings. Macroscopic tumor types are classified according to the Japanese classification of gastric carcinoma-2nd English edition as: Type 0, superficial tumor; Type 1, polypoid tumor; Type 2, ulcerated tumor with a clear margin; Type 3, ulcerated tumor with infiltration; Type 4, diffusely infiltrating tumor; and Type 5, unclassified tumor (18).

Table II. *Relationships between clinicolaboratory characteristics and GPS.*

Variable	GPS 0 (n=298)	GPS 1 (n=99)	GPS 2 (n=28)	*p*-Value
Age (years)	65±11	69±12	70±9	<0.001
Number of tumors	1.1±0.4	1.1±0.4	1.1±0.3	0.822
WBC count ($\times10^3$/mm^3)	5.8±1.6	6.8±2.6	9.5±3.0	<0.001
Neutrophil ratio (%)	58±9	64±12	74±8	<0.001
Lymphocyte ratio (%)	32±8	26±10	18±7	<0.001
Platelet count ($\times10^4$/mm^3)	23±7	26±10	33±14	<0.001
NLR	2.1±1.0	3.3±2.6	5.7±4.1	<0.001
CRP (mg/dl)	0.3±0.1	0.5±0.7	3.5±2.2	<0.001
Albumin (g/dl)	4.0±0.3	3.3±1.6	2.8±0.4	<0.001
CEA (ng/ml)	2.1±1.0	2.4±1.1	2.1±1.2	0.178
CA19-9 (U/ml)	38±164	72±224	93±240	0.422
Operation time (min)	288±87	269±74	278±136	0.138
Bleeding volume (ml)	349±264	469±477	427±393	0.037
Survival period (days)	1787±1165	1085±956	812±993	<0.001

Kruskal-Wallis test, mean±SD.

According to these definitions, we classified the patients' cancers into two types: non-invasive (Types 0, 1 and 2) and invasive (Types 3, 4 and 5).

The pathological types of tumors are also defined as: pap, papillary adenocarcinoma; tub1, well-differentiated adenocarcinoma; tub2, moderately differentiated adenocarcinoma; por, poorly differentiated adenocarcinoma; muc, mucinous adenocarcinoma; sig, signet-ring cell carcinoma (18). According to these definitions, we classified patients into two groups: patients with papillo-tubular-type adenocarcinoma (pap and tub1, 2) and those with other types of carcinoma (por, muc and sig).

Invasion of vessels, *i.e.* lymphatic invasion (ly) and venous invasion (v), is diagnosed as: ly0 (v0), no invasion; ly1 (v1), minimal invasion; ly2 (v2), moderate invasion; ly3 (v3) and severe invasion (18). According to these definitions, we classified patients into two groups: absence (ly0, v0) and presence (ly1-3, v1-3) of vessel invasion.

Stage grouping is defined as ranging from I to IV according to the Japanese classification of gastric carcinoma-2nd English edition (18).

Statistical analysis. Data are presented as mean±standard deviation (SD). Differences among the groups were analyzed using the chi-squared test and Kruskal-Wallis test. Hazard ratio with 95% confidence intervals (C.I.) was calculated by univariate or multivariate analysis using the Cox proportional hazards model. Multivariate analysis was performed using clinical characteristics selected in the univariate analysis at $p<0.05$ to assess those most valuable for predicting postoperative survival.

Deaths before 31 March 2011 were included in this analysis. Statistical analyses were performed using the SPSS statistical software package, version 16.0 (SPSS Inc., Chicago, IL, USA) at a significance level of $p<0.05$.

The Kaplan-Meier analysis and the log rank test were used to compare survival curves for the three GPS groups. Survival curves were described using the StatView software, version 5.0 (Abacus Concepts Inc., Berkeley, CA, USA).

Results

A total of 425 patients were enrolled (men:women=301:124). There were 298 patients with GPS 0, 99 with GPS 1 and 28 with GPS 2.

Table I shows the distribution of the clinical characteristics of the studied patients in the three GPS groups. There were no significant differences among the three groups, except for age (≤70/>70 years) ($p=0.003$), tumor type (0, 1, 2/3, 4, 5) ($p<0.001$), surgical procedures (total gastrectomy/ others) ($p=0.003$), histology (pap and tub1, 2/others) ($p=0.023$), lymphatic invasion (absence/ presence) ($p<0.001$), venous invasion (absence/presence) ($p<0.001$), lymph node metastasis (absence/presence) ($p<0.001$) and stage (I/II/III/IV) ($p<0.001$) (chi-squared test).

Table II shows the relationship between clinicolaboratory characteristics and the GPS. There were significant differences among the three groups in age (years) ($p<0.001$), WBC count ($\times10^3$/mm^3) ($p<0.001$), neutrophil ratio (%) ($p<0.001$), lymphocyte ratio (%) ($p<0.001$), platelet count ($\times10^4$/mm^3) ($p<0.001$), NLR ($p<0.001$), CRP (mg/dl) ($p<0.001$), albumin (g/dl) ($p<0.001$), intraoperative bleeding volume ($p=0.037$) and survival period (days) ($p<0.001$) (Kruskal-Wallis test).

During the observation period, 110 patients died, among whom 33 died of intercurrent disease. Univariate and multivariate analyses were performed to evaluate the relationship between clinical characteristics and overall survival.

The results of univariate analyses demonstrated that age (≤70/>70) (years), gender (men/women), intraoperative bleeding volume (≤315/>315) (ml), surgical procedures (total gastrectomy/others), tumor type (3, 4, 5/0, 1, 2), lymphatic

Table III. *Univariate analysis of clinical characteristics in relation to overall survival.*

Variable	Hazard ratio	95%C.I.	*p*-Value
Age (≤70/>70) (years)	2.436	1.666-3.561	<0.001
Gender (men/women)	0.524	0.322-0.850	0.009
Operation time (≤235/>235) (min)	1.297	0.810-2.076	0.279
Bleeding volume (≤315/>315) (ml)	1.546	1.059-2.257	0.024
Procedures (total gastrectomy/others)	0.544	0.374-0.792	0.002
Tumor location (upper, middle/lower)	0.910	0.618-1.340	0.633
Tumor type (3, 4, 5/0, 1, 2)	0.336	0.230-0.489	<0.001
Number of tumors (≥2/1)	0.990	0.482-2.034	0.979
Histology (pap and tub1, 2/others)	1.429	0.979-2.086	0.064
Lymphatic invasion (presence/absence)	0.457	0.296-0.707	<0.001
Venous invasion (presence/absence)	0.439	0.297-0.648	<0.001
Lymph node metastasis (presence/absence)	0.256	0.174-0.378	<0.001
WBC count (≤6.0/>6.0) ($\times 10^3/mm^3$)	1.459	1.003-2.122	0.048
Neutrophil ratio (≤65/>65) (%)	2.082	1.428-3.034	<0.001
Lymphocyte ratio (≤25/>25) (%)	0.422	0.290-0.615	<0.001
Platelet count (≤35/>35) ($\times 10^4/mm^3$)	2.510	1.543-4.082	<0.001
NLR (≤2.6/>2.6)	2.302	1.580-3.355	<0.001
CRP (≤0.3/>0.3) (mg/dl)	2.182	1.482-3.213	<0.001
Albumin (≤3.6/>3.6) (g/dl)	0.369	0.252-0.541	<0.001
CEA (≤2.0/>2.0) (ng/ml)	1.240	0.853-1.803	0.259
CA19-9 (≤15/>15) (U/ml)	1.564	1.071-2.286	0.021
GPS (0, 1/2)	4.138	2.426-7.058	<0.001

95% C.I., 95% confidence interval; pap, papillary adenocarcinoma; tub1, well-differentiated adenocarcinoma; tub2, moderately differentiated adenocarcinoma.

Table IV. *Multivariate analysis of selected clinical characteristics in relation to overall survival.*

Variable	Hazard ratio	95%C.I.	*p*-Value
Age (≤70/>70) (yr)	2.348	1.570-3.511	<0.001
Gender (men/women)	0.529	0.317-0.881	0.014
Bleeding volume (≤315/>315) (ml)	1.235	0.810-1.883	0.326
Procedure (total/others)	0.882	0.579-1.344	0.560
Tumor type (3, 4, 5/0, 1, 2)	0.541	0.339-0.864	0.010
Lymphatic invasion (presence/absence)	1.768	0.888-3.524	0.105
Venous invasion (presence/absence)	0.923	0.541-1.574	0.769
Lymph node metastasis (presence/absence)	0.304	0.175-0.530	<0.001
WBC count (≤6.0/>6.0) ($x10^3/mm^3$)	0.865	0.548-1.365	0.533
Neutrophil ratio (≤65/>65) (%)	0.764	0.354-1.650	0.493
Lymphocyte ratio (≤25/>25) (%)	1.039	0.304-3.556	0.951
Platelet count (≤35/>35) ($x10^4/mm^3$)	1.910	1.113-3.277	0.019
NLR (≤2.6/>2.6)	1.747	0.424-7.203	0.440
CRP (≤0.3/>0.3) (mg/dl)	1.019	0.623-1.667	0.940
Albumin (≤3.6/>3.6) (g/dl)	0.743	0.476-1.161	0.193
CA19-9 (≤15/>15) (U/ml)	1.150	0.766-1.727	0.501
GPS (0, 1/2)	2.048	1.002-4.185	0.049

95% C.I., 95% confidence interval.

invasion (presence/absence), venous invasion (presence/absence), lymph node metastasis (presence/absence), WBC count (≤6.0/>6.0) ($\times 10^3/mm^3$), neutrophil ratio (≤65/>65) (%), lymphocyte ratio (<25/>25) (%), platelet count (≤35/>35) ($\times 10^4/mm^3$), NLR (<2.6/>2.6), CRP (≤0.3/>0.3) (mg/dl), albumin (≤3.6/>3.6) (g/dl), CA19-9 (≤15/>15) (U/ml) and GPS (0, 1/2) were associated with overall survival (Table III).

Multivariate analysis using the above selected clinical characteristics disclosed that GPS was associated with overall survival (hazard ratio=2.048; 95% C.I.=1.002-4.185; p=0.049)

along with age (≤70/>70) (years) (hazard ratio=2.348; 95% C.I.=1.570-3.511; $p<0.001$), gender (men/women) (hazard ratio=0.529; 95% C.I., 0.317-0.881; $p=0.014$), tumor type (3, 4, 5/0, 1, 2) (hazard ratio=0.541; 95% C.I.=0.339-0.864; $p=0.010$), lymph node metastasis (presence/absence) (hazard ratio=0.304; 95% C.I.=0.175-0.530; $p<0.001$) and platelet count (≤35/>35) ($\times 10^4/mm^3$) (hazard ratio=1.910; 95% C.I.=1.113-3.277; $p=0.019$) (Table IV).

The median and maximum follow-up periods for survivors were 1,489 (9-4,428) and 4,428 days, respectively, and the mean survival period was 1,560±1,162 days (mean±SD).

There were significant differences in the postoperative survival period among patients with GPS 0 (1,787±1,165 days), GPS 1 (1,085±956 days) and GPS 2 (812±993 days) ($p<0.001$, Kruskal-Wallis test) (Table II). The Kaplan-Meier analysis and log rank test demonstrated that there were significant differences in the overall survival among the three groups ($p<0.001$). GPS was able to clearly classify such patients into three independent groups ($p<0.001$) (Figure 1).

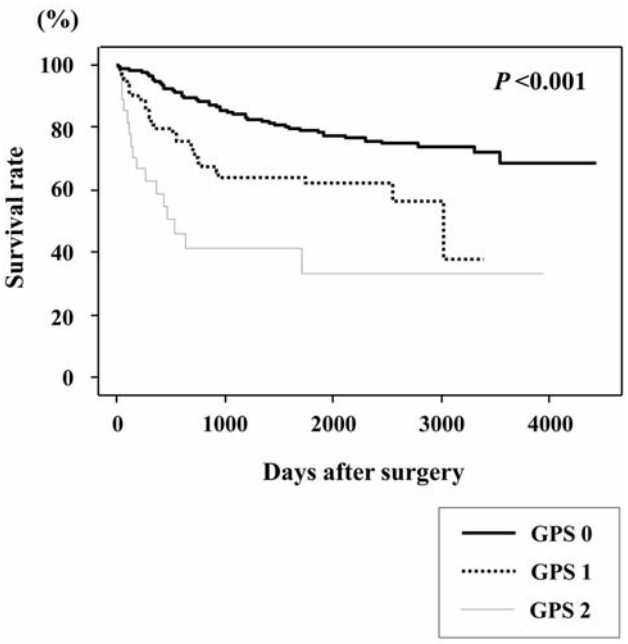

Figure 1. *Relationship between the groups (GPS 0, GPS 1 or 2, from top to bottom) and overall survival in gastric cancer patients with a normal preoperative serum level of CEA (p<0.001).*

Discussion

Various studies have demonstrated that serum CEA levels, similarly to serum CA19-9 levels, is correlated with tumor growth and proliferation in patients with GC (2, 3, 19). Therefore, measurement of the preoperative CEA level is useful for estimation of tumor stage and postoperative survival (2, 4, 6). In fact, our previous analysis of patients with primary gastric cancer undergoing elective surgery revealed that in comparison with a lower preoperative CEA level (≤5.0 ng/ml) (n=448), a higher preoperative CEA level (>5.0 ng/ml) (n=101) was more closely correlated with the presence of invasive tumors, lymphatic invasion, venous invasion, lymph node metastasis and a more advanced clinical stage (data not shown), suggesting that elevation of the CEA level was closely associated with tumor progression. Therefore, it is well acceptable that CEA is useful for not only prognostication of GC but also as an indicator of its progression.

On the other hand, an increased GPS was associated with clinical background characteristics such as advanced patient age, an invasive tumor type, total (rather than partial) gastrectomy, a diffusely differentiated histological type, presence of venous and lymphatic invasion, presence of lymph node metastasis, and an advanced clinical stage. Except for advanced age, all of these characteristics reflect tumor progression. Although total gastrectomy is a desirable treatment option for GC located in the upper stomach, it is the only option that offers a chance of curative resection for diffusely spreading GC, multiple GC or massive, advanced GC (20). Among these clinical characteristics, the most important was the close relationship between an increased GPS and an advanced stage of GC.

In addition, an increased GPS was also associated with not only blood cell components, such as increased WBC count, neutrophil ratio, platelet count (21) and NLR (22, 23), as well as a decreased lymphocyte ratio, but also the levels of serum proteins such as an increased serum CRP level (24) and a decreased serum albumin level (25), along with both an increased intraoperative bleeding volume and a shorter postoperative survival period. Changes in blood cell components have been regarded as SIR-related phenomena (26), as well as adverse changes in the levels of acute-phase proteins, such as an increased CRP level and a decreased albumin level, because the magnitude of SIR depends on the amounts of inflammatory cytokines that are induced by activated immunocytes during tumor *versus* host interactions (27). Therefore, these blood cell components and acute-phase proteins (28) are associated with tumor progression. With regard to intraoperative bleeding volume, in most cases, a higher bleeding volume reflects difficulty with the surgical procedure due to the presence of advanced disease. Among these clinicopathological characteristics, the most important was the close relationship between a higher GPS and shorter survival.

On the basis of these relationships between clinical characteristics and the GPS, the results of multivariate analysis demonstrated that the GPS was an important predictor of overall survival for GC patients with a preoperative normal serum level of CEA, along with

advanced age, male gender, an invasive tumor type, presence of lymph node metastasis and an increased platelet count. These six characteristics were classifiable into three groups.

First, advanced age and male gender characteristics are unique to individual patients. Although a few studies have demonstrated a relationship between male gender and postoperative survival for patients with GC (29), several other studies have demonstrated that advanced age is a risk factor for poor outcome in GC patients (30).

Second, an invasive tumor type and the presence of lymph node metastasis are also important pathological prognostic factors for patients with GC (31). Numerous studies have proved that a strong relationship exists between such pathological factors and the postoperative survival of patients with GC (32-34).

Third, reactive thrombocytosis and the GPS are regarded as SIR-related prognostic factors. Although several previous studies have investigated the relationship between GPS/mGPS and outcome in patients with gastroesophageal cancer (29, 30, 35) including GC (13), three recent important Japanese studies have addressed the relationship between GPS/mGPS and postoperative survival in GC patients. (i) Nozoe et al. demonstrated that the GPS and tumor stage were independently predictive of outcome in 232 GC patients undergoing surgery (11); (ii) Kubota et al. also demonstrated that the GPS was a significant predictor of long-term outcome in patients undergoing curative GC surgery, but not of short-term outcome, in 1,017 GC patients undergoing surgery (12); (iii) Jinag et al. demonstrated that the mGPS was a factor predictive of postoperative mortality in 1,710 GC patients undergoing surgery (14). Several studies have demonstrated a relationship between reactive thrombocytosis and postoperative survival in patients with GC, (21, 36) along with the GPS.

The prognostic significance of tumor markers may differ from that of the systemic inflammation-based GPS because tumor markers may be secreted from the tumor itself, whereas the GPS may reflect the amount of inflammatory cytokines produced, especially interleukin-6 (IL-6) (37, 38), which reflect tumor *versus* host interaction. A recent study has obtained interesting evidence that the levels of IL-6, CEA and CA19-9 are correlated with nodal metastases, whereas that of CRP is correlated with tumor stage, gastric wall invasion and the presence of nodal and distant metastases. It also demonstrated that the area under the ROC curve for IL-6 was larger than those for CRP and tumor markers, such as CEA and CA19-9 (39).

Generally, it is not unusual for GC patients to sometimes have a normal CEA level before surgery, because certain tumors may have a reduced ability to produce CEA even though production of CA 19-9 is not low. Although immune surveillance against malignant tumors does not allow the body to reject them completely, such tumors are nevertheless recognized and this leads to activation of other immunosystems by several types of cytokines. Therefore, when tumor marker levels are within the normal range, it is informative to determine the GPS as an indicator of tumor progression as it is based on inflammation and the levels of inflammatory cytokines.

There is a possibility that early-stage GC patients have increased levels of CEA production when their tumors are growing; in fact the present study included 262 patients with stage I GC (61.6%). However, in GC patients with a normal preoperative CEA level, although the univariate analysis revealed that the level of CA19-9 was related to overall survival, in multivariate analysis this relationship failed to reach statistical significance. Similarly, although the cut-off value for CEA was determined by ROC curve analysis along with CA19-9, the univariate analysis revealed that the serum CEA level was unrelated to overall survival. Therefore, in GC patients with a normal serum level of CEA, there would be no clinical benefits of prognostication (2) or postoperative surveillance for tumor recurrence (6) based on tumor markers.

Our previous study revealed that the GPS was able to predict the postoperative survival of CRC patients with a normal preoperative serum level of CEA and classify such patients into three independent groups before surgery (15). This lends strong support to our present finding that there was no significant difference between GC and CRC in use of the GPS for prognostication and classification of patients with solid tumors and proves our hypothesis that, even if GC patients have a normal serum level of CEA before surgery, the GPS is able to predict their postoperative survival and classify them into three independent groups.

Conflicts of Interest

The Authors have no conflicts of interest to declare. They have received no funding/grant support for this study.

References

1 Wang JY, Tang R and Chiang JM: Value of carcinoembryonic antigen in the management of colorectal cancer. Dis Colon Rectum *37*: 272-277, 1994.

2 Sakamoto J, Nakazato H, Teramukai S, Ohashi Y, Takahashi Y, Mai M, Toge T, Okura H, Kodaira S, Maetani S, Okajima K, Nomoto K, Hattori T and Inokuchi K: Association between preoperative plasma CEA levels and the prognosis of gastric cancer following curative resection. Tumor Marker Committee, Japanese Foundation for Multidisciplinary Treatment of Cancer, Tokyo, Japan. Surg Oncol *5*: 133-139, 1996.

3 Kochi M, Fujii M, Kanamori N, Kaiga T, Kawakami T, Aizaki K, Kasahara M, Mochizuki F, Kasakura Y and Yamagata M: Evaluation of serum CEA and CA19-9 levels as prognostic factors in patients with gastric cancer. Gastric Cancer *3*: 177-186, 2000.

4 Takahashi Y, Takeuchi T, Sakamoto J, Touge T, Mai M, Ohkura H, Kodaira S, Okajima K and Nakazato H: The usefulness of CEA and/or CA19-9 in monitoring for recurrence in gastric cancer patients: a prospective clinical study. Gastric Cancer *6*: 142-145, 2003.
5 Reiter W, Stieber P, Reuter C, Nagel D, Lau-Werner U and Lamerz R: Multivariate analysis of the prognostic value of CEA and CA 19-9 serum levels in colorectal cancer. Anticancer Res *20*: 5195-5198, 2000.
6 Kim DH, Oh SJ, Oh CA, Choi MG, Noh JH, Sohn TS, Bae JM and Kim S: The relationships between perioperative CEA, CA 19-9, and CA 72-4 and recurrence in gastric cancer patients after curative radical gastrectomy. J Surg Oncol *104*: 585-591, 2011.
7 Ishigami S, Natsugoe S, Hokita S, Che X, Tokuda K, Nakajo A, Iwashige H, Tokushige M, Watanabe T, Takao S and Aikou T: Clinical importance of preoperative carcinoembryonic antigen and carbohydrate antigen 19-9 levels in gastric cancer. J Clin Gastroenterol *32*: 41-44, 2001.
8 Kodera Y, Yamamura Y, Torii A, Uesaka K, Hirai T, Yasui K, Morimoto T, Kato T and Kito T: The prognostic value of preoperative serum levels of CEA and CA19-9 in patients with gastric cancer. Am J Gastroenterol *91*: 49-53, 1996.
9 McMillan DC:. Systemic inflammation, nutritional status and survival in patients with cancer. Curr Opin Clin Nutr Metab Care *12*: 223-226, 2009.
10 McMillan DC: The systemic inflammation-based Glasgow Prognostic Score: A decade of experience in patients with cancer. Cancer Treat Rev *39*: 534-540, 2013.
11 Nozoe T, Iguchi T, Egashira A, Adachi E, Matsukuma A and Ezaki T: Significance of modified Glasgow prognostic score as a useful indicator for prognosis of patients with gastric carcinoma. Am J Surg *201*: 186-191, 2011.
12 Kubota T, Hiki N, Nunobe S, Kumagai K, Aikou S, Watanabe R, Sano T and Yamaguchi T: Significance of the inflammation-based Glasgow prognostic score for short- and long-term outcomes after curative resection of gastric cancer. J Gastrointest Surg *16*: 2037-2044, 2012.
13 Dutta S, Crumley AB, Fullarton GM, Horgan PG and McMillan DC: Comparison of the prognostic value of tumour and patient related factors in patients undergoing potentially curative resection of gastric cancer. Am J Surg *204*: 294-299, 2012.
14 Jiang X, Hiki N, Nunobe S, Kumagai K, Kubota T, Aikou S, Sano T and Yamaguchi T: Prognostic importance of the inflammation-based Glasgow prognostic score in patients with gastric cancer. Br J Cancer *107*: 275-279, 2012.
15 Ishizuka M, Nagata H, Takagi K, Iwasaki Y and Kubota K: Inflammation-based prognostic system predicts postoperative survival of colorectal cancer patients with a normal preoperative serum level of carcinoembryonic antigen. Ann Surg Oncol *19*: 3422-3431, 2012.
16 Forrest LM, McMillan DC, McArdle CS, Angerson WJ and Dunlop DJ: Comparison of an inflammation-based prognostic score (GPS) with performance status (ECOG) in patients receiving platinum-based chemotherapy for inoperable non-small-cell lung cancer. Br J Cancer *90*: 1704-1706, 2004.
17 Youden WJ: Index for rating diagnostic tests. Cancer *3*: 32-35, 1950.
18 Japanese classification of gastric carcinoma--2nd English edition – response assessment of chemotherapy and radiotherapy for gastric carcinoma: clinical criteria. Gastric Cancer *4*: 1-8, 2001.
19 Reiter W, Stieber P, Reuter C, Nagel D, Cramer C, Pahl H and Fateh-Moghadam A: Prognostic value of preoperative serum levels of CEA, CA 19-9 and CA 72-4 in gastric carcinoma. Anticancer Res *17*: 2903-2906, 1997.
20 Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric Cancer *14*: 113-123, 2011.
21 Ikeda M, Furukawa H, Imamura H, Shimizu J, Ishida H, Masutani S Tatsuta M and Satomi T: Poor prognosis associated with thrombocytosis in patients with gastric cancer. Ann Surg Oncol *9*: 287-291, 2002.
22 Shimada H, Takiguchi N, Kainuma O, Soda H, Ikeda A, Cho A, Miyazaki A, Gunji H, Yamamoto H and Nagata M: High preoperative neutrophil-lymphocyte ratio predicts poor survival in patients with gastric cancer. Gastric Cancer *13*: 170-176, 2010.
23 Jeong JH, Lim SM, Yun JY, Rhee GW, Lim JY, Cho JY and Kim YR: Comparison of two inflammation-based prognostic scores in patients with unresectable advanced gastric cancer. Oncology *83*: 292-299, 2012.
24 Woo Y, Hyung WJ, Obama K, Kim HI, Pak KH, Son T and Noh SH: Elevated high-sensitivity C-reactive protein, a marker of advanced stage gastric cancer and postgastrectomy disease recurrence. J Surg Oncol *105*: 405-409, 2012.
25 Lien YC, Hsieh CC, Wu YC, Hsu HS, Hsu WH, Wang LS, Huang MH and Huang BS: Preoperative serum albumin level is a prognostic indicator for adenocarcinoma of the gastric cardia. J Gastrointest Surg *8*: 1041-1048, 2004.
26 Ulich TR, del Castillo J and Guo KZ: *In vivo* hematologic effects of recombinant interleukin-6 on hematopoiesis and circulating numbers of RBCs and WBCs. Blood *73*: 108-110, 1989.
27 Wu CW, Wang SR, Chao MF, Wu TC, Lui WY, P'eng FK and Chi CW: Serum interleukin-6 levels reflect disease status of gastric cancer. Am J Gastroenterol *91*: 1417-1422, 1996.
28 Krzystek-Korpacka M, Matusiewicz M, Diakowska D, Grabowski K, Blachut K, Kustrzeba-Wojcicka I, Terlecki G and Gamian A: Acute-phase response proteins are related to cachexia and accelerated angiogenesis in gastroesophageal cancers. Clin Chem Lab Med *46*: 359-364, 2008.
29 Dutta S, Al-Mrabt NM, Fullarton GM, Horgan PG and McMillan DC: A comparison of POSSUM and GPS models in the prediction of post-operative outcome in patients undergoing oesophago-gastric cancer resection. Ann Surg Oncol *18*: 2808-2817, 2011.
30 Crumley AB, McMillan DC, McKernan M, McDonald AC and Stuart RC: Evaluation of an inflammation-based prognostic score in patients with inoperable gastro-oesophageal cancer. Br J Cancer *94*: 637-641, 2006.
31 Shiraishi N, Sato K, Yasuda K, Inomata M and Kitano S: Multivariate prognostic study on large gastric cancer. J Surg Oncol *96*: 14-18, 2007.
32 Siewert JR, Bottcher K, Stein HJ and Roder JD: Relevant prognostic factors in gastric cancer: ten-year results of the German Gastric Cancer Study. Ann Surg *228*: 449-461, 1998.
33 Du C, Zhou Y, Cai H, Zhao G, Fu H and Shi YQ: Poor prognostic factors in patients with stage I gastric cancer according to the seventh edition TNM classification: a comparative analysis of three subgroups. J Surg Oncol *105*: 323-328, 2012.
34 Scartozzi M, Galizia E, Verdecchia L, Berardi R, Graziano F, Catalano V, Giordani P, Mari D, Silva RR, Marmorale C, Zingaretti C and Cascinu S: Lymphatic, blood vessel and perineural invasion identifies early-stage high-risk radically resected gastric cancer patients. Br J Cancer *95*: 445-449, 2006.

35 Crumley AB, Stuart RC, McKernan M, McDonald AC and McMillan DC: Comparison of an inflammation-based prognostic score (GPS) with performance status (ECOG-ps) in patients receiving palliative chemotherapy for gastroesophageal cancer. J Gastroenterol Hepatol *23*: 325-329, 2008.

36 Wang L, Huang X, Chen Y, Jin X, Li Q and Yi TN: Prognostic value of TP/PD-ECGF and thrombocytosis in gastric carcinoma. Eur J Surg Oncol *38*: 568-573, 2012.

37 Ashizawa T, Okada R, Suzuki Y, Takagi M, Yamazaki T, Sumi T, Aoki T, Ohnuma S and Aoki T: Clinical significance of interleukin-6 (IL-6) in the spread of gastric cancer: role of IL-6 as a prognostic factor. Gastric Cancer *8*: 124-131, 2005.

38 Ohsugi Y: Recent advances in immunopathophysiology of interleukin-6: an innovative therapeutic drug, tocilizumab (recombinant humanized anti-human interleukin-6 receptor antibody), unveils the mysterious etiology of immune-mediated inflammatory diseases. Biol Pharm Bull *30*: 2001-2006, 2007.

39 Lukaszewicz-Zajac M, Mroczko B, Gryko M, Kedra B and Szmitkowski M: Comparison between clinical significance of serum proinflammatory proteins (IL-6 and CRP) and classic tumor markers (CEA and CA 19-9) in gastric cancer. Clin Exp Med *11*: 89-96, 2011.

Received August 6, 2014
Revised September 10, 2014
Accepted September 15, 2014