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A Nomogram Combining Neutrophil-to-Lymphocyte Ratio and D-Dimer Predicts Chemosensitivity of Oxaliplatin-Based First-Line Chemotherapy in Patients with Unresectable Advanced Gastric Cancer

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Abstract

Introduction: No effective peripheral blood predictors have been estabioshed for first-line chemotherapy in patients with advanced gastric cancer. In this study, a nomogram combining the neutrophil-to-lymphocyte ratio/D-dimer with gender, number of metastases, and histological grade was established to predict progression-free survival in patients with unresectable advanced gastric cancer. **Methods:** We retrospectively collected baseline clinical characteristics and blood parameters from 153 patients diagnosed with advanced gastric cancer that underwent oxaliplatin-based first-line chemotherapy. Kaplan–Meier analysis and Cox regression analysis were used to determine the factors associated with progression-free survival. The concordance index (C-index) and calibration curve were used to determine the prediction accuracy and discriminative ability of the nomogram as a visual complement to the prognostic score system. **Results:** Determined by the X-tile software, the optimal cut-off points for the neutrophil-to-lymphocyte ratio and D-dimer were 3.18 and 0.56 mg/L, respectively. Multivariate analysis identified four independent prognostic factors: two or more metastatic organs (HR: 1.562, 95% CI: 1.009-2.418, $P = .046$), poor differentiation (HR: 0.308, 95% CI: 0.194-0.487, $P < .001$), neutrophil-to-lymphocyte ratio >3.18 (HR: 1.427, 95% CI: 1.024-1.989, $P = .036$), and D-dimer >0.56 mg/L (HR: 1.811, 95% CI: 1.183-2.773, $P = .006$). Receiver operating characteristic curves showed that the combination of the neutrophil-to-lymphocyte ratio and D-dimer in the prediction model exhibited the highest predictive performance (area under the curve, 0.800). The prognostic nomogram yielded a C-index of 0.800. Decision curve analysis demonstrated that the prognostic nomogram was clinically useful. A nomogram-based risk classification system was also constructed to facilitate risk stratification of advanced gastric cancer for optimal clinical management. **Conclusion:** We identified the neutrophil-to-lymphocyte ratio and D-dimer level as independent prognostic factors for advanced gastric cancer. The prognostic nomogram combining the neutrophil-to-lymphocyte ratio and D-dimer level can be applied in the individualized prediction of treatment outcome in patients with advanced gastric cancer.

Keywords

advanced gastric cancer, NLR, D-dimer, prognostic factor, prognostic model, first-line chemotherapy

Abbreviations

AGC, advanced gastric cancer; AUC, are under the curve; CI, confidence interval; C-index, concordance index; CR, complete response; DCR, disease control rate; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PD,

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progressive disease; PFS, progression-free survival; PR, partial response; RECIST, the Response Evaluation Criteria in Solid Tumors; ROC, receiver operating characteristic; SD, stable disease

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Introduction

Gastric cancer remains the third highest cause of death from malignancy worldwide.[1] In East Asia including Korea, Japan, and Mongolia, the incidence of gastric cancer is high,[2] and China had 478 508 new cases and 373 789 deaths from gastric cancer in 2020.[3] Due to the insidious onset and lack of specific symptoms in the early stage, most patients in developing countries are diagnosed late and cannot undergo radical surgery. Current treatments for advanced gastric cancer (AGC) include palliative gastrectomy, radiation therapy, chemotherapy, molecular targeted therapy, and immunotherapy. At present, oxaliplatin-based chemotherapy remains the main treatment for locally AGC, tumor recurrences, or metastases.[4] However, many patients must give up further treatment for economic reasons in less developed areas. Previous studies have shown that some tumor endogenous factors, such as the differentiation status or gene expression, can influence the effectiveness of chemotherapy. However, whether other affordable pre-treatment predictors can better predict progression-free survival (PFS) in patients with unresectable AGC is unclear. Determining these predictors may help optimize clinical strategies.[5]

Systemic inflammation has been reported to play an important role in the progression of various cancers.[6–8] Circulating inflammatory cells can release a variety of active biological factors, leading to tumor growth, progression, and metastasis.[9–11] Furthermore, abnormal blood clotting is common in cancer patients, and their hypercoagulable state is also related to angiogenesis, tumor growth, spread, and metastasis, resulting in a poor prognosis. For this reason, D-dimers have been found to reflect fibrinolysis and activation of the coagulation cascade. For example, studies have shown that D-dimer can be used as a prognostic marker for tumor indications in colorectal,[12] lung,[13] liver,[14] ovary,[15] and gastric cancer progression.[16] The platelet count is another widely used marker that can be easily obtained from the parameters of whole blood cells. Such prognostic factors are critical to cancer risk stratification, medical treatment, and clinical research. In addition, increasing evidence demonstrates that the neutrophil-to-lymphocyte ratio (NLR) and platelet count can be used to predict gastric cancer.[17,18] Moreover, a high NLR and elevated D-dimer levels can independently predict poor prognosis of gastric cancer. However, evidence on the relationship between NLR, D-dimer levels, and the predictive role of these indicators in patients with AGC receiving oxaliplatin-based first-line chemotherapy is lacking.

In this study, we developed a new prognostic score combining the NLR and D-dimer levels and established a nomogram combining multiple inflammatory indicators to find the best parameters for predicting survival and clinical responses to first-line chemotherapy in patients with metastatic gastric cancer.

Materials and Methods

Patients and Eligibility Criteria

Data from all patients diagnosed with AGC at Anhui Provincial Hospital from January 2016 to December 2020 were retrospectively reviewed. The inclusion criteria for study participation were as follows: (1) age ≥18 years; (2) unresectable locally advanced gastric cancer, metastatic gastric cancer, or gastroesophageal junction adenocarcinoma confirmed by histopathology or cytology; (3) first-line chemotherapy of an oxaliplatin-based regimen; (4) relapsed more than six months after the end of adjuvant/neoadjuvant chemotherapy (oxaliplatin combined with fluorouracil) or not at all; (5) at least one evaluable lesion; (6) at least two cycles of non-targeted drugs (such as trastuzumab, etc) in combination with first-line palliative chemotherapy; and (7) underwent at least one efficacy evaluation. According to Norman et al,[19] the sample size for multivariable analyses had to be >20 times the number of variables, due to the retrospective nature of the study.

Clinical Data Collection

Clinical data including age, gender, tumor metastasis condition, first-line chemotherapy regimen, and first evaluation result were collected. Blood parameters were recorded before chemotherapy, including the white blood cell count, absolute neutrophil count, absolute lymphocyte count, number of red blood cells, hemoglobin concentration, total platelet count, mean platelet volume, albumin, fibrinogen, D-dimer, serum LDH, serum CEA, and serum CA199 levels. Then, the quantitative values of the NLR, platelet-to-lymphocyte ratio, and SII (total platelet count × absolute neutrophil count / absolute lymphocyte count) were calculated. The chemotherapy regimen was an oxaliplatin-based combination chemotherapy regimen consisting of oxaliplatin, leucovorin, and 5-FU (modified FOLFOX); oxaliplatin and capecitabine (XELOX); or oxaliplatin and S-1 (SOX). The RECIST criteria were used to assess chemotherapy efficacy after two cycles. The disease control rate (DCR) was defined as stable disease (SD), partial response (PR), or complete response (CR). Additionally, PFS was defined as the time from randomization to death or disease progression.

Statistical Analysis

Data were analyzed using SPSS (IBM SPSS 26.0, SPSS Inc), R software (version 3.6.1, http://www.r-project.org), and GraphPad Prism (GraphPad Prism 9.0, USA). Additionally, X-tile version 3.6.1 was applied to determine the optimal

cut-off points. The area under the curve (AUC) was used to assess the diagnostic value of the pre-treatment blood indicators, the Chi-squared test or Fisher's exact test was used for rate comparison, and Student's t-test was used for normal distribution data comparison. Univariate and multivariate analyses were performed to identify the independent predictors for PFS, and the *rms* package was used to generate a nomogram based on the logistic regression model. We used the Harrell consistency index (C-index) to determine the discriminative ability of the nomogram. The C-index is a value between 0.5 and 1.0, where 0.5 represents random probability, and 1.0 represents the perfect ability of the model to correctly predict the result. The calibration curve of the nomogram for estimating the PFS was then built, and decision curve analyses were performed. The total points of each patient were determined using the standard logistic model, and three groups of patients with differing prognostic risks (based on total points) were demarcated using the X-tile program. The Kaplan–Meier method was used to illustrate survival curves, which were compared using the log-rank test with the dichotomized risk group as a factor. Every statistical test was two-sided and statistical significance was set at $P < .05$ for all analyses.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Anhui Provincial Hospital. The requirement for informed consent was waived by the ethics committee due to the retrospective nature of the study. Additionally, we de-identified all patient details for this study.

Table 1. The Characteristics of 153 Patients with AGC.

Characteristics	Cases(n)	%
Gender		
Male	110	71.9
Female	43	28.1
Age		
<65	89	58.2
≥65	64	41.8
x ± s	61.24 ± 11.78	
First-line chemotherapeutic regimen		
Sox	72	47.1
Xelox	43	28.1
Folfox	38	24.8
Histologic diffrentiation		
Well and moderate	30	19.6
Poor	123	80.4
Number of distant metastases		
1	126	82.4
≥ 2	27	17.6
First evaluation results		
CR	0	0
PR	18	11.8
SD	110	71.9
PD	25	16.3
Progress-Free Survival (months)		
<6.0	91	59.5
≥6.0	62	40.5
x ± s	5.87 ± 4.55	

Results

Patient Characteristics

A total of 153 patients with AGC were included in this study, of which 110 (71.9%) were male and 43 (28.1%) were female. The median age at diagnosis was 61 years (range 29-86 years). Regarding histologic grade, 123 (80.4%) patients had poorly differentiated tumors, while 30 (19.6%) had moderate or well differentiated tumors. Moreover, a total of 27 patients (27.8%) had at least two distant organ metastases. Additionally, 38 (24.8%), 43 (28.1%), and 72 (47.1%) patients underwent chemotherapy with fluorouracil/leucovorin/oxaliplatin (FOLFOX), capecitabine/oxaliplatin (XELOX), and oxaliplatin/S-1 (SOX), respecitvely. The characteristics of all patients are shown in Table 1. The median values of the pre-treatment NLR and D-dimer levels were 3.84 and 2.09, respectively.

Cut-off Value for NLR and D-Dimer Level

According to the mean PFS value (5.87 ± 4.55 months), the optimal cut-off value for the NLR and D-dimer level was analyzed using X-tile software (survival time cut-off for PFS at six months). The optimal cut-off value of the NLR was calculated to be 3.18 and the D-dimer level was calculated as 0.56 ug/mL. Thus, patients were classified as high NLR (NLR >3.18) (n = 72), low NLR (NLR ≤ 3.18) (n = 81), high D-dimer (D-dimer > 0.58 ug/mL) (n = 122), and low D-dimer (D-dimer ≤ 0.58) (n = 31) (Figure 1).

Association Between Baseline Blood Parameters and Clinical Characteristics

The Chi-squared test demonstrated the difference between the baseline blood parameters and clinical characteristics. Gender, age, chemotherapy regimen, histologic grade, number of distant metastases, and results of the first evaluation showed no difference in blood parameter groups before treatment. However, PFS (≥6 months vs <6 months) among all blood parameter groups showed a significant difference. Moreover, gender differed among the pre-treatment D-dimer groups (Table 2). Finally, the NLR and D-dimer were positively correlated ($r^2 = 0.17$, $P < .0001$; Figure 1C).

PFS in Patients with Various Clinical Characteristics and Blood Parameters

Student's t-test demonstrated the variation of PFS between different clinical and blood parameter groups. PFS showed no statistical difference in gender, age, or platelet count. However, patients with well or moderate differentiation had longer PFS than those with poor differentiation ($P = .001$). Additionally, those with only one distant metastatic organ had longer PFS than those with two or more metastatic organs ($P = .0034$).

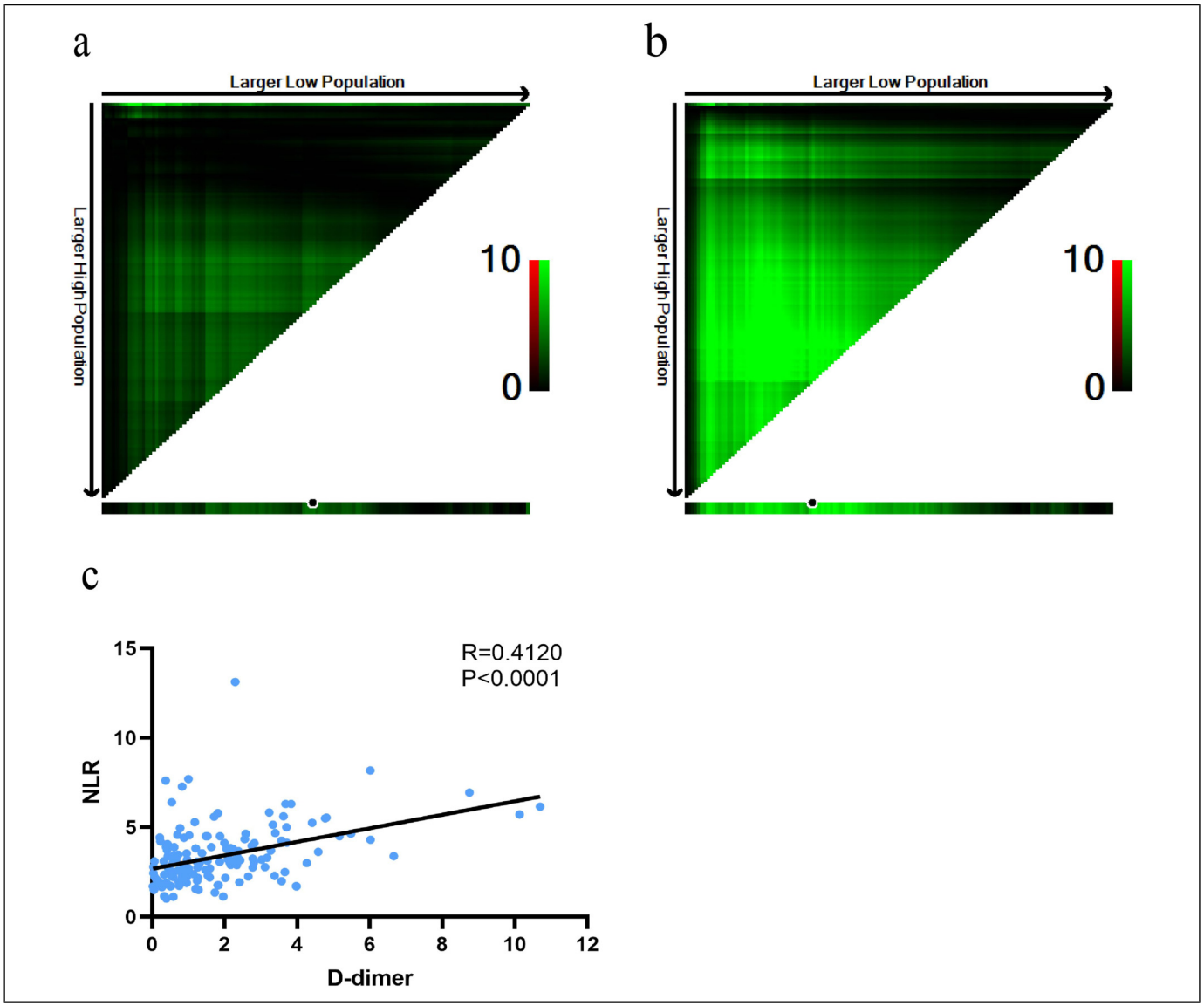

Figure 1. Cut-off values for the pretreatment blood parameters determined by X-tile software Abbreviations: NLR, neutrophil to lymphocyte ratio (A); D-dimer (B), correlation analysis between NLR and D-dimer(C).

Moreover, the first-time evaluation results showed that the ORR group had longer PFS than the no-ORR group ($P = .0461$), and the DCR group had longer PFS than the no-DCR group ($P < .0001$). In the low NLR group (6.785 ± 5.332 months), PFS was longer than in the high NLR group (4.840 ± 3.200 months) ($P = .0064$); similarly, in the low D-dimer group (8.105 ± 4.525 months), PFS was longer than in the high D-dimer group (5.302 ± 4.395 months) ($P = .0020$) (Figure 2).

Kaplan-Meier Analysis among Blood Parameters

Kaplan–Meier analysis showed that PFS of the high NLR group was shorter than that of the low NLR group in 153 patients ($P = .0087$). Additionally, the PFS of patients in the high D-dimer group was shorter than that of those in the low D-dimer group. All survival curves are shown in Figure 3A-E.

Univariate and Multivariate Analysis of Clinical and Blood Parameters

To understand the relationship between clinical features and PFS, univariate analysis including gender, age, histologic grade, number of distant metastases, NLR, and D-dimer was performed. The histologic grade, number of distant metastases, NLR, and D-dimer level were risk factors that significantly influenced PFS (Table 3). Then, gender, histologic grade, number of distant metastases, NLR, and D-dimer level were analyzed by multivariate Cox regression analysis. The results of multivariate analysis indicated that gender (HR: 1.062, 95% CI: 0.721-1.563, $P = .761$), number of distant metastases (HR: 1.562, 95% CI: 1.009-2.418, $P = .046$), histologic grade (HR: 0.308, 95% CI: 0.194-0.487, $P < .001$), NLR (HR: 1.427, 95% CI: 1.024-1.989, $P = .036$), and D-dimer level

Table 2. Correlation Between Hematological Parameters and Clinical Features of 153 Patients with AGC by Chi-Square Test.

Characteristics	NLR			D-dimer		
	NLR ≤ 3.18 N = 81	NLR > 3.18 N = 72	*P*	D-dimer ≤ 0.56 N = 31	D-dimer > 0.56 N = 122	*P*
Gender			.525			.011
Male	60	50		28	82	
Female	21	22		3	40	
Age			.969			.989
≤65 years old	47	42		18	71	
>65 years old	34	30		13	51	
First-line chemotherapeutic regimen			.448			.367
Sox	42	30		15	57	
Xelox	21	22		11	32	
Folfox	18	20		5	33	
Histologic grade						
Well or moderate	16	14	.962	9	21	.139
Poor	65	58		22	101	
Number of distant metastases						
1	66	60	.764	27	99	.438
≥ 2	15	12		4	23	
First evaluation results			.156			.562
DCR(CR + PR + SD)	71	57		27	101	
PD	10	15		4	21	
Progress-Free Survival (months)			.007			<.001
<6.0	40	51		8	83	
≥6.0	41	21		23	39	

(HR: 1.811, 95% CI: 1.183-2.773, $P = .006$) were independent prognostic factors of PFS (Table 3).

Predictive Efficacy of NLR, D-Dimer Level, and Clinical Prognostic Factors

According to the median survival time (six months), the patients were classified as having good or poor prognosis. Receiver operating characteristic (ROC) curve analysis demonstrated the performance of the NLR for the prediction of prognosis to have a specificity and sensitivity of 66.10% and 56.00%, respectively (AUC = 0.618). The AUC of the D-dimer level was 0.67, with a specificity and sensitivity of 40.35% and 90.48%, respectively. For predicting the prognosis of patients with AGC after chemotherapy, the combined model had the highest AUC (AUC = 0.800, 95% CI: 0.737-0.879) (specificity = 90.1%, sensitivity = 58.1%). The ROC curves are presented in Figure 4A.

Development and Performance of the Prognostic Nomogram

The prognostic nomogram was based on gender, histologic grade, number of distant metastases, NLR, and D-dimer level. Each factor was assigned a weighted number of points. The total number of points for each patient was calculated using the prognostic nomogram and was associated with an estimated probability of a short PFS (Figure 4B). The prognostic nomogram yielded a C-index of 0.800. To further assess the predictive accuracy of the nomogram, we plotted a calibration curve with lines drawn close to the diagonal, indicating that the nomogram is accurate relative to the prediction (Figure 4C).

We then used decision curve analysis to assess whether this nomogram could help guide clinical treatment strategies (Figure 4D). The decision curve showed relative performances of the prognostic nomogram consisting of the NLR, gender, histologic grade, number of distant metastases, and D-dimer level. Throughout most of the range of reasonable threshold probabilities, the decision curve analysis showed that the combined model had the most net benefit compared with a "treat all" strategy, a "treat none" strategy, the NLR only model, and the D-dimer only model.

Risk Classification System

In addition to the prognostic nomogram, we also established a risk classification system to classify patients as low-, medium-, and high-risk and rate each patient using the nomogram assessment method based on the total number of patients (Table 4). According to the best cut-off value obtained from the X-tile program, a score of 0–121 indicated low-risk, 122–190 indicated intermediate-risk, and 191–246 indicated high-risk. The Kaplan–Meier curves indicated that the risk classification system could accurately identify the prognosis of different risk groups (Figure 3F). Patients of low-risk had the best prognosis (median 8.6 months), while those of high-risk had the

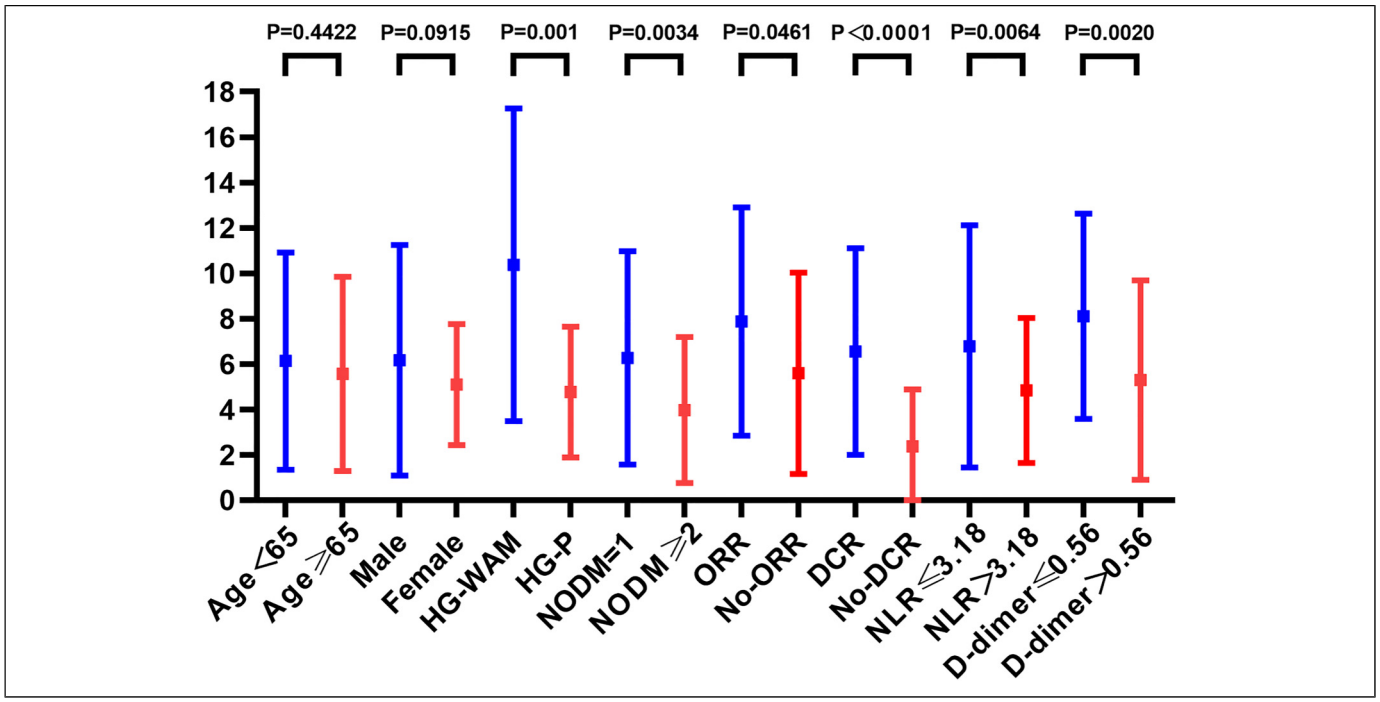

Figure 2. Student's t-test for progress-free survival (PFS) between different clinical features and blood parameters. (A) Comparison of mean progress-free survival (PFS) between the different clinical feature groups; (B) comparison of mean progress-free survival (PFS) between the different blood parameter groups. Abbreviations: HG-WAM group, patient's histologic grade is well or moderate; HG-P group, patient's histologic grade is poor; NODM = 1, patients had a distant organ metastasis; NODM≥ 2 group, patients had 2 or more ≥ 2 metastatic organs; ORR group, the first-time evaluation results was CR or PR; No-ORR group, the first-time evaluation results was SD or PD; DCR group, the first-time evaluation results was CR or PR or SD; No-DCR group, the first-time evaluation results was PD; NLR, neutrophil to lymphocyte ratio.

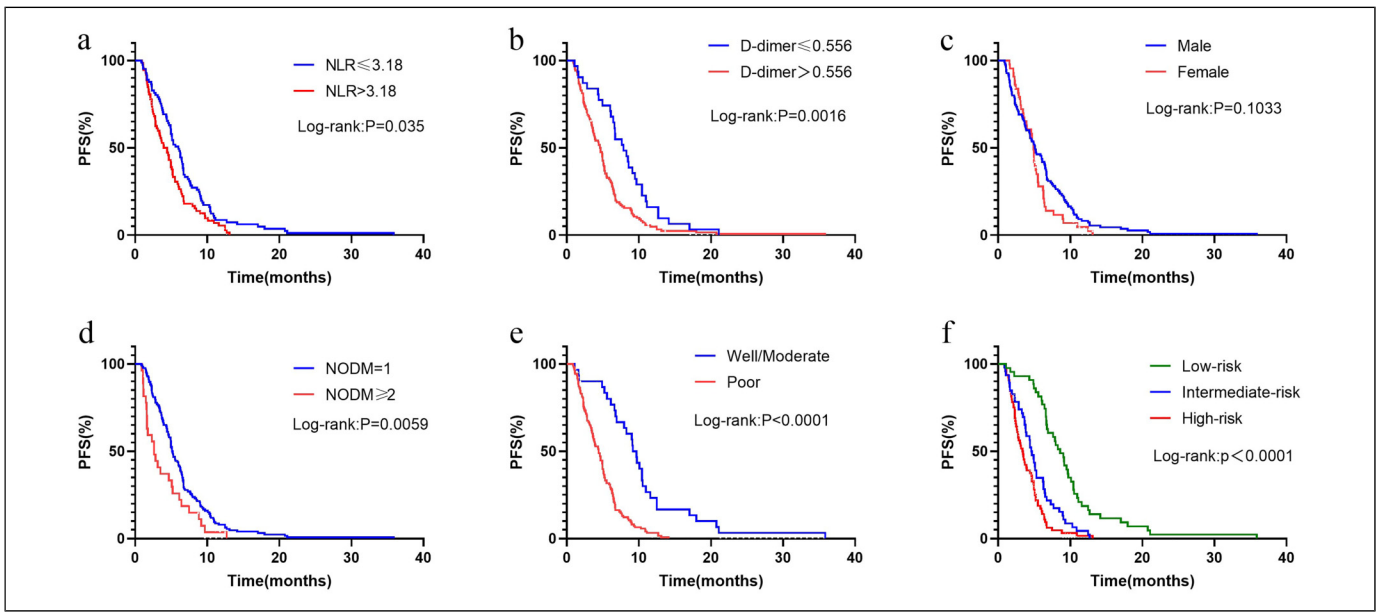

Figure 3. Kaplan–Meier curves demonstrating progress-free survival according to (A) NLR, (B) D-dimer, (C) Gender, (D) NODM, (E) HG, (F) low-, intermediate-, and high-risk patients. Abbreviations: NLR, neutrophil to lymphocyte ratio; NODM, number of distant metastasis; HG, histological grade.

Table 3. Cox Univariate and Multivariate Analyses of Clinical Parameters for PFS Prediction.

Variables	Univariate analysis Hazard ratio	[95% CI]	*P* value	Multivariate analysis Hazard ratio	[95% CI]	*P* value
Gender(male vsfemale)	1.347	[0.939-1.933]	.106	1.062	[0.721-1.563]	.761
Age(≤65y vs>65y)	1.050	[0.758-1.453]	.771			
Metastasis number (1 vs≥2)	1.783	[1.172-2.713]	.007	1.562	[1.009-2.418]	.046
Histologic differentiation (Well to moderate vs Poor)	0.309	[0.198-0.483[	<.001	0.308	[0.194-0.487]	<.001
NLR(≤3.18 vs>3.18)	1.535	[1.108-2.126]	.010	1.427	[1.024-1.989]	.036
D-dimer(≤0.56 vs>0.56)	1.880	[1.259-2.806]	.002	1.811	[1.183-2.773]	.006

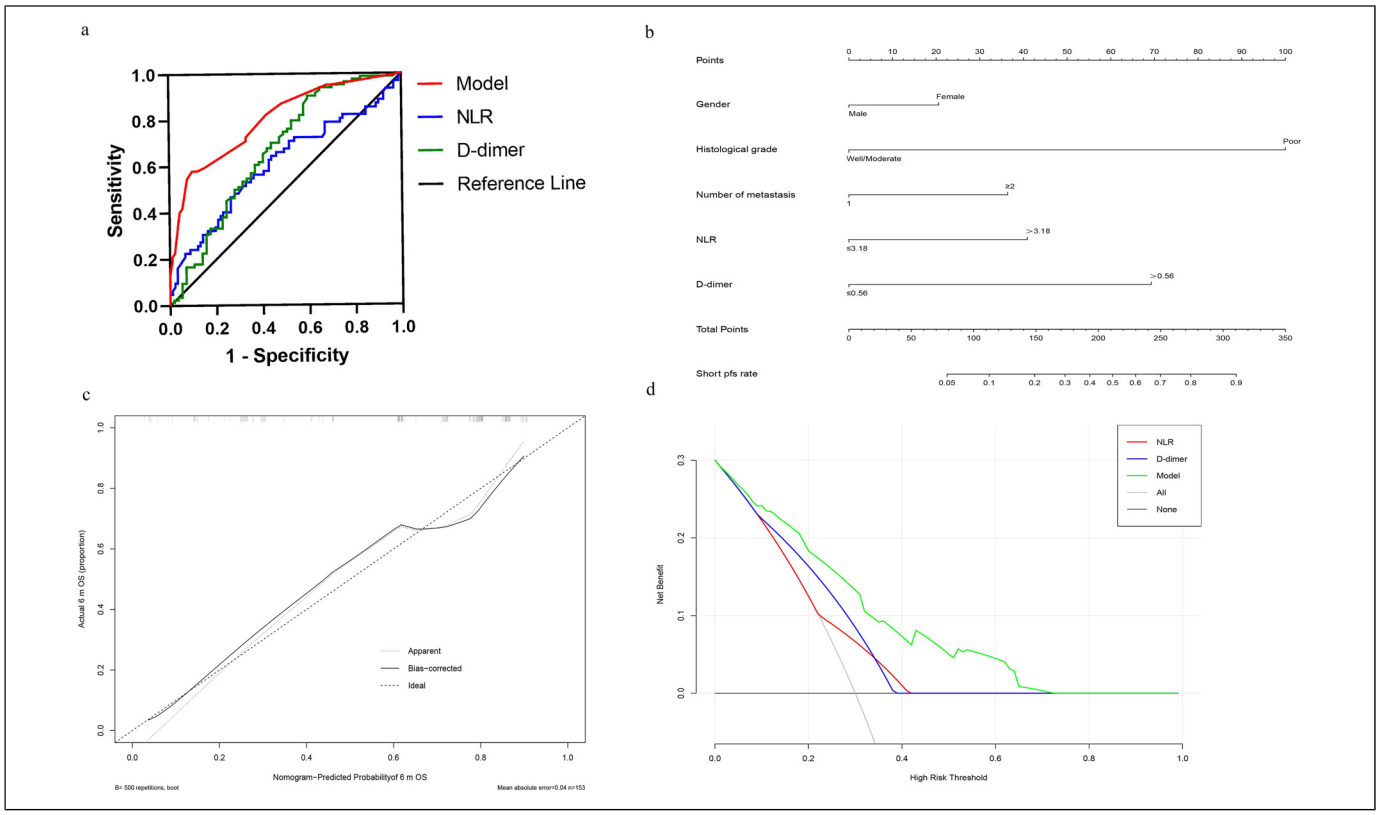

Figure 4. (A) The ROC curves of NLR, D-dimer, and the model for predicting prognosis in patients with AGC before chemotherapy. (B) Nomogram, including gender, histologic grade, number of distant metastases, NLR, and D-dimer, for short PFS rate in patients with AGC before chemotherapy. (C) The calibration curves of the nomogram of the mode. (D) Decision curve analysis (DCAs). The net benefit is shown on the y-axis and the threshold probability is shown on the x-axis. Use of the model (green line) achieves the highest net benefit compared with the NLR (red line), D-dimer (blue line), treat-all strategy (gray line), and the treat none strategy (horizontal black line). Abbreviation: NLR, neutrophil to lymphocyte ratio.

worst prognosis (median 3.4 months), and intermediate-risk patients had a median PFS of 4.7 months.

Discussion

Several studies have evaluated the relationship between blood parameters and gastric cancer; however, most have evaluated the results of surgery, radiotherapy, and postoperative chemotherapy.[20–22] Thus, the relationship between PFS after therapy for AGC and blood parameters had not been fully evaluated. In this study, we developed a nomogram using laboratory markers of pre-chemotherapy hematology and systemic inflammatory response to improve prognostic prediction in patients with AGC after chemotherapy. A nomogram is a graphical representation of a complex mathematical formula, which is simpler and more advanced than analyzing blood parameters. Our study showed that improved serum D-dimer levels and a higher pre-chemotherapy NLR were independent negative

Table 4. Score Assignment and Risk Stratification.

Features	Category	Score
Gender	Male	0
	Female	21
Histologic differentiation	Well and moderate	0
	Poor	100
Metastasis	1	0
	≥2	36
NLR	≤3.18	0
	>3.18	41
D-Dimer	≤0.56	0
	>0.56	69
Risk classification	Low-risk	0-121
	Intermediate-risk	122-190
	High-risk	191-246

predictors of PFS. In previous studies, gender, cell differentiation, and distant metastases have been demonstrated to be prognostic factors.[23–26]

The mechanisms underlying the relationship between NLR preconditioning and prognosis in patients with inoperable gastric cancer receiving systemic therapy are unclear, but many studies provide possible explanations.[27–29] In summary, most neutrophils promote tumor progression by suppressing immune activity, while lymphocytes are considered the most important effector cells in immunotherapy. The NLR is calculated by counting the number of circulating neutrophils to lymphocytes, reflecting the balance between the deleterious effects of neutrophils and the beneficial effects of lymphocyte-mediated immunity.[30] Nevertheless, more research is needed to examine the underlying mechanism of this connection. For gastric cancer patients receiving systemic therapy, other predictive biomarkers carry prognostic value. For example, a recent study showed that the immune checkpoint score system can be used to assess the prognosis of gastric cancer and select adjuvant chemotherapy.[31] In addition, researchers have also recently developed a radiomic signature to predict the prognosis of gastric cancer and the benefits of chemotherapy.[32] Many individual biomarkers, such as IFNGR1,[33] CD47,[34] and CA199[35] have also been reported to be related to the prognosis after systemic treatment of gastric cancer. As a simple and functional biomarker, the NLR is easily obtained from routine blood tests and has powerful applicability in clinical practice.

Impaired fibrinolytic and coagulation systems are another hallmark of cancer, as their components can promote proliferation, survival, and angiogenesis of tumor cells.[36] In particular, coagulation-related molecules such as fibrinogen and D-dimer play a role in gastric cancer growth and progression, and their levels are thought to predict prognosis, treatment response, and risk of thrombosis.[37] Cancer cells express a variety of cytokines and proteins, disrupting normal cell function and the balance of fibrinolysis and anticoagulation, leading to vascular endothelial damage and release of cytokines and agglutinants, which promotes tumor cell migration, invasion, and vascular leakage. Therefore, anticoagulants play an important role in tumor therapy.[36] Among the fibrinolytic and coagulation factors in the tumor microenvironment, fibrinogen and D-dimer are the main components involved in the multi-stage development of tumors. In particular, D-dimer, as a stable fibrin degradation product, can indicate abnormalities in fibrinolysis and coagulation, which are prognostic factors in various malignancies, including GC.[15,38–40] As mentioned above, cancer patients often experience chronic inflammation and hypercoagulation. A high NLR indicates systemic inflammation, and elevated D-dimer levels are associated with excessive inflammation and abnormal coagulation. Moreover, because this study evaluated five variables, a sample size of 153 would meet the most stringent guidelines. Additionally, in our study, the combined model better predicted survival compared to the model of the NLR or D-dimer alone.

Nevertheless, the current study had several limitations. First, based on this particular study population, the cut-off values for the NLR and D-dimer level were 3.18 and 0.58 ug/mL, respectively. Reviewing the literature, cut-off values for biomarkers, rates, and scores differed based on cancer type and study population/region. Therefore, even within a single cancer type, establishing standard cut-offs that are applicable worldwide proves challenging.[21,27,41,42] Second, due to the retrospective nature of this study and the lack of external validation, the prognostic relevance of the combined model in AGC patients requires prospective studies in other populations and larger cohorts. Third, blood cell counts can be affected by several factors; however, we limited some potential confounding factors. Finally, the study lacked follow-up information on overall survival, and the application of other survival outcomes may strengthen our findings.

Conclusion

The NLR and D-dimer level have prognostic value for PFS in patients with AGC receiving first-line palliative chemotherapy. The simple prognostic models based on these independent prognostic factors help identify which patients may benefit from first-line palliative chemotherapy and allow for individualized management of patients with AGC.

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Declaration of Conflicting Interests

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Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Anhui Provincial Hospital (batch no: 2022-RE-029). The requirement for informed consent was waived by the ethics committee because of the study's retrospective nature.

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