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The Value of the C-Reactive Protein-to-Lymphocyte Ratio for Predicting Lymphovascular Invasion Based on Nutritional Status in Gastric Cancer

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Abstract

Preoperative nutrition and inflammation are closely related to tumors (T). Many hematological marker assessment tools comprise nutritional and systemic inflammatory indexes, evaluating essential factors for cancer nutrition, growth, and progression. This study retrospectively investigated whether the C-reactive protein (CRP)-to-lymphocyte ratio (CLR) could predict lymphovascular invasion (LVI) in gastric cancer (GC) patients based on their nutritional status. We included 262 patients who underwent GC surgery between 2019 and 2020. The patient's nutritional status was assessed using the Patient-Generated Subjective Global Assessment (PG-SCA), and patients with scores $\geq$4 were classified as malnourished. First, we examined 7 hematological marker combinations using receiver operating characteristic (ROC) curves to determine which one best predicted malnutrition. The CLR predicted malnutrition more accurately than other ratios (area under the curve: 0.62, 95% confidence interval [CI]: 0.55-0.69, $P = .002$); the optimal cut-off value for malnutrition was 1.04. Next, we evaluated the relationship between the 7 combinations and postoperative LVI. A CLR higher than 1.04 (odds ratio [OR]: 1.81, 95% CI: 1.09-3.00, $P = .021$) and a platelet-to-lymphocyte ratio (PLR) higher than 129.00 (OR: 1.64, 95% CI: 1.00-2.67, $P = .049$) were associated with LVI in the univariate analysis, and the CLR was an independent predictor of LVI in the multivariate analysis (OR: 1.73, 95% CI: 1.04-2.87, $P = .036$). The preoperative CLR can assess nutritional status and independently predict LVI in GC.

Keywords

inflammation mediators, preoperative care, stomach neoplasms, nutritional assessment, hematologic tests

Abbreviations

Alb, albumin; CAR, C-reactive protein-to-albumin ratio; CI, confidence interval; CLR, C-reactive protein-to-lymphocyte ratio; CRP, C-reactive protein; GC, gastric cancer; HALP, hemoglobin, albumin, lymphocyte, and platelet; LVI, lymphovascular invasion; N, node; NAR, neutrophil-to-albumin ratio; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; PAR, platelet-to-albumin ratio; PG-SGA, Patient-Generated Subjective Global Assessment; PLR, platelet-to-lymphocyte ratio; PNI, perineural invasion; ROC, receiver operating characteristic; T, tumor; TNM, tumor, node, metastasis

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Introduction

Gastric cancer (GC) is the fifth most diagnosed cancer and the third leading cause of cancer deaths worldwide.[1] Patients with GC often suffer from malnutrition, which is associated with age, tumor location, tumor (T) and node (N) stages, and the overall tumor, node, metastasis (TNM) stage.[2–4] A patient's nutritional status is also associated with the T stage, postoperative complications, and gastrointestinal cancer.[5–7] The TNM system is a prognostic indicator to guide clinical treatment. In addition, lymphovascular invasion (LVI) is a GC prognostic indicator, identifying GC with high recurrence risk.[8] Thus,

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accurate LVI evaluations are critical, especially before surgery. However, preoperative evaluations are challenging.

A patient's nutritional status and the inflammatory response to cancer have been widely studied. Malnutrition correlates with immune suppression and systemic inflammation. However, it is unclear if inflammation is a cause or result of cancer; in other words, does cancer itself or the anticancer treatment induce inflammation?[9] Regardless, inflammation affects tumor recurrence, progression, and metastasis.[10] Several combinations of hematological markers comprising nutritional and systemic inflammatory indexes have been developed, such as the hemoglobin, albumin, lymphocyte, and platelet (HALP) combination. Many studies have explored their preoperative prognostic value for various cancers, including GC.[11] Other hematological marker combinations include the neutrophil-to-lymphocyte ratio (NLR),[12] the platelet-to-lymphocyte ratio (PLR),[13] the C-reactive protein (CRP)-to-lymphocyte ratio (CLR),[14] the CRP-to-albumin ratio (CAR),[15] the platelet-to-albumin ratio (PAR),[16] and the neutrophil-to-albumin ratio (NAR).[17] Several markers have also been correlated with the T stage and peritoneal metastasis.[18,19]

This study retrospectively investigated patients with GC to determine if the CLR could predict LVI based on the nutritional status.

Materials and Methods

We retrospectively identified patients with GC who underwent curative gastrectomy in our hospital between January 2019 and January 2020. We excluded patients suffering from other malignancies, autoimmune diseases, chronic renal disease, thyroid disorders, and infectious diseases. The postoperative pathology was determined based on the eighth edition of the American Joint Committee on Cancer/Union for International Cancer Control Staging System.[20] This study followed relevant Equator guidelines.[21] All participants provided written informed consent, and an independent ethics committee approved the study.

We used the Patient-Generated Subjective Global Assessment (PG-SGA) to determine each patient's nutritional status. Patients were classified as malnourished if the PG-SGA score was $\geq$4. Before surgery, peripheral blood was collected to analyze hemoglobin, albumin (Alb), lymphocyte, platelet, neutrophil, and CRP levels. We examined the following hematological markers combinations: HALP, NLR, PLR, CLR, CAR, PAR, and NAR. HALP was calculated as: [the hemoglobin level (g/L) $\times$ the Alb level (g/L) $\times$ the lymphocyte count (/L)/platelet count (/L)].[22] NLR was calculated as the neutrophil count (/L) divided by the lymphocyte count (/L), PLR was calculated as the platelet count (/L) divided by the lymphocyte count (/L), and CLR was calculated as the CRP level (mg/L) divided by the lymphocyte count (/L). Furthermore, CAR was calculated as the CRP level (mg/L) divided by the Alb level (g/L), PAR was calculated as the platelet count (/L) divided by the Alb level (g/L), and NAR was calculated as the neutrophil count (/L)divided by the Alb level (g/L). LVI was defined as tumor cell invasion into the vascular wall or tumor emboli in the vascular endothelium. Hematoxylin and eosin staining was performed to evaluate venous invasion. Immunohistochemistry staining for D2-0 was performed using a mouse monoclonal antibody against human lymphatic endothelium antigen to evaluate lymphatic invasion. For this study, samples without lymphatic and venous invasion were classified as LVI negative, and samples with lymphatic or venous invasion were classified as LVI positive.

Statistical analyses were performed using SPSS 20.0 software (IBM Corp.). The Youden index was calculated using a receiver operating characteristic (ROC) analysis to determine the optimal cut-off for preoperative inflammatory markers in malnutrition analyses. The Mann–Whitney U test was used to evaluate the age differences between the groups. The chi-square test was used to analyze the categorized data. We performed univariate analyses using gender, HALP, NLR, PLR, CAR, PAR, NAR, CLR, the Alb level ($\leq$39.93 g/L or >39.93), the platelet count (>199.60×10^9/L or $\leq 199.60 \times 10^9$/L), and the neutrophil count (>3.50×10^9/L or $\leq 3.50 \times 10^9$/L). The multivariate logistic regression analysis included significant variables ($P < .05$) from the univariate analyses. A two-sided P value of <.05 was considered statistically significant.

Results

Clinicopathological Characteristics

Table 1 details the patient's clinical characteristics. We enrolled 262 patients who underwent resection for GC; 188 were men, and 74 were women. The median age was 61.5 (range: 26-80) years, and 171 patients were malnourished. The wall invasion depth of the tumor was pathologically assessed as T1, T2, T3, and T4 in 49 (18.7%), 32 (12.2%), 18 (6.9%), and 163 (62.2%) patients, respectively. Furthermore, 173 patients had a positive nodal status (66.0%).

Table 1. Patient Characteristics.

Features	n = 262
Age [year, median (range)]	61.5 (26-80)
Gender, n(%)	
Male	188 (71.8)
Female	74 (28.2)
Nutritional status, n(%)	
Malnourished (PG-SGA score $\geq$4)	171 (65.3)
Not malnourished (PG-SGA score <4)	91 (34.7)
Open surgery type, n(%)	
Total gastrectomy	109 (41.6)
Distal gastrectomy	135 (51.5)
Proximal gastrectomy	18 (6.9)
Tumor (T) stage, n(%)	
T1	49 (18.7)
T2	32 (12.2)
T3	18 (6.9)
T4	163 (62.2)
Node (N) stage, n(%)	
N0	89 (34.0)
N1	63 (24.0)
N2	53 (20.2)
N3	57 (21.8)

Abbreviation: PG-SGA, patient-generated subjective global assessment.

Table 2. Receiver Operating Characteristic (ROC) Curve Analyses of Hematological Marker Combinations.

Test	AUC	95% confidence interval (CI)	*P* value
HALP	0.37	0.30 to 0.44	.001
NLR	0.54	0.46 to 0.61	.348
PLR	0.58	0.51 to 0.66	.027
CAR	0.61	0.54 to 0.68	.003
CLR	0.62	0.55 to 0.69	.002
PAR	0.56	0.49 to 0.63	.106
NAR	0.51	0.44 to 0.59	.701

Abbreviations: AUC, area under the curve; CAR, C-reactive protein-to-albumin ratio; CLR, C-reactive protein–to-lymphocyte ratio; HALP, hemoglobin, albumin, lymphocyte, and platelet; NAR: neutrophil-to-albumin ratio; NLR, neutrophil-to-lymphocyte ratio; PAR: platelet-to-albumin ratio; PLR, platelet-to-lymphocyte ratio.

Hematological Markers for Malnutrition

Table 2 presents the ROC analysis results for the hematological marker combinations. HALP ($P = .001$), PLR ($P = .027$), CAR ($P = .003$), and CLR ($P = .002$) were accurate malnutrition assessment tools. However, CLR more accurately assessed malnutrition than the other markers (area under the curve: 0.62, 95% confidence interval [CI]: 0.55-0.69; Figure 1). The CLR cut-off value was 1.04, and the sensitivity and specificity were 70.8% and 56.0%, respectively, for predicting malnutrition when the value was above the cut-off.

Relationships Between CLR and Clinical Features

In total, 161 patients (121 men and 40 women) had a high CLR value (CLR >1.04). The CAR value ($P = .000$), T stage ($P = .050$), and LVI ($P = .021$) significantly differed between the high and low CLR groups (Table 3).

A High CLR Value is Associated with LVI

Table 4 presents the results of the univariate and multivariate logistic regression analyses for LVI predictors. The univariate analysis identified a PLR value of >129.00 (odds ratio [OR]: 1.64, 95% CI: 1.00-2.67, $P = .049$) and a CLR value of >1.04 (OR: 1.81, 95% CI: 1.09-3.00, $P = .021$) as significant variables. The multivariate analysis identified a CLR value >1.04

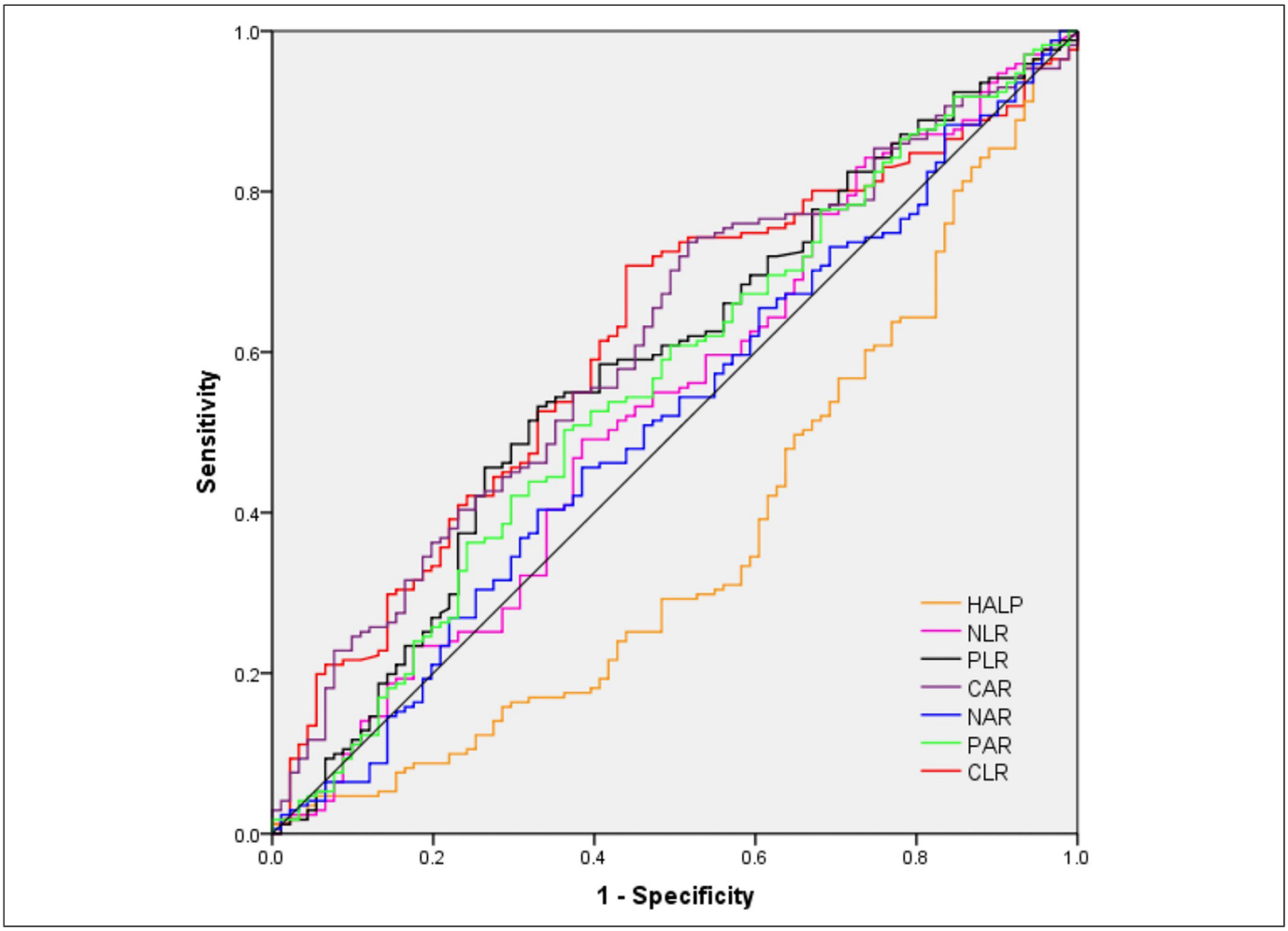

Figure 1. Receiver operating characteristic (ROC) curves for malnutrition using 7 hematological marker combinations.

Table 3. Clinicopathological Characteristic Comparisons Based on the C-Reactive Protein-to-Lymphocyte Ratio (CLR).

Variable	CLR>1.04	CLR≤1.04	*P* value
Age [year, median(range)]	61 (30-80)	62 (26-80)	.774
Gender(n)			.123
Male	121	67	
Female	40	34	
NLR (n)			.056
>2.17	80	38	
≤2.17	81	63	
CAR (n)			.000*
>0.04	158	15	
≤0.04	3	86	
Tumor (T) location (n)			.159
Lower 1/3	50	27	
Middle 1/3	11	14	
Upper 1/3	100	60	
Tumor stage (n)			.050*
T1	27	22	
T2	14	18	
T3	10	8	
T4	110	53	
Node (N) stage (n)			.223
N0	47	42	
N1	41	22	
N2	36	17	
N3	37	20	
LVI (n)			.021*
Positive	89	41	
Negative	72	60	
PNI (n)			.125
Positive	89	46	
Negative	72	55	
Complications (n)			
Pneumonia	14	12	.401
Abdominal infection	7	5	1.000
Lymphorrhagia	1	1	1.000
Anastomotic leakage	3	2	1.000

*Indicates statistical significance (chi-squared test).
Abbreviations: CAR, C-reactive protein-to-albumin ratio; HALP, hemoglobin, albumin, lymphocyte, and platelet; NAR, neutrophil-to-albumin ratio; NLR, neutrophil-to-lymphocyte ratio; LVI, lymphovascular invasion; PAR, platelet-to-albumin ratio; PLR, platelet-to-lymphocyte ratio; PNI, perineural invasion.

as an independent predictor for LVI (OR: 1.73, 95% CI: 1.04-2.87, $P = .036$).

Discussion

Malnutrition and an increased inflammatory response are common in patients with GC. Therefore, malnutrition and inflammatory response markers are recommended for predicting the T stage, metastasis, and prognosis.[10] Furthermore, hematological marker combinations represent a patient's nutritional status and inflammatory condition. This study retrospectively constructed a pathological model based on malnutrition using 7 inflammatory marker combinations, including HALP, NLR, PLR, CAR, PAR, CLR, and NAR. We found that CLR was the most accurate ratio for predicting malnutrition (Table 2).

Previous studies have found significant correlations between CLR and the nutritional status. Okugawa Y et al[23] investigated correlations between CLR and various nutritional markers in 551 GC patients who underwent gastrectomy. They reported that the preoperative CLR value positively correlated with preoperative perineural invasion (PNI) and the Alb level with high collinearity (PNI: $P < .001$, $R = 0.31$; Alb: $P < .001$, $R = 0.55$). Our study found a significant association between the CLR value and the nutritional status, but the sensitivity was 70.8%, and the specificity was 56.0%. This result could be because the combination marker only includes 1 nutritional index, which is not an overall reflection of the body's nutritional status. However, some studies suggest a close relationship between inflammation and nutritional status. We found that the optimal CLR cut-off value for malnutrition was 1.04.

The lymphocyte count is used as a nutritional evaluation index in the clinic. Leandro-Merhi et al[24] reported associations between the total lymphocyte count and nutritional risk and triceps skinfold thickness by multiple linear regression analyses. Numerous studies have also confirmed that quality preoperative nutrition significantly improves the nutritional and immune status, reducing postoperative complications and accelerating recovery.

The combinational markers comprise the systemic inflammatory and nutritional indexes, expanding the breadth but weakening the depth of the nutritional status. Therefore, we selected novel combinational markers based on the nutritional status. The CLR value is not the best predictor of malnutrition, but it can provide clinical guidance. Therefore, CLR may be useful to preliminarily identify malnutrition and guide nutritional intervention.

CLR, calculated as the CRP level divided by the lymphocyte count, is significantly related to prognosis in digestive cancers.[25,26] Inflammation was classified as a hallmark of cancer in 2011.[27] Thus, cancer-related inflammation affects tumor cell proliferation, invasion, and metastasis. CRP secreted from the liver is a positive acute-phase protein, and the CRP level regulated by interleukin-6 reflects the systemic inflammatory response level. The CRP level is also associated with the TNM stage and tumor recurrence.[28] Moreover, lymphocytes play an essential role in the host's cytotoxic immune response. Some studies found that the lymphocyte count was significantly associated with the T stage in GC ($P = .032$).[18] Angin et al[29] showed that the CLR value in stage T4 was higher than in other stages ($P = .025$). A significant negative relationship was also found between CLR and the N stage ($R = -0.500$, $P < .001$). Okugawa et al[23] reported a significant association between high preoperative CLR and an advanced T stage, venous invasion, and lymphatic vessel invasion. We developed a CLR that represented the nutritional, systemic inflammation, and immunological response statuses. In our study, patients with a high CLR value had LVI ($P = .021$), but the T stage, N stage, tumor location, PNI, and postoperative complications did not differ between the groups with high and low CLR values (Table 3).

LVI is when tumor cells invade the lymphatic vessel or vascular wall and is an important way for tumor cells to spread.[30]

Table 4. Univariate and Multivariate Logistic Regression Analyses for Lymphovascular Invasion (LVI) Predictors.

		Univariate analysis			Multivariate analysis		
Variables	n	OR	95% CI	*P* value	OR	95% CI	*P* value
Gender							
Male	188	1			—	—	—
Female	74	1.09	0.41 to 1.20	.560	—	—	—
NLR							
≤2.17	144	1			—	—	—
>2.17	118	1.32	0.81 to 2.14	.269	—	—	—
PLR							
≤129.00	141	1			1		
>129.00	121	1.64	1.00 to 2.67	.049*	1.55	0.94 to 2.54	.085
CAR							
≤0.04	89	1			—	—	—
>0.04	173	1.52	0.91 to 2.55	.109	—	—	—
PAR							
≤4.97	143	1			—	—	—
>4.97	119	1.44	0.89 to 2.35	.14	—	—	—
NAR							
≤0.09	166	1			—	—	—
>0.09	96	1.33	0.81 to 2.21	.263	—	—	—
CLR							
≤1.04	101	1			1		
>1.04	161	1.81	1.09 to 3.00	.021*	1.73	1.04 to 2.87	.036*
Alb≤39.93 (g/L)	128	0.76	1.03 to 2.75	.121	—	—	—
Plt>199.60 ($10^{\wedge 9}$/L)	116	1.32	0.81 to 2.15	.269	—	—	—
Neut>3.50 ($10^{\wedge 9}$/L)	103	0.94	0.69 to 1.85	.692	—	—	—

*Indicates statistical significance.

Abbreviations: Alb, albumin; CI, confidence interval; CAR, C-reactive protein-to-albumin ratio; CLR, C-reactive protein-to-lymphocyte ratio; HALP, hemoglobin, albumin, lymphocyte, and platelet; Neut, neutrophil; NAR, neutrophil-to-albumin ratio; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; PAR, platelet-to-albumin ratio; PLR, platelet-to-lymphocyte ratio; Plt, platelet.

LVI was an independent factor for the resectable GC prognosis, especially for patients with stage N0.[31] LVI was also an effective predictor of lymph node metastasis.[32] A previous study suggested that patients with LVI should receive adjuvant chemotherapy.[33] Thus, an accurate assessment of LVI is critical. Generally, LVI is confirmed by postoperative pathological examination, and it is difficult to know the LVI status preoperatively. However, we found that the CLR value increased with LVI and identified a cut-off value of 1.04. We also found that the CLR was an independent predictor for LVI (Table 4). Although the predictive ability of the CLR value was not high in this study, the results still indicate that the nutritional status and inflammatory reaction are closely related to LVI.

This study had a few limitations. First, some biases exist because of the retrospective nature of this study. Second, we enrolled a small No. of patients from a single institution. Third, we established this model based on malnutrition, and 1.04 may not be the ideal cut-off CLR value for predicting LVI.

Conclusions

The preoperative CLR value based on the patient's nutritional status may be a helpful predictor for LVI in patients with GC.

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Author's Contribution

Rui Xu and Zhi Ding designed the study. Shuo-meng Xiao and Ping Zhao collected and analyzed data. Rui Xu wrote, reviewed, and edited the manuscript. All authors gave final approval of the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics Approval and Consent to Participate

All methods were performed following the relevant guidelines and regulations. The independent Ethics Committee of Sichuan cancer hospital reviewed and approved this study (SCCHEC-02-2018-048). The independent Ethics Committee of Sichuan cancer hospital also approved the requirement for informed consent.

Availability of Data and Materials

The clinical datasets supporting this article's results are available from the corresponding author upon reasonable request.

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