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Prognostic importance of the inflammation-based Glasgow prognostic score in patients with gastric cancer

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BACKGROUND: The inflammation-based Glasgow prognostic score (GPS) has been shown to be a prognostic factor for a variety of tumours. This study investigates the significance of the modified GPS (mGPS) for the prognosis of patients with gastric cancer.

METHODS: The mGPS (0 = C-reactive protein (CRP) $\leqslant 10\,mg\,l^{-1}$, 1 = CRP $> 10\,mg\,l^{-1}$ and 2 = CRP $> 10\,mg\,l^{-1}$ and albumin $< 35\,g\,l^{-1}$) was calculated on the basis of preoperative data for 1710 patients with gastric cancer who underwent surgery between January 2000 and December 2007. Patients were given an mGPS of 0, 1 or 2. The prognostic significance was analysed by univariate and multivariate analyses.

RESULTS: Increased mGPS was associated with male patient, old age, low body mass index, increased white cell count and neutrophils, elevated carcinoembryonic antigen and CA19-9 and advanced tumour stage. Kaplan–Meier analysis and log-rank test revealed that a higher mGPS predicted a higher risk of postoperative mortality in both relative early-stage (stage I; $P < 0.001$) and advanced-stage cancer (stage II, III and IV; $P < 0.001$). Multivariate analysis demonstrated the mGPS to be a risk factor for postoperative mortality (odds ratio 1.845; 95% confidence interval 1.184–2.875; $P = 0.007$).

CONCLUSION: The preoperative mGPS is a simple and useful prognostic factor for postoperative survival in patients with gastric cancer.
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Gastric cancer is the fourth most common cancer worldwide, and the second most frequent cause of mortality (Crew and Neugut, 2006; Kamangar *et al*, 2006). In Japan, although the incidence of gastric cancer has decreased, gastric cancer remains the most frequent cause of morbidity among patients with malignant tumours (Inoue and Tsugane, 2005). Although recent years have seen improvements in surgical techniques and adjuvant chemotherapy, the long-term survival of patients with advanced-stage gastric cancer remains unsatisfactory (Sasako *et al*, 2008).

There is increasing evidence that, in addition to tumour stage and the proliferative activity of tumour cells, the systemic inflammatory response is associated with malignancy (Roxburgh *et al*, 2009; McArdle *et al*, 2010; Richards *et al*, 2010). C-reactive protein (CRP), an acute-phase response protein, has been proven to be an independent prognostic factor for survival in many malignancies, including gastric cancer (Jagdev *et al*, 2010; Roxburgh and McMillan, 2010). In addition, hypoalbuminemia, a typical index of malnutrition, has been reported to be associated with poor survival in advanced cancer (Crumley *et al*, 2010; Lai *et al*, 2010). Recently, the Glasgow prognostic score (GPS), based on serum CRP and albumin levels, was developed to aid in the assessment of cancer prognosis (Ishizuka *et al*, 2009; Richards *et al*, 2010). An elevated GPS has been shown to be associated with worse prognosis for a number of different tumours (McMillan, 2009). Thus, the GPS may be a prognostic marker in cancer, independent of stage and biochemical tumour markers (McMillan, 2009; Roxburgh *et al*, 2009).

The GPS has also been shown to be a prognostic factor in advanced gastrointestinal cancers, including oesophageal and colorectal cancer (Kobayashi *et al*, 2008; Ishizuka *et al*, 2009). However, only few studies have used the GPS for postoperative prognostication of patients with gastric cancer. Thus, in the present study, we collected data retrospectively from 1710 patients with operable gastric cancer and investigated the significance of the preoperative GPS for postoperative survival in these patients.

MATERIALS AND METHODS

The gastric cancer database from the Department of Gastroenterological Surgery at The Cancer Institute Hospital, Tokyo, Japan, was reviewed retrospectively. Patients with gastric adenocarcinoma who had undergone curative (R0 resection) or palliative gastrectomy between January 2000 and December 2007 and for whom preoperative laboratory data for CRP and albumin were available were enrolled into the study. Palliative surgery is defined as the presence of any gross or microscopic residual tumours remaining postoperatively regardless of whether the surgical attempt was originally palliative or curative. Patients who died within 30 days after surgery, or those who died of non-cancer-related causes were excluded from the study. Patients who had other malignancies or who had inflammatory diseases that might have increased CRP levels were also excluded from the study. To remove any influence of neoadjuvant chemo/radiotherapy on survival or GPS, patients who received neoadjuvant chemotherapy

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or radiotherapy were also excluded. Using these criteria, 1710 patients with gastric cancer were enrolled in the present study. Patients were followed according to the established protocol in our hospital, including medical history, physical examination and laboratory studies 1 and 3 months after operation, and then every 6 months.

Pathological tumour stage (pTNM) was determined using the seventh edition of the AJCC cancer staging of stomach (Washington, 2010). Blood samples were collected for routine laboratory measurements of CRP, albumin, complete blood count and tumour markers such as carcinoembryonic antigen (CEA) (cutoff value, $5\,ng\,ml^{-1}$) and CA19-9 (cutoff value, $37\,ng\,ml^{-1}$). The modified GPS (mGPS) was calculated as described previously (Leitch *et al*, 2007). Briefly, patients with elevated CRP ($>10\,mg\,l^{-1}$) were assigned an mGPS of 1 or 2 depending on the absence or presence of hypoalbuminaemia ($<35\,g\,l^{-1}$), whereas patients showing no elevated level of CRP ($\leqslant 10\,mg\,l^{-1}$) are allocated an mGPS of 0, even if hypoalbuminaemia is present.

Statistical analysis

Data are presented as mean and 95% confidence intervals (CI). Differences between groups were analysed using the Kaplan–Meier survival analysis or χ^2 test. Survival analysis was performed using Cox proportional hazards model in a forward stepwise manner. Kaplan–Meier analysis and log-rank test were used to compare mortality for each mGPS. Deaths before 31 July 2010 were included in this analysis. $P<0.05$ was considered significant. All statistical analyses were performed using SPSS version 13.0 (SPSS, Chicago, IL, USA).

RESULTS

During 2000–07, 2601 patients underwent gastric cancer surgery. Of these, 845 were excluded from analysis because data on their CRP and albumin levels were not available, and 46 were excluded because of neoadjuvant chemotherapy, postoperative death or non-cancer death. Of the 1710 included patients with gastric cancer (1157 men; 553 women), 240 (14.0%) had elevated CRP levels ($>10\,mg\,l^{-1}$) and/or hypoalbuminemia ($<35\,g\,l^{-1}$). Of these, 78 (4.6%) were given an mGPS of 1 and 67 (3.9%) were given an mGPS of 2. The median follow-up time was 43.0 (1–123) months. None of the patients was lost to follow-up.

The classified background demographics and their association with overall survival are given in Table 1. There was no significant difference in overall survival in terms of sex (male/female), white cell count ($<11/\geqslant 11\times 10^9\,l^{-1}$) and lymphocytes ($<3/\geqslant 3\times 10^9\,l^{-1}$). Conversely, significant differences in overall survival were found in relation to age ($<65/\geqslant 65$ years), body mass index (BMI; $<18.5/18.5$–$25/>25\,kg\,m^{-2}$), tumour location (upper/middle/lower third), neutrophils ($<7.5/\geqslant 7.5\times 10^9\,l^{-1}$), CEA ($\leqslant 5/>5\,ng\,ml^{-1}$), CA19-9 ($\leqslant 37/>37\,ng\,ml^{-1}$), CRP ($\leqslant 10/>10\,mg\,l^{-1}$), albumin ($<35/\geqslant 35\,g\,l^{-1}$), tumour stage (I/II/III/IV) and mGPS (0/1/2).

The relationship between clinicolaboratory characteristics and mGPS is given in Table 2. Sex, age, BMI, white cell count, neutrophils, CEA, CA19-9 and tumour stage showed significant relationship with the mGPS. Conversely, mGPS was not affected by tumour location and lymphocytes.

Univariate analysis of postoperative mortality is indicated in Table 3. Seven factors were significantly associated with overall survival including age, BMI, neutrophils, CEA, CA19-9, tumour stage and mGPS. On multivariate analysis, factors with $P<0.1$ in univariate analysis were included. Multivariate analysis revealed a significant association between postoperative mortality and age (odds ratio (OR), 1.319; 95% CI, 1.068–1.629; $P=0.010$), tumour stage (OR, 2.909; 95% CI, 2.616–3.234; $P<0.001$) and the mGPS (OR, 1.845; 95% CI, 1.184–2.875; $P=0.007$) (Table 3).

The mean survival of patients with an mGPS of 0, 1 and 2 was 95.8, 62.2 and 35.9 months, respectively (Table 1). Kaplan–Meier analysis and log-rank test demonstrated significant differences among patients with mGPS of 0, 1 and 2 ($P<0.001$), with the mortality rate higher for patients with a higher mGPS (Figure 1).

Table 1 Clinical and laboratory characteristics associated with overall survival

	No. of patients	Overall survival (months), mean (95% CI)	*P*-value[a]
Sex			
Male	1157	90.0 (87.0–93.0)	0.185
Female	553	96.2 (91.9–100.5)	
Age (years)			
<65	885	98.1 (94.7–101.4)	<0.001
⩾65	813	85.9 (82.1–89.8)	
Body mass index ($kg\,m^{-2}$)			
<18.5	261	61.4 (55.8–67.0)	<0.001
18.5–25	1138	96.1 (93.0–99.2)	
⩾25	233	96.1 (91.4–100.9)	
Tumour location			
Upper third	460	79.2 (74.6–83.8)	<0.001
Middle third	772	100.5 (96.9–104.2)	
Lower third	470	88.2 (83.1–93.3)	
White cell count ($\times 10^9 l^{-1}$)			
<11	1682	93.3 (90.7–96.0)	0.156
⩾11	27	60.4 (48.7–72.2)	
Neutrophils ($\times 10^9 l^{-1}$)			
<7.5	1605	94.0 (91.4–96.7)	<0.001
⩾7.5	50	59.2 (46.1–72.3)	
Lymphocytes ($\times 10^9 l^{-1}$)			
<3	1592	92.9 (90.2–95.6)	0.208
⩾3	63	95.0 (85.4–104.6)	
CEA ($ng\,ml^{-1}$)			
⩽5	1433	95.4 (92.7–98.1)	<0.001
>5	233	55.9 (49.9–61.8)	
CA19-9 ($ng\,ml^{-1}$)			
⩽37	1406	94.1 (91.4–96.8)	<0.001
>37	151	48.5 (40.4–56.5)	
CRP ($mg\,l^{-1}$)			
⩽10	1565	95.8 (93.2–98.5)	<0.001
>10	145	51.4 (44.5–58.2)	
Albumin ($g\,l^{-1}$)			
<35	162	38.8 (33.0–44.5)	<0.001
⩾35	1548	97.8 (95.2–100.4)	
Tumour stage (pTNM)			
I	997	113.5 (111.0–116.0)	<0.001
II	200	82.6 (77.2–87.9)	
III	245	68.1 (62.0–74.1)	
IV	268	28.7 (23.9–33.5)	
mGPS			
0	1565	95.8 (93.2–98.5)	<0.001
1	78	62.2 (53.4–71.1)	
2	67	35.9 (27.0–44.8)	

Abbreviations: CEA = carcinoembryonic antigen; CRP = C-reactive protein; mGPS = modified Glasgow prognostic score; pTNM = pathological tumour-node-metastasis staging. [a]Kaplan–Meier survival analysis.

Table 2 Relationships between clinicolaboratory characteristics and mGPS

	mGPS 0 n (%)	mGPS 1 n (%)	mGPS 2 n (%)	*P*-value[a]
Sex				
Male	1045 (90.3)	60 (5.2)	52 (4.5)	0.036
Female	520 (94.0)	18 (3.3)	15 (2.7)	
Age (years)				
<65	831 (93.9)	29 (3.3)	25 (2.8)	0.001
⩾65	723 (88.9)	48 (5.9)	42 (5.2)	
Body mass index ($kg\,m^{-2}$)				
<18.5	212 (81.2)	17 (6.5)	32 (12.3)	<0.001
18.5–25	1059 (93.1)	47 (4.1)	32 (2.8)	
⩾25	221 (94.8)	11 (4.7)	1 (0.4)	
Tumour location				
Upper third	414 (90.0)	22 (4.8)	24 (5.2)	0.069
Middle third	722 (93.5)	29 (3.8)	21 (2.7)	
Lower third	421 (89.6)	27 (5.7)	22 (4.7)	
White cell count ($\times 10\ l^{-1}$)				
<11	1556 (92.5)	70 (4.2)	56 (3.3)	<0.001
⩾11	8 (29.6)	8 (29.6)	11 (40.7)	
Neutrophils ($\times 10^9 l^{-1}$)				
<7.5	1498 (93.3)	65 (4.0)	42 (2.6)	<0.001
⩾7.5	19 (38.0)	12 (24.0)	19 (38.0)	
Lymphocytes ($\times 10^9 l^{-1}$)				
<3	1458 (91.6)	75 (4.7)	59 (3.7)	0.633
⩾3	59 (93.7)	2 (3.2)	2 (3.2)	
CEA ($ng\,ml^{-1}$)				
⩽5	1342 (93.6)	56 (3.9)	25 (2.4)	<0.001
>5	184 (79.0)	20 (8.6)	29 (12.4)	
CA19-9 ($ng\,ml^{-1}$)				
⩽37	1299 (92.4)	57 (4.1)	50 (3.6)	0.006
>37	128 (84.8)	12 (7.9)	11 (7.3)	
Tumour stage				
I	961 (96.4)	30 (3.0)	6 (0.6)	<0.001
II	177 (88.5)	9 (4.5)	14 (7.0)	
III	219 (89.4)	13 (5.3)	13 (5.3)	
IV	208 (77.6)	26 (9.7)	34 (12.7)	

Abbreviations: CEA = carcinoembryonic antigen; mGPS = modified Glasgow prognostic score. [a]χ^2 test.

To clarify whether the mGPS has different prognostic value depending on tumour stage, patients were divided into two groups, namely those with relatively early-stage tumours (stage I; $n=997$) and those with advanced-stage tumours (stage II, III and IV; $n=713$). Significant differences in survival were found for patients with mGPS of 0, 1 and 2 in both groups (both $P<0.001$) (Figures 2 and 3).

DISCUSSION

The present retrospective study analysed individual clinical data for 1710 patients who underwent surgery for a pure cohort of gastric cancer in a high-volume center in Japan. The results demonstrate the prognostic value of the mGPS for gastric cancer. Although the GPS has been reported to have prognostic significance in a variety of cancers, its value in gastric cancer has not been fully investigated (Elahi *et al*, 2004; Crumley *et al*,

Table 3 Univariate and multivariate analyses of overall survival

	Univariate analysis			Multivariate analysis[a]		
	P-value	Odds ratio	95% CI	*P*-value	Odds ratio	95% CI
Sex	0.187	0.869	0.706–1.070	—	—	—
Age	<0.001	1.474	1.217–1.784	0.010	1.319	1.068–1.629
Body mass index	<0.001	0.503	0.419–0.605	0.233	0.884	0.722–1.802
Tumour location	0.088	0.891	0.781–1.017	0.276	0.929	0.813–1.061
White cell count	0.161	1.567	0.837–2.933	—	—	—
Neutrophils	<0.001	2.519	1.668–3.805	0.153	0.681	0.402–1.153
Lymphocytes	0.212	0.693	0.391–1.231	—	—	—
CEA	<0.001	3.121	2.518–3.868	0.107	1.234	0.955–1.595
CA19-9	<0.001	4.059	3.189–5.168	0.177	1.213	0.916–1.605
Tumour stage (I/II/III/IV)	<0.001	2.974	2.724–3.247	<0.001	2.909	2.616–3.234
mGPS (0, 1and 2)	<0.001	4.578	3.324–6.306	0.007	1.845	1.184–2.875

Abbreviations: CEA = carcinoembryonic antigen; mGPS = modified Glasgow prognostic score. [a]Factors <0.10 in univariate analysis were included in the multivariate analysis.

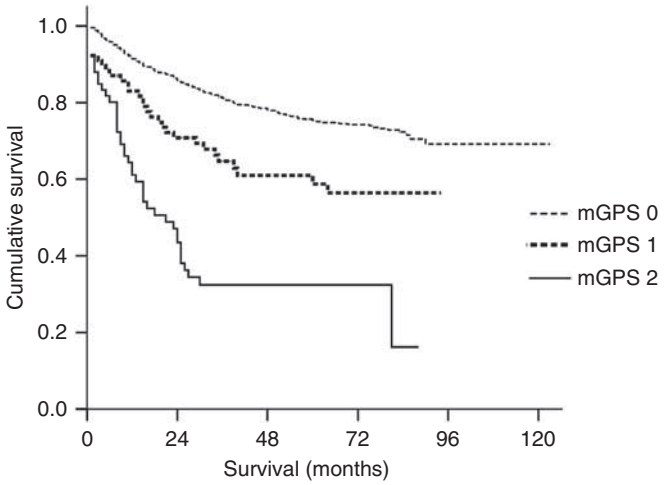

Figure 1 Relationship between the mGPS (mGPS 0, 1, 2 from top to bottom) and overall survival in patients with gastric cancer.

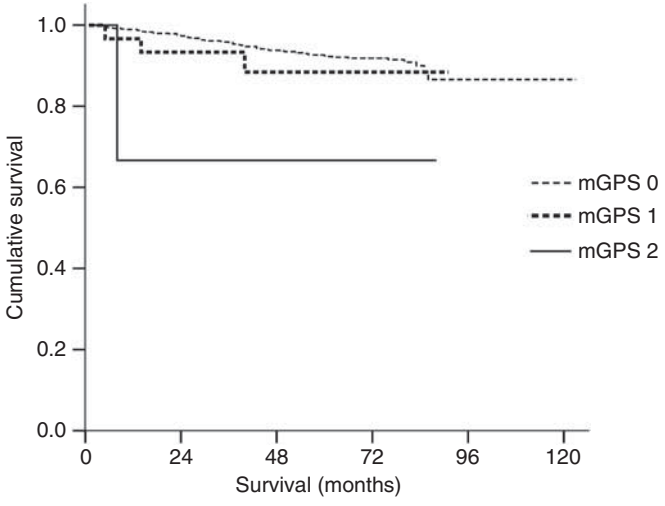

Figure 2 Relationship between the mGPS (mGPS 0, 1, 2 from top to bottom) and overall survival in patients with relatively early gastric cancer (stage I).

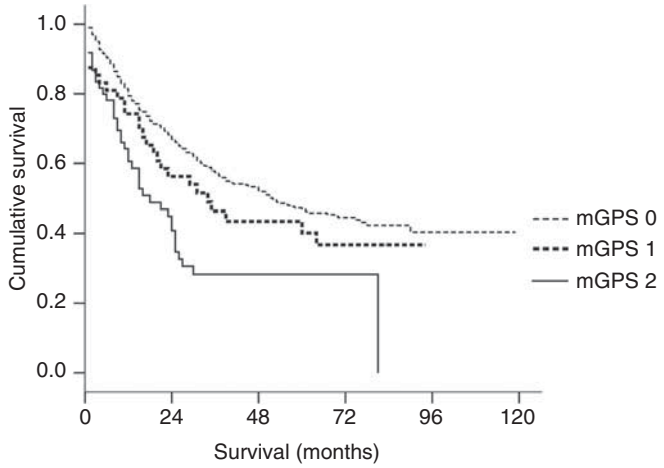

Figure 3 Relationship between the mGPS (mGPS 0, 1, 2 from top to bottom) and overall survival in patients with advanced gastric cancer (stage II, III and IV).

2006; Nozoe *et al*, 2011). Furthermore, the GPS is usually considered to be correlated with postoperative survival only in very advanced cancer (Ishizuka *et al*, 2009; Roxburgh *et al*, 2009; Shimoda *et al*, 2010). The present study included patients with gastric cancer who underwent gastrectomy; and the prognostic value of the mGPS in not only very advanced but also relatively early gastric cancer was evaluated. Currently, pathological TNM is considered the gold standard for predicting postoperative outcome, but it can only be properly evaluated postoperatively. On the other hand, preoperative TNM is not always accurate, and this causes the difficulty and bias for predicting survival preoperatively. The results of the present study indicate that the mGPS can predict postoperative survival for patients with gastric cancer. More importantly, the mGPS can be achieved easily before operation, and it seems not inferior to conventional tumour markers like CEA and CA19-9.

Numerous studies have reported that elevated CRP levels are indicative of a poor outcome in a variety of cancers (Koike *et al*, 2008; Jagdev *et al*, 2010; Roxburgh and McMillan, 2010). For example, elevated CRP levels have been reported to be independent prognostic factors associated with tumour size, cancer stage, cancer cachexia and poor prognosis in many studies (Nozoe *et al*, 2001; Koike *et al*, 2008). Kim *et al* (2009) reported a correlation between CRP levels and depth of invasion, lymph node metastasis and TNM stage in operable gastric cancer. Crumley *et al* (2010) reported that elevated CRP levels were a significant predictor of survival in gastric cancer. In the present study, the mean survival time of patients with elevated CRP levels ($>10\,\mathrm{mg\,l^{-1}}$) was significantly lower than that of patients with normal CRP levels ($\leqslant 10\,\mathrm{mg\,l^{-1}}$), which emphasises the correlation between CRP levels and prognosis.

Hypoalbuminemia is often observed in advanced cancer patients, and is usually regarded as a good index for malnutrition and cachexia. In gastric cancer, hypoalbuminemia is reported to be associated with poorer survival (Lien *et al*, 2004; Crumley *et al*, 2010), which was also observed in the present study. Previous studies have indicated that hypoalbuminemia is likely to develop secondary to increases in serum CRP levels (Al-Shaiba *et al*, 2004). Furthermore, study of Crumley *et al* (2010) demonstrated that the relation of low albumin concentrations and poorer survival in patients with gastric cancer was dependent on the elevated CRP level. In the present study, hypoalbuminemia was significantly correlated with serum elevation of CRP (data not shown). So systemic inflammatory response, as evidenced by elevated CRP level, might have a key role in the progression of malnutrition and even cachexia in gastric cancer (Fearon *et al*, 2006; Crumley *et al*, 2010).

The GPS, which is based on both serum elevation of CRP and hypoalbuminemia, may enable a better appreciation of the effects of the tumour on both ongoing systemic inflammation and malnutrition. The GPS has been introduced to predict the prognosis of patients with very advanced neoplasms (Ishizuka *et al*, 2009; Shimoda *et al*, 2010). Recently, Nozoe *et al* (2011) studied the significance of the GPS in 232 patients with operable gastric cancer and demonstrated the prognostic value of the GPS in these patients. The present study revealed that a higher mGPS was associated with poorer survival in patients with advanced gastric cancer (stage II, III and IV), which is in accordance with the results of previous studies evaluating the prognostic value of the mGPS in gastric and other cancers. In the present study, 268 patients were diagnosed as pathological stage IV gastric cancer according to seventh UICC TNM staging system of gastric cancer. These patients received gastrectomy either because they were not classified as stage IV gastric cancer preoperatively or they needed to receive palliative gastrectomy because of complications related to gastric cancer. On the other hand, interestingly, the present study also showed the significant survival differences depending on the mGPS in patients with relatively early-stage gastric cancer (stage I). In the 997 patients with stage I gastric cancer, the 5-year survival rates for patients with an mGPS of 0 ($n=961$), 1 ($n=30$) and 2 ($n=6$) were 93.0%, 82.8% and 66.7%, respectively (data not shown). Thus, the mGPS might also have prognostic value for survival in patients with relatively early-stage gastric cancer. However, the rate of mGPS 2 in patients with stage I gastric cancer was so low that it is too early to give a definite conclusion. Accumulation of more cases with mGPS 2 in stage I gastric cancer and survey of cancer-specific survival are warranted.

The results of the present study indicate that the mGPS may be a novel and simple biomarker in patients with gastric cancer. The findings of the present study may translate to potential improvements in the therapy of gastric cancer. For example, an mGPS of 2 was associated with very poor survival in the present study, so, for patients with both very advanced gastric cancer and an mGPS of 2, neoadjuvant chemotherapy may be beneficial. Similarly, these patients may require more aggressive adjuvant chemotherapy, such as S-1 plus cisplatin (Kodera *et al*, 2010). On the other hand, as patients with a higher mGPS had inflammatory response and/or malnutrition, anti-inflammatory therapy or nutritional support may have a beneficial effect on prognosis. It remains to be established whether patients with a higher mGPS need more active therapy.

In summary, the preoperative mGPS is a simple and useful prognostic factor for postoperative survival in patients with gastric cancer. The mGPS may be used together with traditional risk factors to individualise treatment strategies and the follow-up of patients with gastric cancer.

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Conflict of interest

The authors declare no conflict of interest.

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