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ORIGINAL RESEARCH

Development and Validation of an Inflammation-Combined Prognostic Index (ICPI)-Based Nomogram for Predicting Overall Survival in Gastric Cancer

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Purpose: This study aims to investigate the correlation between a novel integrated inflammatory marker: The inflammation-combined prognostic index (ICPI), combining NLR, PLR, and MLR, with the clinicopathological characteristics and overall survival (OS) of gastric cancer (GC).

Patients and Methods: Data from 876 patients with GC were retrospectively analyzed from January 1, 2017, to April 30, 2023. PSM was employed to mitigate confounding factors between groups. Receiver operating characteristic (ROC) curves were utilized to determine the optimal cutoff value. Univariate, LASSO, and multivariate regression analyses were executed. Subsequently, a nomogram for predicting OS was developed and validated.

Results: The cohort with a poor prognosis exhibited significantly elevated levels of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and ICPI ($P<0.001$). Similarly, higher levels of NLR, PLR, MLR, and ICPI were associated with a poorer prognosis ($P<0.001$). Following regression analysis, ICPI, T-stage, lymph node ratio (LNR), and primary site were identified as independent risk factors affecting OS. A nomogram was constructed based on these factors to predict 1-, 3-, and 5-year OS, yielding C-indexes of 0.8 and 0.743 for the training and validation sets, respectively. The calibration curves demonstrated close alignment between predicted and actual results, indicating high predictive accuracy. Moreover, the decision curve underscored the practical utility of the model.

Conclusion: The new inflammatory parameter ICPI integrates NLR, PLR and MLR. The ICPI-based nomogram and web calculator accurately predict OS in patients with GC.

Keywords: gastric cancer, ICPI, PSM, nomogram, OS

Introduction

Gastric cancer (GC) ranks fifth and fourth in terms of incidence and mortality rates, respectively, according to statistics from GLOBOCAN (https://gco.iarc.fr/).[1] This malignancy represents a significant global health burden.[2] Despite the widespread clinical use of tumor-node-metastasis (TNM) staging for prognostication, it fails to provide precise predictions of overall postoperative prognosis.[3] Hence, there is a critical and pressing need to establish a dependable model capable of accurately forecasting the prognosis of GC. Such a model would facilitate the development of personalized treatment strategies tailored to individual patient needs.

In recent years, researchers have endeavored to identify a simple, easily accessible, reliable, and inexpensive predictor to assess the efficacy and prognosis of GC treatment. Peripheral blood markers offer advantages of abundant quantity, quality assurance, and easy accessibility. Furthermore, the relationship between inflammation and tumor has garnered

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considerable attention among scholars.[4,5] Consequently, an increasing number of researchers are investigating the association between inflammatory markers and tumors in peripheral blood, with peripheral blood inflammation biomarkers emerging as the simplest method to gauge inflammation levels in patients. Research indicates that alterations in peripheral blood inflammatory markers (eg, neutrophils,[6,7] lymphocytes,[8] platelets,[9] and their derivatives such as neutrophil-to-lymphocyte ratio (NLR),[10] platelet-to-lymphocyte ratio (PLR),[11] monocyte-to-lymphocyte ratio (MLR),[12] etc) can induce changes in the tumor microenvironment (TME) or modulate TME,[13] thereby impacting tumorigenesis, progression, and prognosis.

Owing to the diverse array of peripheral blood inflammatory markers and their derivatives, utilizing a single marker for predicting patient prognosis has inherent limitations. Additionally, the lack of uniformity in selecting cutoff values presents a significant challenge to its widespread application. Some studies[14–16] investigated the association between NLR, PLR, MLR, and the prognosis of advanced GC. Nevertheless, previous studies omitted details regarding potential variations in baseline characteristics between survival and death groups before determining optimal cutoff values for inflammatory parameters. Should disparities exist between these groups in terms of age, histological differentiation, and TNM stage, it casts doubt on the stability of the findings. Propensity score matching (PSM)[17] enhances balance between group differences and mitigates bias and confounding variables in a study, facilitating more rational comparisons.[18]

In summary, this study employed the PSM method to mitigate the impact of confounding factors between survival and death groups, rigorously determined optimal cutoff values for inflammatory parameters, and introduced a novel ICPI. Subsequently, we conducted an analysis to assess the relationship between NLR, PLR, MLR, ICPI, and overall survival (OS) in GC. Finally, utilizing the ICPI, we devised and validated a nomogram to predict OS in GC.

Patients and Methods

Study Subjects and Inclusion Criteria

This study retrospectively analyzed the clinicopathological data of patients diagnosed with GC who underwent radical surgical procedures between January 1, 2017, and April 30, 2023, at the Department of Gastrointestinal Surgery of the First Hospital Affiliated of Chongqing Medical University and the Department of General Surgery of Chongqing University Fuling Hospital. Inclusion criteria: a. postoperative pathologic confirmation of gastric cancer (including adenocarcinoma, mucinous carcinoma, signet-ring cell carcinoma, etc).; b. radical gastric cancer surgery; c. age ≥18 years.

Exclusion Criteria

1. Patients with previous or concurrent multi-site tumors; 2. Patients who underwent neoadjuvant therapy before surgery; 3. Patients with underlying systemic immune diseases or hematologic diseases; 4. Patients with acute infections, recent history of blood transfusion, or gastrointestinal tract hemorrhage; 5. Patients who recently used hormones, anti-inflammatory drugs, or antiplatelet drugs; 6. Patients with incomplete clinicopathologic information.

Clinicopathological Information

Ethnicity, gender, age, marital status, body mass index (BMI), number of underlying diseases, tumor size, primary site, AJCC TNM stage, histological differentiation, pathological classification, number of positive lymph nodes (LN), total number of LN, lymph node ratio (LNR), perineural invasion, vascular invasion, human epidermal growth factor receptor-2 (HER-2) status, and OS. BMI = weight (Kg) / height (m)^2. Given the lack of statistically conclusive evidence regarding the impact of chronic diseases on peripheral blood markers,[19] patients with chronic diseases in a stable stage were not excluded. Regarding underlying diseases, emphasis was placed on hypertension, diabetes, coronary atherosclerotic heart disease, chronic obstructive pulmonary disease (non-acute exacerbation), and history of cerebral infarction. The number of underlying diseases was tallied as follows: If the patient does not have any of the aforementioned five comorbidities, the score is 0. If the patient has one of the five comorbidities, the score is 1. If the patient has any two of the five comorbidities simultaneously, the score is 2. If the patient has any three of the five comorbidities simultaneously, the score is 3, and so five. AJCC TNM stage refers to the 8th edition of TNM staging for GC developed

by the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC). LNR was defined as the ratio of positive lymph nodes to the total number of lymph nodes. OS duration was calculated from the date of surgery to the last follow-up of lost patients, death from any cause, or the follow-up cutoff date.

Inflammatory Biomarkers

Blood sampling and collection of relevant inflammatory markers were conducted within 24 hours of admission for patients diagnosed with GC and scheduled for surgery.[19] NLR = neutrophil count (×10^9/L) / lymphocyte count (×10^9/L). PLR = platelet count (×10^9/L) / lymphocyte count (×10^9/L). MLR = monocyte count (×10^9/L) / lymphocyte count (×10^9/L).

Follow-Up

Follow-up visits were conducted every 3 months during the initial 2 years following surgery, and subsequently, every 6 months. Data collection involved retrieval of medical records from the hospital, as well as phone calls to patients or their families, documenting the date of missed appointments, last known survival status, or date of death. Overall mortality status was characterized by patient death from any cause following surgery.

Obtaining Optimal Cutoff Values for Inflammatory Parameters

To mitigate the presence of confounding variables between groups, we employed the Propensity Score Matching (PSM) method,[20,21] specifically utilizing the Nearest Neighbor Matching Method with a 1:1 ratio and a Caliper of 0.01, to balance baseline characteristics between the survivor and mortality groups. Receiver Operating Characteristic (ROC) curves were employed to ascertain the optimal cutoff value for each parameter[22] (Table 1). Drawing inspiration from the approach outlined by Hirahara,[23] we devised a novel composite index, termed the Inflammation-Combined Prognostic Index (ICPI), which integrates the aforementioned three inflammatory parameters: NLR, PLR, and MLR. The calculation of ICPI is as follows: ICPI = NLR + PLR + MLR. Additionally, if NLR ≥ 3.535, then NLR = 3.535, otherwise NLR = 0; if PLR ≥ 220.67, then PLR = 220.67, otherwise PLR= 0; if MLR ≥ 0.415, then MLR= 0.415, otherwise MLR= 0. Subsequently, we categorized the dataset into two distinct groups, delineated by high and low inflammation levels based on the determined cutoff values for each parameter, and proceeded to compare the OS between these two groups separately.

Statistical Analysis

We conducted univariate, LASSO, and multivariate analyses to identify independent prognostic factors for OS. The patient data were randomly divided into a training set and a validation set at a ratio of 7:3. The training set was utilized to develop a nomogram for OS. Subsequently, the discriminatory and predictive capabilities of the nomogram were assessed in comparison to conventional TNM staging using the Harrell's Concordance Index (C-index) and time-dependent Area Under the Curve (AUC). Calibration curves were generated to evaluate the concordance between the predicted and observed survival rates. Additionally, Decision Curve Analysis (DCA) was employed to assess the net benefit conferred by the model.

Table 1 The Cutoff Values of Inflammatory Parameters

Name	cutoff	AUC	95% CI	p-value
NLR	3.535	0.504	0.431–0.576	0.539
PLR	220.67	0.523	0.451–0.596	0.738
MLR	0.415	0.508	0.435–0.58	0.583
ICPI	3.743	0.559	0.498–0.62	0.971

Abbreviations: NLR, Neutrophil- to- Lymphocyte Ratio; PLR, Platelet-Lymphocyte Ratio; MLR, Monocyte Lymphocyte Ratio; ICPI, Inflammation-Combined Prognostic Index; AUC, Area Under the Curve; CI, Confidence Interval.

Statistical analysis was conducted using R software (version 4.3.1, https://www.r-project.org/). Categorical variables were described using frequencies and percentages and compared using chi-square ($\chi 2$) tests or Fisher's exact probabilities. Continuous variables were described using median and interquartile range (IQR). Student's *t*-test was employed for between-group comparisons of continuous variables with a normal distribution, while the Mann–Whitney *U*-test was used for continuous variables not following a normal distribution. HR and corresponding 95% CI were utilized to present Cox regression results. A significance level of $p < 0.05$ (two-tailed) was considered statistically significant.

Results

Clinicopathologic Characteristics of Patients

We conducted a retrospective analysis of medical record data from 1391 patients and 63 patients diagnosed with GC at the Department of Gastrointestinal Surgery of the First Hospital Affiliated of Chongqing Medical University and the Department of General Surgery of Chongqing University Fuling Hospital, respectively. Following our inclusion and exclusion criteria, information from 876 patients was ultimately obtained (Figure 1). Among them, 210 patients had deceased, while 660 patients were alive. Significant differences in gender, age, BMI, tumor size, histological differentiation, pathological classification, AJCC T stage, AJCC N stage, number of positive LN, LNR, perineural invasion, vascular invasion, and primary site were observed between the two groups. Median age, median tumor size, percentage

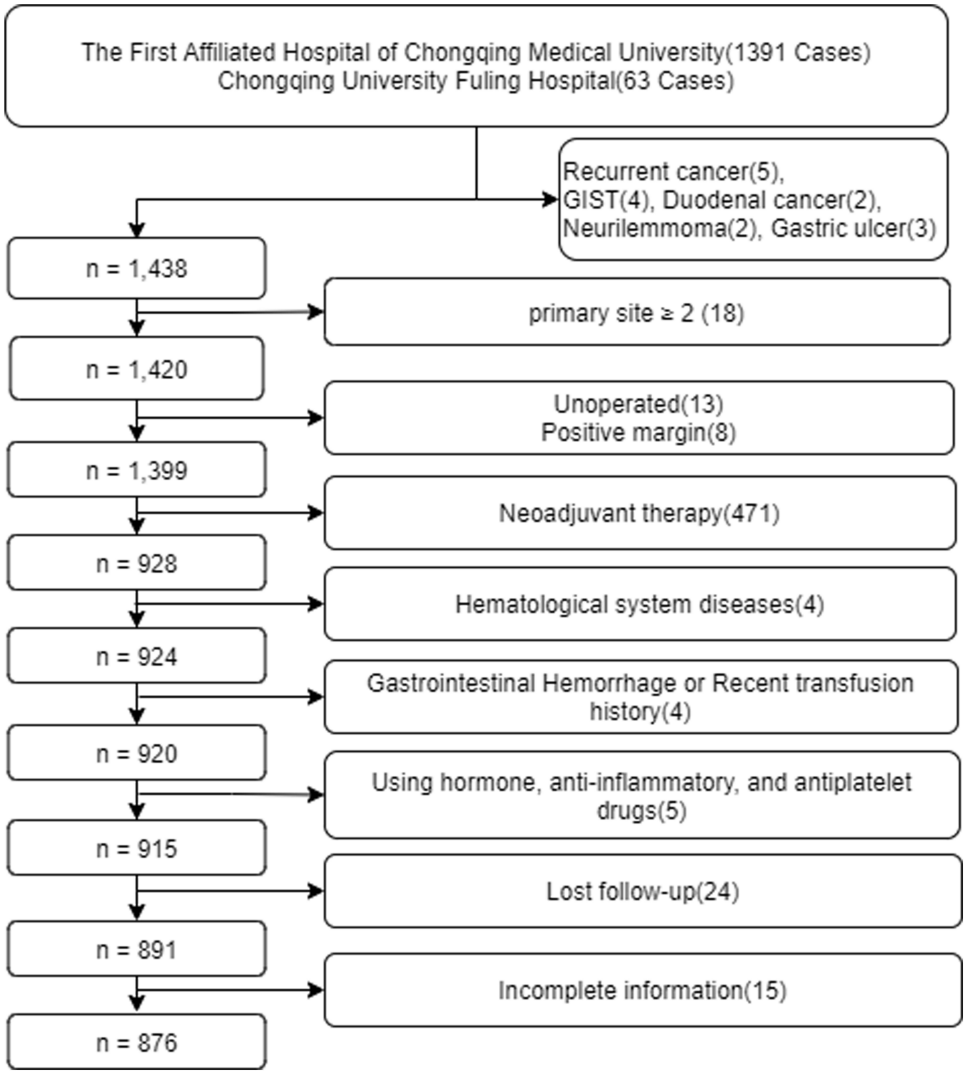

Figure 1 Flowchart showing patients screening process. GIST: GastroIntestinal Stromal Tumor.

of poorly differentiated, percentage of T4 stage, percentage of N3 stage, median number of positive LN, percentage of perineural invasion, and percentage of vascular invasion were significantly higher in the deceased patient group compared to the survival group (Table 2). Statistical differences in NLR, PLR, and MLR were also noted between the two groups (Figure 2A–C). To mitigate potential confounding factors between the groups, we employed the PSM method. Following 1:1 matching, 124 deceased patients and 124 survival patients were finally obtained, respectively. The baseline characteristics of these two groups are presented in Table 2, revealing no statistically significant differences.

Determination of Optimal Cutoff Values for Inflammatory Parameters

The dataset comprising 248 patients post PSM matching was utilized to determine the optimal cutoff values for each inflammatory parameter. Initially, ROC curves were generated, and AUC values were calculated for individual

Table 2 Baseline Characteristics of GC Patients Before and After PSM

Characteristics	Before PSM			After PSM		
	Death N 210	Survival N = 666	p-value	Death N 124	Survival N = 124	p-value
Ethnic (%)			0.11			>0.9
Hans	205 (98%)	661 (99%)		122 (98%)	122 (98%)	
Miao	1 (0.5%)	1 (0.2%)		0 (0%)	0 (0%)	
Tu	4 (1.9%)	4 (0.6%)		2 (1.6%)	2 (1.6%)	
Gender (%)			0.038			0.9
Female	54 (26%)	222 (33%)		37 (30%)	36 (29%)	
Male	156 (74%)	444 (67%)		87 (70%)	88 (71%)	
Age, median (IQR)	67 (61, 74)	65 (57, 71)	<0.001	67 (61, 75)	68 (60, 73)	>0.9
Marital status (%)			0.8			>0.9
Married	208 (99%)	661 (99%)		124 (100%)	124 (100%)	
Single	0 (0%)	2 (0.3%)		0 (0%)	0 (0%)	
Widowed	2 (1.0%)	3 (0.5%)		0 (0%)	0 (0%)	
Underlying diseases (%)			0.051			0.8
0	136 (65%)	474 (71%)		86 (69%)	81 (65%)	
1	50 (24%)	143 (21%)		26 (21%)	28 (23%)	
2	24 (11%)	41 (6.2%)		12 (9.7%)	14 (11%)	
3	0 (0%)	6 (0.9%)		0 (0%)	1 (0.8%)	
4	0 (0%)	2 (0.3%)				
BMI, median (IQR)	21.9 (19.7, 24.0)	22.8 (20.7, 24.8)	<0.001	22.48 (20.16, 24.18)	22.01 (19.68, 24.01)	0.3
Tumor size, median (IQR)	3.50 (3.00, 5.00)	2.50 (1.50, 3.50)	<0.001	3.50 (2.73, 4.50)	3.50 (2.50, 4.58)	0.7
Histological differentiation (%)			0.001			0.9
Well differentiated	0 (0%)	13 (2.0%)		0 (0%)	0 (0%)	
Moderately differentiated	41 (20%)	152 (23%)		27 (22%)	32 (26%)	
Poorly differentiated	164 (78%)	451 (68%)		94 (76%)	89 (72%)	
Unclassified	5 (2.4%)	50 (7.5%)		3 (2.4%)	3 (2.4%)	
Pathological classification (%)			0.006			0.8
Adenocarcinoma	181 (86%)	544 (82%)		108 (87%)	111 (90%)	
Mucinous carcinoma	5 (2.4%)	12 (1.8%)		5 (4.0%)	4 (3.2%)	
Signet-ring cell carcinoma	19 (9.0%)	74 (11%)		10 (8.1%)	8 (6.5%)	
Adenosquamous carcinoma	1 (0.5%)	2 (0.3%)		0 (0%)	1 (0.8%)	
Squamous cell carcinoma	3 (1.4%)	2 (0.3%)		0 (0%)	0 (0%)	
Carcinoma	1 (0.5%)	32 (4.8%)		1 (0.8%)	0 (0%)	

(*Continued*)

Table 2 (Continued).

Characteristics	Before PSM			After PSM		
	Death N 210	Survival N = 666	p-value	Death N 124	Survival N = 124	p-value
AJCC T_Stage (%)			<0.001			>0.9
Tis	2 (1.0%)	78 (12%)		2 (1.6%)	3 (2.4%)	
T1	9 (4.3%)	200 (30%)		9 (7.3%)	12 (9.7%)	
T2	17 (8.1%)	107 (16%)		13 (10%)	10 (8.1%)	
T3	4 (1.9%)	5 (0.8%)		3 (2.4%)	3 (2.4%)	
T4	178 (85%)	276 (41%)		97 (78%)	96 (77%)	
AJCC N_Stage (%)			<0.001			0.9
N0	52 (25%)	416 (62%)		43 (35%)	43 (35%)	
N1	32 (15%)	95 (14%)		24 (19%)	29 (23%)	
N2	45 (21%)	78 (12%)		26 (21%)	25 (20%)	
N3	81 (39%)	77 (12%)		31 (25%)	27 (22%)	
Positive_LN, median (IQR)	5.0 (1.0, 10.0)	0.0 (0.0, 2.0)	<0.001	2.0 (0.0, 6.3)	2.0 (0.0, 6.0)	0.9
Total_LN, median (IQR)	22 (17, 27)	22 (18, 28)	0.5	23 (17, 28)	23 (18, 28)	0.9
LNR, median (IQR)	0.20 (0.03, 0.52)	0.00 (0.00, 0.09)	<0.001	0.08 (0.00, 0.26)	0.08 (0.00, 0.29)	>0.9
Vascular invasion (%)			<0.001			0.4
Negative	153 (73%)	581 (87%)		97 (78%)	102 (82%)	
Positive	57 (27%)	85 (13%)		27 (22%)	22 (18%)	
Perineural invasion (%)			0.001			0.6
Negative	168 (80%)	590 (89%)		99 (80%)	102 (82%)	
Positive	42 (20%)	76 (11%)		25 (20%)	22 (18%)	
HER2 (%)			0.12			>0.9
Negative	195 (93%)	584 (88%)		115 (93%)	115 (93%)	
1+	9 (4.3%)	48 (7.2%)		4 (3.2%)	5 (4.0%)	
2+	6 (2.9%)	24 (3.6%)		5 (4.0%)	4 (3.2%)	
3+	0 (0%)	10 (1.5%)		0 (0%)	0 (0%)	
Primary site (%)			0.003			0.7
Gastric cardia	42 (20%)	74 (11%)		26 (21%)	20 (16%)	
Gastric fundus	13 (6.2%)	36 (5.4%)		9 (7.3%)	7 (5.6%)	
Gastric antrum	63 (30%)	240 (36%)		38 (31%)	43 (35%)	
Gastric corpus	91 (43%)	296 (44%)		50 (40%)	51 (41%)	
Gastric angle	1 (0.5%)	20 (3.0%)		1 (0.8%)	3 (2.4%)	

Abbreviations: GC, Gastric Cancer; PSM: Propensity Score Matching; IQR, InterQuartile Range; BMI: Body Mass Index; LN, Lymph Nodes; LNR, Lymph Node Ratio; HER2, Human Epidermal growth factor Receptor-2.

inflammatory parameters (Table 1 and Supplementary Figure 1). The optimal cutoff value for NLR was 3.535; however, the AUC was only 0.504. For PLR, the optimal cutoff value was 220.67, yielding the highest AUC of 0.523. The optimal cutoff value for MLR was 0.415, resulting in an AUC of 0.508. Despite PLR exhibiting the highest AUC value, all AUC values for NLR, PLR, and MLR were deemed unsatisfactory. Consequently, drawing upon the methodology proposed by Hirahara,[23] a new parameter, ICPI, was formulated, integrating NLR, PLR, and MLR, and ICPI values were computed for each patient. The optimal cutoff value for ICPI was determined to be 3.743, achieving an AUC of 0.559 (Table 1), notably higher than those of NLR, PLR, and MLR. The Restricted Cubic Spline diagram (RCS) illustrated that as NLR, MLR, and ICPI exceeded their respective cutoff values, the risk of death from GC increased proportionally (Figure 3A, B, C). Conversely, this trend was not clearly observed in PLR (Figure 3D).

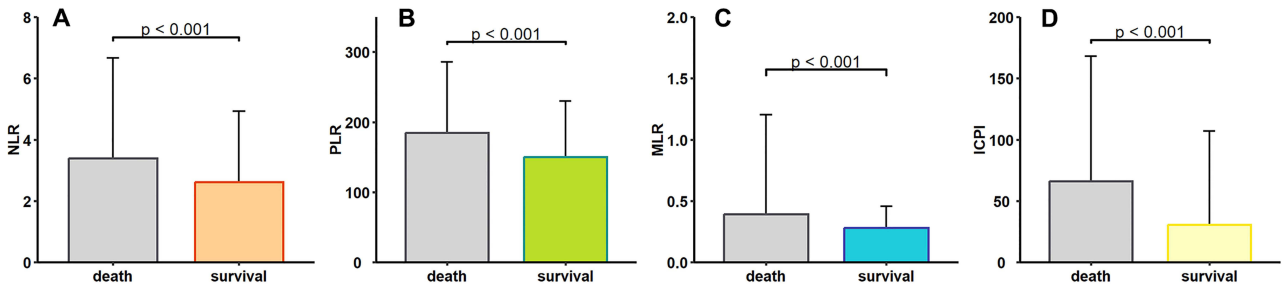

Figure 2 Bar charts (**A–D**) depicting the significant difference in inflammatory status between the death group (N = 210) and the survival group (N = 666) (P < 0.001). (**A**) NLR was notably higher in death patients compared to survival patients. (**B**) PLR exhibited a significant elevation in death patients compared to survival patients. (**C**) MLR displayed a significant increase in death patients compared to survival patients. (**D**) ICPI showed a substantial elevation in death patients compared to survival patients.
Abbreviations: NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-Lymphocyte Ratio; MLR, Monocyte-to-Lymphocyte Ratio; ICPI, Inflammation-Combined Prognostic Index.

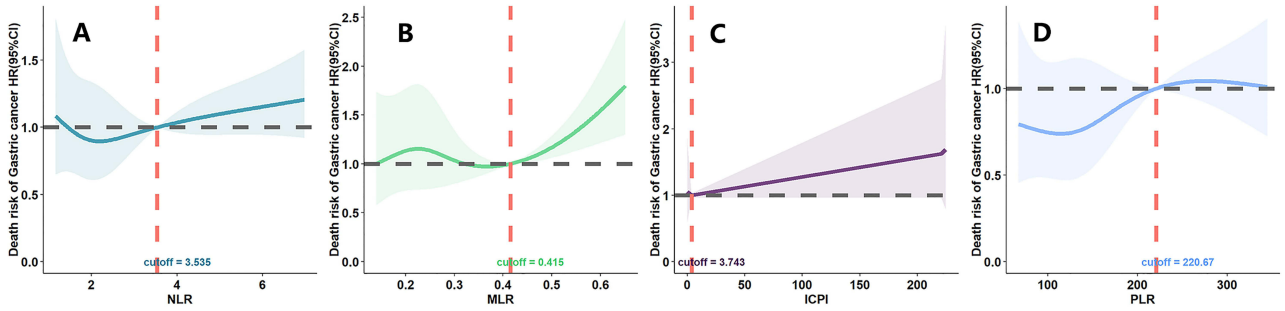

Figure 3 Relationship between each inflammatory parameter and risk of death in GC. (**A**) When NLR <3.535, the risk of death in GC patients remained insignificantly influenced by NLR; however, after NLR ≥3.535, the risk of death significantly increased with the rise in NLR. (**B**) When MLR <0.415, the risk of death remained insignificantly altered with MLR; however, after MLR ≥0.415, the risk of death significantly increased with the rise in MLR. (**C**) When ICPI <3.743, the risk of death remained insignificantly influenced by ICPI; conversely, after ICPI ≥3.743, the risk of death significantly increased with the rise in ICPI. (**D**) The risk of death exhibited no significant alteration with PLR.
Abbreviations: NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-Lymphocyte Ratio; MLR, Monocyte-Lymphocyte Ratio; ICPI, Inflammation-Combined Prognostic Index.

Survival Analysis

Initially, we computed the ICPI for 876 patient data based on the optimal cutoff values of NLR, PLR, and MLR determined in Determination of Optimal Cutoff Values for Inflammatory Parameters (Figure 2D). Subsequently, we classified the patient data into two groups representing high and low inflammation levels according to the cutoff values of each inflammation parameter. The survival disparities between these two groups were then separately assessed. Our analysis revealed that patient groups characterized by elevated inflammation levels (High-NLR, High-PLR, High-MLR, and High-ICPI) exhibited notably poorer overall prognoses compared to those with lower inflammation levels (Low-NLR, Low-PLR, Low-MLR, and Low-ICPI), with corresponding HRs of 0.45, 0.43, 0.46, and 0.42, respectively. This disparity was statistically significant (P < 0.001) (Figure 4).

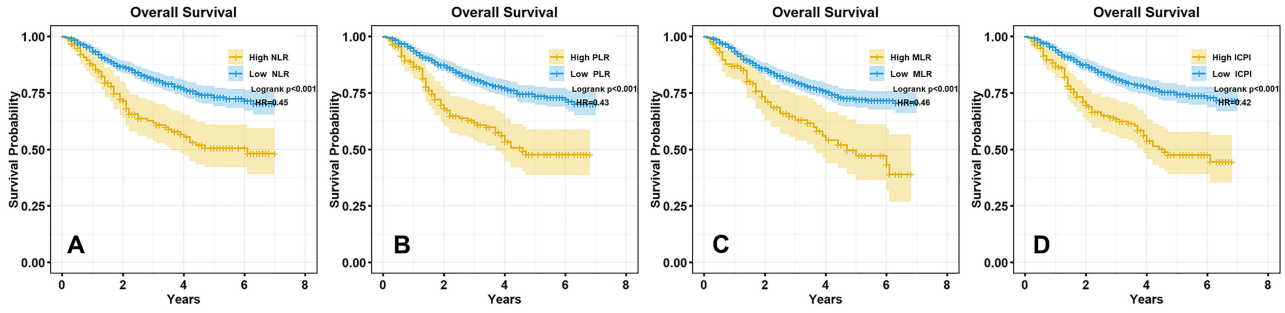

Figure 4 Comparison of long-term survival outcomes among GC patients in two groups categorized by high and low levels of inflammation status. (**A**) The low NLR group exhibited superior long-term survival outcomes compared to the high NLR group. (**B**) The low PLR group demonstrated better long-term survival outcomes than the high PLR group. (**C**) The low MLR group displayed improved long-term survival outcomes compared to the high MLR group. (**D**) The low ICPI group manifested better long-term survival outcomes than the high ICPI group.
Abbreviations: NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-Lymphocyte Ratio; MLR, Monocyte-Lymphocyte Ratio; ICPI, Inflammation-Combined Prognostic Index.

Univariate, LASSO and Multivariate Regression Analysis

To ascertain whether ICPI served as an independent risk factor influencing the prognosis of GC, we conducted univariate, LASSO, and multivariate regression analyses. Preceding the analysis, we partitioned the data of 867 patients into a training set and a validation set at a 7:3 ratio (Supplementary Table 1). Subsequently, we initially performed univariate analysis in the training set to assess the parameters correlated with OS in GC. Our findings indicated that 14 parameters, including marital status, BMI, tumor size, AJCC T stage, LNR, vascular invasion, primary site, NLR, ICPI, AJCC N stage, perineural invasion, PLR, number of positive LN, and MLR, exhibited correlations with patient OS (Table 3). To mitigate overfitting of the multivariate model, we conducted LASSO regression analysis on the aforementioned 14 parameters prior to multivariate analysis. Upon reaching the minimum λ value, we retained 9 parameters with non-zero coefficients (Marital status, BMI, Tumor size, AJCC T_Stage, LNR, Vascular invasion, Primary site, NLR, ICPI) for subsequent analysis (Figure 5). Finally, we conducted multivariate analysis on the 9 parameters obtained in the preceding step. Our analysis identified ICPI (HR: 0.64, 95% CI: 0.43–0.96), AJCC T-stage (HR: 1.7, 95% CI: 1.37–2.11), LNR (HR: 10.93, 95% CI: 5.63–21.24), and primary site (HR: 0.84, 95% CI: 0.72–0.97) as independent risk factors for OS in patients with GC, whereas NLR, PLR, and MLR were not independent risk factors for OS (Table 3).

Establishment and Validation of the Nomogram

Although the AUC value of ICPI was higher than that of NLR, PLR, and MLR, it still did not meet our expectations, and its application alone to predict the prognosis of GC patients was still unconvincing. Therefore, we constructed a nomogram for predicting 1-, 3-, and 5-year OS in GC based on the results of multivariate analysis with four independent risk factors (Figure 6). Initially, we used the C-index to evaluate the discriminative ability of the nomogram. In the training set, the C-index of this predictive model was 0.8 (95% CI: 0.763–0.838), while the C-index of the

Table 3 Univariate and Multivariate Analysis

Characteristics	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Marital status	2.14	1.03–4.43	0.041	1.69	0.81–3.52	0.16
BMI	0.92	0.87–0.97	0.002	0.97	0.92–1.02	0.26
Tumor size	1.27	1.17–1.36	<0.001	1.03	0.94–1.14	0.52
AJCC T_Stage	2.2	1.8–2.68	<0.001	1.7	1.37–2.11	<0.001
LNR	27.91	16.01–48.66	<0.001	10.93	5.63–21.24	<0.001
Vascular invasion	2.63	1.83–3.78	<0.001	1.08	0.72–1.6	0.71
Primary site	0.8	0.69–0.93	0.003	0.84	0.72–0.97	0.02
NLR	1.1	1.05–1.14	<0.001	1.02	0.96–1.08	0.5
ICPI	0.39	0.28–0.55	<0.001	0.64	0.43–0.96	0.03
Ethnic	1.28	0.62–2.61	0.5			
Gender	1.45	0.99–2.13	0.054			
Age	1.01	1–1.03	0.17			
Histological differentiation	1.02	0.76–1.35	0.91			
Underlying diseases	1.2	0.96–1.52	0.12			
Total_LN	0.99	0.97–1.01	0.34			
AJCC N_Stage	1.92	1.67–2.2	<0.001			
Perineural invasion	2.01	1.33–3.03	<0.001			
Pathological classification	0.87	0.73–1.03	0.1			
PLR	0.4	0.28–0.56	<0.001			
Positive_LN	1.08	1.07–1.1	<0.001			
HER2	0.92	0.73–1.15	0.45			
MLR	0.46	0.31–0.68	<0.001			

Abbreviations: BMI, Body Mass Index; LN, Lymph Nodes; LNR, Lymph Node Ratio; NLR, Neutrophil- to-Lymphocyte Ratio; PLR, Platelet-Lymphocyte Ratio; MLR, Monocyte- Lymphocyte Ratio; ICPI, Inflammation-Combined Prognostic Index; HER2, Human Epidermal growth factor Receptor-2.

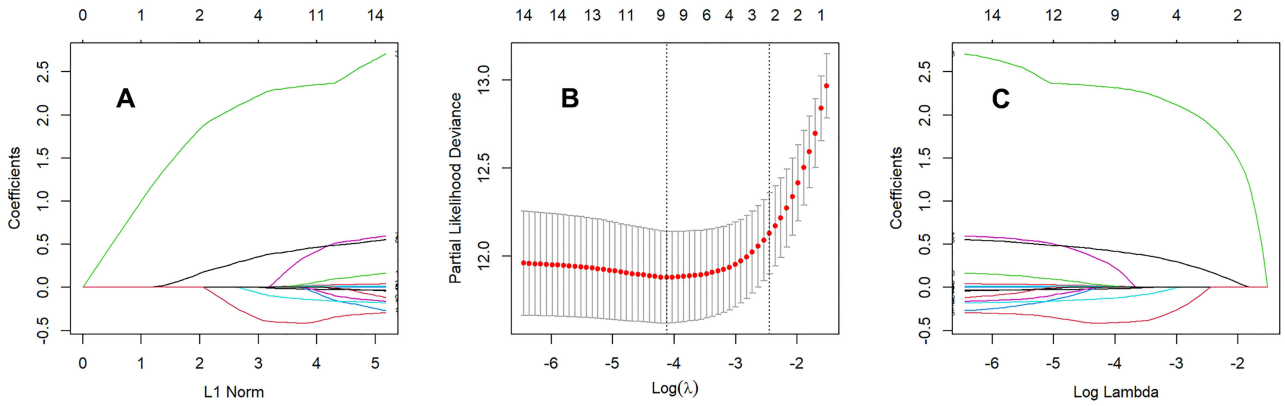

Figure 5 Nine clinical and pathological features were selected through LASSO regression analysis at the minimum λ. (**A**) LASSO Path Plot. (**B**) LASSO Cross-Validation Plot. (**C**) LASSO Coefficients Plot.

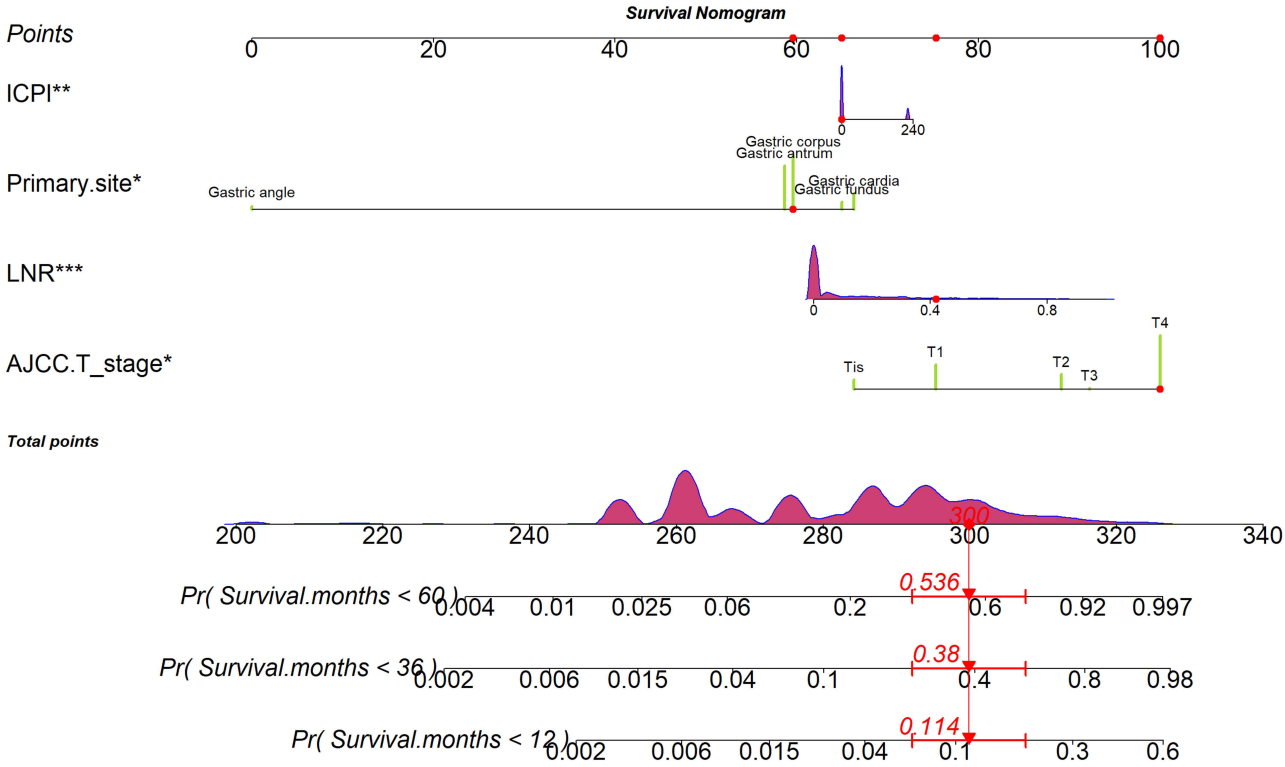

Figure 6 Predicted nomogram of 1-, 3- and 5-year all-cause mortality in patients with GC. *p < 0.05; **p < 0.01; ***p < 0.001. Each parameter in the graph has a corresponding Point value above it, and we add the Point values corresponding to the four parameters of the patient to get a Total point value, and finally we look for the predicted probability that corresponds to the Total point value directly below it. For example, a patient with gastric corpus cancer who has ICPI=0, LNR=0.42, and AJCC T-stage of T4, his Total point is 300, corresponding to 1-year, 3-year, and 5-year all-cause mortality rates of 0.114,0.38, and 0.536, respectively; and the corresponding 1-year, 3-year, and 5-year survival rates of 0.886, 0.62, and 0.464. LNR: Lymph Node Ratio; ICPI: Inflammation-Combined Prognostic Index.

traditional TNM model was 0.718 (95% CI: 0.679–0.754). In the validation set, the C-index of this nomogram was 0.743 (95% CI: 0.705–0.78), whereas the C-index of the traditional TNM model was 0.669 (95% CI: 0.63–0.705). Concurrently, we depicted the time-dependent AUC curve to evaluate the predictive performance of the nomogram. In the training set, the 1-year, 3-year, and 5-year AUCs and their 95% CIs were 0.808 (0.751–0.864), 0.833 (0.792–0.873), and 0.84 (0.793–0.886), respectively. Correspondingly, in the validation set, the 1-year, 3-year, and 5-year AUCs and their 95% CIs were 0.689 (0.558–0.819), 0.717 (0.637–0.798), and 0.769 (0.687–0.852), respectively (Figure 7). This suggests that the predictive performance of the nomogram remains relatively stable over time and may even tend to

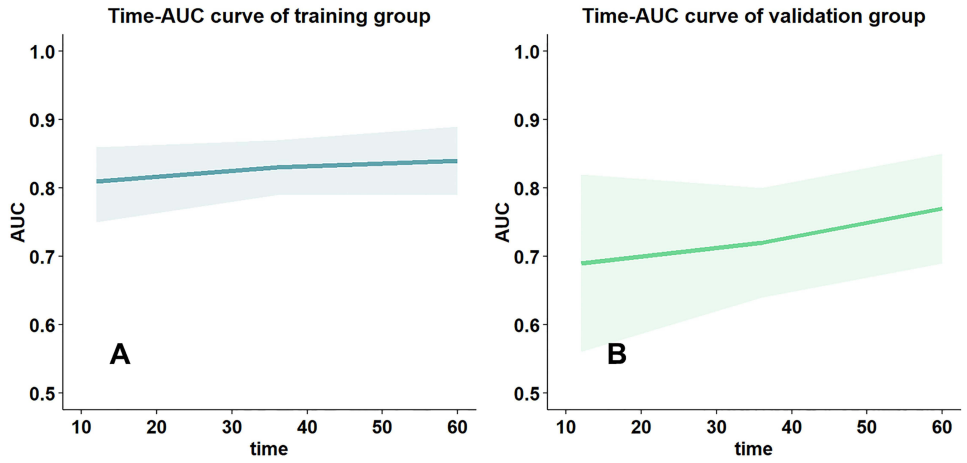

Figure 7 Time-AUC curve analysis between training set (**A**) and validation set (**B**).

improve. The calibration curves show that the model predictions are close to the actual results in the training and validation sets (Figure 8). Finally, a decision curve analysis was employed to evaluate the clinical utility of the nomogram. The findings revealed that the nomogram conferred a superior net benefit in comparison to conventional TNM staging (Figure 9).

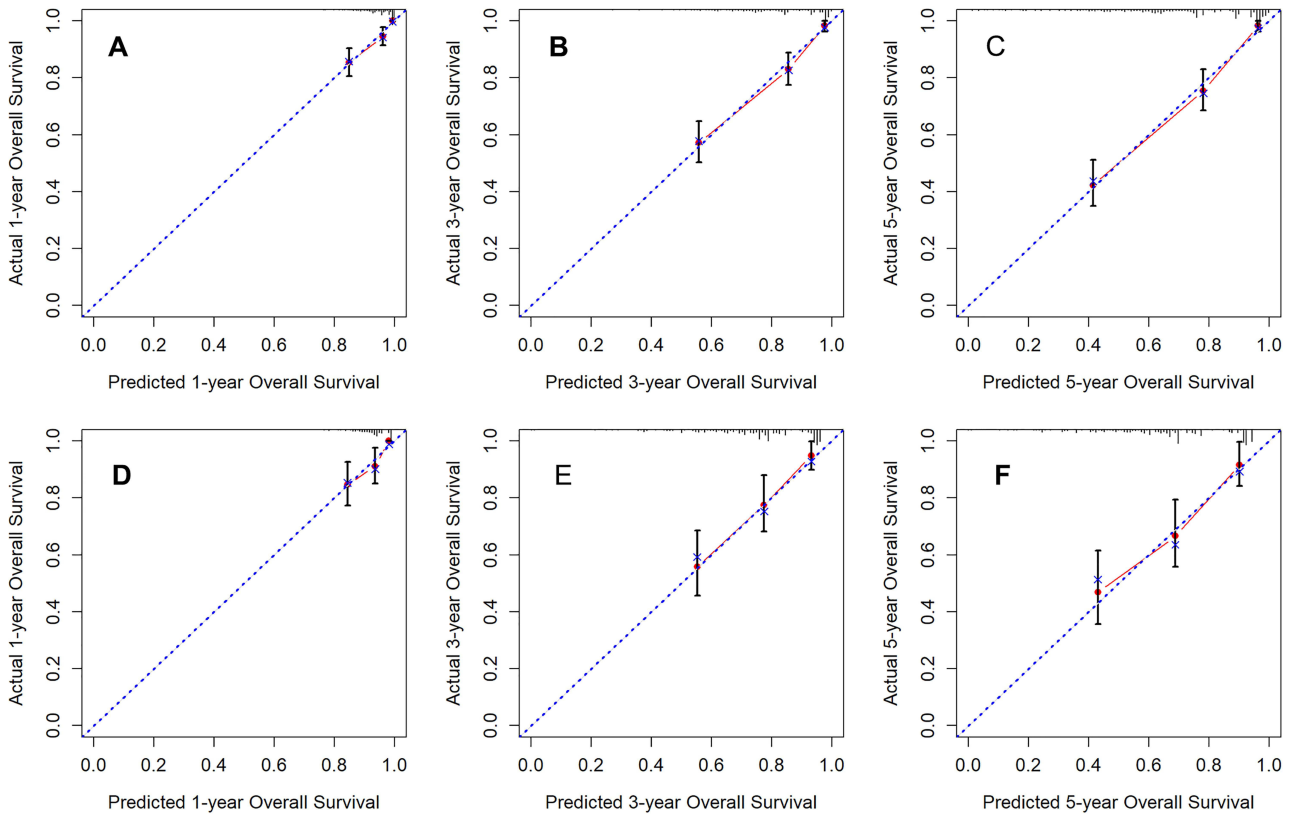

Figure 8 Calibration curves illustrating the predicted OS of the prognostic model in both the training and validation sets. (**A**–**C**) Depict the calibration curves for 1-year, 3-year, and 5-year OS, respectively, in the training set. (**D**–**F**) Represent the calibration curves for 1-year, 3-year, and 5-year OS, respectively, in the validation set. The x-axis represents the OS predicted by the model, whereas the y-axis denotes the actual OS. The proximity of the blue reference line to the middle signifies better calibration.

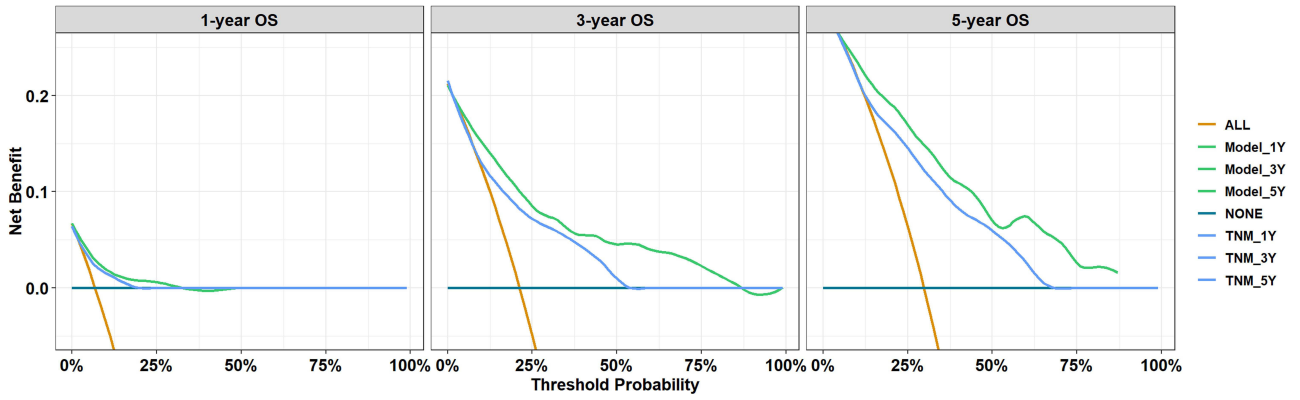

Figure 9 Decision curve analysis of the prognostic model and the traditional TNM stage model. x-axis is the threshold probability of OS for patients at 1, 3 and 5 years. y-axis is the net patient benefit. The brown line indicates that no patients died and the dark blue line indicates that all patients died. The 1-, 3-, and 5-year net benefit of this model exceeds that of the traditional TNM stage model.

Web Calculator

To ensure ease of use for clinicians in the office, we endeavored to create a straightforward nomogram. As a result, we have designed a web-based dynamic nomogram calculator (https://jasonidea.shinyapps.io/gc_icpi/). This tool enables clinicians to promptly predict a patient's 1-, 3-, and 5-year survival rates by inputting the relevant parameters as soon as the patient's test results become available in the clinic (Supplementary Figure 2).

Discussion

In recent years, significant attention has been directed towards understanding the interplay between inflammation and tumors. Cancer-associated inflammation has emerged as the seventh hallmark of cancer.[24] The seminal work of Virchow in the 19th century first systematically reported the relationship between inflammation and tumors, catalyzing a growing body of research into the role of systemic inflammation within the TME.[24,25] Some studies[26,27] assert that the systemic inflammatory response (SIR) constitutes a pivotal component of cancer, with evidence indicating its association with patient survival across various cancer types. The precise mechanisms underlying SIR in tumor patients remain elusive. Dzobo[28] proposed that SIR might manifest as a nonspecific response secondary to tumor hypoxia/necrosis or local tissue injury. Nevertheless, the body's response to systemic inflammation exhibits heterogeneity. Hibino's[29] investigation delineated numerous alterations in neuroendocrine metabolism, encompassing endocrine hormones, as well as hematopoietic changes, including interleukins, interferons, hematopoietic growth factors, and acute-phase proteins. Moreover, Kim's[30] study uncovered associations between inflammatory and immune cells in peripheral blood—such as neutrophils, lymphocytes, and monocytes—and tumor cell invasion and metastasis. Concurrently, some studies[29,31] elucidated how inflammation fosters tumor cell genesis, invasion, and metastasis by furnishing diverse bioactive molecules to the TME. In clinical settings, direct evaluation of patients' inflammatory status through monitoring relevant endocrine hormones and cytokine levels entails significant expense. Conversely, indirect assessment of patients' inflammatory status via monitoring changes in inflammation-related indicators in peripheral blood[32] is a cost-effective, easily accessible approach with acceptable reproducibility, thereby garnering patient acceptance. Therefore, in this study, we investigated the correlation of peripheral blood inflammatory parameters (NLR, PLR and MLR) with clinicopathological features and prognosis of GC. To evaluate the inflammatory status of patients more comprehensively, we integrated NLR, PLR and MLR into a new inflammatory parameter: ICPI. Finally, we constructed and validated a nomogram based on ICPI for predicting OS in GC, demonstrating superior predictive ability compared to the traditional TNM prediction model.

In this investigation, we conducted an analysis to elucidate the correlation between inflammatory status and OS in patients with GC. Notably, we employed the PSM method for the first time to mitigate potential confounding factors between the compared groups before determining the optimal cutoff values for inflammatory parameters. Despite the relatively low final AUC values for each inflammatory parameter, we maintain confidence in the stability and reliability of their cutoff values. Our findings revealed significantly elevated levels of inflammatory parameters—including NLR,

PLR, MLR, and ICPI—in the death group compared to the survival group. Moreover, upon stratifying patients based on the identified optimal cutoff values for inflammatory parameters, we observed substantially diminished OS in groups characterized by high NLR, high PLR, high MLR, and high ICPI, in contrast to their counterparts with low values. Our study findings align with those of Matsas,[14] Zhang,[11] and Wang,[12] suggesting a consistent trend. This phenomenon may be attributed to inflammation's multifaceted influence on tumorigenesis, progression, invasion, and metastasis,[31,33] consequently impacting the overall prognosis of GC.

Neutrophils are capable of secreting various inflammatory mediators that suppress the lymphocyte-mediated immune response, thereby facilitating tumor proliferation.[34,35] Additionally, neutrophils produce hydrogen peroxide and arginase 1, which directly impede lymphocyte activity within the cancer context.[6,36] Furthermore, neutrophils contribute to the promotion of adhesion and distant metastasis of circulating tumor cells (CTCs).[37] Platelets play a pivotal role in promoting Epithelial-Mesenchymal Transition (EMT) in tumor cells, thereby fostering cancer metastasis.[9] Moreover, platelets down-regulate the cytokine NKG2D on the surface of natural killer (NK) cells, thereby shielding tumor cells from immune system surveillance. Additionally, platelets possess the ability to recruit and activate granulocytes within tumor tissue.[38] Monocytes release an array of cytokines and chemokines to suppress the immune response and modulate the TME, thereby fostering tumor proliferation, angiogenesis, and progression.[39] Lymphocytes, pivotal constituents of the cytotoxic immune response, play a central role in cellular immune surveillance. They inhibit cancer cell proliferation and migration by stimulating the growth of cytotoxic cells and secreting cytokines.[8,25]

Hence, NLR, PLR, and MLR, each focusing on different aspects of host inflammation and immunity, serve as valuable indicators. Our novel parameter, ICPI, amalgamates these three ratios, rendering it more comprehensive in evaluating patients' inflammatory and immune statuses. Notably, ICPI exhibits superior predictive and diagnostic capabilities, as evidenced by its significantly higher AUC compared to NLR, PLR, and MLR. While all parameters—NLR, PLR, MLR, and ICPI—demonstrated associations with OS in univariate analyses, only ICPI emerged as an independent risk factor for OS in both LASSO and multivariate regression analyses.

Our primary objective is to provide practical solutions for clinical settings rather than dwell solely in theoretical realms. Recognizing the potential complexity associated with calculating the ICPI, we acknowledge its potential challenges for implementation in clinical practice. Therefore, we developed a nomogram for predicting OS in GC based on ICPI and three other independent prognostic parameters derived from multivariate analysis. This nomogram has been validated to possess high predictive accuracy and practical utility. To enhance accessibility for clinical users, we designed a straightforward web calculator based on this nomogram, prioritizing simplicity, convenience, and efficiency while ensuring stability and reliability. By eliminating the need for arduous and tedious calculations, users can promptly obtain results by inputting available parameters. Given the continuous generation of data from GC patients, we envision equipping the model with self-learning and self-updating capabilities in the future. This will enable the model to maintain a stable predictive capacity through continual self-correction and potentially enhance its predictive accuracy over time.

This study is not without its shortcomings and limitations, necessitating cautious interpretation of its findings. 1). it is a retrospective study, thus susceptible to selective bias. 2). the sample size was relatively small, and the follow-up period was relatively short. 3). the decision to administer neoadjuvant and adjuvant therapy in patients with stage II and above significantly influences patient prognosis. However, we opted to exclude patients undergoing neoadjuvant therapy from our analysis due to its potential impact on inflammatory parameters. Additionally, we did not account for postoperative adjuvant therapy in our analysis, despite emerging evidence suggesting that adjuvant chemotherapy may not independently affect prognosis in GC patients.[15,23] 4). external validation of our findings using independent datasets was not conducted. Future research endeavors should prioritize multicenter prospective studies with larger sample sizes, diverse patient populations, and extended follow-up periods to validate our findings comprehensively.

Conclusion

In this study, we validated the efficacy of a novel inflammatory parameter, ICPI, developed a nomogram, and introduced a web calculator to predict OS in patients diagnosed with GC. Our findings revealed that patients with poorer prognoses exhibited higher levels of NLR, PLR, MLR, and ICPI. Conversely, patients with elevated levels of NLR, PLR, MLR, and ICPI also displayed inferior prognoses. Moreover, we identified ICPI, AJCC T stage, LNR, and primary site as independent risk factors influencing

patients' OS. The transition from identifying independent risk factors to establishing the nomogram signifies a crucial progression from theory to clinical application. Simultaneously, the introduction of the web calculator has simplified and enhanced the clinical applicability of the model, transitioning it from a complex and cumbersome tool to one that is simple and reliable.

Data Sharing Statement

The author has no right to disclose the research data. However, if scholars have academic needs, they can request it from the author.

Ethical Recognition

The study adhered to the principles outlined in the Declaration of Helsinki (revised 2013) and received approval from the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (K2023-542) and the Ethics Committee of Chongqing University Fuling Hospital (2024CDFSFLYYEC-011). Given that this study is retrospective, the ethics committee granted a waiver for the requirement of written informed consent. The data utilized in this study are de-identified, preventing the recognition of individual participants. We are committed to upholding the confidentiality of all patient information.

Consent for Publication

All authors agree to publish.

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 declare that they have no conflicts of interest in this work.

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