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Original article

Systemic prognostic score and nomogram based on inflammatory, nutritional and tumor markers predict cancer-specific survival in stage II–III gastric cancer patients with adjuvant chemotherapy

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SUMMARY

Background: To investigate the clinical utility of several established inflammatory, nutritional and tumor markers, and to construct a new scoring system based on preoperative prognostic markers to predict outcomes in gastric cancer (GC).

Methods: We retrospectively assessed 688 consecutive patients who underwent curative resection followed by adjuvant chemotherapy for stage II–III GC from 2000 to 2012.

Results: On multivariate analysis, C-reactive protein/albumin (CRP/Alb) ratio (>0.2), prognostic nutritional index (PNI) (score 1), preoperative body weight loss (>6%) and carbohydrate antigen 19-9 (CA 19-9) (>27 U/mL) independently predicted unfavorable cancer-specific survival (CSS). These 4 preoperative prognostic markers were allocated 1 point each. Then, a new systemic prognostic score (SPS) was constructed based on the total score. Multivariate analysis revealed that SPS was an independent predictor of CSS ($P < 0.001$). Patients with a SPS of 0, 1, 2, or 3/4 had a 5-year CSS rates of 67.2%, 45.3%, 29.0%, and 10.6%, respectively (0 *vs.* 1 [$P < 0.001$], 1 *vs.* 2 [$P = 0.031$] and 2 *vs.* 3/4 [$P = 0.004$]). The median survival times for SPS 0, SPS 1, SPS 2 and SPS 3/4 were 68.7, 47.1, 28.3 and 16.3 months, respectively. The area under the receiver operating characteristics (ROC) curve for SPS was higher than other markers ($P < 0.001$). Furthermore, a nomogram that integrated TNM stage, tumor location and SPS exhibited superior discrimination power compared with the TNM stage alone (C-index, 0.714 *vs.* 0.630, respectively; $P < 0.001$).

Conclusion: The preoperative SPS combining inflammatory, nutritional and tumor markers independently predicted postoperative survival in stage II–III GC patients treated with adjuvant chemotherapy.

1. Introduction

Despite the decreasing trend of the incidence and mortality in recent decades, gastric cancer (GC) remains the second most frequent cause of cancer death worldwide [1,2]. In China, GC is still considered as a major public health problem. It is the second most common malignancy in men and fifth most common in women, and is the second leading cause of cancer-related mortality [3]. Although multidisciplinary treatment has improved in recent years, the postoperative long-term survival still remains poor, even in those patients undergoing curative resection followed by adjuvant chemotherapy [4–6]. Therefore, the identification of independent

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prognostic markers for individualized risk stratification and follow-up procedures has become a hot topic in the field of the GC research.

There is increasing evidence that cancer-associated systemic inflammation and malnutrition are common in the majority of patients with malignancy, which is closely linked to tumor progression [7–9]. Over the past decades, it has been recognised that such measurements of abnormal status are consistently associated with adverse prognosis independent of tumor stage [10,11]. It is also of interest that several scoring systems have been reported repeatedly to have independent prognostic role in a variety of cancers, such as the neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), lymphocyte monocyte ratio (LMR), C-reactive protein to albumin (CRP/Alb) ratio, Prognostic Nutritional Index (PNI), body mass index (BMI) and preoperative body weight loss [12-14]. This has raised the possibility that these cumulative scores may be modified to further improve the prognostic value and clinical utility. Furthermore, several most common tumor markers, including carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA 19-9), and CA 72-4, are routinely applied in the screening, diagnosis, and postsurgical follow-up of GC [15,16]. Numerous studies, especially a recent meta-analysis of 33 studies, have proved their potential prognostic value [17]. Given these results, we postulated that combining inflammatory, nutritional and tumor markers might provide more comprehensive prognostic information than individual markers.

In this study, we aimed to investigate the independent prognostic factors and establish a new scoring system using the newly identified factors to predict outcomes in stage II–III GC patients treated with adjuvant chemotherapy.

2. Material and methods

2.1. Patient characteristics

We performed a retrospective review of a database including 688 consecutive GC patients undergoing curative resection followed by adjuvant chemotherapy. All surgical procedures (R0 resection plus D2 lymphadenectomy) were uniform and performed by the same team at the Department of Gastric Surgery, Sun Yat-sen University Cancer Center, between 2000 and 2012. By multidisciplinary discussion, all patients routinely received 5-fluorouracil-based (5-FU) adjuvant chemotherapy for more than four cycles after surgery [18]. In principle, patients were treated until disease progression or unacceptable side effects occurred.

All enrolled patients fit the following criteria: 1) stage II–III gastric adenocarcinoma confirmed by histopathology, 2) complete clinicopathological and follow-up data, 3) no preoperative chemoradiotherapy or other adjuvant chemoradiotherapy, and 4) no parenteral nutrition, acute infections or other inflammatory conditions within 2 weeks before surgery.

Our study complied with the standards of the Declaration of Helsinki. Ethical approval was obtained from the Sun Yat-sen University Cancer Center research ethics committee, who deemed informed consent unnecessary.

2.2. Patient follow-up

In our center, patients were followed up by telephone or outpatient visit, every 3 months during the first 2 years, and every 6 months thereafter. Follow-up assessment included physical examination, electronic gastroduodenoscope, and dynamic computed tomography (CT) scan, laboratory testing of CEA, CA199, and CA724, etc. The latest follow-up date was February 2016. After a median follow-up of 36 months (range 3–162), we used cancer-specific survival (CSS) as the primary outcome for this study. CSS was calculated from the date of surgery until death of GC or last follow-up.

2.3. Prognostic scores evaluation

Routine laboratory measurements were carried out within 2 weeks before surgery. Unintentional preoperative weight loss during the 6 months before diagnosis was recorded at the initial

Table 1
The clinicopathological characteristics of 688 gastric cancer patients.

	No. of patients (%)
Age (years)	
<60	411 (59.7%)
≥60	277 (40.3%)
Sex	
Female	239 (34.7%)
Male	449 (65.3%)
Tumor size (cm)	
<5	350 (50.9%)
≥5	338 (49.1%)
Tumor location	
Lower third	276 (40.1%)
Upper/Middle third	412 (59.9%)
Histological grade	
Well differentiated	93 (13.5%)
Poorly differentiated	595 (86.5%)
TNM stage	
II	193 (28.1%)
III	495 (71.9%)
Complications	
No	528 (76.7%)
Yes	160 (23.3%)
NLR	
<2.6	476 (69.2%)
≥2.6	212 (30.8%)
PLR	
<130	299 (43.5%)
≥130	389 (56.5%)
LMR	
>3.5	421 (61.2%)
≤3.5	267 (38.8%)
CRP/Alb ratio	
<0.2	552 (80.2%)
≥0.2	136 (19.8%)
PNI	
0	608 (88.4%)
1	80 (11.6%)
Performance status	
0	166 (24.1%)
1/2	522 (75.9%)
BMI	
≥18.5	400 (58.1%)
<18.5	288 (41.9%)
Preoperative body weight loss	
≤6%	511 (74.3%)
>6%	177 (25.7%)
CEA	
Normal	535 (77.8%)
Elevated	153 (22.2%)
CA19-9	
Normal	532 (77.3%)
Elevated	156 (22.7%)
CA72-4	
Normal	517 (75.1%)
Elevated	171 (24.9%)
Fibrinogen (mg/dL)	
≤400	548 (79.7%)
>400	140 (20.3%)

Abbreviations: TNM = tumor-node-metastasis staging; NLR = neutrophil lymphocyte ratio; PLR = platelet lymphocyte ratio; LMR = lymphocyte monocyte ratio; CRP/Alb ratio = C-reactive protein/albumin ratio; PNI = Prognostic Nutritional Index; BMI = body mass index; CEA = carcinoembryonic antigen; CA = carbohydrate antigen.

visit. As reported previously, the prognostic scores BMI and PNI were constructed using standard thresholds [19]. According to the manufacturer's instructions, grouping of the continuous variables CEA (5 ng/mL), CA 19-9 (27 U/mL), CA 72-4 (5 U/mL) and fibrinogen (400 mg/dL) were carried out using widely accepted thresholds. For the prognostic markers NLR, PLR, LMR, CRP/Alb ratio and preoperative weight loss, established thresholds do not exist for the current study population. The optimal cutoff value was determined by receiver operating characteristic (ROC) curve analyses, as shown in Table 1.

2.4. Statistical methods

Data were processed with SPSS 19.0 software package (SPSS, Chicago, IL, USA) and R software package (http://www.r-project.org). The CSS rate was compared by the Kaplan–Meier methodology and log-rank test. Significant associations and differences between groups were examined using the Chi-square test for categorical variables. The optimal cutoff value was determined by ROC curve analyses on the basis of joint sensitivity and specificity. To identify the independent factors, a final multivariate Cox

Table 2
Univariate and multivariate analyses for cancer-specific survival in 688 patients with gastric cancer.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (years)		0.044		0.368
<60	1.00		1.00	
≥60	1.267 (1.007, 1.594)		1.156 (0.843, 1.585)	
Sex		0.271		
Female	1.00			
Male	0.876 (0.691, 1.109)			
Tumor size (cm)		0.002		0.059
<5	1.00		1.00	
≥5	1.448 (1.151, 1.821)		0.721 (0.514, 1.012)	
Tumor location		<0.001		0.005
Lower third	1.00		1.00	
Upper/Middle third	1.610 (1.263, 2.052)		1.577 (1.147, 2.169)	
Histological grade		0.251		
Well differentiated	1.00			
Poorly differentiated	1.230 (0.864, 1.750)			
TNM stage		<0.001		<0.001
II	1.00		1.00	
III	5.150 (3.508, 7.562)		5.036 (3.021, 8.396)	
Complications		0.867		
No	1.00			
Yes	0.977 (0.747, 1.278)			
NLR		0.001		0.999
<2.6	1.00		1.00	
≥2.6	1.478 (1.166, 1.873)		1.000 (0.691, 1.447)	
PLR		0.013		0.908
<130	1.00		1.00	
≥130	1.343 (1.063, 1.697)		1.020 (0.726, 1.433)	
LMR		0.002		0.534
>3.5	1.00		1.00	
≤3.5	1.454 (1.148, 1.840)		1.119 (0.785, 1.595)	
CRP/Alb ratio		<0.001		0.019
<0.2	1.00		1.00	
≥0.2	1.924 (1.442, 2.568)		1.593 (1.080, 2.351)	
PNI		<0.001		0.001
0	1.00		1.00	
1	1.793 (1.316, 2.443)		2.135 (1.351, 3.372)	
Performance status		0.289		
0	1.00			
1/2	0.883 (0.703, 1.111)			
BMI		0.279		
≥18.5	1.00			
<18.5	1.135 (0.902, 1.429)			
Preoperative body weight loss		<0.001		0.001
≤6%	1.00		1.00	
>6%	1.883 (1.478, 2.400)		1.771 (1.282, 2.445)	
CEA		0.008		0.199
Normal	1.00		1.00	
Elevated	1.432 (1.098, 1.868)		1.275 (0.880, 1.846)	
CA19-9		<0.001		0.017
Normal	1.00		1.00	
Elevated	1.646 (1.247, 2.173)		1.503 (1.075, 2.102)	
CA72-4		0.021		0.588
Normal	1.00		1.00	
Elevated	1.420 (1.054, 1.913)		1.102 (0.775, 1.566)	
Fibrinogen (mg/dL)		0.024		0.814
≤400	1.00		1.00	
>400	1.363 (1.043, 1.782)		1.049 (0.704, 1.563)	

Abbreviations: TNM = tumor-node-metastasis staging; NLR = neutrophil lymphocyte ratio; PLR = platelet lymphocyte ratio; LMR = lymphocyte monocyte ratio; CRP/Alb ratio = C-reactive protein/albumin ratio; PNI = Prognostic Nutritional Index; BMI = body mass index; CEA = carcinoembryonic antigen; CA = carbohydrate antigen.

proportional hazards model was performed, using all variables in which p value was less than 0.05 in the univariate analysis. A nomogram was generated by R software, with the discriminative ability assessed by the concordance index (C-index), which ranges from 0.5 (perfect discordance) to 1 (perfect concordance). Calibration plots were performed to compare the predicted probability of CSS with the observed outcome. A two-tailed P value of <0.05 was considered to be statistically significant. All data in our study have been recorded at Sun Yat-sen University Cancer Center for future reference (number RDDA2018000570).

3. Results

Of the 688 enrolled patients, 239 (34.7%) were women and 449 (65.3%) were men; 193 (28.2%) were stage II and 495 (71.9%) were stage III (Table 1); The median age at the time of diagnosis was 57 years, with an age range from 21 to 86 years. During a median follow-up period of 36 months, 296 GC deaths were observed.

Results from the multivariate analysis indicated that CRP/Alb ratio (HR: 1.593; 95% CI: 1.080–2.351; P = 0.019), PNI (HR: 2.135; 95% CI: 1.351–3.372; P = 0.001), preoperative body weight loss (HR: 1.771; 95% CI: 1.282–2.445; P = 0.001) and CA 19-9 (HR: 1.503; 95% CI: 1.075–2.102; P = 0.017) were independent prognostic factors of CSS as well as tumor location (HR: 1.577; 95% CI: 1.147–2.169; P = 0.005) and TNM stage (HR: 5.036; 95% CI: 3.021–8.396; P < 0.001; Table 2).

Kaplan–Meier analysis indicated that the elevated CRP/Alb ratio (>0.2), PNI (score 1), preoperative body weight loss (>6%) and CA 19-9 (>27 U/mL) were both associated with shorter CSS (All P < 0.05). These 4 preoperative prognostic markers were allocated 1 point each. Based on the total score, we developed a new systemic prognostic score (SPS), with scores ranging from SPS 0 to SPS 4 (Fig. 1). Overall, 317 (46.1%) patients were SPS 0, whereas 233 (33.9%), 107 (15.6%), 29 (4.2%) and 2 (0.3%) patients were SPS 1, SPS 2, SPS 3 and SPS 4, respectively. Because only 2 patients scored SPS 4, SPS 3 and SPS 4 were combined when the CSS rates were calculated. Patients with a SPS of 0, 1, 2, or 3/4 had a 5-year CSS rates of 67.2%, 45.3%, 29.0%, and 10.6%, respectively (0 vs. 1 [P < 0.001], 1 vs. 2 [P = 0.031] and 2 vs. 3/4 [P = 0.004]; Fig. 2). The median survival times for SPS 0, SPS 1, SPS 2 and SPS 3/4 were 68.7, 47.1, 28.3 and 16.3 months, respectively. When the CRP/Alb ratio, PNI, preoperative body weight loss and CA 19-9 were replaced by the SPS, multivariate analysis revealed that the SPS were independent predictors of CSS (HR for SPS 1: 1.774, 95% CI: 1.235–2.548, P = 0.002; HR for SPS 2: 2.546, 95% CI: 1.626–3.984, P < 0.001; HR for SPS 3/4: 5.309, 95% CI: 2.810–10.031, P < 0.001; P < 0.001), along with tumor location and TNM stage (S1 Table). In stage-matched analysis, the prognostic significance of SPS was still maintained in patients with stage II (P = 0.001) and stage III (P < 0.001) GC (Fig. 3).

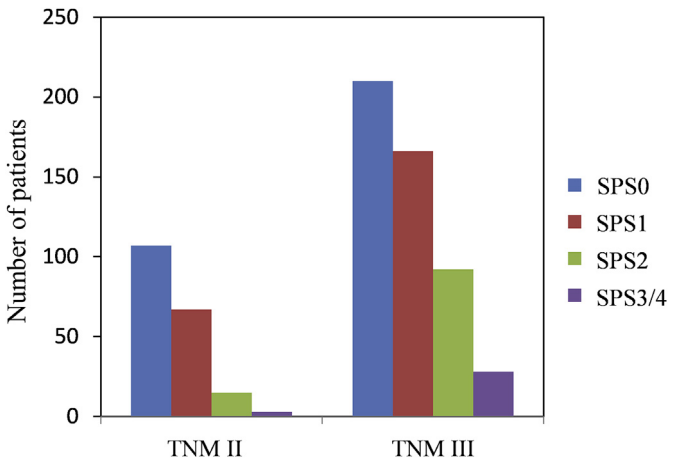

Fig. 1. Distribution of the preoperative SPS in different TNM stage. SPS = systemic prognostic score.

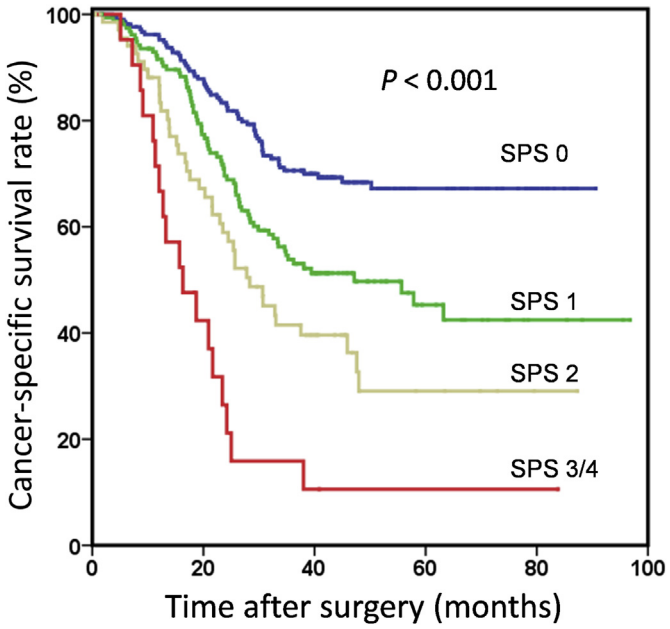

Fig. 2. Cancer-specific survival based on SPS in stage II–III GC patients treated with adjuvant chemotherapy. SPS = systemic prognostic score; GC = gastric cancer.

The relationships between the SPS and clinicopathological features are summarized in Table 3. An elevated SPS correlated significantly with larger tumor size (P < 0.001), poorer histological grade (P < 0.001), higher TNM stage (P < 0.001), elevated NLR (P < 0.001), elevated PLR (P < 0.001), lower LMR (P < 0.001), lower BMI (P < 0.001), elevated CEA (P = 0.017) and elevated fibrinogen level (P < 0.001).

To further assess their discrimination ability, ROC analysis was performed to compare the areas under-the-curve (AUC) values. The SPS had a higher AUC value (0.646; P < 0.001) than other individual prognostic marker, including the CRP/Alb ratio (0.563), PNI (0.547), preoperative body weight loss (0.579) and CA 19-9 (0.562).

To better make individualized predictions of clinical outcomes, we performed a prognostic nomogram that integrated all independent prognostic factors including TNM stage, tumor location and SPS (Fig. 4). The nomogram can obtain an estimate of the expected survival by summing the scores identified on the points scale for each predictor. A higher total score reveals a worse clinical prognosis. By internal validation, calibration plots of the nomogram predicting 1-, 3- and 5-year CSS performed well with the ideal model (Fig. 5A–C). The accuracy of our nomogram was higher than that of the seventh AJCC TNM classification or SPS. The C-index of our prognostic model was 0.714 (95% CI: 0.680–0.749) and higher than TNM stage (C-index 0.630; P < 0.001) or SPS (C-index 0.632; P < 0.001).

4. Discussion

Currently, surgical resection remains the cornerstone of treatment for patients with GC. However, despite after curative resection and adjuvant chemotherapy, stage II–III GC patients often experience early recurrence or metastasis within 5 years. Thus, it is

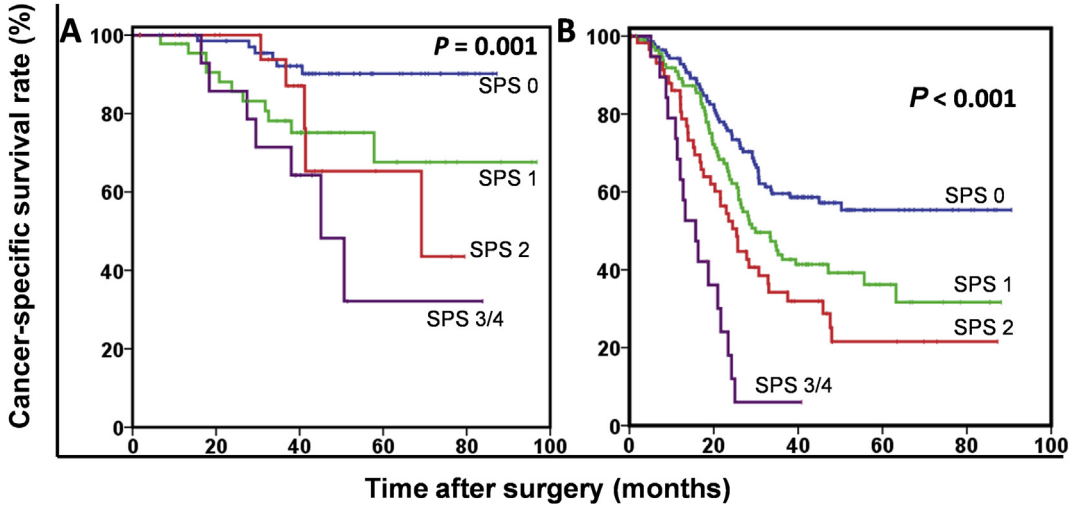

Fig. 3. Cancer-specific survival based on SPS in patients with stage II (A) and stage III (B) gastric cancer, respectively. SPS = systemic prognostic score.

Table 3
The clinicopathological characteristics stratified by SPS.

	SPS 0 (n = 317)	SPS 1 (n = 233)	SPS 2 (n = 107)	SPS 3 (n = 31)	P value
Age (years)					0.377
<60	199	137	59	16	
≥60	118	96	48	15	
Sex					0.524
Female	117	76	38	8	
Male	200	157	69	23	
Tumor size (cm)					<0.001
<5	205	106	33	6	
≥5	112	127	74	25	
Tumor location					0.089
Lower third	139	94	34	9	
Upper/Middle third	178	139	73	22	
Histological grade					<0.001
Well differentiated	27	35	27	4	
Poorly differentiated	290	198	80	27	
TNM stage					<0.001
II	108	67	15	3	
III	209	166	92	28	
Complications					0.561
No	246	174	86	22	
Yes	71	59	21	9	
NLR					<0.001
<2.6	251	157	59	9	
≥2.6	66	76	48	22	
PLR					<0.001
<130	158	108	27	6	
≥130	159	125	80	25	
LMR					<0.001
>3.5	215	146	54	6	
≤3.5	102	87	53	25	
Performance status					0.055
0	90	53	18	5	
1/2	227	180	89	26	
BMI					<0.001
≥18.5	204	133	55	8	
<18.5	113	100	52	23	
CEA					0.017
Normal	263	170	81	21	
Elevated	54	63	26	10	
CA72-4					0.077
Normal	252	170	73	22	
Elevated	65	63	34	9	
Fibrinogen (mg/dL)					<0.001
≤400	262	195	70	21	
>400	55	38	37	10	

Abbreviations: SPS = systemic prognostic score; TNM = tumor-node-metastasis staging; NLR = neutrophil lymphocyte ratio; PLR = platelet lymphocyte ratio; LMR = lymphocyte monocyte ratio; BMI = body mass index; CEA = carcinoembryonic antigen; CA = carbohydrate antigen.

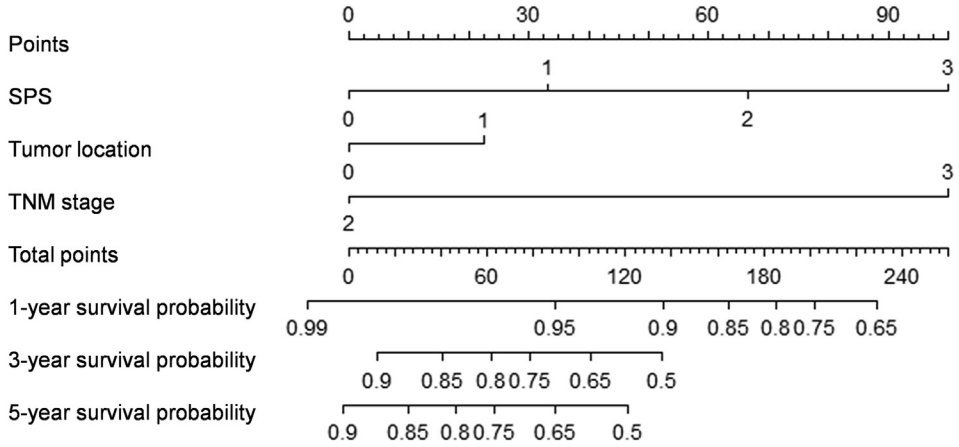

Fig. 4. Postoperative nomogram for predicting 1-, 3- and 5-year cancer-specific survival in stage II–III GC patients treated with adjuvant chemotherapy. SPS = systemic prognostic score.

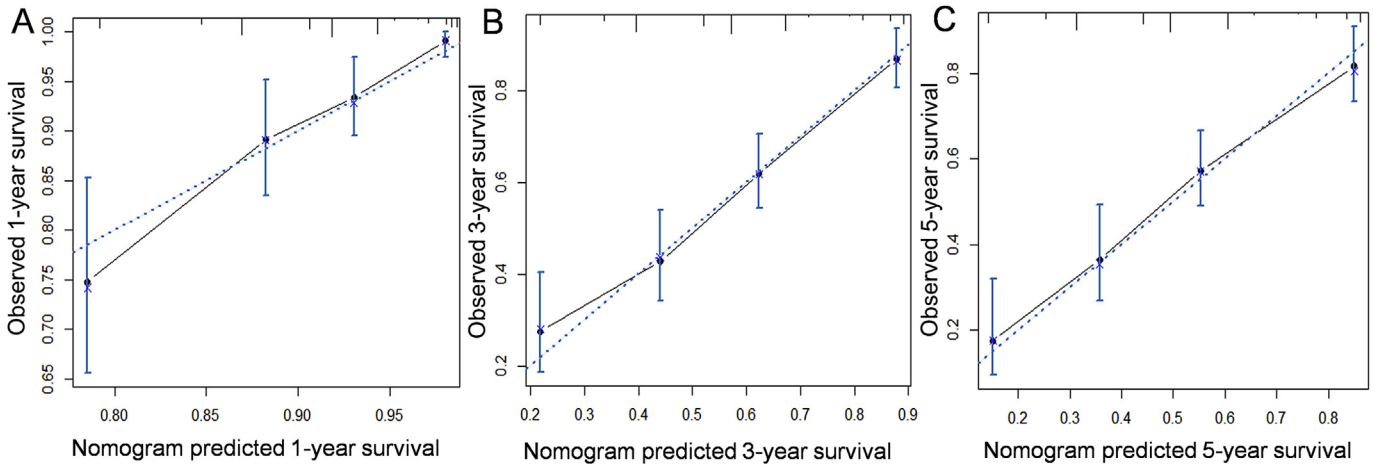

Fig. 5. Calibration plots of the nomogram for 1-year (A), 3-year (B) and 5-year (C) cancer-specific survival. The x-axis represents the nomogram-predicted survival, and the y-axis represents actual survival and 95% confidence intervals. Circles, predict survival in subcohorts of the original database; cross symbol, predict survival in subcohorts of 200 bootstrap samples. The dotted line represents the ideal correlationship between predicted and actual survival.

important to understand the biological mechanisms of tumor progression and to identify independent prognostic factors to optimize postoperative Rational adjuvant treatments

In recent years, it has been recognised that the systemic inflammatory response has a major role in carcinogenesis and determining disease progression [20]. Numerous studies have proved that the activation and maintenance of the systemic inflammatory response consistently confers the compromised immune function, upregulation of growth factors and tumor revascularization [21]. Moreover, the tumor microenvironment orchestrated by inflammatory cells can facilitate tumor growth, invasion and metastasis [22]. Numerous studies showed a clear association between an elevated systemic inflammatory response and adverse prognosis [23,24]. Over the last decade, several established systemic inflammation-based scores have been routinely incorporated into clinical care, including NLR, PLR, LMR and CRP/Alb ratio.

Furthermore, nutritional status has been reported repeatedly to greatly affect survival in cancer patients [25]. Cancer-associated malnutrition is a common feature in patients with cancer, with the global incidence ranging from 30% to 85%. Cancer-associated malnutrition is a complex, multifactorial syndrome, which contributes to diminished immunological function and the activation of systemic inflammatory response [26]. Meanwhile, studies have indicated that malnutrition leads to poor life quality, reduced therapeutic efficacy, and various severe postoperative complications [27]. Several promising nutritional-based indices, such as PNI, BMI and preoperative body weight loss, have been used to triage patients in clinical care [28]. Similarly, tumor markers, such as CEA, CA 19-9 and CA 72-4, are widely applied in patient counseling/management and, more recently, for prognosis prediction as well [29].

In the present study, we assessed the prognostic role of these established prognostic scores, along with the clinicopathological features. We found only CRP/Alb ratio, PNI, preoperative body weight loss and CA 19-9 independently predicted CSS as well as tumor location and TNM stage. We postulated that combination of these four scores, named SPS, could conceal their individual shortcomings and emphasize the merit of each score. Results of multivariate analysis showed that SPS was an independent predictor of CSS for stage II–III GC patients with adjuvant chemotherapy. Furthermore, its prognostic value was substantially stable in stage II and stage III patients. Kaplan–Meier analysis indicated that SPS could effectively classify patients into four independent groups. These data suggested SPS might provide additional prognostic information that would complement to the present TNM stage.

In fact, our results of the present study were also in line with those of previous reports. Kusunoki M et al. found that a high CRP/Alb ratio predicted surgical site infection, early recurrence and poor prognosis in GC [30]. Furthermore, our previous study also revealed that preoperative body weight loss might be a superior predictor of prognosis compared with other established nutritional-based markers in GC [31]. A recent meta-analysis of 10 studies suggested that PNI was a significant predictive indicator of prognosis and postoperative complications in patients with GC [10]. Similarly, another meta-analysis including 38 studies, shown that elevated CA19-9 serum levels were associated with poorer prognosis in GC [32]. Of note, we also found that PNI and preoperative body weight loss were independent predictors of CSS for stage II–III GC patients with adjuvant chemotherapy. We speculated that some of these nutritional parameters might be modifiable with the aim of increasing long term survival in GC. Zietarska M et al. found that high protein nutritional support improved nutritional status assessed by part of nutritional parameters in precachectic oncologic patients [33]. However, considering the influence of postoperative diet, life quality and adjuvant chemotherapy, we believe further exploration of postoperative nutritional status is needed in future studies. Moreover, patients with malnutrition may benefit from perioperative proactive nutritional interventions [34,35]. Despite promising results of targeted nutritional intervention in various cancers, no large-scale prospective studies exist assessing the role of nutrition support in GC patients post operatively [36,37]. Therefore, prospective randomized controlled studies are warranted as validation studies.

More importantly, we found SPS, a new scoring system based on the 4 significant factors, could further classify patients into four risk subgroups in different TNM stage. By incorporating the SPS into clinicopathological factors, a nomogram was established well with internal validation, and the calibration was excellent. This prognostic model may have important clinical usefulness in patient management, risk stratification, therapeutic intervention, and postoperative surveillance strategies. In addition, it can enhance risk communication between clinicians and patients, help to selecting candidates for whom prospective clinical studies can be developed. However, our model needs to be validated with different institutional datasets and in a prospective manner.

There are some limitations inherent to the study. First, the major limitations of the present study were its single-center retrospective nature. Second, there was lack of external validation in large-scale prospective randomized controlled studies. Third, our conclusions may have been strengthened by the use of additional outcome measures, such as progression-free survival and recurrence-free survival.

5. Conclusions

We have demonstrated that the SPS is an independent predictor of CSS in stage II–III GC patients with adjuvant chemotherapy. As a simple, conventionally available and cost-effective marker, it may have important clinical utility in improving prognostic prediction and guiding treatment strategies.

Disclosures and funding sources

The authors declare no conflicts of interest to the paper.

Authors' contributions

ZZW and SXW contributed to the conception and design of the study; WZM and LEZ, performed the literature search, data extraction and quality assessment. WZM performed the statistical analyses; LXC composed the first draft of the manuscript; LW, CYB and SXW read and critically revised the manuscript. All authors read and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2018.07.015

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