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ORIGINAL RESEARCH

Prognostic values of preoperative platelet-to-lymphocyte ratio, albumin and hemoglobin in patients with non-metastatic colon cancer

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Purpose: Preoperative platelet-to-monocyte ratio (PLR), albumin and hemoglobin are suggested prognostic indicators in various malignancies. However, the prognostic values of PLR, albumin and hemoglobin remain elusive. The objective of the present study was to evaluate the prognostic values of PLR, albumin and hemoglobin in stage I-III colon cancer.

Patients and methods: A total of 312 patients with non-metastatic colon cancer undergoing curative resection were enrolled in this study. The prognostic values of PLR, albumin and hemoglobin were identified by receiver operating characteristics, and univariate and multivariate analyses.

Results: Univariate analysis revealed that preoperative PLR, albumin and hemoglobin were significantly associated with overall survival (OS) and that preoperative PLR and albumin were significantly associated with progression-free survival (PFS). Multivariate analysis revealed that preoperative PLR was significantly associated with OS.

Conclusion: Reduced preoperative PLR was significantly associated with better OS in patients with stage I-III colon cancer. Preoperative PLR was an independent prognostic indictor for OS in patients with colon cancer undergoing curative resection.

Keywords: platelet-to-lymphocyte ratio, albumin, hemoglobin, colon cancer, prognosis

Introduction

Colon cancer is one of the leading causes of cancer-related mortality worldwide, with increasing incidence and mortality.[1] Curative resection was the primary cure for non-metastatic colon cancer, and 5-year survival rates ranged from 44.3% to 93.2% depending on their risk of recurrence and metastasis.[2] Clinical stage and tumor differentiation are widely used to predict the clinical outcomes of colon cancer. However, a large proportion of the population with the same clinical stage and tumor differentiation exhibit different clinical outcomes. Therefore, additional prognostic indicators are needed to identify the high-risk subgroup and optimize therapeutic strategies for colon cancer.

Cumulative evidence supports that systemic inflammation is closely associated with tumorigenesis and tumor progression via the promotion of tumor proliferation, angiogenesis and migration.[3–5] Based on this theory, several biomarkers of systemic inflammation, such as neutrophil-to-lymphocyte ratio (NLR),[6] lymphocyte-to-monocyte ratio (LMR),[7] platelet-to-lymphocyte ratio (PLR),[8,9] albumin and hemoglobin, are associated with clinical outcomes. Because these biomarkers are easily obtained from preoperative routine examinations, they have attracted increasing attention. PLR was calculated as

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peripheral platelet count divided by lymphocyte count, which reflects the host immune response and tumor burden. Several studies demonstrated that PLR was significantly associated with clinical outcomes in various malignancies, such as breast cancer,[10] lung cancer,[11] and gastric cancer.[12] However, other studies did not support this conclusion.[13] Albumin is the most abundant plasma protein, and it plays an important role in maintaining colloid osmotic pressure. Decreased preoperative albumin levels are associated with clinical outcomes in various malignancies.[14] PLR, hemoglobin and albumin are potential prognostic indicators in various malignancies, but the prognostic values of these biomarkers were not well evaluated in patients with colon cancer undergoing curative resection.

Therefore, the objective of the present study was to evaluate the prognostic values of PLR, albumin and hemoglobin in stage I-III colon cancer and to identify an accurate prognostic indicator for the predicting of clinical outcomes and optimizing therapeutic strategies.

Patients and methods

Patients

We recruited a total of 312 patients who were diagnosed with colon cancer based on pathological examination at West China Hospital from February 2012 to March 2014. The Ethics Committee of West China Hospital of Sichuan University approved this study, and all patients signed an informed consent. This study was conducted in accordance with the Declaration of Helsinki. The present study used the following enrolment criteria: (1) all patients had non-metastatic disease; (2) all patients underwent curative resection; (3) patients did not receive preoperative antitumor treatment, such as chemotherapy or radiotherapy; (4) all patients had complete medical records and laboratory data; and (5) survival time exceeded 3 months. The following exclusion criteria were applied: (1) alive with a follow-up of <3 months; (2) medical history of haemopathy or synchronous malignancy; or (3) with metastasis, recurrent colon cancer, or multifocal lesions.

Methods

We retrospectively extracted clinical characteristics from medical records, such as age, gender, clinical stage, tumor location, differentiation, and medical history. Clinical stage was determined according to the 7th edition of the American Joint Committee on Cancer (AJCC) staging system. Preoperative routine examination, including platelet count, lymphocyte count, albumin and hemoglobin, were performed within one week before curative resection. PLR was calculated as peripheral absolute platelet count divided by absolute lymphocyte count. All patients were regularly followed up at the first month after surgery, every 3 months during the following 3 years, and every 6 months in subsequent years. Overall survival (OS) was calculated from the date of surgery to the date of death by any cause. Progression-free survival (PFS) was calculated from the date of surgery to the date of recurrence or metastasis. The last follow-up date was the end of October 2017.

Statistical analysis

We used SPSS 19.0 software (SPSS, Inc., Chicago, IL, USA) to perform all statistical analyses. A two-sided *P*-value less than 0.05 was considered statistically significant. Categorical variable data were presented as a frequency or rate. Continuous variable data were presented as the median with quartile range or the mean with 95% confidence interval (CI). Receiver operating characteristic (ROC) curve analysis was performed to quantify the area under the ROC curve (AUC). An independent-samples *t*-test or a nonparametric test was performed to compare continuous variables between different groups. The chi-square test was performed to compare categorical data. The Kaplan–Meier method with a log-rank test was used to perform univariate analysis. The hazard ratio (HR) and 95% CI estimated from the multivariate Cox analysis were reported.

Results

A series of 312 patients were enrolled in the present study. Baseline characteristics of all patients are presented in Table 1. There were 176 (56.4%) males and 136 (43.6%) females, with a median age of 62 years (range 19–94). The median follow-up period was 49 months (range 4–69). The mean values of preoperative PLR, albumin and hemoglobin were 158.4 (119.5–220.4), 38.9 (35.6–42.3) and 111.0 (85.0–129.0), respectively. During the follow-up period, 42 (13.5%) patients died, and 48 (15.4%) patients experienced tumor recurrence. The one-, three- and five-year OS rates of the 312 patients were 97.4%, 91.9% and 86.5%, respectively. The one-, three- and five-year PFS rates of 312 patients were 94.2%, 85.9% and 84.6%, respectively.

ROC curves were performed to evaluate the clinical utilities of PLR, albumin and hemoglobin. The AUC for OS in PLR, albumin and hemoglobin was 0.628 (*P*=0.008), 0.644 (*P*=0.003) and 0.629 (*P*=0.007), respectively (Figure 1). The AUC for PFS in PLR, albumin and hemoglobin was 0.570 (*P*=0.121), 0.611 (*P*=0.015) and 0.575 (*P*=0.099), respectively (Figure 2).

Table 1 Baseline characteristics of patients with colon cancer

Variable	PLR			Hemoglobin (g/L)			Albumin (g/L)		
	<260	≥260	*P*-value	<100	≥100	*P*-value	<38	≥38	*P*-value
Age (years)			0.408			0.509			0.000
<60	109	20		46	83		40	89	
≥60	148	35		72	111		95	88	
Gender			0.544			0.918			0.512
Male	147	29		67	109		79	97	
Female	110	26		51	85		56	80	
CEA (U/mL)	2.82	4.32		3.42	2.93		4.13	2.79	
CA199 (U/mL)	13.57	15.58		13.37	13.85		13.98	13.57	
CA125 (U/mL)	13.44	18.44		14.87	13.81		17.60	12.97	
Tumor location			0.005			0.000			0.005
Right colon	139	41		94	86		90	90	
Left colon	118	14		24	108		45	87	
Tumor invasion depth			0.013			0.016			0.102
T1+T2	35	1		7	29		11	25	
T3+T4	222	54		111	165		125	152	
Lymph involvement			0.119			0.065			0.583
No	186	34		76	144		93	127	
Yes	71	21		42	50		42	50	
Clinical stage			0.119			0.065			0.583
I+II	186	34		76	144		93	127	
II	71	21		42	50		42	50	
Tumor grade			0.005			0.025			0.005
Low	76	27		48	55		56	47	
Middle, high	181	28		70	139		79	130	
Hypertension			0.595			0.838			0.059
No	207	46		95	158		103	150	
Yes	50	9		23	36		32	27	
Diabetes mellitus			0.975			0.561			0.370
No	238	51		108	181		123	166	
Yes	19	4		10	13		12	11	

Abbreviations: CEA, carcino-embryonic antigen; PLR, platelet-to-lymphocyte ratio.

The optimal cut-off level was calculated as the maximal Youden Index for OS. The respective cut-off levels of PLR, albumin and hemoglobin were 260, 38 and 100. PLR was decreased in 257 patients (82.4%) and increased in 55 patients (17.6%). Albumin was decreased in 135 patients (43.3%) and increased in 177 patients (56.7%). Hemoglobin was decreased in 118 patients (37.8%) and increased in 194 patients (62.2%). Patients in the decreased PLR group had significantly better OS and PFS than those in the increased PLR group (Figure 3A, B). Patients in the increased albumin group had significantly better OS and PFS than those in the decreased albumin group (Figure 3C,D). Patients in the increased hemoglobin group had significantly better OS than those in the decreased hemoglobin group (Figure 3E,F). We also performed subgroup analyses on the basis of clinical stage to evaluate the prognostic values of PLR, albumin and hemoglobin. Statistically significant differences in the stage I-II group were found in albumin for OS and in PLR for OS and PFS. (Figure 4A-L)

Univariate analysis demonstrated that tumor location, differentiation, lymph node involvement, clinical stage, diabetes mellitus, PLR, albumin and hemoglobin were significantly associated with OS. Only clinical stage was entered into the multivariate analysis because clinical stage is derived from tumor invasion depth and lymph node

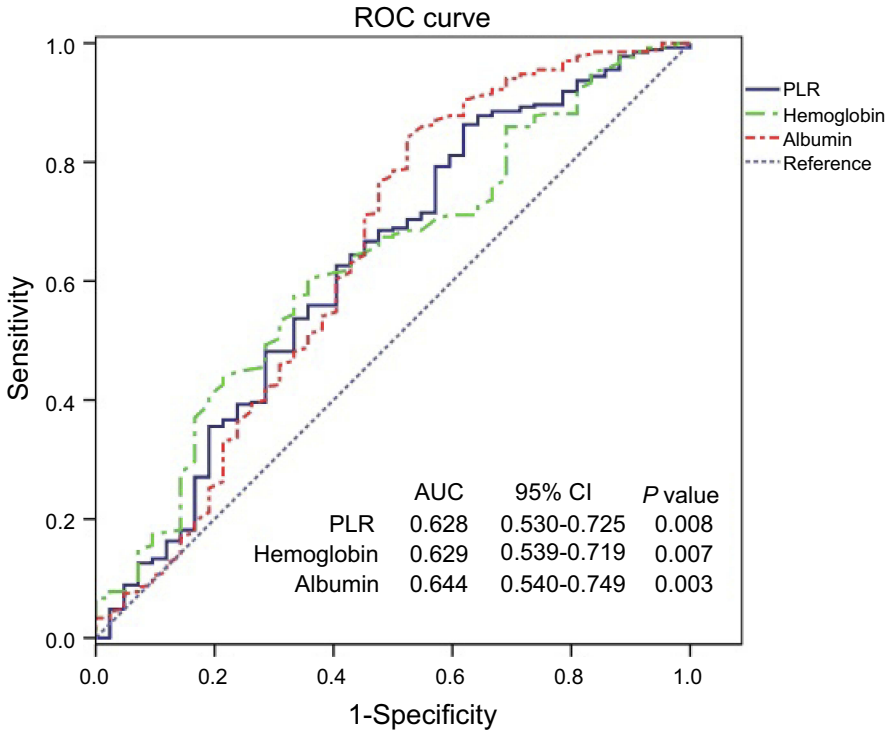

Figure 1 ROC curves for preoperative PLR, hemoglobin and albumin according to OS.
Abbreviations: AUC, area under the ROC curve; ROC, receiver operating characteristics; PLR, platelet-to-lymphocyte ratio; OS, overall survival.

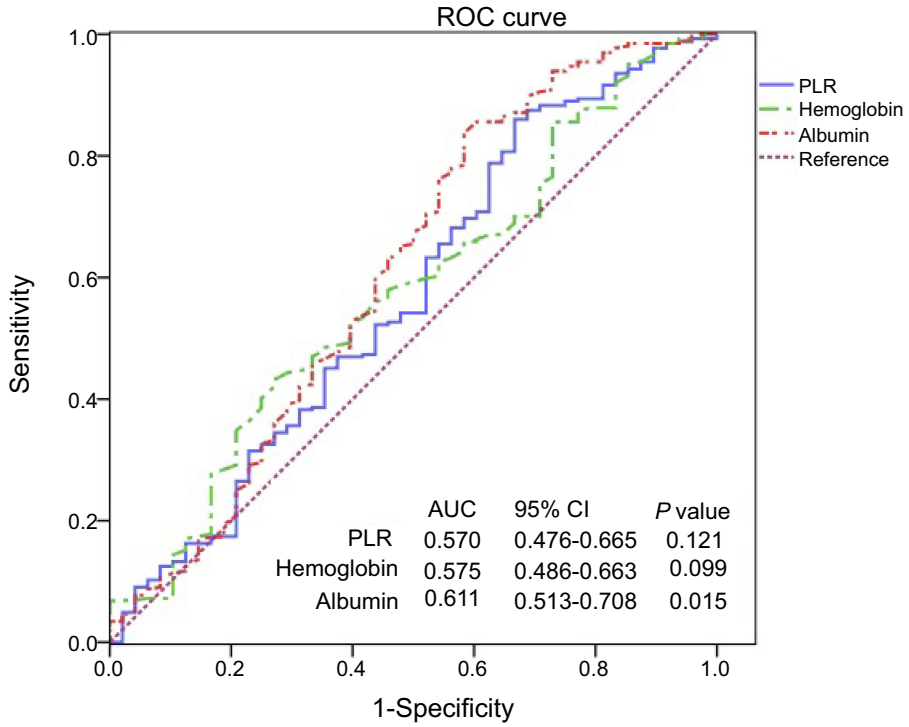

Figure 2 ROC curves for preoperative PLR, hemoglobin and albumin according to PFS.
Abbreviations: AUC, area under the ROC curve; ROC, receiver operating characteristics; PLR, platelet-to-lymphocyte ratio; PFS, progression-free survival.

involvement. Multivariate analysis demonstrated that tumor differentiation (HR, 0.439; 95% CI: 0.234-0.822, *P*=0.010), clinical stage (HR, 2.229; 95% CI: 1.189-4.178, *P*=0.012), diabetes mellitus (HR, 2.500; 95% CI: 1.075-5.815, *P*=0.033) and PLR (HR, 0.446; 95% CI: 0.229-0.870, *P*=0.018) were all independent prognostic indicators for

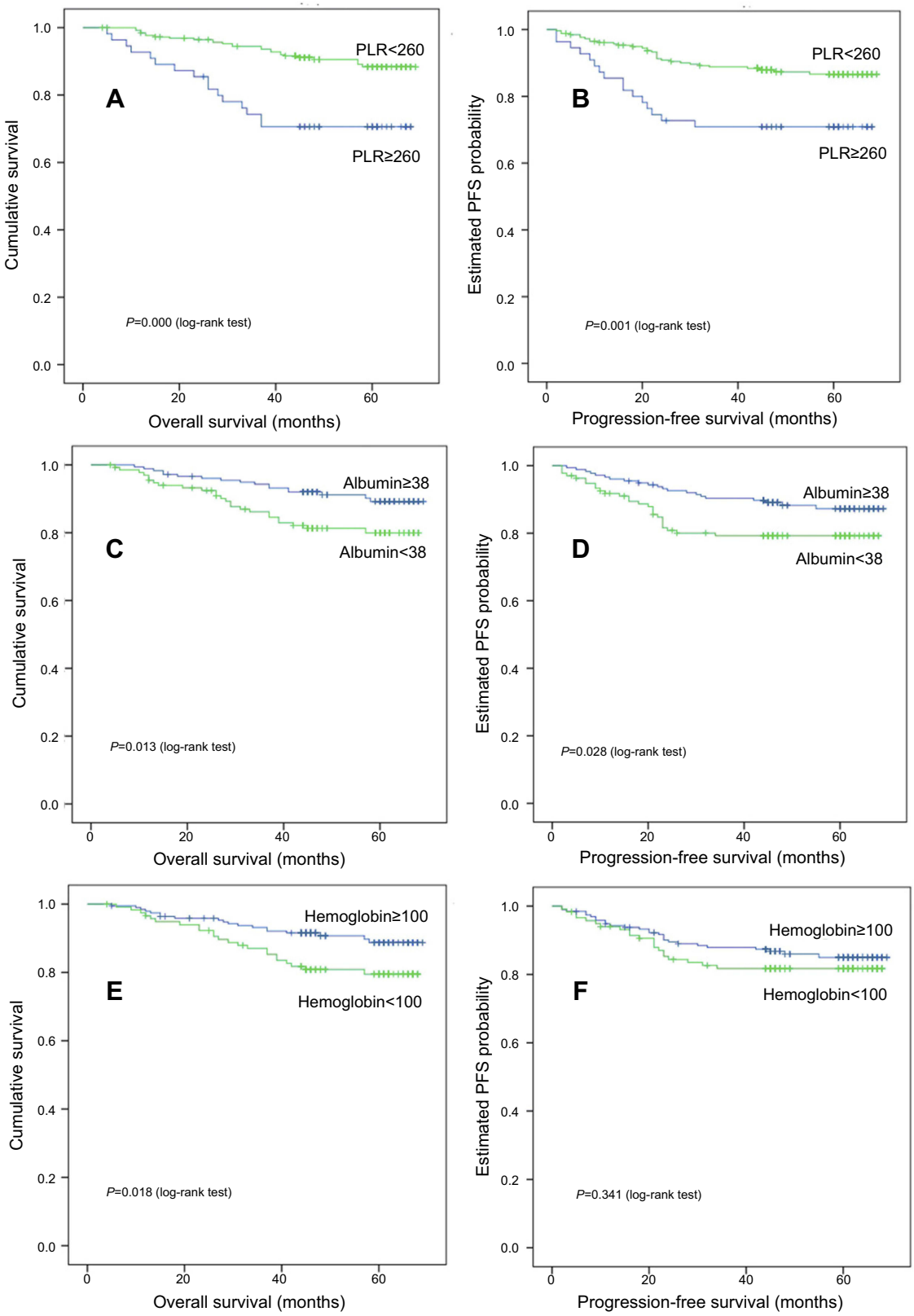

Figure 3 Kaplan-Meier curves of PLR, albumin and hemoglobin according to overall survival and progression-free survival.(**A** and **B**) are the survival curves of PLR for overall survival and progression-free survival; (**C** and **D**) are the survival curves of albumin for overall survival and progression-free survival; (**E** and **F**) are the survival curves of hemoglobin for overall survival and progression-free survival.

Abbreviation: PLR, platelet-to-lymphocyte ratio.

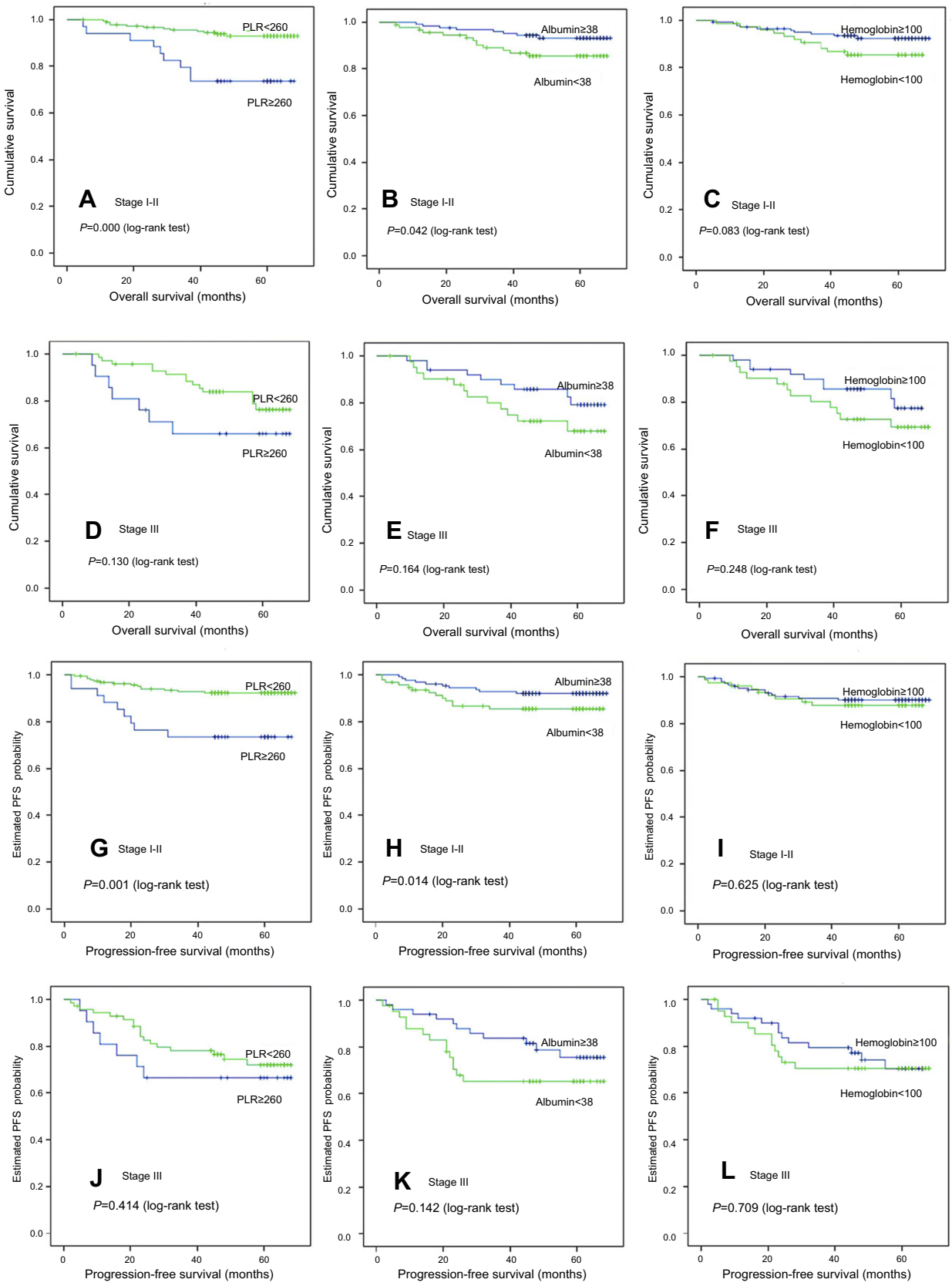

Figure 4 Kaplan-Meier curves of PLR, albumin and hemoglobin according to clinical stage.(**A, B** and **C**) are the survival curves of PLR, albumin and hemoglobin for overall survival in stage I-II; (**D, E** and **F**) are the survival curves of PLR, albumin and hemoglobin for overall survival in stage III; (**G, H** and **I**) are the survival curves of PLR, albumin and hemoglobin for progression-free survival in stage I-II; (**J, K** and **L**) are the survival curves of PLR, albumin and hemoglobin for progression-free survival in stage III.
Abbreviation: PLR, platelet-to-lymphocyte ratio.

OS (Table 2). Similarly, univariate analysis demonstrated that tumor differentiation, lymph node involvement, clinical stage, diabetes mellitus, PLR and albumin were significantly associated with PFS. Multivariate analysis demonstrated that tumor differentiation (HR, 0.445; 95% CI: 0.249-0.798, *P*=0.007) and clinical stage (HR, 2.375; 95% CI: 1.331-4.237, *P*=0.003) were also defined as independent prognostic indicators for PFS. (Table 3)

Discussion

It is well known that the tumor microenvironment, including inflammatory cells and host immune cells, are significantly associated with tumor progression. Circulating inflammatory immune cells, serum albumin and hemoglobin are considered potential prognostic indicators for predicting clinical outcomes of various malignancies. The inflammatory status of the tumor microenvironment is easily measured by using peripheral blood biomarkers. Therefore, peripheral blood biomarkers, such as PLR, albumin and hemoglobin, were considered useful prognostic indicators for clinical outcomes. Several studies have discussed the relationship between systemic inflammation and clinical outcomes, but these results were inconclusive in various malignancies.[15–17]

In the present study, we evaluated the prognostic values of PLR, albumin and hemoglobin in colon cancer, which extends and refines the relationship between peripheral blood biomarkers and clinical outcomes. We identified several clinicopathological features, such as tumor differentiation, clinical stage and diabetes mellitus, that affected clinical outcomes. Our results revealed that increased preoperative PLR was significantly associated with poor OS, which is an independent prognostic indicator for OS in colon cancer. Notably, PLR, albumin and hemoglobin did not correlate with PFS in multivariate analysis.

Several studies have demonstrated the prognostic value of PLR on survival for colorectal cancer and other tumors. Bailon-Cuadrado et al[18] examined 201 patients with colon

Table 2 Univariate and multivariate analyses of prognostic factors for overall survival

Variables		Univariate analysis	Multivariate analysis	
		P-value	HR (95% CI)	*P*-value
Age (years)	<60	0.128		
	≥60			
Gender	Male	0.411		
	Female			
Tumor location	Right colon	0.045	1	0.106
	Left colon		0.563(0.280–1.130)	
Differentiation	Low	0.000	1	0.010
	Middle, high		0.439(0.234–0.822)	
Tumor invasion depth	T1 + T2	0.152		
	T3+T4			
Lymph node involvement	No	0.002		
	Yes			
Clinical stage	I+II	0.002	1	0.012
	III		2.229(1.189–4.178)	
Hypertension	No	0.142		
	Yes			
Diabetes mellitus	No	0.012	1	0.033
	Yes		2.500(1.075–5.815)	
Adjuvant chemotherapy	Yes	0.779		
	No			
PLR	≥260	0.000	1	0.018
	<260		0.446(0.229–0.870)	
Hemoglobin (g/L)	≥100	0.018	1	0.845
	<100		1.070(0.540–2.121)	
Albumin (g/L)	≥38	0.013	1	0.277
	<38		1.450(0.742–2.835)	

Abbreviation: PLR, platelet-to-lymphocyte ratio.

Table 3 Univariate and multivariate analyses of prognostic factors for progression-free survival

Variables		Univariate analysis	Multivariate analysis	
		P-value	HR (95% CI)	*P*-value
Age (years)	<60	0.059		
	≥60			
Gender	Male	0.530		
	Female			
Tumor location	Right colon	0.278		
	Left colon			
Differentiation	Low	0.000	1	0.007
	Middle, high		0.445(0.249–0.798)	
Tumor invasion depth	T1 + T2	0.091		
	T3+T4			
Lymph node involvement	No	0.000		
	Yes			
Clinical stage	I+II	0.000	1	0.003
	III		2.375(1.331–4.237)	
Hypertension	No	0.097		
	Yes			
Diabetes mellitus	No	0.027	1	0.096
	Yes		2.007(0.883–4.562)	
Adjuvant chemotherapy	Yes	0.534		
	No			
PLR	≥260	0.001	1	0.066
	<260		0.552(0.293–1.040)	
Hemoglobin (g/L)	≥100	0.341		
	<100			
Albumin (g/L)	≥38	0.028	1	0.283
	<38		1.388(0.762–2.528)	

Abbreviation:PLR, platelet-to-lymphocyte ratio.

cancer who underwent curative resection and reported that increased PLR was negatively associated with OS and PFS. Peng et al[19] performed a meta-analysis of 3542 patients with colorectal cancer and reported that increased PLR was significantly associated with poor OS and PFS. Portale et al[13] investigated 152 patients with rectal cancer undergoing curative resection and reported that PLR was not an independent prognostic indicator. Chen et al[12] examined 1080 patients with gastric cancer and reported that increased PLR was significantly associated with peritoneal metastasis. Our results support PLR an independent prognostic indicator for OS.

The exact mechanism of the relationship between systemic inflammation and tumor progression is not fully understood. The following theories contribute to the interpretation of the relationship. Platelets play an important role in tumor progression via the promotion of tumor proliferation, angiogenesis, degradation of the extracellular matrix and the release of vascular endothelial growth factors,[11,20,21] and these cells protect tumor cells from cytolysis and promote metastasis.[22] Anti-platelet drugs inhibit the invasiveness of tumor cells by decreasing metalloproteinase-9 secretion.[23] In addition, the tumor microenvironment releases proinflammatory mediators, including IL-1, IL-3 and IL-6, which promote the proliferation of megakaryocytes.[24] Megakaryocytes are platelet progenitor cells, which indicates that thrombocytosis reflects the status of systemic inflammation in the tumor microenvironment. Lymphocytes inhibit tumor proliferation and metastasis by enhancing cytotoxic cell death and cytokine production.[25] Peripheral lymphocytopenia is marked by a decrease in $CD4^+$ helper lymphocytes and an increase in $CD8^+$ suppressor lymphocytes,[26] which may lead to the insufficient immunological response and contribute to poor clinical outcomes after curative resection.

Malnutrition is significantly associated with increased postoperative morbidity and mortality.[27] Malnutrition, which is partially mirrored by hypoalbuminemia, is involved in antitumor therapy and the host

immune response. Serum albumin produced in the liver is the most abundant blood plasma protein, and it is often used to assess a patient's nutritional status. Many studies have combined systemic inflammatory indicators and albumin to create new prognostic indicators, such as the prognostic nutritional index, the albumin-to-fibrinogen ratio,[28] and the C-reactive protein-to-albumin ratio.[29] These prognostic indicators are associated with clinical outcomes. Serum albumin is one of the most important indicators of nutritional status, and it is an independent prognostic indicator in various malignancies, such as gastric cancer,[30] colorectal cancer,[31] breast cancer,[32] ovarian cancer[33] and cervical cancer.[34] Hemoglobin is a clinical characteristic that is a prognostic indicator in various malignancies, such as anal cancer[35] and head and neck cancer.[36,37] It was hypothesized that anaemia may enhance tumor hypoxia and increase tumor cell resistance to therapy to promote distant metastasis.[35–37] Franco et al reported that preoperative hemoglobin level was an independent prognostic indicator for OS, but not PFS.[35] Our results of the multivariate analyses did not reveal albumin or hemoglobin as independent prognostic indicators for OS or PFS. Our results are likely true and reliable based on our sample size of 300 patients who were only diagnosed with colon cancer.

It must be acknowledged that there were several limitations in the present study that should be considered. First, this study was a retrospective observational study in a single institution, and selection bias cannot be fully excluded. Second, the sample size was relatively small, and the results may not be generalized. Third, we used the same cut-off levels for both OS and PFS to simplify the calculation, which may be less powerful than the use of respective cut-off levels. Fourth, several factors, such as vascular invasion, perineural invasion and microsatellite instability, were also reported as prognostic indicators. These factors were not evaluated in our study because of a deficiency of the abovementioned data. Therefore, our results should be carefully interpreted.

Conclusion

In conclusion, we identified preoperative PLR as an independent prognostic indicator for OS in patients with stage I-III colon cancer who underwent curative resection. Decreased preoperative PLR was significantly associated with better OS. Nevertheless, large-scale, better-designed studies are needed to evaluate the prognostic indicators and elucidate the exact mechanisms of systemic inflammation, nutrition status and clinical outcome.

Author contributions

ZGL, YZ and ZFX designed the study and wrote the manuscript. ZGL, YQH, YPC and RZ retrieved data from the database. XTW interpreted the data and proofread the final version. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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