Clinical Significance of Peripheral Blood-Derived Inflammation Markers in Advanced Gastric Cancer after Radical Resection

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Abstract

Background and objective: The prognostic significance of peripheral blood-derived inflammation markers in patients with gastric cancer (GC) has not been elucidated. This study aimed to investigate the relationship between systemic inflammatory markers and GC prognosis.

Methods: A prospective observational cohort study involving 598 patients was conducted to analyze the prognosis of GC based on systemic inflammatory markers. The following peripheral blood-derived inflammation markers were evaluated: the neutrophil-lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), systemic immune-inflammation index (SII), C-reactive protein/albumin (CRP/Alb) ratio, Glasgow Prognostic Score (GPS), modified Glasgow Prognostic Score (mGPS), prognostic nutrition index (PNI), and prognostic index (PI). The receiver operating characteristics (ROC) curve and the Youden index were used to determine the optimal cutoff values. Univariate and multivariate analysis of prognostic factors was conducted accordingly.

Results: The optimal cutoff values of the PNI, fibrinogen, NLR, PLR, SII, and CRP/Alb were 49.5, 397ng/dl, 2.5, 154, 556, and 0.05, respectively. Multivariate analysis showed that age, PLR, TNM stage, and chemotherapy were the independent prognostic factors for advanced gastric cancer (AGC). Adjuvant chemotherapy improved the long-term prognosis of patients with PLR ≥154, but chemotherapy had no significant effect on the survival of patients with PLR <154.

Conclusions: Our findings show that higher PLR (≥154) is an independent risk factor for poor prognosis in GC patients. Besides, PLR can predict adjuvant chemotherapy (oxaliplatin/5-fluorouracil combination) response in patients with GC after surgery.

Introduction

Gastric cancer (GC) is one of the most common malignant tumors and that poses a serious threat to human health, especially in Asia. Approximately 300,000 deaths and 400,000 new cases of GC occur in China every year[1]. Despite the advancement in diagnostic and treatment methods, the prognosis of advanced gastric cancer (AGC) patients has remained poor[2]. Tumor, Node, Metastasis (TNM) staging based on the International Union Against Cancer (UICC)/American Joint Committee on Cancer (AJCC) guidelines is currently the standard approach of determining the prognosis of GC patients[3]. However, several prognostic factors related to GC have been proposed, which include peripheral blood-derived inflammation markers, such as neutrophil-lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), systemic immune-inflammation index (SII), C-reactive protein/albumin (CRP/Alb) ratio, and Glasgow Prognostic Score (GPS)[4–6].

Some studies have combined the TNM staging system with GC related risk factors to improve the accuracy of the long-term prognosis of the disease[7]. Routine peripheral blood-derived inflammation markers are closely associated with the pathogenesis of GC[8]. Moreover, the use of these markers as

prognostic factors is advantageous because most of the peripheral blood-derived inflammation markers belong to the routine test items; the test cost is cheap and does not require special equipment.

Park indicated that preoperative body mass index (BMI) and prognostic nutritional index (PNI), as well as their postoperative changes, are related to the prognosis of stage II/III GC[9]. Also, Jagadesham reported that the combination of one or more markers of systemic inflammation could precisely predict the prognosis of advanced adenocarcinoma of the esophagus[10]. Studies have suggested that combining NLR and PLR could significantly improve the accuracy of predicting the first-line chemosensitivity in AGC[11]. Contrarily, Xu et al. indicated that CRP/Alb might be a promising predictor of early recurrence (recurrence within 12 months after radical gastrectomy) and postoperative chemotherapy in stage III GC[12].

Unfortunately, most of these findings are based on small sample retrospective studies with insufficient evidence, which could be the reason for the inconsistencies among the various reports. Herein, we designed a prospective observational cohort to examine the relationship between peripheral blood-derived inflammation markers and the prognosis of GC. Also, we hypothesized that derangements in one or more systemic inflammation markers may be associated with poor disease outcomes and the ineffectiveness of chemotherapy.

Methods

Study population

This was a prospective observational cohort study involving patients who underwent radical gastrectomy from January 2013 to December 2016 at HwaMei Hospital, University of Chinese Academy of Sciences. And was approved by the Ethics Committee of the HwaMei Hospital and the University of Chinese Academy of Sciences (approval NO. PJ-NBEY-KY-2019-153-01). Written consent was obtained from all patients before enrollment. The inclusion criteria were: (1) patients with histologically proven primary adenocarcinoma of the stomach; (2) patients without a history of gastrectomy or other malignant tumor; (3) patients without inflammatory or hematological diseases; (4) patients with pathologically negative resection margins (R0); (5) patients without neoadjuvant chemoradiotherapy; (6) follow-up of at least 36 months. Treatment with 5-fluorouracil (5-FU)-based or platinum-based adjuvant chemotherapy was recommended for all patients with stage II-III of the disease[13].

Systemic inflammatory markers and histological examination

The whole blood and clinicopathological data were obtained one week before initial treatment. Blood samples were collected for routine laboratory tests, which included complete blood count, CRP, albumin, fibrinogen, and tumor markers, such as carcinoembryonic antigen (CEA). The following common peripheral blood-derived inflammation markers were included based on previous studies: NLR, PLR, SII, CRP/Alb, GPS, modified Glasgow Prognostic Score (mGPS), PNI, and prognostic index (PI).

All surgical resection specimens were assessed according to the handling guideline of the third edition of the Japanese classification of gastric carcinoma. And the staging was conducted by pathologists using the 8th edition of the UICC/AJCC TNM staging system[3].

Follow-up

All patients were followed up every 3–6 months for the first two years and annually thereafter until death or at least five years after surgery. Disease-free survival (DFS) was defined as the time from surgery to death, loco-regional recurrence or distant recurrence. Disease-specific survival (DSS) was defined as the time from surgery to death as a result of GC. Patients for whom none of these events was recorded were censored at the date of their last known contact. The median follow-up time for the entire cohort was 50 months (range 4–83 months), and follow-up of all patients was stopped in December 2019.

Statistical analysis

Continuous variables were compared using the independent sample t-test or Wilcoxon rank-sum test, whereas categorical variables were compared using Pearson's chi-squared test or Fisher's exact test, as appropriate. The receiver operating characteristics (ROC) curve was calculated, and the Youden index (maximum = sensitivity + specificity − 1) was used to determine the optimal cutoff value for the number of lymph nodes retrieved, PNI, fibrinogen, NLR, PLR, SII, and CRP/Alb. The potentially relevant factors obtained from the univariate analysis were assessed in the multivariate model using Cox's regression. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated. The DFS and DSS were calculated using the Kaplan-Meier method, and the log-rank test was employed to determine the significance. All statistical tests were performed 2-sided, and a $p < 0.05$ was considered statistically significant. All the analyses were performed using SPSS software (version 25.0, SPSS Inc. IL, USA).

Results

A total of 598 patients were recruited from January 2013 to December 2016. The 5-year DFS and DSS rates of all patients were 72.6% and 75.4%, respectively. Male patients were about twice as many as female patients, and the tumors in the distal stomach accounted for 77% of all the tumors. Concerning the GC staging, patients with GC stage I, II, and III were 119, 113, and 366, respectively. The 5-year DFS and DSS rates after surgery for stage I patients were 97% and 98%, respectively, whereas, for stage II patients, the rates were 81.4% and 85.8%, respectively. For stage III patients, the rates were 52.1% and 55.6%, respectively (Supplementary Table 1).

A total of 376 patients received adjuvant chemotherapy, of which 239 received SOX regimen [14] and 112 XELOX[15]. The remaining 25 patients received other chemotherapy treatments[16].

Optimal cutoff analysis

The optimal cutoff value of the number of lymph nodes retrieved, PNI, fibrinogen, NLR, PLR, SII, and CRP/Alb were 30, 49.5, 397 ng/dl, 2.5, 154, 556, and 0.05, respectively.

Clinicopathological factors and survival analysis

A total of 23 potential risk factors were selected. According to univariate analysis, the following 17 clinicopathological characteristics were found to be significantly associated with the 5-year DFS rate in all enrolled patients: age, tumor location, type of gastrectomy, tumor size, perineural invasion, lymphovascular invasion, T stage, N stage, chemotherapy, PNI, fibrinogen, NLR, PLR, SII, GPS, CRP/Alb, and CEA (Table 1). Multivariate Cox proportional hazards model analysis showed that age, T stage, N stage, number of lymph nodes retrieved, and PLR were independent prognostic factors for GC (Table 1).

Table 1

1 Univariate and multivariate analysis of prognostic factors in patients with gastric cancer

Clinicopathological	Univariate analysis			Multivariate analysis		
feature	HR	95% CI	*p* value	HR	95% CI	*p* value
Age (years)						
≤ 60	1			1		
> 60	1.62	1.16−2.25	**0.005**	1.63	1.15−2.31	**0.007**
Gender						
Male	1					
Female	1.01	0.73−1.40	0.967			
BMI						
≤ 24 kg/m^2	1					
> 24 kg/m^2	0.77	0.52−1.13	0.175			
Tumor location						
Upper third	1					
Middle third	0.53	0.29−0.98	**0.041**			
Lower third	0.47	0.31−0.71	**< 0.001**			
Two-thirds or more	0.76	0.27−2.15	0.600			
Gastrectomy						
Distal	1					
Total	1.57	1.10−2.23	**0.013**			
Proximal	NA					
Tumor size						
≤ 5 cm	1					
> 5 cm	2.60	1.90−3.54	**< 0.001**			
Histologic type						
Differentiated	1					
Undifferentiated	1.29	0.95−1.76	0.106			
Perineural invasion						

Clinicopathological	Univariate analysis			Multivariate analysis		
Absence	1					
Presence	2.73	2.00-3.72	< 0.001			
Lymphovascular invasion						
Absence	1					
Presence	2.78	2.02−3.83	< 0.001			
T category						
T1	1			1		
T2	4.30	1.56−11.83	0.005	3.04	1.08−8.57	0.036
T3	2.04	0.25−16.92	0.510	1.69	0.20−14.50	0.633
T4a	15.79	6.97−35.76	< 0.001	8.22	3.26−20.75	< 0.001
T4b	28.21	9.78−81.36	< 0.001	13.05	3.98−42.82	< 0.001
N category						
N0	1			1		
N1	3.22	1.76−5.90	< 0.001	1.70	0.88−3.26	0.112
N2	4.71	2.75−8.05	< 0.001	2.09	1.15−3.81	0.016
N3a	11.35	6.82−18.89	< 0.001	5.38	3.00-9.65	< 0.001
N3b	24.19	13.27−44.07	< 0.001	11.01	5.50-22.04	< 0.001

2 Univariate and multivariate analysis of prognostic factors in patients with gastric cancer

Clinicopathological	Univariate analysis			Multivariate analysis		
feature	HR	95% CI	*p* value	HR	95% CI	*p* value
Chemotherapy						
No	1			1		
Yes	1.58	1.12−2.22	**0.009**	0.70	0.48−1.01	0.059
Number of lymph nodes retrieved						
≤ 15	1			1		
16−29	0.75	0.50−1.13	0.169	0.46	0.30−0.70	**< 0.001**
≥ 30	1.36	0.88−2.11	0.166	0.52	0.32−0.84	**0.008**
PI						
0	1					
1	1.54	0.96−2.49	0.075			
PNI						
< 49.5	1					
≥ 49.5	0.40	0.27−0.59	**< 0.001**			
Fibrinogen						
< 397 ng/dl	1					
≥ 397 ng/dl	2.06	1.51−2.81	**< 0.001**			
NLR						
< 2.5	1			1		
≥ 2.5	1.69	1.24−2.31	**0.001**	0.70	0.48−1.01	0.059
PLR						
< 154	1			1		
≥ 154	2.21	1.62−3.01	**< 0.001**	1.70	1.20−2.42	**0.003**
SII						

HR, hazard ratios; CI, confidence interval; BMI, Body mass index; PNI, Prognostic nutritional index; PI, Prognostic index; GPS, Glasgow Prognostic Score; mGPS, Modified Glasgow Prognostic Score; NLR, Neutrophil-lymphocyte ratio; PLR, Platelet-lymphocyte ratio; CRP/Alb, C-reactive protein/albumin; SII, Systemic immune-inflammatory index

Clinicopathological	Univariate analysis			Multivariate analysis
< 556	1			
≥ 556	1.94	1.43−2.64	**< 0.001**	
GPS				
0	1			
1	1.76	1.24−2.49	**0.002**	
2	1.89	1.04−3.43	**0.037**	
mGPS				
0	1			
1	1.53	0.68−3.46	0.307	
2	1.66	0.92-3.00	0.091	
CRP/Alb				
< 0.05	1			
≥ 0.05	1.91	1.40−2.60	**< 0.001**	
CEA				
≤ 5 ng/mL	1			
> 5 ng/mL	1.76	1.16−2.68	**0.008**	

HR, hazard ratios; CI, confidence interval; BMI, Body mass index; PNI, Prognostic nutritional index; PI, Prognostic index; GPS, Glasgow Prognostic Score; mGPS, Modified Glasgow Prognostic Score; NLR, Neutrophil-lymphocyte ratio; PLR, Platelet-lymphocyte ratio; CRP/Alb, C-reactive protein/albumin; SII, Systemic immune-inflammatory index

Risk factors for advanced gastric cancer

Considering the close correlation between the TNM stage and the 5-year DFS, the number of lymph nodes retrieved may be related to the prognosis. Lymph nodes less than 16 is considered inadequate lymph node dissection, especially for AGC. Therefore, only patients with the AGC lymph nodes ≥ 16 were included in the analysis. Multivariate analysis showed that age, PLR, and TNM stages were associated with 5-year DFS. Also, age, PLR, TNM stage, and chemotherapy were associated with 5-year DSS (Table 2).

Table 2
Multivariate analysis of prognostic factors in patients with advanced gastric cancer

Clinicopathological	Multivariate analysis DFS			Multivariate analysis DSS		
feature	HR	95% CI	*p* value	HR	95% CI	*p* value
Age (years)						
≤ 60	1			1		
> 60	1.61	1.10−2.35	**0.014**	1.61	1.06−2.42	**0.024**
PLR						
< 154	1			1		
≥ 154	2.00	1.40−2.84	**< 0.001**	2.09	1.43−3.04	**< 0.001**
TNM						
II	1			1		
III	4.46	2.51−7.91	**< 0.001**	5.94	3.01−11.74	**< 0.001**
Chemotherapy						
No	1			1		
Yes	0.70	0.48−1.04	0.074	0.66	0.45−0.99	**0.043**
DFS, disease-free survival; DSS, disease-specific survival; HR, hazard ratios; CI, confidence interval; PLR, platelet-lymphocyte ratio						

Risk factors associated with stage II and III gastric cancer

Kaplan-Meier curves were used to determine the long-term disease outcomes of GC patients in stage II and stage III. In GC stage II, the 5-year DFS rates were similar among patients with age ≤ 60 and age > 60 ($p = 0.213$). However, in stage III, the 5-year DFS rate of GC patients aged > 60 was worse than those aged ≤ 60 ($p = 0.016$). Similarly, in GC stage III, the 5-year DFS rate of patients with PLR ≥ 154 was worse than those with PLR < 154 ($p < 0.001$). But this phenomenon was not observed in GC stage II ($p = 0.153$). The effect of chemotherapy on the prognosis of patients with stage II GC was not statistically significant ($p = 0.260$). In contrast, chemotherapy significantly improved the 5-year DFS in patients with stage III GC ($p = 0.017$) [Figure 1].

With the 5-year DSS as a long-term prognostic index, age, PLR, and chemotherapy had the same effect on the prognosis of stage II and III GC patients as 5-year DFS, except that chemotherapy also improved the 5-year DSS of stage II GC patients ($p = 0.033$) [Figure 2].

Combined with the above observations, PLR was found to be an independent risk factor for the prognosis of AGC. Patients with AGC were divided into the PLR < 154 and PLR ≥ 154 subgroups. Further analysis of the clinicopathological factors between the two groups revealed that tumor lesions in the PLR < 154

group were smaller than those in the PLR ≥ 154 group. But, there was no other difference between the groups (Table 3). Further analysis of the relationship between chemotherapy and PLR showed that chemotherapy improved the long-term prognosis of patients in the PLR ≥ 154 group, including 5-year DFS and DSS ($p = 0.026$, $p = 0.014$, respectively). Notably, chemotherapy had no significant effect on the long-term prognosis of patients in the PLR < 154 group (Fig. 3).

Table 3
Association between PLR and the patients' characteristics

	PLR < 154	PLR ≥ 154	*p* value
Age (year)			0.223
≤ 60	78	55	
>60	110	103	
Gender			0.818
Male	128	105	
Female	60	53	
Tumor location			0.941
Upper third	26	47	
Middle third	23	17	
Lower third	133	116	
Two-thirds or more	6	4	
Tumor size			**< 0.001**
≤ 5 cm	135	73	
> 5 cm	53	85	
Histologic type			0.156
Differentiated	74	75	
Undifferentiated	114	83	
Perineural invasion			0.194
Absence	79	78	
Presence	109	80	
Lymphovascular invasion			0.509
Absence	77	59	
Presence	111	99	
T category			0.835
T1	7	4	

PLR, Platelet-lymphocyte ratio

	PLR < 154	PLR ≥ 154	p value
T2	15	10	
T3	7	6	
T4a	153	135	
T4b	6	3	
N category			0.416
N0	35	28	
N1	39	29	
N2	58	41	
N3a	45	43	
N3b	11	17	
CEA			0.275
≤ 5 ng/mL	166	133	
> 5 ng/mL	22	25	
PLR, Platelet-lymphocyte ratio			

Discussion

Many studies have been conducted to investigate the correlation between peripheral blood-derived inflammation markers and tumor prognosis[17, 18]. Liu showed that CRP/Alb was an independent prognostic marker for patients with ovarian cancer[19]. Also, the NLR and PLR are prognostic factors in patients with non-small cell lung cancer after stereotactic radiation therapy[20]. The independent risk factors for poor GC prognosis include NLR, PLR, fibrinogen, PNI, GPS, CRP/Alb, among others. Also, some studies have combined these systemic inflammatory markers with or without TNM stage to provide new prognostic tools[21–23]. However, most of these studies were retrospective, and reported inconsistent results, particularly on the significance of each inflammatory index and the threshold value.

Therefore, in addition to the peripheral blood-derived inflammation markers reported in previous studies, this study further explored the prognostic value of some conventional systemic inflammatory marker in patients with GC. We prospectively analyzed 598 GC patients after radical surgery and found that independent risk factors for poor prognosis of GC included age, T stage, N stage, number of lymph nodes retrieved, and PLR. Currently, TNM staging is the standard prognostic tool for GC. Given the excellent prognosis of early gastric cancer, our focus was to analyze the prognosis of patients with AGC (stage II/III). Many studies have demonstrated that the number of lymph node dissection has an impact on the

prognosis of GC; therefore, we further excluded patients with an inadequate amount of lymph node dissection (less than 16)[24–26].

Independent risk factors for AGC included age, PLR, TNM stages, and chemotherapy. Previous studies have investigated the effect of age on GC prognosis; however, most of these studies found no significant association between age and GC prognosis[27–29]. Takatsu analyzed 5000 GC cases and found that early-onset GC (age < 40 years) was likely to present lymph node metastases. But the survival rate of young GC patients was equivalent to that of older GC patients (age ≥ 60 years)[30]. In the present study, older GC patients (age > 60 years) had a worse prognosis, which was closely related to tumor recurrence.

Nutritional status is associated with survival in patients with malignant tumors, including GC. Preoperative underweight and low PNI are considered poor prognostic factors. Park suggested that careful nutritional intervention after surgery could improve the survival rate[9]. Besides, a meta-analysis concluded that a low PNI is significantly associated with poor overall survival except for stage IV GC[31]. However, consistent with the results of Li et al.[32], we observed that PNI was not associated with prognosis. Also, our results did not show a correlation between fibrinogen and the prognosis of GC. Recent studies have shown that fibrinogen is one of the risk factors for poor prognosis in upper gastric cancer[33]. Fibrinogen is the primary acute-phase protein, and as a critical component of the hemostatic system, it regulates the systemic inflammatory state and cancer progression. However, its clinical significance in the prognosis of GC has not been elucidated.

The NLR and PLR are the most extensively studied markers of peripheral blood-derived inflammation, which are associated with the prognosis of GC. Accumulating evidence has shown that NLR and PLR are associated with distant metastases during GC progression[34, 35]. Kim reported that although both the PLR and NLR could reflect the prognosis, the NLR was more predictive of overall survival than the PLR in GC[36]. Also, they suggested that NLR and PLR might be associated with lymph node metastasis in early gastric cancer[37]. On the contrary, Zhu et al. indicated that NLR and PLR could not predict lymph node metastasis and prognosis in early gastric cancer[38]. In the present study, PLR was significantly correlated with the prognosis of GC, but there was no statistical difference between NLR and prognosis of GC. This observation seems to be inconsistent with previous studies, but the exact mechanism is still unclear. However, the inconsistencies could be because most previous studies focused on overall survival as the primary outcome, whereas herein, we used tumor recurrence and tumor-related mortality as observational indicators, which seem to be more accurate. In addition, the clinicopathological characteristics were similar between the PLR elevating group (PLR < 154) and the PLR decreasing group (PLR ≥ 154), except for tumor size, which further suggested that PLR might influence the prognosis of tumor through other mechanisms. A recent meta-analysis has revealed that PLR is associated with prognosis of GC[39].

Abnormal levels of CRP and Alb have been related to poor prognosis of tumor patients. It is noteworthy that the combinations of these two indicators can enhance the accuracy to predict the recurrence of multiple tumors. Among them, the most common evaluation criteria after combination include GPS and

CRP/Alb. Besides, many studies have used GPS to predict the prognosis of various tumors, including GC. Hsueh recently recommended the use of GPS as a predictive and prognostic factor in patients with GC. A significant correlation was observed between the GPS, short-term postoperative complications, and long-term survival outcomes in patients with GC undergoing D2 gastrectomy[40]. Some studies have indicated that GPS and mGPS, used either alone or in combination, represent an independent prognostic factor for long-term outcome in resected GC[41, 42]. However, Walsh's results did not show a correlation between prognosis of patients and mGPS levels, although mGPS was associated with advanced GC stage[17]. Liu et al. retrospectively analyzed 455 patients with resectable GC and showed that CRP/Alb, rather than GPS and mGPS, was associated with overall survival[43]. Similarly, Xu[12] and Lu[44] et al. also observed that CRP/Alb and CRP/prealbumin were associated with recurrence of GC based on the data from a phase III randomized clinical trial. On the contrary, our results showed that although CRP/Alb and GPS were associated with prognosis in the univariate analysis, the multivariate analysis showed that both were not related to long-term survival.

Consistent with the results of previous clinical trials, our findings showed that chemotherapy could significantly improve the prognosis of AGC, especially for patients with stage III GC[45, 46]. Moreover, many studies have investigated the correlation between peripheral blood-derived inflammation markers and the effects of chemotherapy, to guide the selection of chemotherapy-sensitive patients. A study suggested that the sensitivity of chemotherapy (oxaliplatin/5-fluorouracil combination) might be closely related to NLR, PLR, and their changes in metastatic gastric cancer[47]. Hirahara believed that the combination of NLR and PLR might be more effective in predicting the chemotherapy response in patients with metastatic gastric cancer[48]. Besides, Tang[49] and Chen[50] concluded that PLR could predict the efficacy of neoadjuvant chemotherapy of GC patients treated with oxaliplatin and capecitabine regimens. In the current study, PLR effectively predicted adjuvant chemotherapy (oxaliplatin/5-fluorouracil combination) response in patients with AGC after surgery. For patients with PLR $\geq$ 154, chemotherapy significantly improved long-term survival, including DFS and DSS; however, patients with PLR < 154 did not benefit from adjuvant chemotherapy. Thus, we recommend that AGC patients with PLR $\geq$ 154 should actively receive adjuvant chemotherapy (oxaliplatin/5-fluorouracil combination) after surgery, whereas patients with PLR < 154 need to be cautious when choosing adjuvant chemotherapy.

This study systematically evaluated the relationship between peripheral blood-derived inflammation markers and the prognosis of GC. Notably, the potential ability of inflammatory markers to predict the effects of chemotherapy was further demonstrated. However, this study had a few limitations. Importantly, this was an observational study and was therefore influenced by other confounding factors. Also, the sample size was relatively small, and this may have reduced the reliability of the findings. Thus, these results need to be further validated by large multicenter randomized clinical trials.

Conclusion

Our findings show that PLR is significantly correlated with the prognosis of GC, especially for stage III. That is, higher PLR (≥ 154) is an independent risk factor for poor long-term survival rate of GC patients. Moreover, PLR can be used to predict adjuvant chemotherapy (oxaliplatin/5-fluorouracil combination) response in patients with GC after surgery.

Abbreviation

GC, gastric cancer; AGC, advanced gastric cancer; UICC, International Union Against Cancer; AJCC, American Joint Committee on Cancer; NLR, neutrophil-lymphocyte ratio; PLR, platelet lymphocyte ratio; SII, systemic immune-inflammation index; CRP/Alb, C-reactive protein/albumin ratio; GPS, Glasgow Prognostic Score; mGPS, modified Glasgow Prognostic Score; BMI, body mass index; PNI, prognostic nutritional index; PI, prognostic index; DFS, disease-free survival; DSS, disease-specific survival; ROC, receiver operating characteristics; HR, hazard ratios; CI, confidence intervals

Declarations

Conflict of interest

The authors declare no conflict of interest.

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Author contributions

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References

1. Allemani C, Matsuda T, Di Carlo V et al. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet 2018; 391: 1023-1075.
2. Macdonald JS, Smalley SR, Benedetti J et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001; 345: 725-730.
3. Japanese gastric cancer treatment guidelines 2014 (ver. 4). Gastric Cancer 2017; 20: 1-19.

4. Shi H, Jiang Y, Cao H et al. Nomogram Based on Systemic Immune-Inflammation Index to Predict Overall Survival in Gastric Cancer Patients. Dis Markers 2018; 2018: 1787424.

5. Miyamoto R, Inagawa S, Sano N et al. The neutrophil-to-lymphocyte ratio (NLR) predicts short-term and long-term outcomes in gastric cancer patients. Eur J Surg Oncol 2018; 44: 607-612.

6. Zhang LX, Wei ZJ, Xu AM, Zang JH. Can the neutrophil-lymphocyte ratio and platelet-lymphocyte ratio be beneficial in predicting lymph node metastasis and promising prognostic markers of gastric cancer patients? Tumor maker retrospective study. Int J Surg 2018; 56: 320-327.

7. Petrillo A, Laterza MM, Tirino G et al. Systemic-inflammation-based score can predict prognosis in metastatic gastric cancer patients before first-line chemotherapy. Future Oncol 2018; 14: 2493-2505.

8. Zheng L, Zou K, Yang C et al. Inflammation-based indexes and clinicopathologic features are strong predictive values of preoperative circulating tumor cell detection in gastric cancer patients. Clin Transl Oncol 2017; 19: 1125-1132.

9. Park SH, Lee S, Song JH et al. Prognostic significance of body mass index and prognostic nutritional index in stage II/III gastric cancer. Eur J Surg Oncol 2019.

10. Jagadesham VP, Lagarde SM, Immanuel A, Griffin SM. Systemic inflammatory markers and outcome in patients with locally advanced adenocarcinoma of the oesophagus and gastro-oesophageal junction. Br J Surg 2017; 104: 401-407.

11. Huang Z, Liu Y, Yang C et al. Combined neutrophil/platelet/lymphocyte/differentiation score predicts chemosensitivity in advanced gastric cancer. BMC Cancer 2018; 18: 515.

12. Xu BB, Lu J, Zheng ZF et al. The predictive value of the preoperative C-reactive protein-albumin ratio for early recurrence and chemotherapy benefit in patients with gastric cancer after radical gastrectomy: using randomized phase III trial data. Gastric Cancer 2019; 22: 1016-1028.

13. Bang YJ, Kim YW, Yang HK et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet 2012; 379: 315-321.

14. Boku N, Ryu MH, Kato K et al. Safety and efficacy of nivolumab in combination with S-1/capecitabine plus oxaliplatin in patients with previously untreated, unresectable, advanced, or recurrent gastric/gastroesophageal junction cancer: interim results of a randomized, phase II trial (ATTRACTION-4). Ann Oncol 2019; 30: 250-258.

15. Ryu MH, Yoo C, Kim JG et al. Multicenter phase II study of trastuzumab in combination with capecitabine and oxaliplatin for advanced gastric cancer. Eur J Cancer 2015; 51: 482-488.

16. Rao S, Starling N, Cunningham D et al. Matuzumab plus epirubicin, cisplatin and capecitabine (ECX) compared with epirubicin, cisplatin and capecitabine alone as first-line treatment in patients with advanced oesophago-gastric cancer: a randomised, multicentre open-label phase II study. Ann Oncol 2010; 21: 2213-2219.

17. Walsh SM, Casey S, Kennedy R et al. Does the modified Glasgow Prognostic Score (mGPS) have a prognostic role in esophageal cancer? J Surg Oncol 2016; 113: 732-737.

18. Song S, Li C, Li S et al. Derived neutrophil to lymphocyte ratio and monocyte to lymphocyte ratio may be better biomarkers for predicting overall survival of patients with advanced gastric cancer. Onco Targets Ther 2017; 10: 3145-3154.

19. Liu Y, Chen S, Zheng C et al. The prognostic value of the preoperative c-reactive protein/albumin ratio in ovarian cancer. BMC Cancer 2017; 17: 285.

20. Cannon NA, Meyer J, Iyengar P et al. Neutrophil-lymphocyte and platelet-lymphocyte ratios as prognostic factors after stereotactic radiation therapy for early-stage non-small-cell lung cancer. J Thorac Oncol 2015; 10: 280-285.

21. Yu L, Lv CY, Yuan AH et al. Significance of the preoperative neutrophil-to-lymphocyte ratio in the prognosis of patients with gastric cancer. World J Gastroenterol 2015; 21: 6280-6286.

22. Hu D, Zhang H, Lin X et al. Elevated preoperative neutrophil-to-lymphocyte ratio can predict poor survival in early stage gastric cancer patients receiving radical gastrectomy: The Fujian prospective investigation of cancer (FIESTA) study. J Cancer 2017; 8: 1214-1222.

23. Liu X, Wu Z, Lin E et al. 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. Clin Nutr 2019; 38: 1853-1860.

24. Kulig J, Sierzega M, Kolodziejczyk P, Popiela T. Ratio of metastatic to resected lymph nodes for prediction of survival in patients with inadequately staged gastric cancer. Br J Surg 2009; 96: 910-918.

25. Lee HJ, Hyung WJ, Yang HK et al. Short-term Outcomes of a Multicenter Randomized Controlled Trial Comparing Laparoscopic Distal Gastrectomy With D2 Lymphadenectomy to Open Distal Gastrectomy for Locally Advanced Gastric Cancer (KLASS-02-RCT). Ann Surg 2019.

26. Shoda K, Ichikawa D, Arita T et al. Risk Stratification According to the Total Number of Factors That Meet the Indication Criteria for Radical Lymph Node Dissection in Patients with Early Gastric Cancer at Risk for Lymph Node Metastasis. Ann Surg Oncol 2016; 23: 792-797.

27. Lu J, Chen Y, Liu Y et al. Clinical significance of prognostic score based on age, tumor size, and grade in gastric cancer after gastrectomy. Cancer Manag Res 2018; 10: 4279-4286.

28. Song M, Kang D, Yang JJ et al. Age and sex interactions in gastric cancer incidence and mortality trends in Korea. Gastric Cancer 2015; 18: 580-589.

29. Zhang J, Gan L, Xu MD et al. The prognostic value of age in non-metastatic gastric cancer after gastrectomy: a retrospective study in the U.S. and China. J Cancer 2018; 9: 1188-1199.

30. Takatsu Y, Hiki N, Nunobe S et al. Clinicopathological features of gastric cancer in young patients. Gastric Cancer 2016; 19: 472-478.

31. Yang Y, Gao P, Song Y et al. The prognostic nutritional index is a predictive indicator of prognosis and postoperative complications in gastric cancer: A meta-analysis. Eur J Surg Oncol 2016; 42: 1176-1182.

32. Li J, Xu R, Hu DM et al. Prognostic Nutritional Index Predicts Outcomes of Patients after Gastrectomy for Cancer: A Systematic Review and Meta-Analysis of Nonrandomized Studies. Nutr Cancer 2019;

71: 557-568.

33. Cong X, Li S, Zhang Y et al. The combination of preoperative fibrinogen and neutrophil-lymphocyte ratio is a predictive prognostic factor in esophagogastric junction and upper gastric cancer. J Cancer 2019; 10: 5518-5526.

34. Miyatani K, Saito H, Kono Y et al. Combined analysis of the pre- and postoperative neutrophil-lymphocyte ratio predicts the outcomes of patients with gastric cancer. Surg Today 2018; 48: 300-307.

35. Nora I, Shridhar R, Huston J, Meredith K. The accuracy of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio as a marker for gastrointestinal malignancies. J Gastrointest Oncol 2018; 9: 972-978.

36. Kim EY, Lee JW, Yoo HM et al. The Platelet-to-Lymphocyte Ratio Versus Neutrophil-to-Lymphocyte Ratio: Which is Better as a Prognostic Factor in Gastric Cancer? Ann Surg Oncol 2015; 22: 4363-4370.

37. Lou N, Zhang L, Chen XD et al. A novel scoring system associating with preoperative platelet/lymphocyte and clinicopathologic features to predict lymph node metastasis in early gastric cancer. J Surg Res 2017; 209: 153-161.

38. Zhu GS, Tian SB, Wang H et al. Preoperative Neutrophil Lymphocyte Ratio and Platelet Lymphocyte Ratio Cannot Predict Lymph Node Metastasis and Prognosis in Patients with Early Gastric Cancer: a Single Institution Investigation in China. Curr Med Sci 2018; 38: 78-84.

39. Cao W, Yao X, Cen D et al. The prognostic role of platelet-to-lymphocyte ratio on overall survival in gastric cancer: a systematic review and meta-analysis. BMC Gastroenterol 2020; 20: 16.

40. Hsueh SW, Liu KH, Hung CY et al. Significance of the Glasgow Prognostic Score in Predicting the Postoperative Outcome of Patients with Stage III Gastric Cancer. J Clin Med 2019; 8.

41. Melling N, Gruning A, Tachezy M et al. Glasgow Prognostic Score may be a prognostic index for overall and perioperative survival in gastric cancer without perioperative treatment. Surgery 2016; 159: 1548-1556.

42. Jiang X, Hiki N, Nunobe S et al. Prognostic importance of the inflammation-based Glasgow prognostic score in patients with gastric cancer. Br J Cancer 2012; 107: 275-279.

43. Liu X, Sun X, Liu J et al. Preoperative C-Reactive Protein/Albumin Ratio Predicts Prognosis of Patients after Curative Resection for Gastric Cancer. Transl Oncol 2015; 8: 339-345.

44. Lu J, Xu BB, Zheng ZF et al. CRP/prealbumin, a novel inflammatory index for predicting recurrence after radical resection in gastric cancer patients: post hoc analysis of a randomized phase III trial. Gastric Cancer 2019; 22: 536-545.

45. Koizumi W, Takiuchi H, Yamada Y et al. Phase II study of oxaliplatin plus S-1 as first-line treatment for advanced gastric cancer (G-SOX study). Ann Oncol 2010; 21: 1001-1005.

46. Al-Batran SE, Hartmann JT, Hofheinz R et al. Biweekly fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) for patients with metastatic adenocarcinoma of the stomach or esophagogastric

junction: a phase II trial of the Arbeitsgemeinschaft Internistische Onkologie. Ann Oncol 2008; 19: 1882-1887.

47. Lee S, Oh SY, Kim SH et al. Prognostic significance of neutrophil lymphocyte ratio and platelet lymphocyte ratio in advanced gastric cancer patients treated with FOLFOX chemotherapy. BMC Cancer 2013; 13: 350.

48. Hirahara T, Arigami T. Combined neutrophil-lymphocyte ratio and platelet-lymphocyte ratio predicts chemotherapy response and prognosis in patients with advanced gastric cancer. BMC Cancer 2019; 19: 672.

49. Tang C, Cheng X, Yu S et al. Platelet-to-lymphocyte ratio and lymphocyte-to-white blood cell ratio predict the efficacy of neoadjuvant chemotherapy and the prognosis of locally advanced gastric cancer patients treated with the oxaliplatin and capecitabine regimen. Onco Targets Ther 2018; 11: 7061-7075.

50. Chen L, Hao Y, Cong X et al. Peripheral Venous Blood Platelet-to-Lymphocyte Ratio (PLR) for Predicting the Survival of Patients With Gastric Cancer Treated With SOX or XELOX Regimen Neoadjuvant Chemotherapy. Technol Cancer Res Treat 2019; 18: 1533033819829485.

Figures
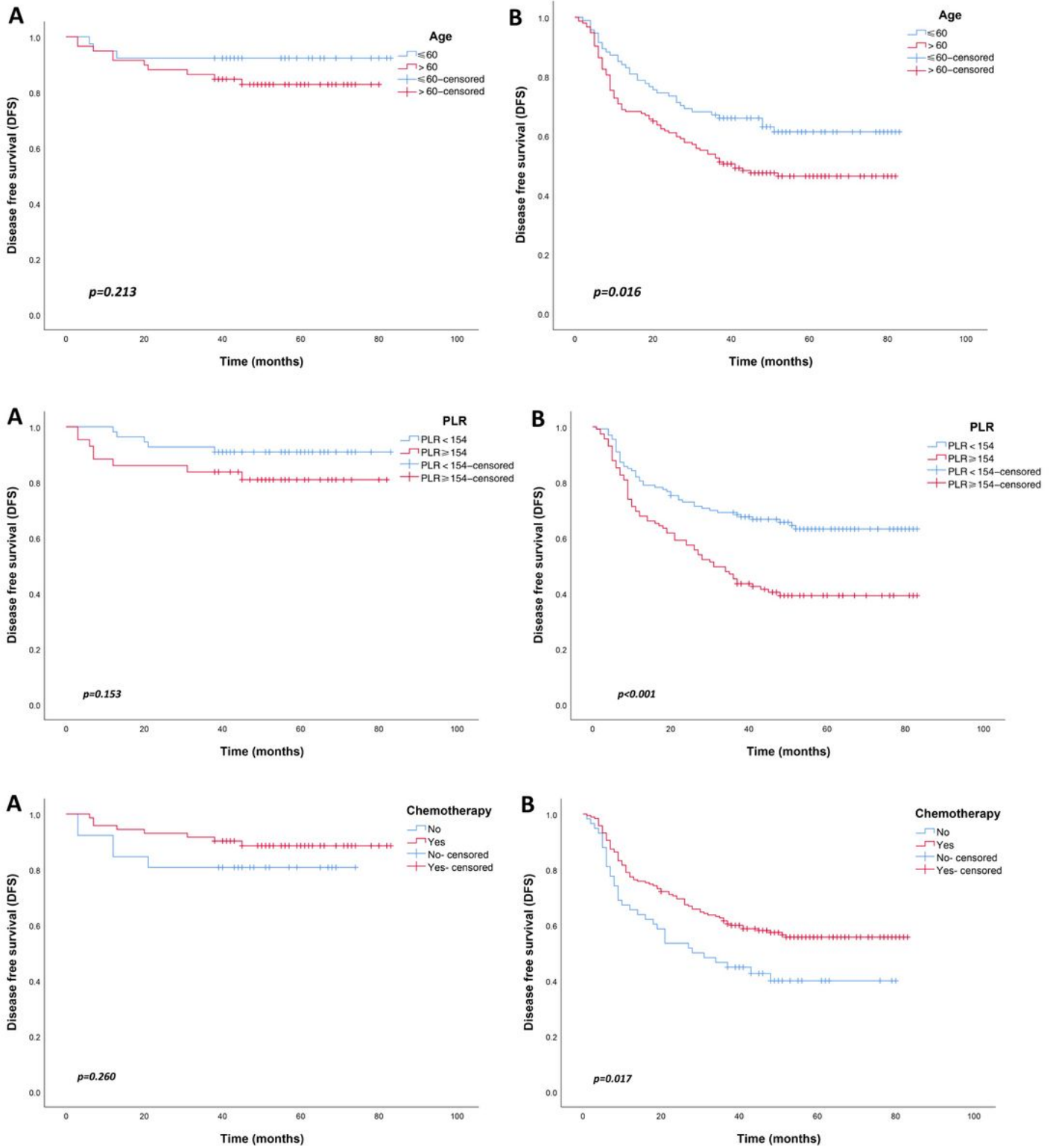
Figure 1

Disease-free survival (DFS) of patients with advanced gastric cancer according to the risk factors. (A) stage II; (B) stage III.
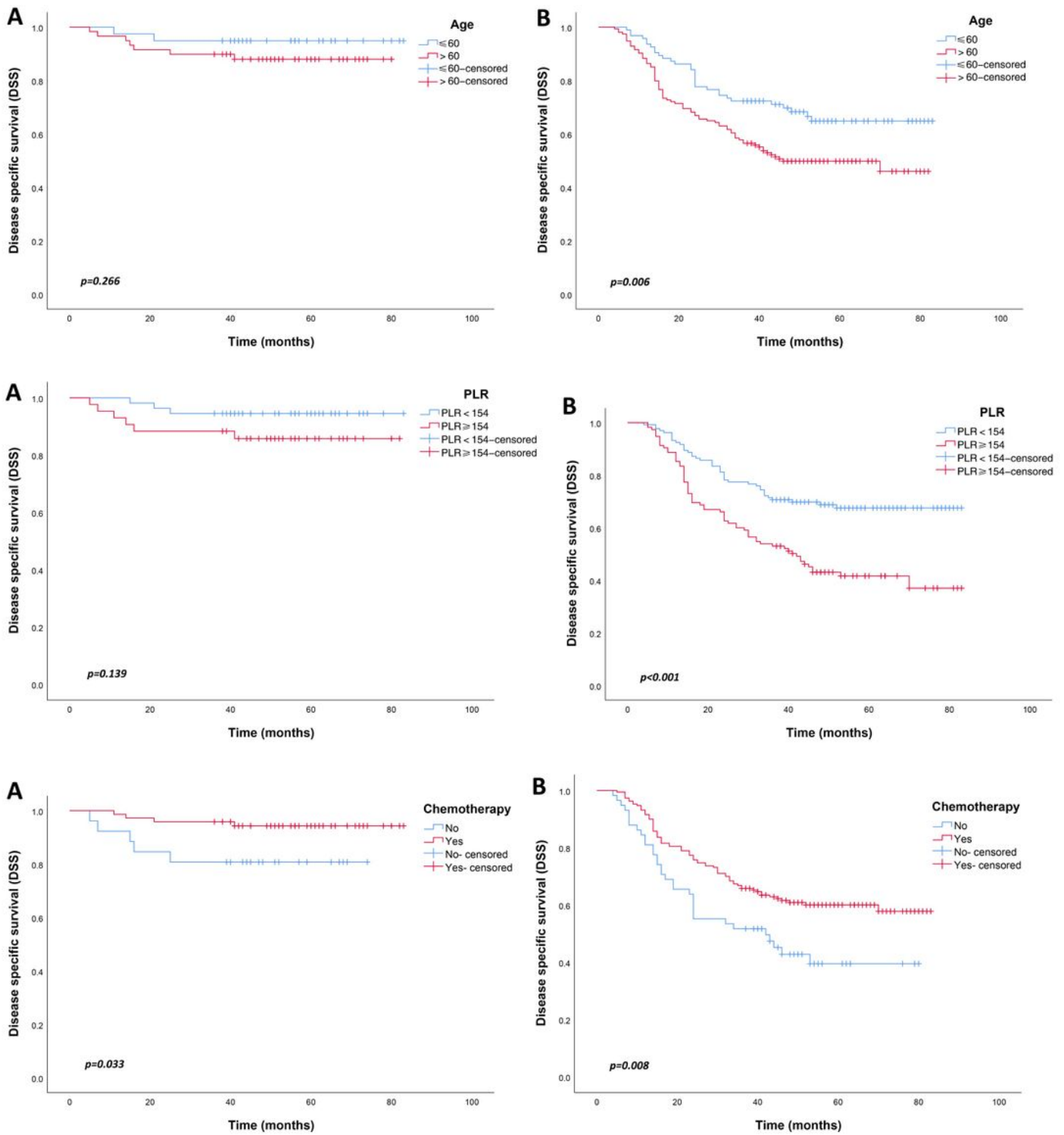
Figure 2

Disease-specific survival (DSS) of patients with advanced gastric cancer according to the risk factors. (A) stage II; (B) stage III.
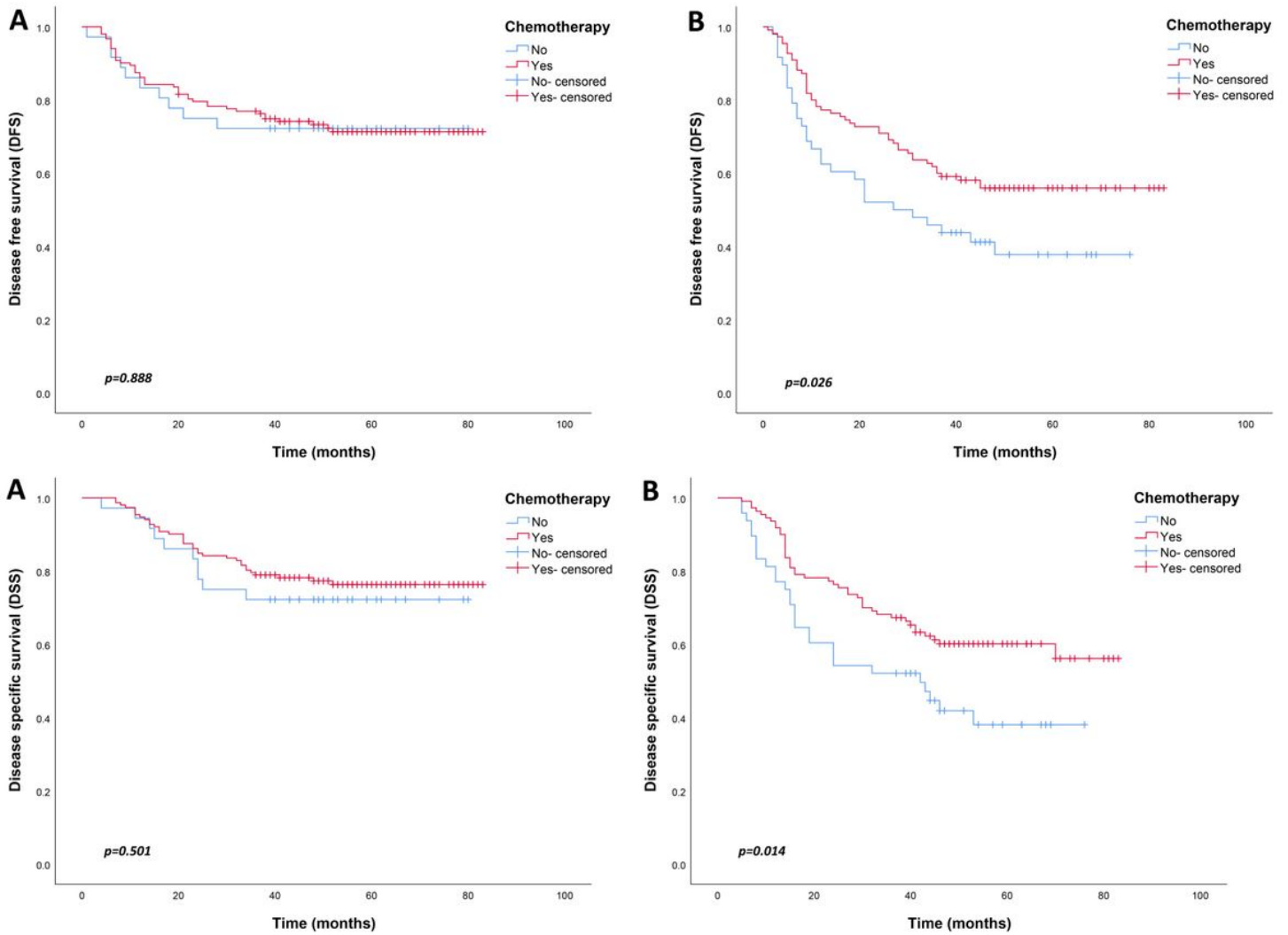
Figure 3

Comparison of survival curves between patients with or without chemotherapy in advanced gastric cancer. (A) PLR <154; (B) PLR ≥154.