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ORIGINAL RESEARCH

Fibrinogen-to-Lymphocyte Ratio Was an Independent Predictor of Lymph Node Metastasis in Patients with Clinically Node-Negative Advanced-Stage Gastric Cancer

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Purpose: Various hematological indicators have been reported to predict lymph node metastasis (LNM) in gastric cancer (GC) patients, but the relationship between FLR and LNM has not been studied. Therefore, the aim of this study was to evaluate the role of preoperative fibrinogen-to-lymphocyte ratio (FLR) in predicting LNM in patients with clinically node-negative (cN0) advanced gastric cancer (AGC).

Patients and Methods: We retrospectively reviewed 571 eligible patients with primary AGC adenocarcinoma who underwent radical gastrectomy (discovery cohort). Patients were divided into high and low FLR groups according to the optimal cutoff value determined by Youden index. FLR is an independent predictor of LNM determined by logistic regression and validated in the validation cohort of 207 patients. Receiver operating characteristic (ROC) curve analysis was used to evaluate the predictive value of FLR for LNM. The nonlinear relationship between FLR and LNM risk was assessed using restricted cubic spline. Sensitivity analyses were performed according to FLR quartiles to further assess the robustness of the results. The nomogram was built based on FLR and clinicopathological characteristics, and was evaluated by calibration curves, ROC curve analysis and decision curve analysis.

Results: In the discovery cohort, the area under the curve (AUC) value for FLR to predict LNM was 0.592. There is a linear relationship between the FLR value and the risk of LNM, and the risk of LNM increased with FLR value. High FLR level is an independent risk factor for LNM, and the results of sensitivity analysis robust this finding. The nomogram for individual risk assessment performed well. Furthermore, we verified the FLR was an independent predictor of LNM in the validation cohort.

Conclusion: FLR was an independent predictor of LNM in patients with cN0 AGC.

Keywords: advanced gastric cancer, clinically node-negative, lymph node metastasis, fibrinogen-to-lymphocyte ratio, nomogram

Introduction

Gastric cancer (GC) is one of the most common malignant tumors worldwide, with more than 1 million new cases and 769,000 deaths recorded in 2020.[1] GC accounts for 7.7% of all global deaths and ranks fifth and fourth in terms of morbidity and mortality, respectively.[1] Although there has been significant progress in the early diagnosis and treatment of GC in recent years, advanced-stage gastric cancer (AGC) still accounts for approximately 70% of all cases, and its 5-year survival rate is only approximately 30%.[2] Lymph node metastasis (LNM) is an independent indicator of poor prognosis in GC, and the incidence rate of LNM in patients with AGC patients can be as high as 80%.[3] Currently, surgical resection is the preferred treatment option for AGC. Previous papers indicated that neoadjuvant chemotherapy is beneficial for AGC, and it can reduce tumor stage, particularly among patients with LNM, thereby improving the rates of complete (R0) resection.[4,5] Therefore, the early and accurate prediction of LNM can help establish preoperative individualized treatment plans and improve prognosis. Currently, contrast-enhanced abdominal computed tomography (CT) scan is the most commonly used method in

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the preoperative assessment of LNM. However, there are still issues in terms of accuracy and consistency rates, which generally vary from 40% to 70%.[6,7] In addition, several protein markers that can be used for predicting LNM in GC are still assessed. However, these are expensive and complex and are challenging to perform clinically.[8,9] Therefore, it is necessary to actively search for convenient and effective biomarkers for predicting LNM before surgery.

Inflammation plays an important role in tumor pathogenesis, and systemic inflammation contributes to tumor progression and metastasis by inhibiting apoptosis and promoting angiogenesis.[10] Various hematological indicators have been reported to predict LNM in GC, such as prognostic nutritional index, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and lymphocyte-monocyte ratio cell ratio.[11–13]

Fibrinogen is a 340-kDa glycoprotein produced by hepatocytes that regulate the process of coagulation and thrombosis. Further, it plays an important role in hemostasis, cell adhesion, and systemic inflammatory responses.[14] Hyperfibrinogenemia can increase the risk of LNM in GC.[15] Recently, fibrinogen-to-lymphocyte ratio (FLR) was found to be associated with prognosis in different types of cancers. Moreover, it could be a predictor of peritoneal metastasis in GC.[16–20] However, there are no relevant reports focusing on the association between FLR and LNM in patients with GC. Therefore, the current study aimed to assess the predictive value of FLR in LNM in patients with clinically node-negative (cN0) AGC.

Materials and Methods

Patients

Patients with primary AGC (T2-T4) with adenocarcinoma pathologically who underwent curative R0 gastrectomy at our hospital from January 2018 to January 2021 were reviewed in this study (n = 1207, discovery cohort). The exclusion criteria were as follows: 1) patients with a history of other types of malignant tumors or gastrectomy, 2) those who had distant metastases or who received neoadjuvant chemotherapy, 3) those with < 15 surgically cleared lymph nodes, 4) those who did not undergo CT scan at our institution, 5) those with emergency admission, 6) those with diseases or oral medications that can affect preoperative hematological parameters, 7) those with clinically positive lymph node (cN+), and 8) those with incomplete clinicopathological and laboratory data. Based on the same criteria, we recruited patients as the validation cohort between February 2021 and January 2022. Figure 1 shows the specific screening process. This study was approved by the institutional review board of Yijishan Hospital of Wannan Medical College (2022–027). The need for informed consent was waived given the retrospective nature of this study. Identifying information was removed to protect patient confidentiality.

Data Collection

Data on the following clinicopathological features were obtained from the medical records: sex, age, presence of hypertension and diabetes mellitus, tumor size and site, T stage, tumor grade, Lauren type, number of dissected and positive lymph nodes, and preoperative hematological parameters. Tumor size was measured as the largest diameter of the tumor, and tumor sites were classified as upper (cardia and fundus), middle (body and angle), lower (antrum), and overlap. According to the American Joint Committee on Cancer/International Union Against Cancer TNM staging system (8th edition), the T stage was divided into T2 (muscularis propria), T3 (subserosal and serosal layers), and T4 (invasion of adjacent organs). Tumor grade was categorized into high/moderate differentiation and low differentiation, and the least differentiated components were used for analysis among patients with multiple differentiation types.[13] The preoperative hematological parameters included fibrinogen, lymphocyte, and carbohydrate antigen 19–9 levels. These parameters were measured within 1 week before surgery, and the results of the first blood test after admission were considered the main results.[21]

Definition

FLR was defined as fibrinogen level (g/L) divided by lymphocyte level (10^9/L).[17] The patients were divided into the high and low groups based on the optimal cutoff value of FLR determined using the Youden index.[22] Clinical N stage (cN)

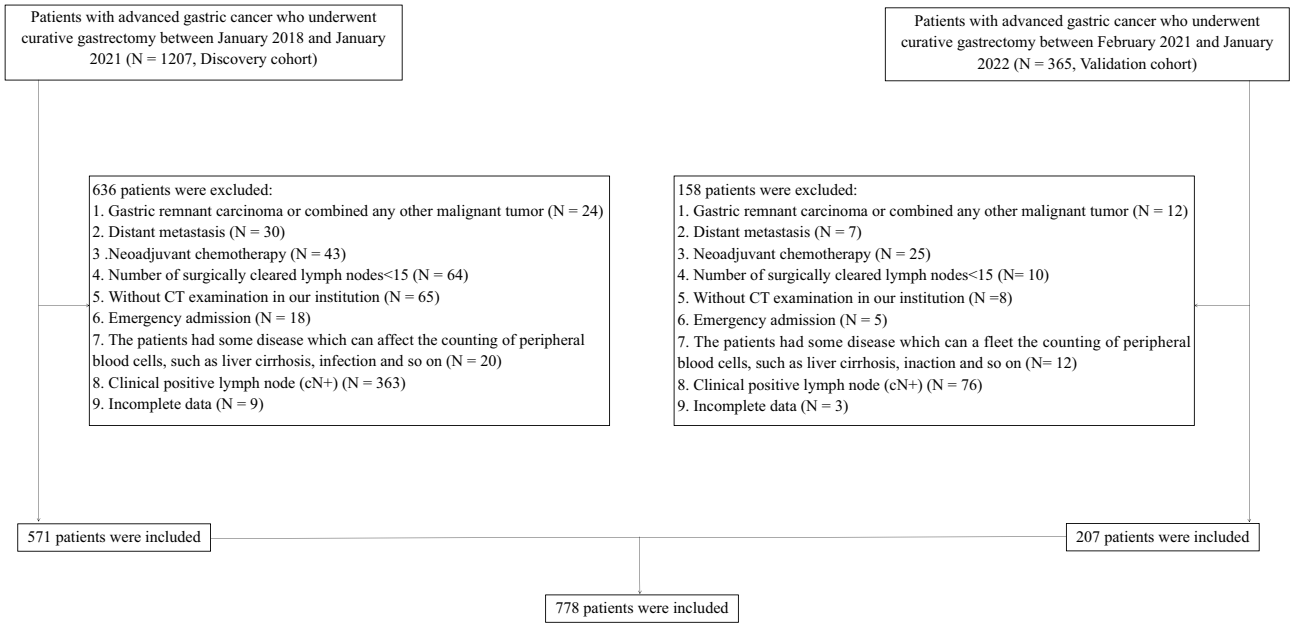

Figure 1 Screening flowchart.

was identified using a contrast-enhanced abdominal CT scan. Based on previous studies, cN+ was defined as lymph nodes with a short-axis diameter of ≥ 8 mm or a long-axis diameter of ≥ 10 mm[23,24] and cN0 as the absence of LNM.

Statistical Analysis

The median and interquartile ranges were used to describe non-normally distributed quantitative data. The chi-square test and Mann–Whitney *U*-test were used to compare categorical and continuous variables between the two groups, respectively. Receiver operating characteristic (ROC) curves were drawn to assess the predictive power of preoperative FLR for LNM, and the Youden index was utilized to determine the optimal cutoff value of FLR. Variables with P values of < 0.05 in the univariate logistic regression analysis were included in the multivariate analysis to identify the independent indicators of LNM. The association between FLR and the risk of LNM was evaluated on a continuous scale using restricted cubic spline curves based on the multivariate analysis.[25] Sensitivity analysis was performed according to FLR quartiles to further assess the robustness of the results. A nomogram was established based on independent indicators and was then assessed via area under the curve (AUC), calibration curve, and decision curve analysis.[26] The bootstrap method was used to resample 1000 times to obtain the corrected concordance index (C-index) for internal validation.[27] The Delong test was used to compare the AUC value.[28] The Statistical Package for the Social Sciences software for Windows (version 26.0) and R version 4.0.2 were used in this study. All analyses were two-sided, and a P value of < 0.05 was considered statistically significant.

Results

Characteristics of the Patients

The current study enrolled 571 eligible patients in the discovery cohort. Table 1 shows the baseline characteristics of the participants. The incidence rate of LNM in patients with cN0 AGC was 63.0%. The lower portion of the stomach (35.2%) was the common site, followed by the middle portion (31.9%) and the upper portion (21.7%). Approximately 56.9% of the patients presented with T3 stage disease. Meanwhile, 23.8% and 19.3% of patients had T2 and T4 stage disease, respectively. In terms of tumor grade and Lauren type, the patients mainly presented with low differentiation (72.3%) and intestinal type (71.6%), respectively. The positivity rate of LNM was significantly high in the subgroups with a tumor size of ≥ 5 cm (71.7%), CA199 level of ≥ 37 (74.2%), low differentiation (70.2%), and high FLR group (68.9%).

Table 1 Clinicopathological Variables of Patients with cN0 Advanced Gastric Cancer

Variables	Discovery Cohort			P	Validation Cohort			P
	Total	Positive (n = 360)	Negative (n = 211)		Total	Positive (n = 152)	Negative (n = 55)	
Sex				0.226				0.513
Male	450	278	172		150	112	38	
Female	121	82	39		57	40	17	
Age (years)	66 (57–72)	66 (57–72)	66 (58–72)	0.971	67 (60–72)	67 (61–72)	67 (57–71)	0.381
Median (IQR)								
Hypertension				0.916				0.677
No	418	263	155		146	106	40	
Yes	153	97	56		61	46	15	
Diabetes mellitus				0.756				0.281
No	539	339	200		193	140	53	
Yes	32	21	11		14	12	2	
Tumor size (cm)				0.002				0.041
<5	380	223	157		115	78	37	
≥5	191	137	54		92	74	18	
Tumor site				0.265				0.177
Upper	124	79	45		57	41	16	
Middle	182	114	68		55	35	20	
Lower	201	120	81		78	62	16	
Overlap	64	47	17		17	14	3	
T stage				<0.001				0.008
T2	136	37	99		41	23	18	
T3	325	237	88		119	89	30	
T4	110	86	24		47	40	7	
Grade				<0.001				<0.001
Low	413	290	123		161	131	30	
High/Moderate	158	70	88		46	21	25	
Lauren type			1	0.112				0.113
Intestinal type	409	247	162		123	84	39	
Diffuse type	65	45	20		26	22	4	
Mixed type	97	68	29		58	46	12	
Number of dissected nodes	28 (22–35)	29 (23–36)	26 (22–33)	0.010	26 (21–32)	26 (21–32)	26 (21–33)	0.995
Median (IQR)								
CA199 (u/mL)				0.012				0.733
<37	474	288	186		170	124	46	
≥37	97	72	25		37	28	9	
FLR				<0.001				<0.001
Low	221	119	102		38	18	20	
High	350	241	109		169	134	35	

Abbreviations: FLR, fibrinogen-to-lymphocyte ratio; CA19-9, carbohydrate associated antigen 19–9; IQR, interquartile range.

ROC Curve Analysis

As depicted in Figure 2A, based on the ROC curve, the AUC value of FLR for predicting LNM in patients with cN0 AGC was 0.592. The sensitivity and specificity of FLR for predicting LNM were 66.9% and 48.3%, respectively. Further, patients were divided into the high and low groups based on the optimum FLR cutoff value (1.78). In addition, the Delong test analysis showed that the FLR had comparable predictive ability with the CA199 (p value > 0.05) (Figure 2B).

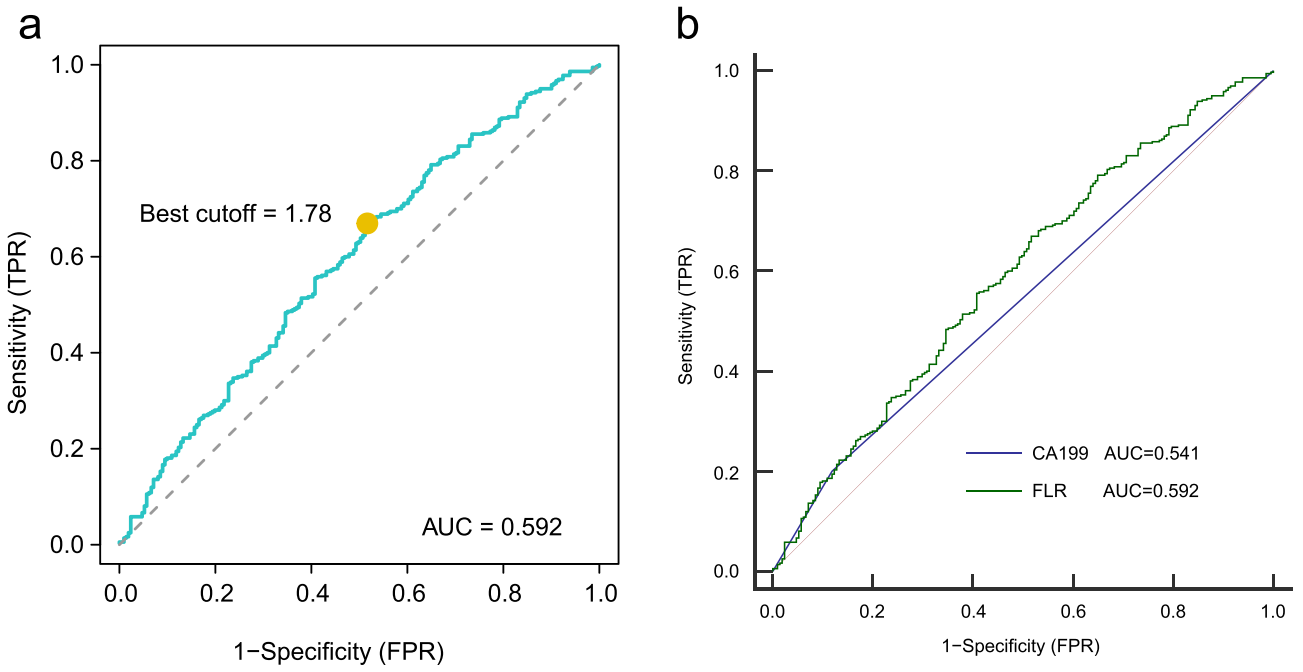

Figure 2 (**A**) The ROC curve of FLR for predicting LNM in patients with cN0 AGC. (**B**) Receiver operating curves of the FLR and the CA199 for prediction of LNM in patients with cN0 AGC.
Abbreviations: FLR, fibrinogen-to-lymphocyte ratio; ROC, receiver operating characteristic; LNM, lymph node metastasis; AGC, advanced-stage gastric cancer.

Univariate and Multivariate Logistic Regression Analyses

According to the results of the univariate analysis, T stage, grade, tumor size, number of dissected nodes, CA199 level, and FLR were significantly correlated with LNM (all $P < 0.05$). The multivariate analysis showed that T stage ($P < 0.001$), grade ($P < 0.001$), and FLR ($P = 0.009$) were independent risk indicators of LNM (Table 2). Furthermore, the sensitivity analysis confirmed the robustness of these findings (P for trend = 0.013) (Supplementary Table 1). As shown in Supplementary Figure 1, based on the restricted cubic spline curve, there was a linear association between FLR and the risk of LNM (P for non-linearity > 0.05). Moreover, the risk of LNM increased with a higher FLR.

Table 2 Logistic Analyses the Predictors of Lymph Node Metastasis in Patients with cN0 Advanced Gastric Cancer

Variables	Discovery Cohort				Validation Cohort	
	Univariate Analysis		Multivariate Analysis		Multivariate Analysis	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Sex						
Female	Ref					
Male	0.77 (0.50–1.17)	0.226				
Age (years)	1.00 (0.98–1.02)	0.933				
Median (IQR)						
Hypertension						
No	Ref					
Yes	1.02 (0.70–1.50)	0.916				
Diabetes mellitus						
No	Ref					
Yes	1.13 (0.54–2.47)	0.756				

(*Continued*)

Table 2 (Continued).

Variables	Discovery Cohort				Validation Cohort	
	Univariate Analysis		Multivariate Analysis		Multivariate Analysis	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Tumor size (cm)						
< 5	Ref		Ref		Ref	
≥ 5	1.79 (1.23–2.61)	0.002	1.01 (0.66–1.56)	0.958	1.33 (0.61–2.93)	0.478
Tumor site						
Upper	Ref					
Middle	0.95 (0.59–1.53)	0.849				
Lower	0.84 (0.53–1.34)	0.471				
Overlap	1.57 (0.82–3.12)	0.180				
T stage						
T2	Ref		Ref		Ref	
T3	7.21 (4.63–11.41)	<0.001	6.70 (4.19–10.91)	<0.001	1.63 (0.66–4.01)	0.284
T4	9.59 (5.40–17.59)	<0.001	7.08 (3.84–13.44)	<0.001	2.40 (0.74–8.26)	0.151
Grade						
High/Moderate	Ref		Ref		Ref	
Low	2.96 (2.03–4.34)	<0.001	2.65 (1.73–4.06)	<0.001	4.91 (2.28–10.80)	<0.001
Lauren type		0.114				
Intestinal type	Ref					
Diffuse type	1.48 (0.85–2.64)	0.175				
Mixed type	1.54 (0.96–2.51)	0.077				
Number of dissected nodes	1.02 (1.01–1.04)	0.010	1.02 (1.00–1.04)	0.056	0.99 (0.95–1.03)	0.651
Median (IQR)						
CA199 (u/mL)						
< 37	Ref		Ref		Ref	
≥ 37	1.86 (1.15–3.09)	0.013	1.40 (0.82–2.45)	0.233	0.72 (0.29–1.88)	0.483
FLR						
Low	Ref		Ref		Ref	
High	1.90 (1.34–2.69)	<0.001	1.70 (1.14–2.53)	0.009	4.54 (1.99–10.60)	<0.001

Abbreviations: CA19-9, carbohydrate associated antigen 19–9; FLR, fibrinogen-to-lymphocyte ratio; OR, odds ratio; CI, confidence interval.

Comparison of Clinicopathological Characteristics Between the High and Low FLR Group

As shown in Supplementary Table 2, there were no significant differences in terms of sex, presence of hypertension and diabetes mellitus, tumor site and grade, Lauren type, and the number of dissected nodes between the high and low FLR groups. However, age, tumor size, T stage, CA199 levels, and incidence rates of LNM significantly differed between the two groups. The distribution of FLR value significantly differed among the subgroups classified according to T stage ($P = 0.027$) and tumor size ($P < 0.001$) (Figure 3).

Establishment and Validation of the Nomogram

T stage, grade, and FLR are the independent indicators in the multivariate analysis. These parameters were selected to establish a nomogram for predicting LNM in patients with cN0 AGC (Figure 4A). According to the calibration curve, the predicted probabilities of the model were consistent with the actual probabilities (Hosmer−Lemeshow test, $P = 0.503$) (Figure 4B). In addition, the C-index of internal validation was 0.755. The AUC of the nomogram was 0.741 (95% confidence interval: 0.703–0.777), and it was significantly better than that of T stage (0.696; 95% confidence interval: 0.656–0.0.733, $P < 0.001$) or grade (0.611; 95% confidence interval: 0.570–0.652, $P < 0.001$) alone (Figure 4C). Decision curve analysis revealed that the model had higher clinical usefulness than T stage, grade, or FLR alone (Figure 4D).

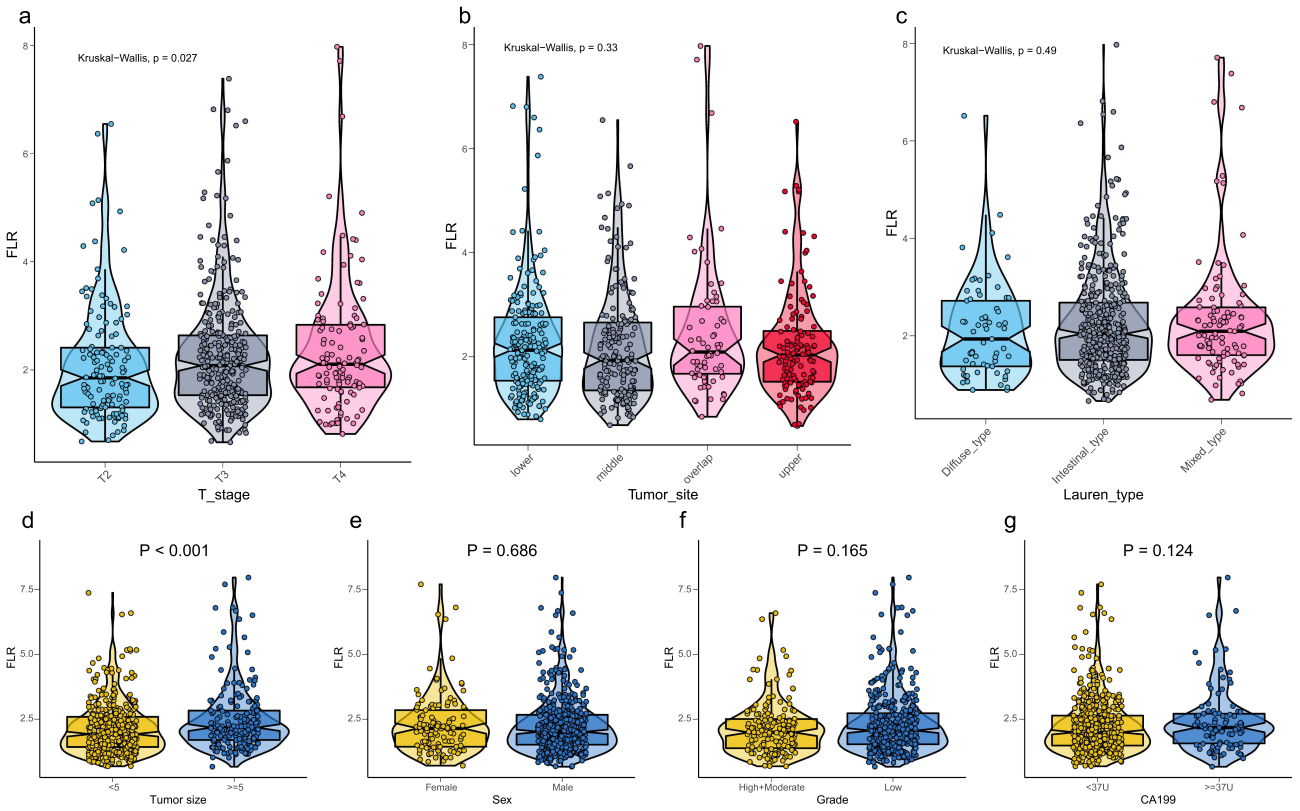

Figure 3 Distribution of FLR in terms of different clinicopathological variables. (**A**) T stage. (**B**) Tumor site. (**C**) Lauren type. (**D**) Tumor size. (**E**) Sex. (**F**) Grade. (**G**) CA199.

Abbreviation: FLR, fibrinogen-to-lymphocyte ratio.

FLR is a Independent Risk Indicator in the Validation Cohort

In the validation cohort, we divided patients into high and low FLR groups according to the cutoff value of discovery cohort. The multivariate analysis validated that FLR ($P < 0.001$) was an independent indicator of LNM (Table 2).

Discussion

The current study reported the use of FLR, a novel indicator, for independently predicting LNM in patients with cN0 AGC. Results showed that patients with a high FLR level are more likely to develop LNM, and the risk of LNM increases with high FLR. In addition, a nomogram for individual risk assessment based on FLR and clinicopathological characteristics showed good performance.

Tumor cells can activate the hemostatic system via different mechanisms, including the release of procoagulant tissue factors, cancer procoagulants and microparticles, soluble factors, and direct adhesive contact to activate the host's hemostatic cells (endothelial cells and platelets).[29] Fibrinogen, a hemostatic factor, is an important determinant of the metastatic potential of tumor cells, and its mechanisms of action are as follows: acts as a bridge to support the adhesion of tumor cells to the vascular endothelium; combines with other proteins and deposited on the extracellular matrix to form a stable scaffold; and promotes tumor proliferation and stimulates angiogenesis by supporting the binding of various growth factors to tumor cells.[30,31] As early as 2005, Yamashita et al retrospectively analyzed the preoperative plasma fibrinogen levels of 649 patients with GC undergoing surgery. Results showed that hyperfibrinogenemia may provide a favorable environment for cancer cell metastasis via the lymphatic system.[15] Previous studies have shown that fibrinogen can increase the metastatic potential by disrupting the clearance of tumor cells by natural killer cells, and it also reflects the connection between fibrinogen and the immune system in the process of cancer metastasis.[32] Recently, a multivariate analysis evaluated 136 patients with GC undergoing surgery. Results showed that fibrinogen levels were significantly associated with lymph node involvement in patients with GC.[33]

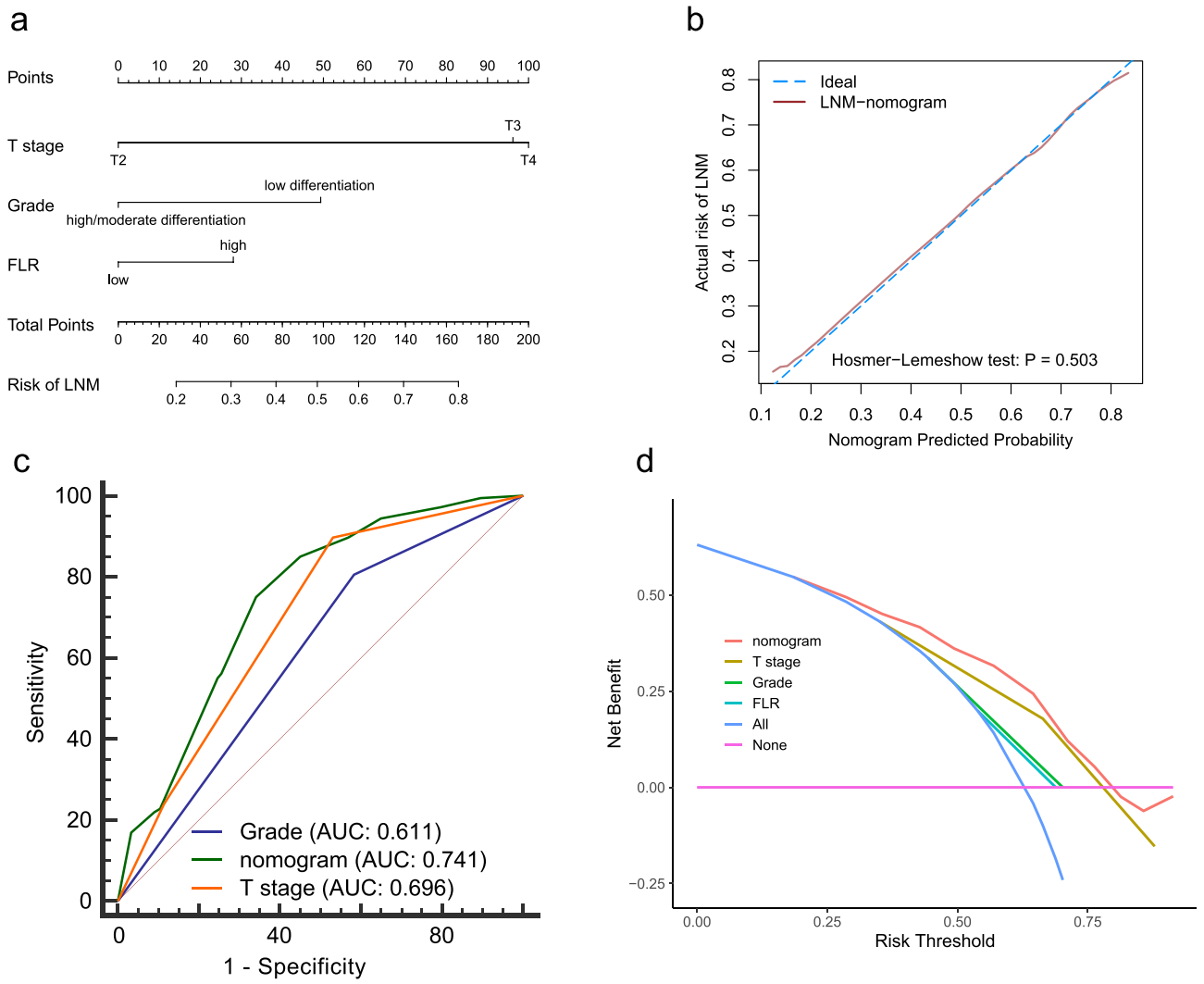

Figure 4 Development and evaluation of the nomogram for predicting LNM in patients with cN0 AGC. (**A**) Nomogram. (**B**) Calibration curves. (**C**) ROC curves. (**D**) Decision curve analysis.

Lymphocytes are an important component of the immune system, can destruct tumor cells, and can participate in mediating anti-tumor host immune responses in the tumor microenvironment.[34] Tumor-infiltrating lymphocytes (TILs) mainly include T cells, B cells, and natural killer cells, and the low expression of TILs will promote tumor invasion and metastasis.[35] Kim et al found that low TILs and submucosal invasion were independent predictors of LNM in early-stage GC.[34] In recent years, lymphocytes are often selected to construct some novel predictive biomarkers and are widely used in the prediction of LNM in patients with GC. Kosuga et al found that the preoperative neutrophil-to-lymphocyte ratio may be a useful complementary diagnostic tool for predicting LNM in AGC.[36] Du et al showed that a low preoperative lymphocyte-to-monocyte ratio was positively correlated with LNM in patients with GC.[13] Tong et al used the derived monocyte-to-lymphocyte ratio for predicting LNM in patients with gastric signet ring cell carcinoma.[21]

FLR, combined with hemagglutination and inflammation markers, have a potential prognostic value in different types of cancers, such as non-small cell lung cancer, esophageal cancer, liver cancer, and head and neck adenoid cystic carcinoma.[16–19] In addition, Huang et al found that a high FLR level was a risk factor for peritoneal metastasis in GC.[20] The current study first reported the association between FLR and LNM in patients with AGC.

An accurate assessment of preoperative lymph node status in patients with AGC is important for determining whether to provide neoadjuvant chemotherapy and the extent of surgical lymph node dissection. Due to the low accuracy of imaging assessment of cN, in patients with cN0 stage, the use of FLR to assist imaging examinations, such as contrast-

enhanced abdominal CT scan, to identify unsuspected LNM involvement has clinical value. Moreover, this indicator can be obtained by collecting blood samples from the peripheral veins, which has the advantages of simple procedures, less invasiveness and low cost.[37]

The current study had several limitations. First, this was a retrospective study, and selection bias could not be avoided. Second, the study only included patients from a single hospital, which limits the generalisability of our findings. Therefore, prospective large-scale multicenter studies should be performed to validate our findings. Third, this study only included patients who underwent radical gastrectomy, which may not be representative of the overall population of AGC patients. Fourth, in the current study, the predictors of T stage and grade were determined via postoperative pathological examination. Although preoperative ultrasound gastroscopy and gastroscopic biopsy have good power to obtain preoperatively evaluation parameters in terms of them, there are still certain differences between preoperative diagnosis and pathological results.[38] The inclusion of postoperative parameters in the preoperative assessment might have caused some bias.

Conclusion

We found that FLR is a low-cost, accessible, and potentially novel serological marker that independently predicts LNM in patients with cN0 AGC.

Ethical Statement

This study was approved by the institutional review board of Yijishan Hospital of Wannan Medical College (2022-027). The need for informed consent was waived given the retrospective nature of this study. Identifying information was removed to protect patient confidentiality. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Disclosure

The authors report no conflicts of interest in this work.

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