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ORIGINAL RESEARCH

The Value of the Preoperative Hematological Inflammatory Markers for Predicting Lymphovascular Invasion in Gastric Cancer

Cong Li[1,*], Yanyan Wang[1,*], Shumei Liang[2,*], Huina Shi[1], Xuelian Mao[1], Xiao Wang[3], Dongping Mo[1,4]

[1]Department of Clinical Laboratory, Jiangsu Cancer Hospital & Nanjing Medical University Affiliated Cancer Hospital & Jiangsu Institute of Cancer Research, Nanjing, People's Republic of China; [2]Department of Clinical Laboratory, the Third People's Hospital of Chengdu, Chengdu, People's Republic of China; [3]Department of CT, Jiangsu Cancer Hospital & Nanjing Medical University Affiliated Cancer Hospital & Jiangsu Institute of Cancer Research, Nanjing, People's Republic of China; [4]Jiangsu Key Laboratory of Molecular and Translational Cancer Research, Nanjing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Dongping Mo, Department of Clinical Laboratory, Jiangsu Cancer Hospital & Nanjing Medical University Affiliated Cancer Hospital & Jiangsu Institute of Cancer Research, Nanjing, People's Republic of China, Email moxiaoyubang@163.com

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Background: Gastric cancer (GC) is a prevalent malignant tumor of the digestive system, with high morbidity and mortality. Lymphovascular invasion (LVI) is a risk factor for recurrence and metastasis of GC and an independent predictor of poor postoperative prognosis in GC patients. Accumulating evidence suggests that blood-based inflammatory indicators are linked with the pathogenesis of GC. The study delves into hematological inflammatory markers to explore their potential applications in preoperative LVI in GC.

Methods: We retrospectively collected and analyzed data from inpatients diagnosed GC at our hospital from December 2020 to October 2024, with LVI confirmed by pathological examination after surgery. Preoperative hematological inflammatory indicators were calculated from peripheral blood samples. Lasso logistic regression and multivariate logistic regression analyses were utilized to verify independent risk factors for LVI-positive GC patients and constructed the nomogram model. The correlation between hematological inflammatory indicators and clinical TNM staging was assessed through Spearman's analysis.

Results: In the study, 624 patients were pathological diagnosed with LVI-positive. The variables screened by Lasso logistic regression including CA199, PLR, SII, PNI, cT staging, and cN staging. Multivariate logistic regression analysis confirmed that CA199 (OR = 1.349, 95% CI: 1.016–1.790), PLR (OR = 1.396, 95% CI: 1.005–1.939), PNI (OR = 0.706, 95% CI: 0.515–0.968), cT staging (OR = 1.737, 95% CI: 1.511–1.996) and cN staging (OR = 2.272, 95% CI: 1.975–2.613) were independent risk factors of LVI-positive. PLR was positively correlated with cT and cN staging, while PNI was negatively correlated with both. The C-statistic of the nomogram model was 0.845, with a sensitivity of 86.86% and a specificity of 69.90%.

Conclusion: We provided a new perspective on the clinical application of preoperative hematological inflammatory markers in the auxiliary diagnosis of LVI-positive in GC patients.

Keywords: gastric cancer, lymphovascular invasion, inflammatory marker, nomogram model

Introduction

According to recent statistics, gastric cancer has become the fifth most frequently diagnosed cancer and the third-leading cause of cancer deaths worldwide, with high morbidity and mortality.[1,2] Owing to the deficiency of representative symptoms and effective markers, gastic cancer is typically diagnosed at an advanced stage, which results in a poor prognosis.[3] Postoperative distant metastasis, along with the drug resistance to chemotherapy and resistance to immunotherapy, contribute to a 5-year survival rate of under 30% among advanced gastric cancer patients.[4,5] Lymphovascular invasion (LVI) is defined as the invasion of vessel walls by tumor cells and/or the presence of tumor emboli within an

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endothelial-lined space, which leads to vascular function and blood circulation disorders, and often indicated poor prognosis for various tumors.[6–8] In gastric cancer, regional LVI is closely related to patient recurrence and prognosis, with LVI-positive patients having a higher recurrence rate and a lower 5-year survival rate.[9,10] At present, gastric cancer patients are mainly stratified based on TNM staging. Due to the crucial role of LVI in determining treatment regimen and its impact on the prognosis of gastric cancer, studies suggested that incorporating LVI into the TNM staging system might have a better efficiency for predicting the overall survival rate of gastric cancer patients.[11,12] Currently, the status of LVI can only be obtained from histopathologic examination after surgery, which is invasive, time-consuming, and unsuitable for preoperative decision-making.[13] Therefore, in the clinical treatment of gastric cancer, it is necessary to find a reliable preoperative predictive method to guide surgery or adjuvant therapy.

An increasing number of studies have indicated that the malignant progression of gastric cancer is closely associated with the tumor inflammatory microenvironment.[14,15] There are various inflammatory cells such as neutrophils, lymphocytes, macrophages, and monocytes in tumor inflammatory microenvironment.[16] During inflammation, these cells are often abnormally expressed, manifested in abnormal peripheral blood routine.[17,18] It is believed that neutrophils infiltrating within the tumor tissue can produce various inflammatory mediators and inflammatory factors to promote the formation of the tumor microenvironment, facilitating tumor growth, invasion, angiogenesis, and metastasis.[19–21] During the invasion and metastasis of tumor cells, platelets and macrophages facilitate angiogenesis, basement membrane rupture, and extracellular matrix remodeling, enabling tumor cells to invade and infiltrate blood vessels and lymphatic vessels for distant metastasis.[22] Lymphocytes can not only activate other immune cells such as macrophages to assist in killing tumor cells, but also play a role in tumor immune evasion, promoting vascular growth and proliferation, increasing tumor growth and metastasis,[23] and providing favorable conditions for the formation of LVI. Growing evidence suggested that the complete blood count-derived inflammatory markers, such as platelet to lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), and systemic immune inflammation index (SII), have been proved to be related to the prognosis and progression of a variety of tumors.[24–26] Importantly, all of the above indicators can be easily measured through routine blood tests for cancer patients. In our previous research, we confirmed that CEA, FLR, D-dimer, PLR, CA199, and CA724 as independent risk factors for gastric cancer patients with perineural invasion. Meanwhile, a prediction model with good discrimination and accuracy has been successfully established and validated.[27] Currently, imaging techniques are commonly employed for preoperative prediction of LVI in gastric cancer patients.[28,29] However, imaging methods struggle to accurately identify subclinical lymph node micrometastasis and hematogenous micrometastasis. Therefore, this raises the question of whether inflammatory markers derived from peripheral blood can also offer clinical application for LVI assessment in gastric cancer. To our knowledge, there are few studies on LVI and hematological indicators in gastric cancer.

In this study, we performed a retrospective analysis to evaluate the clinical significance of inflammatory markers derived from peripheral blood test results in gastric cancer patients with LVI. Additionally, we employed the Lasso regression to screen parameters and calculated the optimal cut-off value for LVI and established a nomogram based on multivariate logistic regression results. Our present study may provide a new non-invasive auxiliary method for preoperative diagnosis of gastric cancer patients with LVI. The prediction of LVI in preoperative assessment of whether the tumor has reached a locally advanced stage, offering supportive evidence for the administration of neoadjuvant therapy and holding significant potential for improving the prognosis of gastric cancer patients.[30,31]

Materials and Method

Study Patients and Processing

We retrospectively collected and analyzed data from inpatients diagnosed gastric cancer at the Jiangsu cancer hospital from December 2020 to October 2024. The present study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Ethical Committee of Jiangsu cancer hospital (No. KY-2024-012-GZ-01 and No. KY-2024-119). Patients were included if they met the following criteria: (1) Age over 20 years old; (2) Primary gastric cancer; (3) Not receiving any anti-tumor therapeutic before admission; (4) Complete clinical and laboratory data; (5) Received upper endoscopy, barium meal examination, computed tomography or magnetic resonance imaging prior to

therapeutic. Patients were excluded if they presented with the following: (1) History of other malignant tumors; (2) Distant metastasis; (3) Recurrent tumors or residual gastric cancer; (4) Gastrointestinal stromal tumor; (5) History of serious immune disorders, malignant hematologic disease; (6) History of severe hepatic or renal disease. After applying these criteria, 1232 gastric cancer patients were included in the present study. The clinical stage of all patients was determined by clinical examination and the imaging examinations.[32] All patients were staged according to the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) 8th edition staging system. The clinicopathological characteristics of these cases were shown in Table S1.

The research procedures of this study were as follows: Firstly, we obtained laboratory data, clinical data and pathological characteristics in gastric cancer patients treated with curative gastrectomy. Then, we calculated inflammation markers based on laboratory data, and analyzed laboratory indicators that showed differences between LVI-negative and LVI-positive groups. Thirdly, lasso logistic regression was used to screen variables, and receiver operating characteristic (ROC)–area under curve (AUC) analysis was employed to calculate the optimal cut-off value for LVI. Finally, we formulated the nomogram based on multivariate logistic regression results. A flow diagram of subjects enrolled in this study is provided in Figure 1.

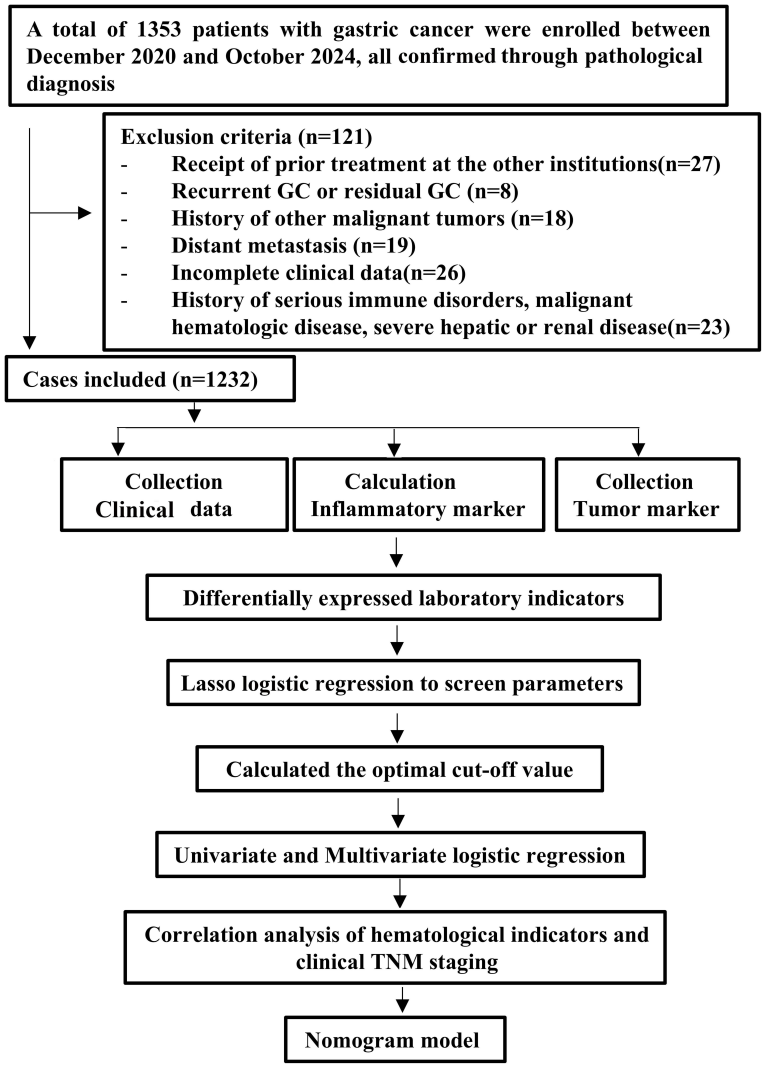

Figure 1 The flowchart of the study design and analysis.
Abbreviations: GC, gastric cancer; TNM, tumor-node-metastasis.

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Laboratory Data Collection and Calculation

Blood samples were collected from all patients in the morning. All laboratory indicators were checked before the cases received clinical treatment. The laboratory indicators included neutrophils count (NE), lymphocytes count (LY), monocytes count (MO), platelets count (Plt), albumin (Alb), carcinoembryonic antigen (CEA) and carbohydrate antigen 199 (CA199). The calculation formula of peripheral blood derived inflammatory markers according to the following equations: neutrophil to lymphocyte ratio (NLR) = NE/LY, PLR = Plt/LY, LMR = LY/MO, albumin-to-lymphocyte ratio (ALR) = Alb/LY, SII = (NE×Plt)/LY, prognostic nutritional index (PNI) = Alb(g/L)+5×LY, systemic inflammation response index (SIRI) = (NE×MO)/LY, aggregate index of systemic inflammation (AISI) = (NE×Plt×MO)/LY, (neutrophil + monocyte)-to-lymphocyte ratio (NMLR) = (NE+MO)/LY.

Histopathological Evaluations of LVI

All surgical specimen were processed according to standard pathological procedures and stained with hematoxylin-eosin (HE). For each specimen, three independent representative tissue sections were prepared. The pathological diagnosis was determined after a discussion between two experienced pathologists. LVI was defined as the invasion, destruction, or intraluminal thrombosis of small veins, arteriole, or lymphatic vessels of the tumor.[33] All patients were divided into an LVI-positive group (624 cases, 50.65%) and an LVI-negative group (608 cases, 49.35%) in the present study.

Statistical Analysis

All data in the present study were tested for a normal distribution using the Kolmogorov–Smirnov test. Continuous variables were presented as means ± standard deviations or medians (interquartile range [IQR]), and the results were compared using Student's *t*-test or Mann–Whitney *U*-test, when appropriate. Categorical variables were presented as count (%) and compared with Chi-square tests or Fisher's exact test. Lasso logistic regression was employed for variable selection. The ROC-AUC was employed to evaluated the diagnostic accuracy of all variables for patients with LVI. Univariate and multivariate logistic regression analyses of relative risks for patients with LVI, and OR and 95% CI were calculated. Spearman's analysis was used to assess the correlations between variables and cTNM stage. Finally, Nomogram model was developed to evaluate LVI-positive gastric cancer based on multivariate logistic regression results. A *P*-value less than 0.05 was considered statistically significant, and all statistical test were two-sided. All statistical analysis was performed using IBM SPSS Statistics Version 20.0, GraphPad Prism v9.4.1 and R version 4.2.1.

Results

Analysis of Patient Clinical Characteristics According to Status of LVI

Based on the status of LVI, the 1232 patients were categorized into two groups. Compared with the LVI-negative groups, the medians of age and preoperative CEA, CA199, NLR, PLR, ALR, SII, SIRI, NMIR and SIRI were significantly increased ($P < 0.05$), and the medians of LMR and PNI were markedly decreased ($P < 0.01$). What's more, there were statistically significant difference in clinical T staging and N staging between patients with LVI-negative and those with LVI-positive ($P < 0.001$). All detailed data were shown in Table 1.

Prediction Model Built Based on Lasso Logistic Regression

In order to prevent overfitting, we utilized Lasso logistic regression for parameter selection during model construction. There are 14 variables that differences between LVI-negative and LVI-positive groups, including age, CEA, CA199, NLR, PLR, ALR, SII, SIRI, NMIR, SIRI, cT staging and cN staging. Herein, a 10-fold cross-validation was implemented to determine to optimal penalty term lambda, with a more stringent selection to minimize the number of covariates. Figure 2A displays the coefficient distributions of predictors, and Figure 2B shows the cross-validation error plot of the Lasso model. Finally, six non-zero variables with optimal lambda ($\lambda = 0.012$) in the Lasso model were cT staging, cN staging, CA199, PLR, SII and PNI.

Table 1 Comparison of Characteristics According to Status of LVI in Gastric Patients

Characteristics	LVI-Negative (n = 608)	LVI-Positive (n = 624)	*P* value
Demographic Data			
Age (years)	63 (56–70)	65 (57–70)	0.034*
Gender			0.568
Women	174 (28.62%)	169 (27.08%)	
Men	434 (71.38%)	455 (72.92%)	
Laboratory Data			
CEA (ng/mL)	2.12 (1.37–3.32)	2.35 (1.36–4.09)	0.015*
CA199 (U/mL)	8.56 (5.72–15.25)	10.15 (6.07–19.1)	0.002**
NLR	1.92 (1.49–2.48)	2.10 (1.61–2.89)	<0.001***
PLR	126.4 (94.51–164.67)	140.8 (107.96–192.06)	<0.001***
LMR	4.04 (3.14–5.07)	3.60 (2.76–4.65)	<0.001***
ALR	25.78 (21.01–31.75)	26.98 (21.87–33.82)	0.020*
SII	385.49 (276.22–557.31)	463.84 (316.83–698.18)	<0.001***
PNI	51.60 (47.80–54.75)	49.78 (45.69–53.2)	<0.001***
SIRI	0.80 (0.55–1.17)	0.89 (0.61–1.39)	<0.001***
NMLR	2.20 (1.69–2.80)	2.37 (1.85–3.24)	<0.001***
AISI	160.68 (105.28–257.13)	201.04 (121.86–337.58)	<0.001***
Clinical TNM staging			
cT staging			<0.001***
T1	278 (45.72%)	38 (6.09%)	
T2	81 (13.32%)	52 (8.33%)	
T3	133 (21.88%)	186 (29.81%)	
T4	116 (19.08%)	348 (55.77%)	
cN staging			<0.001***
N0	410 (67.43%)	86 (13.78%)	
N1	95 (15.63%)	122 (19.55%)	
N2	55 (9.05%)	165 (26.44%)	
N3	48 (7.89%)	251 (40.23%)	

Notes: The measurement data were expressed as the median and quartile (25%–75%), and the enumeration data were expressed as frequency and rate (%). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Abbreviations: LVI, lymphovascular invasion; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 199; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; ALR, albumin-to-lymphocyte ratio; SII, systemic immune-inflammation index; PNI, prognostic nutritional index; SIRI, the systemic inflammation response index; AISI, aggregate index of systemic inflammation; NMLR, (neutrophil + monocyte)-to-lymphocyte ratio; TNM, tumor-node-metastasis.

Diagnostic Efficiency of Hematological Indicators for Patients with LVI

ROC curve analysis was conducted to determine the ability of hematological indicators to distinguish LVI-positive patients. The cut-off value of the CA199 was 10.25 U/mL (AUC = 0.551, 95% CI: 0.519–0.583, sensitivity: 49.36%, specificality: 59.70%). The cut-off value of the PLR was 171.43 (AUC = 0.597, 95% CI: 0.565–0.628, sensitivity: 35.42%, specificality: 78.95%). And then, the cut-off value of SII and PNI were 387.77 and 47.78, respectively. The AUC of SII was 0.591, the 95% CI was 0.559–0.622, the sensitivity was 63.62%, and the specificity was 50.66%. The AUC of PNI was 0.593, the 95% CI was 0.562–0.596, the sensitivity was 38.46%, and the specificity was 75.66%. Details of the accuracy, positive predictive value, negative predictive value and Youden's index are shown in Table 2.

Univariate Logistic Regression Analysis for LVI in GC Patients

Perform univariate logistic regression analysis with the occurrence of LVI as the dependent variable (negative = 0, positive = 1), CA199 (≤10.25U/mL = 0, >10.25U/mL = 1), PLR (≤171.43 = 0, >171.43 = 1), SII (≤387.77 = 0, >387.77

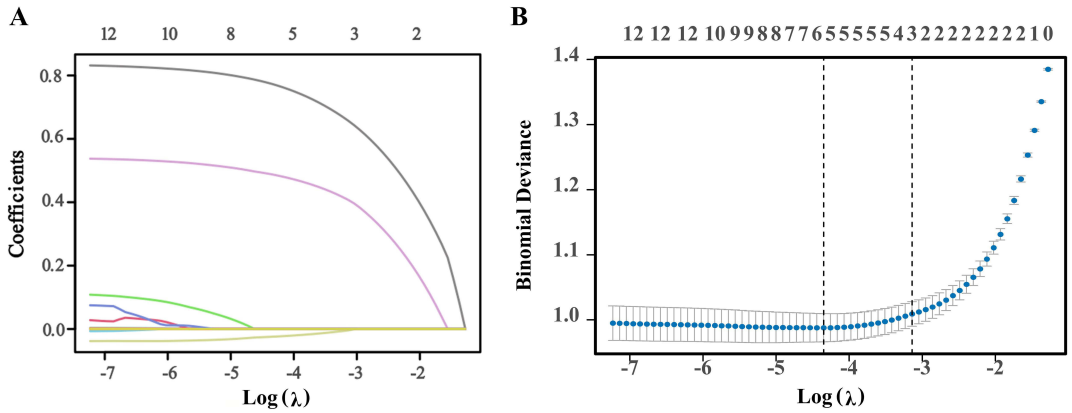

Figure 2 Screening of variables based on Lasso logistic regression. (**A**) Lasso regression coefficient path plot for 14 variables. X-axis is log (lambda) and Y-axis is partial regression coefficients. (**B**) Lasso regression cross-validation plot. The optimal parameter (lambda) in the Lasso model was selected using a 10-fold cross validation based on the minimum criterion.

= 1), PNI (≤47.78 = 0, >47.78 = 1), cT staging (T1 = 0, T2 = 1, T3 = 2, T4 = 3), and cN staging (N0 = 0, N1 = 1, N2 = 2, N3 = 3) as independent variables. The results displayed that the above variables were significantly correlated with LVI-positive patients (Table 3).

Table 2 Diagnostic Efficiency of Hematological Indicators for Patients with LVI

Variables	AUC (95% CI)	Se (%)	Sp (%)	Ac (%)	PPV (%)	NPV (%)	Cutoff value	Youden's index
CA199 (U/mL)	0.551 (0.519–0.583)	49.36	59.70	54.46	55.70	53.46	10.25	0.091
PLR	0.597 (0.565–0.628)	35.42	78.95	55.11	63.32	54.36	171.43	0.144
SII	0.591 (0.559–0.622)	63.62	50.66	57.22	56.96	57.57	387.77	0.143
PNI	0.593 (0.562–0.596)	38.46	75.66	56.82	61.86	54.40	47.78	0.141

Abbreviations: LVI, lymphovascular invasion; AUC, area under curve; CI, confidence interval; Se, sensitivity; Sp, specificity; Ac, accuracy; PPV, positive predictive value; NPV, negative predictive value; CA199, carbohydrate antigen 199; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; PNI, prognostic nutritional index.

Table 3 Univariate Logistic Regression Analysis of LVI in Gastric Cancer Patients

Variables	OR	95% CI	*P* value
CA199 (U/mL)			0.002**
≤10.25	1		
>10.25	1.417	1.131–1.776	
PLR			<0.001***
≤171.43	1		
>171.43	2.042	1.583–2.638	
SII			<0.001***
≤387.77	1		
>387.77	1.796	1.430–2.255	
PNI			<0.001***
≤47.78	1		
>47.78	0.515	0.403–0.658	
cT staging			
T1	1		
T2	6.697	2.889–7.636	<0.001***

(*Continued*)

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Table 3 (Continued).

Variables	OR	95% CI	*P* value
T3	10.231	6.820–15.347	<0.001***
T4	21.947	14.729–32.703	<0.001***
cN staging			
N0	1		
N1	6.122	4.293–8.731	<0.001***
N2	14.302	9.745–20.990	<0.001***
N3	24.930	16.938–36.692	<0.001***

Notes: **$P < 0.01$, ***$P < 0.001$.
Abbreviations: LVI, lymphovascular invasion; OR, odds ratio; CI, confidence interval; CA199, carbohydrate antigen 199; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; PNI, prognostic nutritional index.

Multivariate Regression Analysis for LVI in GC Patients

Subsequently, we included variables with $P < 0.05$ in the univariate regression analysis into the multivariate regression analysis, employing a likelihood ratio test with maximum partial likelihood estimation (forward: LR). The results showed that CA199 (OR = 1.349, 95%: 1.016–1.790, $P = 0.038$), PLR (OR = 1.396, 95%: 1.005–1.939, $P = 0.046$), PNI (OR = 0.706, 95%: 0.515–0.968, $P = 0.030$), cT staging (OR = 1.737, 95%: 1.511–1.996, $P < 0.001$), and cN staging (OR = 2.272, 95%: 1.975–2.613, $P < 0.001$) were independent risk factors of LVI-positive patients (Table 4). Then, we obtained a classification discriminant equation using the above results to ascertain whether gastric cancer patients with LVI-positive, as follow: logit (P) = −2.504+0.299*CA199+0.334*PLR-0.348*PNI+0.552*cT+0.821*cN ($\chi^2 = 506.73$, $P < 0.001$), for which the critical value is 0.50, thus, if the logit (*P*) of a case is larger than 0.50, it belongs to LVI-positive patients. Otherwise, it belongs to the LVI-negative groups. And the model prediction accuracy is 77.10%.

Correlation Analysis of Hematological Indicators and Clinical TNM Staging

The Spearman correlation test was used to examine the correlation between levels of CA199, PLR and PNI. There was a negative correlation between PLR and PNI ($r = -0.450$, $P < 0.001$; Figure 3A). However, there is no significant correlation between CA199 and PLR or PNI ($P > 0.05$). Immediately after, we divided all subjects into 4 group cohorts: cT1, cT2, cT3 and cT4 according to the cT staging. As shown in Figure 3B and C, PLR was positively correlated with cT staging ($r = 0.180$, $P < 0.001$), while PNI was negatively correlated with cT staging ($r = -0.159$, $P < 0.001$). When we grouped the all subjects based on cN staging (cN0, cN1, cN2 and cN3), the similar results were found (CA199: $r = 0.065$, $P = 0.023$; PLR: $r = 0.139$, $P < 0.001$; PNI: $r = -0.127$, $P < 0.001$; Figure 3D–F).

Table 4 Multivariate Analysis of Logistic Regression Model for Predicting LVI

Variables	β	SE	Wals	*P* value	OR	95% CI
CA199	0.299	0.144	4.291	0.038*	1.349	1.016–1.790
PLR	0.334	0.167	3.970	0.046*	1.396	1.005–1.939
PNI	−0.348	0.161	4.668	0.030*	0.706	0.515–0.968
cT staging	0.552	0.071	60.490	<0.001***	1.737	1.511–1.996
cN staging	0.821	0.071	132.212	<0.001***	2.272	1.975–2.613
Constant	−2.504	0.249	100.834	<0.001***	0.082	–

Notes: *$P < 0.05$, ***$P < 0.001$.
Abbreviations: β, Beta coefficient; SE, standard error; OR, odds ratio; CI, confidence interval; CA199, carbohydrate antigen 199; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index.

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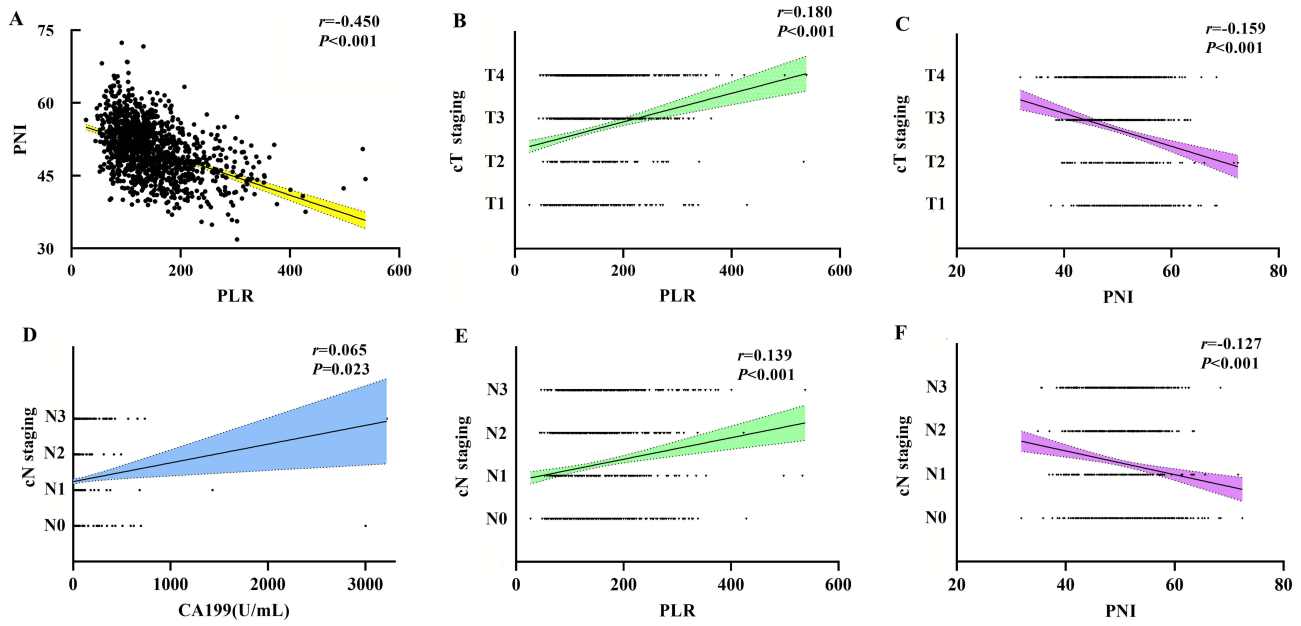

Figure 3 Correlation analysis of hematological indicators and clinical TNM staging. (**A**) Correlation analysis between PLR and PNI. (**B** and **C**) Association between the cT staging and PLR, PNI. (**D**–**F**) Association between the cN staging and CA199, PLR, PNI.
Abbreviations: CA199, carbohydrate antigen 199; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index.

Nomogram Model for Risk Assessment of GC with LVI

Based on the results of multivariable logistic regression, we establish a nomogram model for LVI-positive patients using the R language rms package. The C statistic for the nomogram was 0.845, with a sensitivity of 86.86% and a specificity of 69.90%, indicating that the model had certain accuracy (Figure 4A). Hosmer-Lemeshow goodness of fit test was used to evaluated the calibration ability of the model, and the results indicated that there was no statistically significant difference between the predicted values of the model and the actual observed values (χ^2= 13.80, P = 0.087, Figure 4B). Besides, the DCA suggested that the clinical net benefit of intervention based on the predicted probability of the model is highest when the threshold probability is between 0.12 and 0.83 (Figure 4C). And then, the plotting function was constructed, and the nomogram was plotted (Figure 4D). That is, a score of cT4 staging was 70 points, while a score of cT1 staging was 0 points; a score of cN3 staging was 100 points, while a score of cN0 staging was 0 points; a score of CA199 = 2000 U/mL was 47.5 points; a score of PLR = 450 was 50 points; a score of PNI = 30 was 57.5 points. The total score was 205 points, suggesting that the probability of LVI-positive in gastric cancer was greater than 80%. The risk of LVI-positive can be predicted based on the total points (Table 5).

Discussion

Actually, we have displayed that PLR, cT staging and cN staging were independent risk factors for LVI in gastric cancer patients in our previous research, with a total of 341 cases at that time.[34] The present study expanded the sample size on the basis of the original, established a nomogram model to obtain more reliable results. Similarly, apart from PLR, cT staging and cN staging, CA199 and PNI also serve as independent predictors for LVI in gastric cancer in this study. Some individual markers, such as CA199, PNI or PLR, have limited predictive power on their own, whereas combinations of markers demonstrated better predictive performance within the model. Compared to previous study, the present study has elevated the prediction accuracy from 67.26% to 77.10%, and the C-statistic from 0.733 to 0.845. In short, our study provided a simple and effective non-invasive auxiliary method for predicting preoperative LVI patients with gastric cancer.

LVI refers to the invasion of tumors into lymphatic vessels and/or blood vessels, which is an important pathway for local metastasis.[35] It plays an important role in tumor recurrence and lymph node metastasis, and increases the risk of micrometastasis.[36] In the present study, the rate of LVI positivity was 50.65%, which is consistent with LVI detection rate

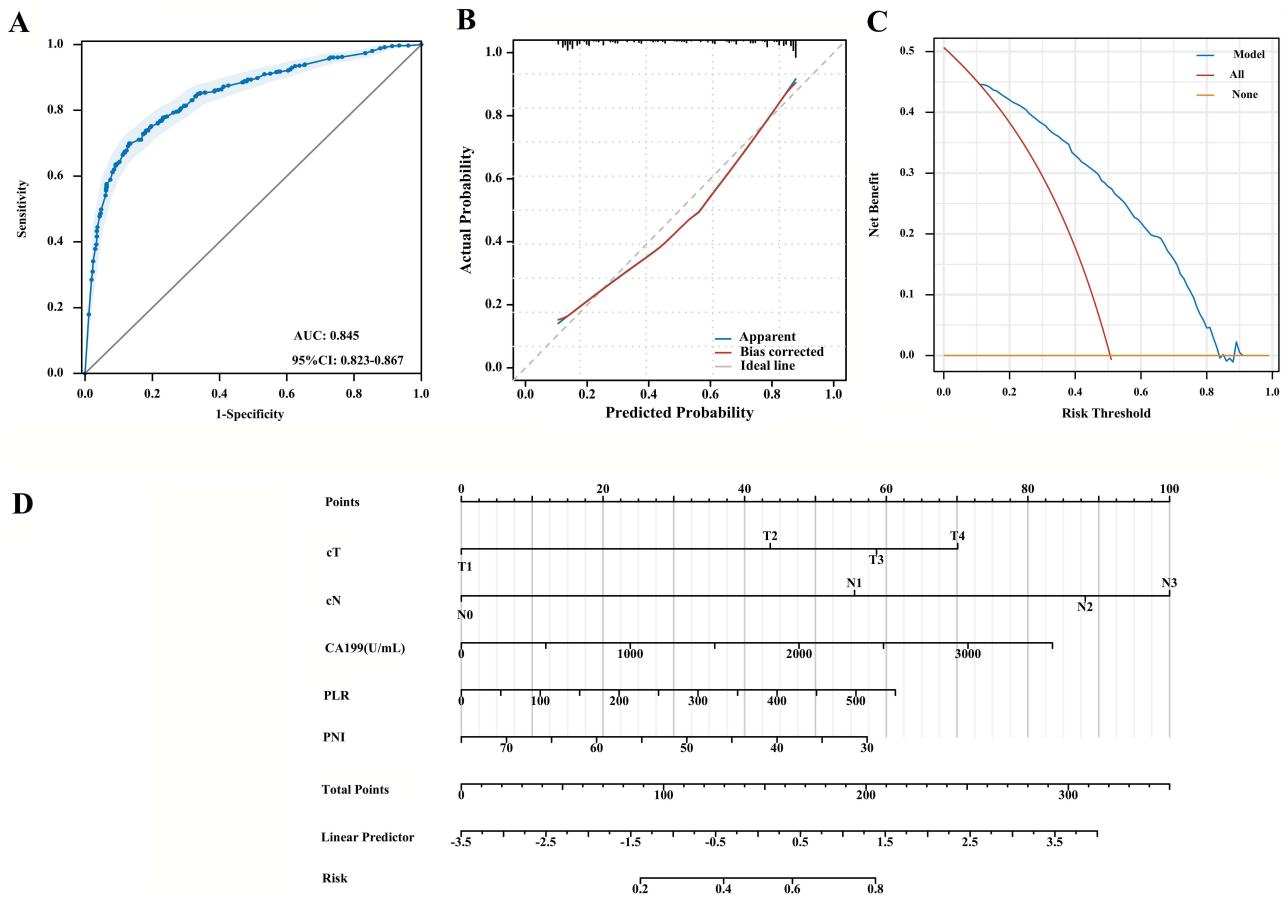

Figure 4 Prediction model for risk assessment of gastric cancer with LVI. (**A**) ROC curve of the combined factors; (**B**) Calibration curve of mo (**C**) DCA of mo (**D**) Nomogram of the logistic regression model.

Abbreviations: LVI, Lymphovascular Invasion; AUC, area under the curve; CI, confidence interval; CA199, carbohydrate antigen 199; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; DCA, decision curve analysis.

of 55.60% reported in previous study.[37,38] Previous studies have shown that gastric cancer patients with LVI have a higher degree of malignancy and lower postoperative survival rate, and LVI is an independent risk factor affecting patient prognosis.[9,39] Currently, preoperative LVI prediction remains challenging due to its histopathological nature, which is associated with biologically aggressive diseases and can only be confirmed through postoperative histopathological examination.[40]

Therefore, there is a need for a convenient and accurate tool to comprehensively predict LVI status in gastric cancer patients. Some studies revealed that radiomics features of positron emission tomography/computed tomography (PET/CT) and enhanced CT can evaluate the preoperative status of LVI in gastric cancer.[41,42] Hematological indicators are

Table 5 Relationship Between Total Points and Risk of LVI for Gastric Cancer Patients

Total Points	Risk of LVI-Positive (%)
<90	<20
90-130	20-40
130-163	41-60
163-205	61-80
>205	>80

Abbreviation: LVI, Lymphovascular Invasion.

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renowned for their simplicity and clinical practicality in tumor screening and have become a common method for cancer evaluation. At present, the clinical potential significance of derived inflammatory markers of peripheral blood in gastric cancer patients with LVI is still limited. This study explores the correlation between derived inflammatory indicators and LVI, hoping that they could become an auxiliary diagnostic tool beyond imaging examinations.

Nowadays, with the deepening of research on the interaction between tumor microenvironment and immune response, the close relationship between inflammatory response and tumor occurrence and development has been gradually emerged. Inflammation alters the tumor microenvironment, creating a suitable environment for the proliferation of cancer cells.[43] LVI means that the invasion and accumulation of cancer cells in the blood vessels and lymphatic system during growth, proliferation, and metastasis, leading to a series of pathological and physiological changes. When the body undergoes an inflammatory response, blood inflammatory indicators such as neutrophils, platelets, and lymphocytes often show abnormal expression. Tumor stroma can recruit various inflammatory cells through chemokines, forming an important component of the tumor microenvironment and promoting tumor cell proliferation and infiltration. Among them, platelets utilize the encapsulation function of blood clots to protect circulating tumor cells (CTCs) from immune system surveillance, avoiding antigen presentation by mononuclear macrophages and dissolution and elimination by natural killer cells.[44] To enhance the adhesion and aggregation between tumor cells and platelets, tumor cells produce a series of special mechanisms to activate platelets. This is also the main reason why cancer patients have a high coagulation state and a high risk of thrombosis.[45] Activated platelets release lysophosphatidic acid (LPA), which plays a significant role in enhancing the invasive ability of tumor cells, vascular permeability, and promoting transendothelial migration.[46] Lower levels of lymphocytes indicate insufficient immune response to tumors and weakened ability to delay cancer cell infiltration.[47] Besides, low levels of serum albumin are often associated with tumor related inflammatory reactions and affect the prognosis of malignant tumors.[48] In our study, PLR and PNI were independent risk factors for LVI-positive patients, indicating an increase in platelets, a decrease in lymphocytes and albumin levels, and a corresponding increase in the risk of LVI in gastric cancer. Moreover, PLR was positively correlated with cT staging and cN staging, while the PNI was negatively correlated with both. The results suggested that LVI-positive patients with high infiltration and lymph node metastases have higher platelets, lower lymphocyte and worse nutritional status. Unfortunately, SII was not an independent risk factor for LVI-positive patients. SII is associated with peripheral blood neutrophils, but there was no significant difference in the median neutrophils between LVI-negative group and LVI-positive group in this study (3.18 vs 3.33, $P > 0.05$). The occurrence of such results may be attributed to the fact that multivariate analysis incorporates multiple variables into the model simultaneously. The statistical model automatically assigns the influence to stronger variables, such as PLR and PNI in this study, while excluding SII from the model. Given that this study is a single-center investigation, a multi-center analysis will be conducted in future studies to verify the impact of the aforementioned variables.

A previous study showed that PLR > 129 (OR: 1.64, 95% CI: 1.00–2.67) is associated with LVI in the univariate logistic analysis, but not an independent risk factor for LVI in gastric cancer patients. The analysis may be due to the small sample size (N = 262).[49] The present study has over 1000 research subjects, and the results are more convincing. In our previous research, we displayed that PNI could be used as screening biomarker in diagnosing gastric cancer, especially in the early stage.[50] Beyond that, higher PNI was markedly associated with better overall survival in gastric cancer, and higher PNI patients had a protective effect regarding postoperative morbidity and mortality.[48] Because of this, lower PNI is more likely to present in LVI-positive gastric patients, indicating poor prognosis. The therapeutic strategy for gastric cancer, including the extent of gastric resection and lymphadenectomy, is determined based on cT (T1 or T2-T4) and cN (N0 or N+).[51] Therefore, this study included clinical cTNM staging for model construction, and the results suggested that cT staging and cN staging were also independent risk factors for LVI-positive patients. The underlying reason could be that as the tumor progresses, tumor cells infiltrate and invade blood vessels, subsequently proliferating at the infiltrated vascular sites and continuously releasing tiny cancer emboli into the circulation. In addition, gastric cancer patients with LVI-positive exhibit elevated levels of vascular endothelial growth factor (VEGF) within their tumor tissues.[52] The production of VEGF stimulates neovascularization, and the incomplete basement membrane of these newly formed vessels enhances the likelihood of cancer cell invasion into the vascular system, thereby increasing the counts of vascular cancer thrombus and lymph node metastasis also increases.[53] This offers an explanation for the correlation between LVI and both tumor infiltration and lymph node metastasis.

Finally, we establish a nomogram model for gastric cancer with LVI-positive. The C-statistic of the nomograms model evaluation was 0.845, with a sensitivity of 86.86% and a specificity of 69.90%, indicating that the model had certain accuracy. The calibration curve also indicated that the predictive results were good in accordance with the actual results. What's more, assign a score to each value level of each indicator based on their contribution to the outcome variable in the model. And then add up these scores to obtain the total score, which can be transformed into a function of the probability of clinical outcome events to ultimately calculate the predicted value of a specific event.[54] Nomograms have significantly benefited in diagnosis of gastric cancer. For instance, Tong et al[38] have established a nomogram based on Borrmann classification, CA724, tumor thickness, and iodine concentration in the venous phase, with an AUC of 0.864 for LVI patients with gastric cancer. But CA199 and PLR were not included in the model of this study, potentially due to factors such as inclusion criteria, sample size, and detection methods. Besides, Zhang et al[28] have also reported a nomogram model for predicting LVI in gastric cancer patients, consisting of vascular entry sign, clinical T stage, and clinical N stage. The AUC of this model is 0.878, similar to the results obtained in this study, and both offer valuable tools for clinical decision-making and the formulation of personalized treatment approaches. Although the AUC of the prediction model in the present study is largely consistent with previous research findings, it can be further enhanced by integrating imaging and comprehensive clinical pathological data in subsequent stages to improve the diagnostic efficacy for LVI patients gastric with cancer.

The main limitation of this study was that data from a single center were retrospectively analyzed, although we have a relatively large sample size. There were biases in participant selection and clinical data extraction, thereby potentially impacting the study's conclusions to some extent. Secondly, the cut-off value of laboratory data was only calculated only by mathematical methods, and their clinical potential should be further validated through multi-center studies with larger sample sizes. Moreover, the LVI group was not differentiated into lymphatic cancer emboli, vascular cancer emboli, and microvascular cancer emboli, which will be the focus of future research endeavors.

Conclusions

In summary, the predictive model for LVI-positive patients, established by combining CA199, PLR, PNI, cT staging, and cN staging, exhibits significant clinical value, providing supportive evidence for clinicians in developing surgical plans and implementing neoadjuvant therapy. Furthermore, we have initiated a multi-center retrospective analysis and will further refine data from auxiliary diagnostic tools such as laboratory testing and medical imaging examinations, aiming to enhance the accuracy and reliability of LVI prediction. We aspire for hematological indicators to become an additional auxiliary diagnostic method for predicting LVI patients with gastric cancer patients.

Data Sharing Statement

The data that support the results of this study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Clinical Research Ethics Committee of Jiangsu Cancer Hospital (No. KY-2024-012-GZ-01 and No. KY-2024-119). Due to retrospective characteristics of the study, informed consent was waived. All patient data was treated with confidentiality.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors have no conflicts of interest to declare for this work.

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