RESEARCH ARTICLE

Neutrophil Count and the Inflammation-based Glasgow Prognostic Score Predict Survival in Patients with Advanced Gastric Cancer Receiving First-line Chemotherapy

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Abstract

Purpose: To explore the value of systemic inflammatory markers as independent prognostic factors and the extent these markers improve prognostic classification for patients with inoperable advanced or metastatic gastric cancer (GC) receiving palliative chemotherapy. Methods: We studied the prognostic value of systemic inflammatory factors such as circulating white blood cell count and its components as well as that combined to form inflammation-based prognostic scores (Glasgow Prognostic Score (GPS), Neutrophil-Lymphocyte Ratio (NLR), Platelet Lymphocyte Ratio (PLR), Prognostic Index (PI) and Prognostic Nutritional Index (PNI)) in 384 patients with inoperable advanced or metastatic gastric cancer (GC) receiving first-line chemotherapy. Univariate and multivariate analyses were performed to examine the impact of inflammatory markers on overall survival (OS). Results: Univariate analysis revealed that an elevated white blood cell, neutrophil and/or platelet count, a decreased lymphocyte count, a low serum albumin concentration, and high CRP concentration, as well as elevated NLR/PLR , GPS, PI, PNI were significant predictors of shorter OS. Multivariate analysis demonstrated that only elevated neutrophil count (HR 3.696, p=0.003) and higher GPS (HR 1.621, p=0.01) were independent predictors of poor OS. Conclusion: This study demonstrated elevated pretreatment neutrophil count and high GPS to be independent predictors of shorter OS in inoperable advanced or metastatic GC patients treated with first-line chemotherapy. Upon validation of these data in independent studies, stratification of patients using these markers in future clinical trials is recommended.

Keywords: Systemic inflammation - Glasgow Prognostic Score (GPS) - gastric cancer - overall survival

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Introduction

Gastric cancer is the fourth most frequent malignancy and the second leading cause of cancer-related mortality (Herszenyi et al., 2010). Since the early stages of the disease are often asymptomatic, diagnosis is frequently made at an advanced stage (Maconi et al., 2008). Palliative chemotherapy for advanced or metastatic disease can improve survival and quality of life in patients with gastric cancer (Murad et al., 1993; Pyrhonen et al., 1995; Glimelius et al., 1997).

Risk-directed treatment strategies are widely employed in the management of patients with cancer. Advanced stage, immature differentiation, low KPS score, and associated tumor-related factors are the primary factors in treatment consideration. However, the true benefit of chemotherapy remains unclear, with median overall survival often less than 1 year together with significant side effects (Oba et al., 2013). Therefore, there is continuing interest in prognostic factors to permit more accurate patient stratification and which will improve clinical decision making.

A growing body of evidence demonstrates that patient outcomes in cancer are determined not only by tumor-related factors but also by host-related factors, particularly, the systemic inflammatory response (Colotta et al., 2009; Hanahan et al., 2011). Several recent studies have revealed a correlation between clinical outcomes with common solid tumors (colorectal cancer, lung cancer, breast cancer and pancreatic cancer, etc) and systemic inflammatory response, including plasma C-reactive protein (CRP), hypoalbuminemia, and a selective combination of C-reactive protein and albumin termed as Glasgow Prognostic Score (GPS) (Leitch et al., 2007; Hwang et al., 2011; Jiang et al., 2012; Fox et al., 2013; McMillan, 2013). There were also many studies reporting that haematological markers of systemic inflammatory response such as white blood cell count or its components (neutrophil, lymphocyte, neutrophil-lymphocyte ratio (NLR)), platelet, and platelet-lymphocyte ratio (PLR) are

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Table 1. Systemic Inflammation-based Prognostic Scores

Combined marker	Score
The Glasgow Prognostic Score(GPS)	
C-reactive protein<1.0mg/dL and albumin≥35g/L	0
C-reactive protein<1.0mg/dL and albumin<35g/L	1
C-reactive protein≥1.0mg/dL and albumin≥35g/L	1
C-reactive protein≥1.0mg/dL and albumin<35g/L	2
Neutrophil Lymphocyte Ratio(NLR)	
<2.75	1
≥2.75	2
Platelet Lymphocyte Ratio(PLR)	
<163	1
≥163	2
Prognostic Index(PI)	
C-reactive protein<1.0mg/dL and white cell count<11×10^9/l	0
C-reactive protein≥1.0mg/dL and white cell count<11×10^9/l	1
C-reactive protein<1.0mg/dL and white cell count≥11×10^9/l	1
C-reactive protein≥1.0mg/dL and white cell count≥11×10^9/l	2
Prognostic Nutritional Index(PNI)	
Albumin(g/L)+5×total lymphocyte count×10^9/l≥45	0
Albumin(g/L)+5×total lymphocyte count×10^9/l<45	1

also prognostic indicators for cancer clinical outcomes (Yamanaka et al., 2007; Cho et al., 2009; Kishi et al., 2009; Sarraf et al., 2009; Kwon et al., 2012; Dalpiaz et al., 2013; Fox et al., 2013). In addition, other inflammatory factor combinations such as Prognostic Index (PI) and Prognostic Nutritional Index (PNI) have also been linked with prognosis of malignancies (Kasymjanova et al., 2010; Nozoe et al., 2010; Kanda et al., 2011). However, the value of these markers as independent prognostic factors and the extent these markers improve prognostic classification for patients with inoperable advanced or metastatic GC receiving first-line chemotherapy remains uncertain.

Therefore, we examined these questions in a population of patients treated with first-line chemotherapy to determine which marker had the greatest prognostic value.

Materials and Methods

Patients

Detailed clinical data for patients treated at the Gastrointestinal Oncology Department of the Peking University Cancer Hospital were recorded in a regularly updated electronic database. Eligibility criteria included: (1) chemotherapy-naïve patients with pathologically confirmed, inoperable locally advanced or metastatic GC; (2) received first-line chemotherapy; (3) life expectancy ≥3 months. Patients who received adjuvant chemotherapy within 6 months before recurrence and those showing clinical evidence of infection or other inflammatory conditions (e.g., connective tissue disorders, rheumatologic diseases, vasculitis) were excluded from the study. All patients provided written informed consent before receiving chemotherapy. The study was approved by the Research Ethics Committee of Peking University Cancer Hospital.

Inflammation-based variables determination

Routine laboratory measurements of complete blood count, platelets, albumin and CRP were carried out at the time of first visits. The detection limit of CRP was <0.1mg/L, with the upper limit of normal at <10mg/L and the coefficients of variation at <5%.

The laboratory variables were analyzed as categorical variables using standard thresholds. Dichotomization of these variables was based on the upper (white blood cells, neutrophils, platelets and CRP) and the lower (albumin and lymphocytes) ranges of normal measurements for these markers.

Previous studies used a cut-off point ranging from 2.5 to 5.0 for NLR (Yamanaka et al., 2007; Kao et al., 2010; Chua et al., 2011; Fox et al., 2013; Lee et al., 2013) and 150 to 300 for PLR (Aliustaoglu et al., 2010; Asher et al., 2011; He et al., 2013) in advanced malignancies. We used the medians of distribution as cut-off points for dichotomization. The GPS, NLR, PLR, PI and PNI were constructed as described in Table 1.

Statistical analysis

SPSS (version 16.0) statistical software was used for the statistical analysis. Differences between study groups in baseline characteristics and clinical outcomes were assessed with the use of two-sided Fisher's exact tests and chi-square tests for categorical variables. Objective response to treatment was classified using the Response Evaluation Criteria in Solid Tumors (RECIST 1.0) every 6 weeks. Progression-free survival (PFS) and overall survival (OS) were calculated from the date of the first visit to the date of disease progression and death respectively. Univariate survival analysis was performed using the Kaplan–Meier method with the log-rank test. Multivariate survival analysis and calculation of hazard ratios (HR) were performed using a Cox regression model including those factors that were significant (p <0.05) on univariate analysis. Chi-square tests were used for comparison of categorical data. All p-values were two-sided and p<0.05 was considered significant.

Results

Patient characteristics

From April 2004 to September 2011, 384 patients were eligible for the study. The last follow-up time was September 1, 2012, and 21 patients (5.5%) were lost. Two hundred and sixty-four patients (68.8%) died and the median survival time was 13.9 months. Three hundred and seventy-six patients provided complete pretreatment data of white blood cell count and its components, including PNI in 372 patients, and GPS and PI in 216 patients. Detailed clinicopathological characteristics of the patients are listed in Table 2. The majority of patients were male (71.1%), younger than 65 years (75.3%) and had metastatic disease (75.0%). Ninety-six patients (25.0%) had inoperable locally advanced disease, among which fifty patients received gastrectomy with extended lymph node dissection (D2) after first-line chemotherapy. One hundred and seventy-five patients (45.6%) presented with more than one metastatic site. The majority of patients showed lymph node metastasis while 34.4% (n = 132) patients were afflicted with liver, 22.1% (n = 85) with peritoneal, and 8.1% (n=31) with lung metastasis. Two hundred and thirty-six patients (61.5%) had a KPS > 80.

Table 2. Clinicopathological and Systemic Inflammatory Characteristics Associated with Progression Free Survival and Overall Survival

	PFS			OS		
	No. of patients (%)	months (95% CI[a])	*p*-value	No. of patients (%)	months (95% CI[a])	*p*-value
Gender			0.022			0.673
Male	244 (73.0)	5.8 (5.2-6.3)		273 (71.1)	13.9 (12.4-15.4)	
Female	90 (27.0)	4.7 (3.6-5.9)		111 (28.9)	14.5 (11.0-18.0)	
Age			0.24			0.811
>65yrs	82 (24.6)	6.6 (5.3-7.9)		95 (24.7)	13.4 (12.2-14.7)	
≤65yrs	252 (75.4)	5.3 (4.5-6.1)		289 (75.3)	14.4 (12.4-16.4)	
KPS[b]			0.007			<0.001
≤80	135 (40.4)	5.2 (4.5-5.9)		148 (38.5)	12.0 (10.6-13.3)	
>80	199 (59.6)	6.1 (5.4-6.7)		236 (61.5)	16.1 (14.0-18.2)	
Pathology grade			0.591			0.037
Poorly differentiated	255 (76.3)	5.5 (4.8-6.1)		295 (76.8)	13.2 (11.9-14.5)	
Well/moderately differentiated	79 (23.7)	5.9 (4.8-6.9)		89 (23.2)	16.7 (13.8-19.5)	
Stage			0.329			0.001
Locally advanced	63 (18.9)	6.2 (4.4-8.1)		96 (25.0%)	19.2 (12.5-25.7)	
Metastatic disease	271 (81.1)	5.5 (4.9-6.1)		288 (75.0%)	13.4 (12.0-14.7)	
Liver metastasis			0.452			0.074
Yes	128 (38.3)	5.8 (5.0-6.5)		132 (34.4)	13.2 (11.6-14.8)	
No	206 (61.7)	5.5 (4.7-6.3)		252 (65.6)	14.6 (12.6-16.7)	
Peritoneal metastasis			0.002			<0.001
Yes	79 (23.7)	4.6 (3.8-5.3)		85 (22.1)	11.5 (8.3-14.7)	
No	255 (76.3)	6.0 (5.4-6.5)		299 (77.9)	14.5 (12.6-16.4)	
Lung metastasis			0.196			0.362
Yes	29 (8.7)	7.3 (5.0-9.6)		31 (8.1)	14.5 (11.6-17.5)	
No	305 (91.3)	5.5 (4.9-6.1)		353 (91.9)	13.8 (12.1-15.6)	
No. of metastatic sites			0.104			0.002
1	165 (49.4)	5.8 (4.7-6.9)		209 (54.4)	17.0 (13.4-20.7)	
≥2	169 (50.6)	5.5 (4.8-6.2)		175 (45.6)	12.3 (10.6-14.0)	
Chemotherapy cycles			<0.001			0.029
<4 cycles	114 (34.1)	2.2 (1.5-2.9)		141 (36.7)	10.3 (8.3-12.3)	
≥4 cycles	220 (65.9)	6.6 (6.1-7.2)		243 (63.3)	16.0 (14.1-18.0)	
Gastrectomy after chemotherapy			NA			<0.001
Yes	NA	NA		50 (13.0)	24.7 (11.7-37.7)	
No	NA	NA		334 (87.0)	13.2 (12.2-14.2)	
White blood cell count			0.007			<0.001
$<10\times10^9$/l	299 (91.7)	5.8 (5.3-6.3)		348 (92.5)	14.6 (12.9-16.2)	
$\geq10\times10^9$/l	27 (8.3)	3.3 (1.4-5.3)		28 (7.5)	9.8 (3.2-16.5)	
Neutrophil count			0.011			0.003
$<8\times10^9$/l	307 (94.2)	5.8 (5.3-6.3)		357 (95%)	14.5 (12.9-16.1)	
$\geq8\times10^9$/l	19 (5.8)	3.1 (2.0-4.3)		19 (5%)	9.8 (3.3-16.4)	
Lymphocyte count			0.003			0.046
$<1\times10^9$/l	47 (14.4)	3.7 (2.6-4.8)		52 (13.8)	11.6 (8.3-14.9)	
$\geq1\times10^9$/l	279 (85.6)	6.1 (5.5-6.7)		324 (86.2)	14.5 (12.9-16.2)	
Platelet count			0.014			0.05
$<350\times10^9$/l	277 (85.0)	6.0 (5.5-6.5)		324 (86.2)	14.5 (12.9-16.1)	
$\geq350\times10^9$/l	49 (15.0)	4.3 (2.9-5.8)		52 (13.8)	11.6 (8.7-14.5)	
NLR[c]			<0.001			0.003
<2.75	165 (50.6)	6.7 (5.9-7.5)		188 (50)	17.1 (14.6-19.7)	
≥2.75	161 (49.4)	4.6 (3.8-5.3)		188 (50)	12.5 (10.9-14.1)	
PLR[d]			<0.001			0.013
<163	162 (49.7)	6.5 (5.6-7.3)		188 (50)	16.7 (14.0-19.3)	
≥163	164 (50.3)	5.0 (4.2-5.8)		188 (50)	12.5 (11.3-13.7)	
Albumin			0.001			0.021
<35 g/L	23 (7.1)	3.0 (1.8-4.2)		23 (6.2)	11.1 (6.3-15.8)	
≥35 g/L	301 (92.9)	5.8 (5.3-6.3)		349 (93.8)	14.4 (12.8-16.0)	
CRP[e]			0.041			0.003
<10 mg/L	129 (67.5)	6.2 (5.4-7.1)		151 (69.6)	14.4 (12.1-16.7)	
≥10 mg/L	62 (32.5)	4.3 (2.9-5.8)		66 (30.4)	9.8 (5.9-13.7)	
GPS[f]			0.002			0.006
0	123 (64.8)	6.2 (5.3-7.2)		145 (67.1)	14.5 (12.0-17.0)	
1	62 (32.6)	4.4 (3.1-5.8)		66 (30.6)	11.1 (7.9-14.3)	
2	5 (2.6)	1.7 (1.6-1.7)		5 (2.3)	4.2 (0-9.7)	
PI[g]			0.038			0.001
0	128 (67.4)	6.2 (5.6-6.9)		150 (69.4)	14.4 (12.1-16.7)	
1	57 (30.0)	4.6 (3.5-5.6)		61 (28.2)	9.8 (5.5-14.1)	
2	5 (2.6)	0.8 (0.5-1.1)		5 (2.3)	2.9 (0-12.5)	
PNI[h]			<0.001			0.008
0	250 (77.2)	6.2 (5.6-6.8)		291 (78.2)	15.5 (13.9-17.2)	
1	74 (22.8)	3.5 (2.7-4.3)		81 (21.8)	11.1 (7.9-14.3)	

CI[a], confidence interval; KPS[b], Karnofsky Performance Status Scale; NLR[c], neutrophil-lymphocyte ratio; PLR[d], platelet-lymphocyte ratio; CRP[e], C-reactive protein; GPS[f], Glasgow prognostic scoring; PI[g], Prognostic Index; PNI[h], Prognostic Nutritional Index; NA, not applicable

Table 3. Multivariate Analyses of Overall Survival (n=216)

	Hazard ratio (95% CI[a])	*p*-value
KPS[b] (>80/≤ 80)	0.642(0.453-0.908)	0.012
Chemotherapy cycles (≥4 cycles /<4 cycles)	0.447(0.314-0.637)	<0.001
Gastrectomy after chemotherapy (yes/no)	0.289(0.139-0.601)	0.001
Neutrophil count ($\geq 8\times10^9$/$<8\times10^9$)	3.696(1.555-8.784)	0.003
GPS[c] (≥1/0)	1.621(1.124-2.339)	0.01

CI[a], confidence interval; KPS[b], Karnofsky Performance Status Scale; GPS[c], Glasgow prognostic scoring

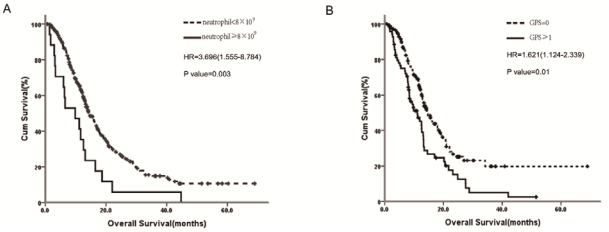

Figure 1. Overall Survival According to Neutrophil Count (A) and GPS (B). Good prognosis is represented by solid-dash line, and poor prognosis is represented by solid line. GPS=Glasgow prognostic scoring

Inflammation-based variables

Most patients' white blood cell, neutrophil, lymphocyte, platelet count, albumin, and CRP concentrations were in the normal range. Specifically, only 28 (7.5%), 19 (5%) and 52 (13.8%) patients presented elevated white blood cell count, neutrophil count and platelet count individually. Similarly, 52 patients (13.8%) showed decreased lymphocyte count. The median values of NLR and PLR were 2.75 and 163, respectively. A total of 66 patients (30.4%) had an elevated CRP concentration (≥10 mg/L) and 23 patients (6.2%) had hypoalbuminemia (<35 g/L). Accordingly, 66 patients (30.6%) had GPS of 1, and only 5 (2.3%) had GPS of 2. Similarly, 61 patients (28.2%) had PI of 1, and only 5 (2.3%) had PI of 2. Eighty-one patients (21.8%) had elevated PNI (1). Details are listed in Table 2.

Impact of inflammation-based variables on PFS and OS

The relationship between clinicopathological characteristics, markers of systemic inflammation and survival is shown in Table 2 and Table 3. The univariate analysis demonstrated that white blood cell count, neutrophil count, lymphocyte count, platelet count, NLR, PLR, serum CRP, albumin concentration, GPS, PI, PNI, KPS, stage, pathology grade, number of metastatic sites, peritoneal metastasis, first-line chemotherapy cycles and gastrectomy after chemotherapy were significantly associated with OS. PFS was analyzed among patients without gastrectomy after chemotherapy (n=334). The univariate analysis demonstrated that white blood cell count, neutrophil count, lymphocyte count, platelet count, NLR, PLR, serum CRP, albumin concentration, GPS, PI, PNI, KPS, gender, peritoneal metastasis, and first-line chemotherapy cycles were significantly associated with PFS.

Multivariate analysis demonstrated that neutrophil count, GPS, KPS, first-line chemotherapy cycles and gastrectomy after chemotherapy were independent prognostic factors for survival. Figure 1 shows the survival curves of patients according to neutrophil count (A) and GPS (B).

GPS/Neutrophil count and clinicopathological characteristics

We also analysed the relationship between clinicopathological features and GPS in gastric cancer patients. It was demonstrated that GPS was significantly associated with gender ($p = 0.016$), stage ($p = 0.002$), metastatic sites ($p = 0.03$), liver ($p < 0.001$) and peritoneal ($p = 0.038$) metastasis, as well as the circulating white blood cell-related markers. We also found that neutrophil count was significantly associated with peritoneal metastasis ($p = 0.003$), metastatic sites ($p = 0.037$), white blood cell count ($p < 0.001$), platelet count ($p = 0.003$), NLR ($p < 0.001$) and PLR ($p = 0.034$).

Discussion

Established risk factors are of limited prognostic value due to the tremendous heterogeneity in the length of survival among patients with inoperable locally advanced or metastatic GC. Procter et al. (Proctor et al., 2011) reported the superior prognostic value of mGPS and PI with regard to PNI, NLR and PLR. It was also demonstrated that higher NLR and mGPS were important predictors of poor survival in patients with gastric cancer receiving palliative chemotherapy; however, PI and PNI were not analyzed (Jeong et al., 2012). In the present study, we examined the correlation between comprehensive systemic inflammatory markers including haematological markers of systemic inflammatory response, NLR, PLR, PI, PNI as well as GPS and overall survival in chemotherapy-naïve patients with inoperable advanced or metastatic GC. We found that in addition to traditional clinicopathological parameters such as KPS, radical surgery and relatively adequate chemotherapy, neutrophil count and GPS were also independent predictors of survival in those patients.

Previous reports indicated a significant correlation between the neutrophil count or neutrophil-lymphocyte ratio and survival in a variety of clinical settings including gastric cancer (Yamanaka et al., 2007; Kishi et al., 2009; Jung et al., 2011; Dalpiaz et al., 2013; Fox et al., 2013; Lee et al., 2013; Sugiura et al., 2013). However, in the present study, we found that only elevated neutrophil count was an independent predictor of poor survival in multivariate analysis. Since the NLR may be increased due to an increase in neutrophils, or a decrease in lymphocytes or both (Leitch et al., 2007), higher NLR might correlate with decreased lymphocyte primarily in this study. We therefore, speculated that neutrophil count might better serve as a prognostic factor and play a vital role in cancer progression.

Several mechanisms mediate the association between elevated neutrophil count and poor prognosis. First, cancer cells release myeloid growth factors (e.g., granulocyte colony-stimulating factor) resulting in production of neutrophils (Lord et al., 1989). Second, circulating neutrophils secrete various cytokines, including vascular

endothelial growth factor (VEGF), tumor necrosis factor-α, and interleukins, which contribute to the progression of cancer (Ulich et al., 1987; Mahmoud et al., 2002; Kusumanto et al., 2003; Fondevila et al., 2004). Further, we found that elevated neutrophil count was associated with poor pathological differentiation, more advanced stage, more metastatic sites, peritoneal metastasis and higher GPS, all of which are associated with poor prognosis, suggesting that higher neutrophil count was probably related to great tumor burden.

CRP is a nonspecific but sensitive marker of systemic inflammatory response, and expressed in selected tumor cells. Many recent studies indicate that elevated CRP is a predictor of poor prognosis in malignant tumors including gastric cancer (Crumley et al., 2010; He et al., 2013; Szkandera et al., 2013; Xia et al., 2013). Serum concentration of CRP in tumor-bearing patients is known to be upregulated by proinflammatory cytokines including interleukin-1, interleukin-6, and tumor necrosis factor (Mahmoud et al., 2002). The inflammatory environment in tumors might substantially influence the malignant potential and thus the prognosis.

Hypoalbuminemia is often observed in advanced cancer patients, and is usually regarded as an index of malnutrition and cachexia. In gastric cancer, hypoalbunemia is reported to be associated with poor survival (Crumley et al., 2010; Jiang et al., 2012). Evidence also suggested that the development of hypoalbuminemia was a consequence of systemic inflammation, and might be secondary to elevation of CRP (Al-Shaiba et al., 2004; Onate-Ocana et al., 2007). Therefore, an inflammation-based prognostic score, the GPS, composed of serum elevation of CRP and hypoalbuminemia, representing the coexistence of ongoing systemic inflammation and host malnutrition might provide additional prognostic information.

Other studies have comprehensively validated the prognostic value of mGPS/GPS in a variety of advanced malignancies, including gastric cancer (Leitch et al., 2007; Hwang et al., 2011; Jiang et al., 2012; Fox et al., 2013; McMillan 2013).The results of the present study are consistent with previous reports, and suggest that GPS showed superior prognostic value to NLR in locally advanced or metastatic gastric cancer. In our study, only five patients had a GPS of 2, with a poor outcome consistent with previous evidence (Crumley et al., 2006; Hwang et al., 2011).

We also analyzed other inflammation-based prognostic scores, such as PI and PNI. Although multivariate analysis demonstrated no prognostic significance, both markers showed great tendency to be associated with survival. We speculated that absolute neutrophil count may be an appropriate addition to the comprehensively validated GPS.

Overall, our study demonstrated the predictive value of systemic inflammation in the survival of inoperable gastric cancer patients, although the underlying mechanism is unclear. Mantovani et al. (Mantovani et al., 2008) reported that activated extrinsic (pre-existing inflammation) or intrinsic pathway (oncogene activation) results in mobilization of transcription factors and inflammatory mediators. It may lead to recruitment of inflammatory cells including neutrophils. The resulting cascade of inflammation mediators leads to tumor progression. Further, the presence of a systemic inflammatory response and the associated nutritional decline may affect therapeutic compliance. Evidence showed that cancer is associated with a comprehensive systemic inflammation long before metastasis becomes clinically evident (Fox et al., 2013). Abrogation of systemic inflammation may occur in response to effective therapies. In fact, contemporary clinical trials have demonstrated that anti-inflammatory therapy improves patient survival (Rothwell et al., 2011).

In summary, this study indicated that neutrophil count and GPS are independent, cost-effective, and universal predictors of survival in patients with inoperable advanced or metastatic GC. Upon validation of these data in independent studies, stratification of patients using these markers in future clinical trials is recommended.

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