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ORIGINAL RESEARCH

# Prognostic Enhancement in Gastric Cancer Through the Integration of Inflammatory Indices into the pTNM-Inflammation Staging System (pTNM-I)

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**Background:** The prognostic discriminative ability of the pathological tumor-node-metastasis (pTNM) staging system for gastric cancer (GC) still requires further improvement. This study aimed to develop a pTNM-Inflammation (pTNM-I) staging system by integrating pTNM staging with peripheral inflammatory status to enhance the prognostic stratification capability of pTNM.

**Methods:** This study retrospectively analyzed 4,049 patients who underwent curative surgery for GC. Receiver Operating Characteristic (ROC) analysis was used to determine the optimal cutoff values of the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) for different pTNM stages, and the pTNM-I staging system was constructed. Kaplan-Meier survival curves were used to evaluate the impact of pTNM-I on prognosis. Cox regression analysis was employed to identify independent risk factors affecting patient outcomes. Finally, a nomogram was constructed based on pTNM-I staging and clinical pathological characteristics.

**Results:** After constructing the pTNM-I staging system based on the optimal cutoff values of NLR, PLR, and SII, the 5-year survival rates for stages I-a to III-c were 97.6%, 88.0%, 84.2%, 92.5%, 77.5%, 71.3%, 74.3%, 45.3%, and 27.5% ($P < 0.001$). ROC analysis showed that the predictive ability of pTNM-I was superior to that of pTNM (AUC: 0.798 vs 0.743). Cox analysis revealed that pTNM-I was an independent prognostic factor associated with patient outcomes ($P < 0.001$). The nomogram based on pTNM-I also demonstrated better predictive performance compared to the traditional pTNM staging (AUC: 0.808 vs 0.743).

**Conclusion:** The pTNM-I staging system provided more robust prognostic discriminative ability. As a simple, economical, and routine prognostic tool, it is worthy of clinical application.

**Keywords:** gastric cancer, pTNM, inflammation, prognosis

## Introduction

Gastric cancer (GC) is a highly heterogeneous digestive tract tumor. Although its incidence has decreased, it remains one of the most common malignancies.[1] Surgery is the primary treatment for GC, but the five-year survival rate for GC remains low, at less than 50%.[2] The postoperative pathological tumor-lymph node-metastasis (pTNM) staging system is the gold standard for evaluating the prognosis of GC.[3] However, reports based on tumor macroscopic anatomy are limited,[3] and patients with the same pTNM stage often exhibit significant differences in prognosis.[3,4] Additionally, the TNM staging system for GC is continuously being refined and improved.[4] Therefore, further refinement of the pTNM staging system is crucial for accurately predicting prognosis, given its utility and limitations.



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Since the seed and soil theory was proposed,[5] changes in the tumor microenvironment have received widespread attention. The presence of chronic inflammation has also been observed in the development of GC.[6] Some common inflammatory markers, such as the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR), play important roles in the prognosis of GC.[7,8] Moreover, Systemic immune-inflammation index (SII) has been reported as a predictor of patient prognosis in multiple cancer types, including lung cancer, colorectal cancer, and esophageal cancer.[9–11] The diagnostic and prognostic performance of inflammatory markers differs significantly across different stages. For example, NLR can predict the prognosis of early-stage GC,[12] while PLR helps predict the prognosis of advanced-stage GC.[13] Furthermore, the combination of multiple markers provides comprehensive inflammatory information.[14] Therefore, considering the application value of inflammatory markers at different stages, combining inflammatory indices with the traditional pTNM staging system can provide comprehensive micro-prognostic information. However, such studies are currently lacking.

In this study, we retrospectively analyzed patients with gastric cancer who underwent radical surgery in the Department of Gastrointestinal Oncology at Harbin Medical University Cancer Hospital. Based on traditional inflammatory indices, including NLR, PLR, and the systemic immune-inflammation index (SII), we investigated the prognostic value of these inflammatory indices at different pTNM stages. We combined these indices with the pTNM staging system to construct the pTNM-inflammatory staging (pTNM-I) system and thoroughly explored its prognostic value, providing a potential supplement to the pTNM staging system.

# Materials and Methods

## Patients

This study retrospectively analyzed patients with gastric cancer (GC) who underwent curative surgery at Harbin Medical University between January 2012 and December 2016. The diagnosis of GC was based on preoperative gastroscopy, intraoperative rapid frozen section, and postoperative pathology. All patients underwent routine preoperative examinations, including blood tests, biochemical tests, abdominal CT, and ultrasound, upon admission to the Department of Gastrointestinal Oncology. Patient data were stored in the electronic medical record system of Harbin Medical University Cancer Hospital, which included detailed records of patient general information, treatment, and follow-up. The pTNM staging was determined according to the 8th edition of the AJCC staging manual.

Exclusion criteria included: (1) severe infections; (2) autoimmune diseases; (3) preoperative use of antiplatelet drugs; (4) abnormal liver or kidney function; (5) hematological diseases; (6) other systemic malignancies; (7) patients with incomplete clinical or pathological information.

## Follow-Up

All patients underwent regular follow-up, which included blood tests, gastroscopy, and imaging studies. After discharge, patients followed medical advice and underwent examinations at local hospitals or Harbin Medical University Cancer Hospital. Specifically, patients with stage I disease were followed up every 12 months, stage II patients every 6–12 months, and stage III patients every 3–6 months. Follow-up information was recorded in detail by professional follow-up staff and attending physicians and stored in the gastric cancer information management system of Harbin Medical University Cancer Hospital.

## Inflammatory Markers

We used three traditional inflammatory markers: NLR, PLR, and SII. These were calculated based on the first blood test performed after hospital admission and before surgery. NLR was calculated as the peripheral neutrophil count divided by the lymphocyte count. PLR was calculated as the peripheral platelet count divided by the lymphocyte count. SII was calculated as the peripheral neutrophil count multiplied by the platelet count divided by the lymphocyte count. The calculation methods and application values of these inflammatory indices have been detailed in previous studies.[7,8,12,13,15]

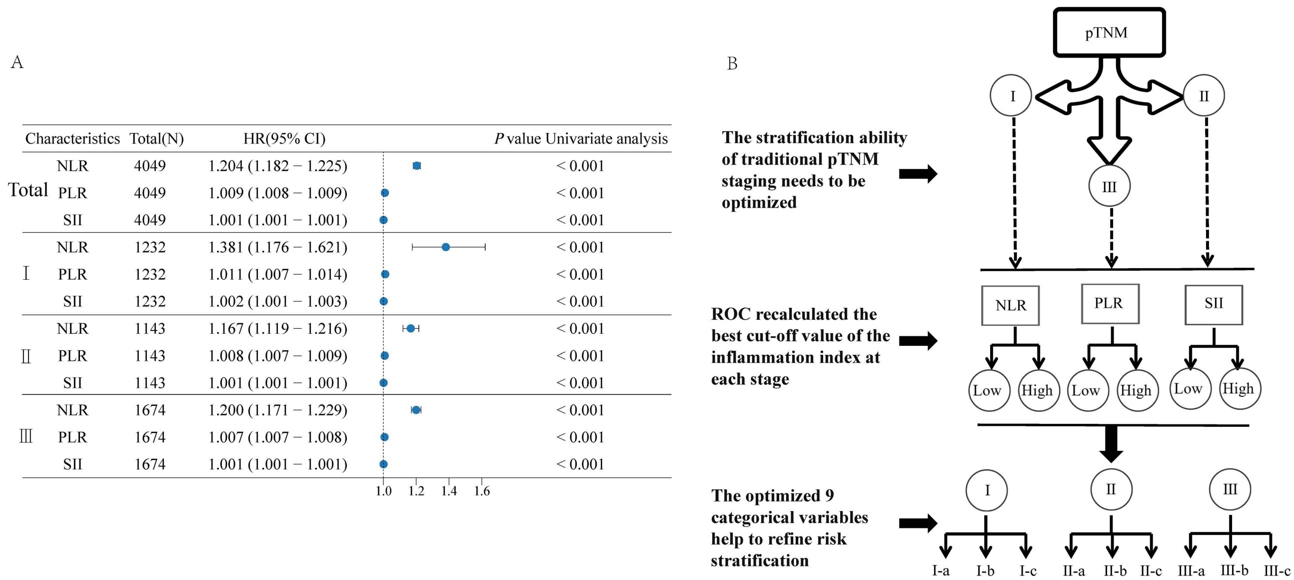


**Figure 1** Schematic diagram of the pTNM-I staging construction. (**A**) Effect of different inflammatory indices on prognosis in univariate cox analysis. (**B**) Construction process of pTNM-I staging.

**Abbreviations**: NLR, Neutrophil to Lymphocyte Ratio; PLR, Platelet to Lymphocyte Ratio; SII, Systemic Immune-Inflammation Index; ROC, Receiver Operating Characteristic; pTNM-I, pTNM-inflammation.

## Construction of pTNM-I

Given the importance of inflammatory indices in the prognosis of GC, we reevaluated the prognostic value of inflammatory indices according to different pTNM stages (I–III). Specifically, we used receiver operating characteristic (ROC) curves to determine the optimal cutoff values of inflammatory markers for each pTNM stage. The optimal cutoff values were calculated using the Youden index. The area under the ROC curve (AUC) was used to assess the diagnostic performance of the inflammatory markers. After calculating the cutoff values for the inflammatory markers, patients were grouped based on these values. Patients with values below the optimal cutoff were assigned to the low group (score 0), while those above the cutoff were assigned to the high group (score 1). For detailed inflammatory grouping, all inflammatory markers with a score of 0 were classified as group "a", those with a score of 1 as group "c", and the remainder as group "b". Therefore, all patients were ultimately categorized into groups I-a, I-b, I-c, II-a, II-b, II-c, III-a, III-b, and III-c (Figure 1B). Further details are shown in Figure 1.

## Statistical Analysis

We used the 5-year survival status as the study endpoint. Overall survival (OS) was defined as the time from surgery to the last follow-up. Chi-square test was used to analyze the relationship between pTNM-I and clinicopathological characteristics. Receiver operating characteristic (ROC) curves and time-dependent ROC curves were used to evaluate the predictive performance of prognostic markers. Both ROC curves (based on 5-year survival status) and time-dependent ROC curves were used to evaluate the prognostic performance of NLR, PLR, and SII. Kaplan-Meier survival curves were used to analyze patient prognosis, and the Log rank test was applied for comparison. Cox regression analysis was performed to determine independent risk factors associated with patient prognosis, expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). Variables with $P < 0.05$ in univariate Cox analysis were included in the multivariate analysis. Nomogram models were created based on significant factors ($P < 0.05$) in multivariate Cox regression using the rms package in R Project. Calibration curves, decision curves, and the C-index were used to evaluate the predictive performance of the nomograms. All statistical analyses were performed using SPSS (v 25.0) and R Project (v 4.3.0).


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# Results

## Patient Characteristics

Finally, this study included 4,049 patients who underwent curative surgery for GC (Table 1). Among them, 2,938 (72.56%) were male, and 1,111 (27.44%) were female. The mean age was 58.14 years. According to the pTNM staging system, 1,232 (30.43%), 1,143 (28.23%), and 1,674 (41.34%) patients were classified as stage I, II, and III, respectively.

## Prognostic Value of Inflammatory Indices

For different stages, NLR, PLR, and SII all demonstrated certain prognostic value (Figure 1A). Based on ROC calculations, the optimal cutoff values for NLR, PLR, and SII were 2.71, 110.36, and 427.46, respectively. The AUC values were 0.603, 0.723, and 0.710 (Figure 2A), which also indicated that these inflammatory indices had good prognostic value for predicting GC outcomes. Time-dependent ROC analysis also showed that NLR, PLR, and SII maintained good predictive performance during the 1–5 year observation period (Figure 2B). After grouping based on the optimal cutoff values, we found that higher inflammatory states were associated with poor prognosis (Figure 2C–E).

## Prognostic Value of Inflammatory Indices Across Different Stages

For stage I patients, the optimal cutoff values for NLR, PLR, and SII were 3.21, 121.68, and 605.82, respectively. The AUC values were 0.560, 0.604, and 0.720 (Figure 3A). Time-dependent ROC analysis revealed that NLR, PLR, and SII maintained good predictive performance during the observation period (Figure 3B). After grouping based on the optimal cutoff values, we found that elevated inflammatory levels were associated with poor prognosis in stage I patients (Figure 3C–E). When grouped based on NLR, PLR, and SII, the 5-year survival rates for stage I-a, I-b, and I-c patients were 97.5%, 88.0%, and 84.2%, respectively ($P < 0.001$) (Figure 3F). This indicated that inflammatory staging could significantly predict the prognosis of stage I patients.

For stage II patients, the optimal cutoff values for NLR, PLR, and SII were 2.45, 99.04, and 583.88, respectively. The AUC values were 0.575, 0.677, and 0.692 (Figure 4A). Time-dependent ROC analysis showed that NLR, PLR, and SII maintained good predictive performance during the observation period (Figure 4B). After grouping based on the optimal

**Table 1** Baseline Characteristics Table of Patients

| Characteristics | Total (N=4049) |
|---|---|
| Sex | |
| Male | 2938 (72.56%) |
| Female | 1111 (27.44%) |
| Age (Mean±SD) | 58.14±10.09 |
| CEA (Mean±SD) | 6.53±35.33 |
| CA 19–9 (Mean±SD) | 35.96±120.96 |
| Tumor location | |
| Upper | 439 (10.84%) |
| Middle | 612 (15.11%) |
| Lower | 2927 (72.29%) |
| Total | 71 (1.75%) |
| pTNM | |
| I | 1232 (30.43%) |
| II | 1143 (28.23%) |
| III | 1674 (41.34%) |
| Tumor size (mm) | |
| ≤50 | 2571 (63.50%) |
| >50 | 1478 (36.50%) |

**Abbreviations**: CEA, carcinoembryonic antigen; CA 19–9, carbohydrate antigen 19–9; SD, standard deviation.

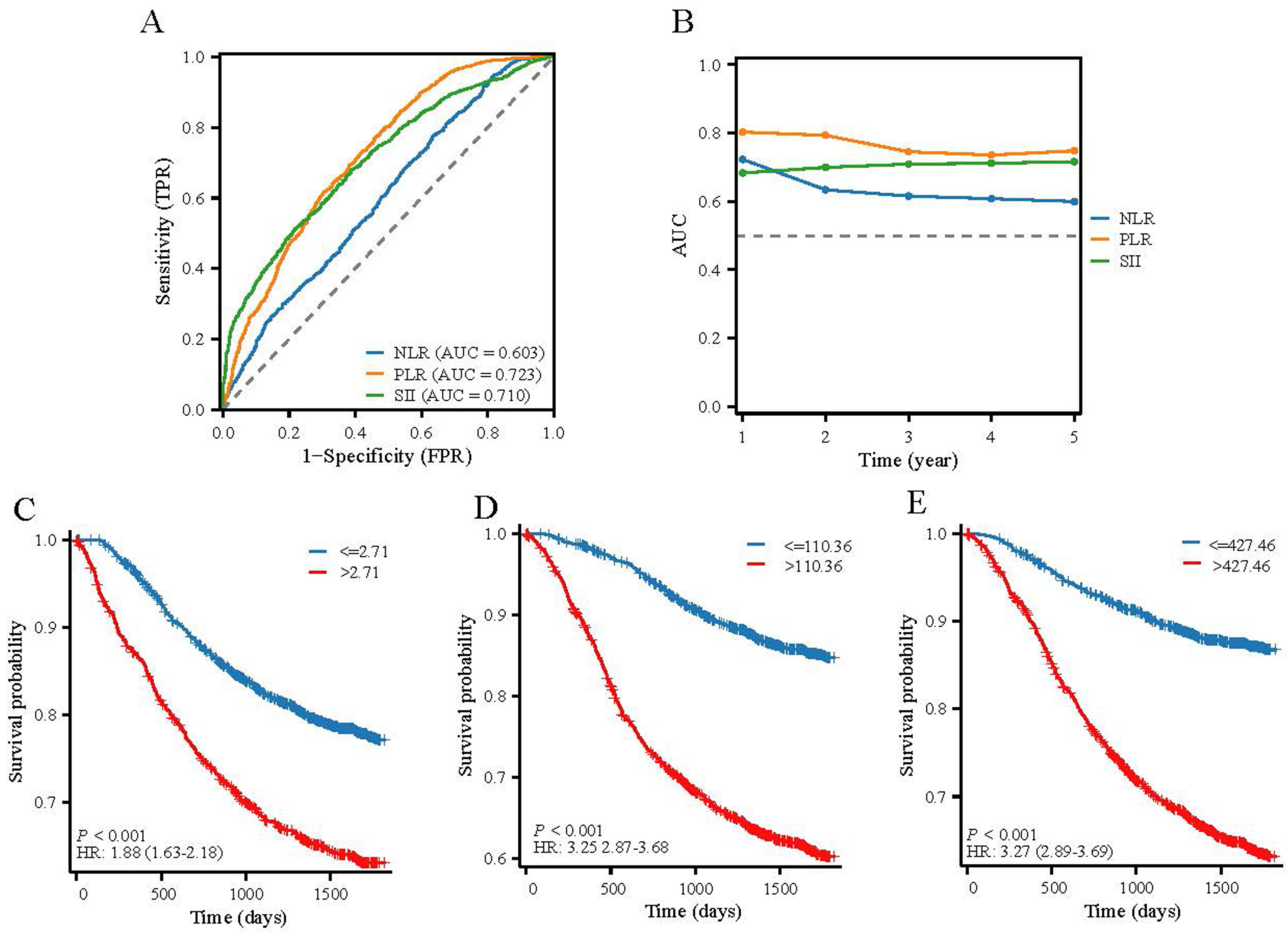


**Figure 2** The prognostic significance of inflammation indices for overall patients. (**A**) ROC shows the predictive performance of different inflammation indices. (**B**) Time-ROC demonstrates the dynamic predictive performance of inflammation indices during the observation period. (**C**) The impact of NLR on prognosis based on the optimal cutoff value. (**D**) The impact of PLR on prognosis based on the optimal cutoff value. (**E**) The impact of SII on prognosis based on the optimal cutoff value.
**Abbreviations**: NLR, Neutrophil to Lymphocyte Ratio; PLR, Platelet to Lymphocyte Ratio; SII, Systemic Immune-Inflammation Index; ROC, Receiver Operating Characteristic; Time-ROC, Time-dependent Receiver Operating Characteristic.

cutoff values, we found that elevated inflammatory levels were associated with poor prognosis in stage II patients (Figure 4C–E). When grouped based on NLR, PLR, and SII, the 5-year survival rates for stage II-a, II-b, and II-c patients were 92.5%, 77.5%, and 71.3%, respectively ($P < 0.001$) (Figure 4F). This indicated that inflammatory staging could significantly predict the prognosis of stage II patients.

For stage III patients, the optimal cutoff values for NLR, PLR, and SII were 2.71, 131.48, and 497.66, respectively. The AUC values were 0.598, 0.733, and 0.690 (Figure 5A). Time-dependent ROC analysis demonstrated that NLR, PLR, and SII maintained good predictive performance during the observation period (Figure 5B). After grouping based on the optimal cutoff values, we found that elevated inflammatory levels were associated with poor prognosis in stage III patients (Figure 5C–E). When grouped based on NLR, PLR, and SII, the 5-year survival rates for stage III-a, III-b, and III-c patients were 74.2%, 45.3%, and 27.5%, respectively ($P < 0.001$) (Figure 5F). This indicated that inflammatory staging could significantly predict the prognosis of stage III patients.

## Construction of pTNM-I

Based on the prognostic value of NLR, PLR, and SII for stage I–III GC patients, we constructed the pTNM-I staging system according to the optimal cutoff values for each marker (Figure 6A). Kaplan-Meier analysis showed that pTNM-I could significantly stratify patients by prognosis, with 5-year survival rates for groups I-a to III-c being 97.6%, 88.0%, 84.2%, 92.5%, 77.5%, 71.3%, 74.3%, 45.3%, and 27.5%, respectively ($P < 0.001$) (Figure 6C). After comparing the

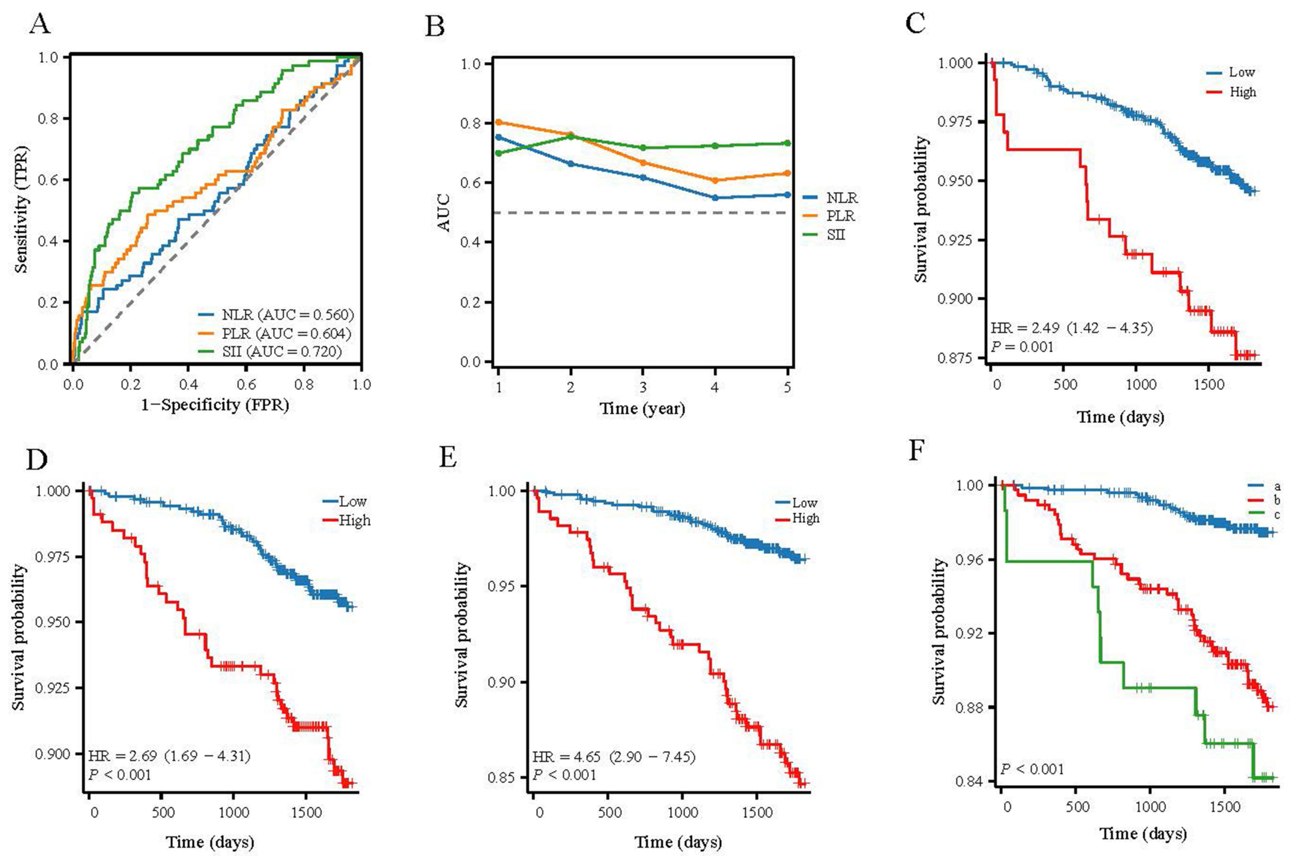


**Figure 3** The prognostic significance of inflammation indices for stage I patients. (**A**) ROC shows the predictive performance of different inflammation indices. (**B**) Time-ROC demonstrates the dynamic predictive performance of inflammation indices during the observation period. (**C**) The impact of NLR on prognosis based on the optimal cutoff value. (**D**) The impact of PLR on prognosis based on the optimal cutoff value. (**E**) The impact of SII on prognosis based on the optimal cutoff value.
**Abbreviations**: NLR, Neutrophil to Lymphocyte Ratio; PLR, Platelet to Lymphocyte Ratio; SII, Systemic Immune-Inflammation Index; ROC, Receiver Operating Characteristic; Time-ROC, Time-dependent Receiver Operating Characteristic.

traditional pTNM with pTNM-I, we found that pTNM-I had superior predictive ability compared to pTNM (AUC: 0.798 vs 0.743) (Figure 6D). For time-dependent ROC analysis, pTNM-I showed higher AUC values than pTNM during the 1–5 year observation period (Figure 6E). This indicated that pTNM-I had good predictive value. Chi-square analysis revealed that pTNM-I was associated with gender ($P = 0.020$), tumor location ($P < 0.001$), pTNM stage ($P < 0.001$), and tumor size ($P < 0.001$) (Table 2).

## Univariate and Multivariate Analysis of Prognostic Factors

In the univariate analysis, age, CEA, CA19-9, tumor location, tumor size, and pTNM-I were significantly associated with the prognosis of GC patients (All $P < 0.05$). In the multivariate analysis, age ($P < 0.001$), CA19-9 ($P = 0.002$), tumor location ($P < 0.001$), tumor size (P < 0.001), and pTNM-I ($P < 0.001$) were identified as independent prognostic factors for patient outcomes (Table 3).

## Development of a Prognostic Nomogram Based on pTNM-I

Based on the results of the multivariate Cox analysis, we constructed a nomogram to predict the prognosis of GC patients by integrating pTNM-I with clinical pathological characteristics (Figure 7A). The ROC curve indicated that the nomogram had superior predictive performance compared to the traditional pTNM staging system (AUC: 0.808 vs 0.743) (Figure 7B). Time-dependent ROC analysis demonstrated that during the 1–5 year observation period, the nomogram consistently outperformed the pTNM staging system, with higher AUC values (Figure 7C). The calibration plots revealed that the nomogram performed well in predicting the 1-year, 3-year, and 5-year prognosis of patients

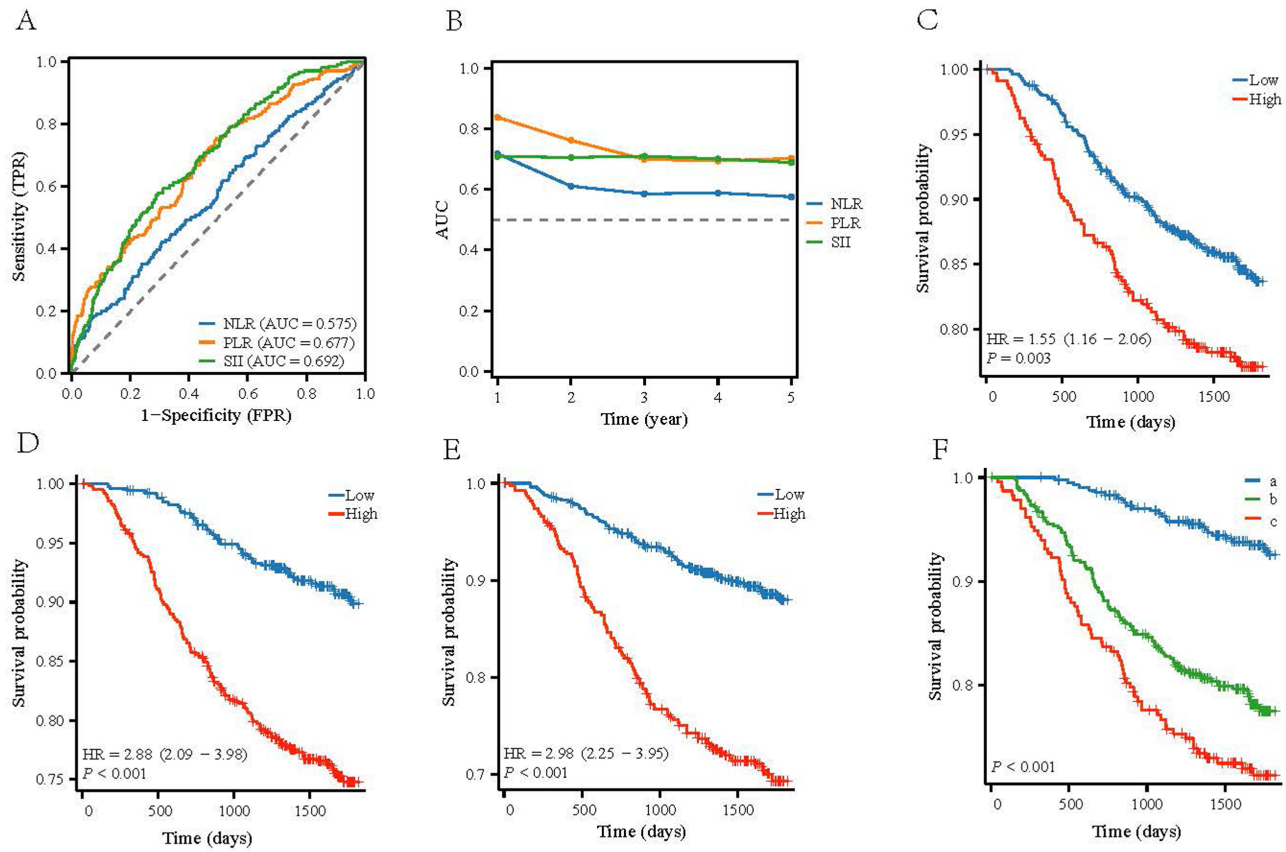


**Figure 4** The prognostic significance of inflammation indices for stage II patients. (**A**) ROC shows the predictive performance of different inflammation indices. (**B**) Time-ROC demonstrates the dynamic predictive performance of inflammation indices during the observation period. (**C**) The impact of NLR on prognosis based on the optimal cutoff value. (**D**) The impact of PLR on prognosis based on the optimal cutoff value. (**E**) The impact of SII on prognosis based on the optimal cutoff value.
**Abbreviations**: NLR, Neutrophil to Lymphocyte Ratio; PLR, Platelet to Lymphocyte Ratio; SII, Systemic Immune-Inflammation Index; ROC, Receiver Operating Characteristic; Time-ROC, Time-dependent Receiver Operating Characteristic.

(Figure 7D). Furthermore, the nomogram achieved excellent predictive accuracy for the 1–5 year survival outcomes, with c-index values of 0.810, 0.802, 0.797, 0.789, and 0.780, respectively (Figure 7E). These results underscore the nomogram's outstanding predictive capability. Additionally, decision curves for predicting the 1-year, 3-year, and 5-year outcomes showed that the nomogram's predictive performance was consistently better than that of the traditional pTNM staging system (Figure 7F–H). Therefore, the nomogram, constructed using pTNM-I staging and clinical pathological characteristics, holds significant application value in prognosis prediction.

## Discussion

In this study, we developed the pTNM-I staging system for the first time. Compared to the traditional pTNM staging system, pTNM-I staging incorporates more prognostic information, allowing for a more comprehensive assessment of the inflammatory status in patients at different stages. Moreover, pTNM-I staging demonstrates superior predictive performance compared to the traditional pTNM staging system. Based on the traditional pTNM three-class system, pTNM-I staging refines patient prognosis into nine classification variables, offering a more detailed risk stratification. Additionally, we constructed a nomogram based on pTNM-I staging and patients' clinical pathological characteristics, which demonstrated good predictive performance. These results indicate that the pTNM-I staging system has excellent clinical application value.

Inflammatory markers have been widely applied in the prognosis prediction of GC. However, traditional inflammatory markers exhibit significant differences in their prognostic abilities.[7,16,17] Clearly, these differences in prognostic capability suggest the heterogeneity of the disease process in GC, which is not only reflected in the macroscopic

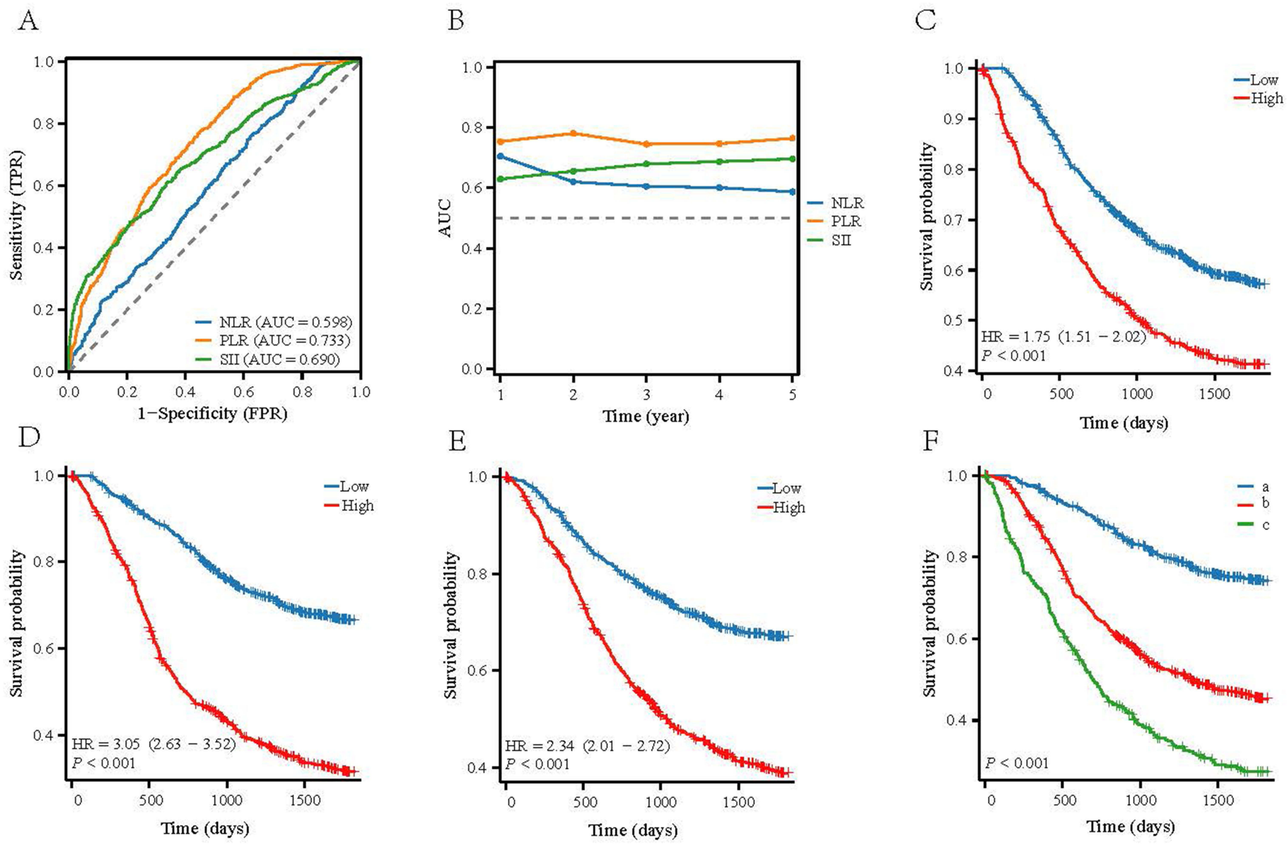


**Figure 5** The prognostic significance of inflammation indices for stage III patients. (**A**) ROC shows the predictive performance of different inflammation indices. (**B**) Time-ROC demonstrates the dynamic predictive performance of inflammation indices during the observation period. (**C**) The impact of NLR on prognosis based on the optimal cutoff value. (**D**) The impact of PLR on prognosis based on the optimal cutoff value. (**E**) The impact of SII on prognosis based on the optimal cutoff value.

**Abbreviations**: NLR, Neutrophil to Lymphocyte Ratio; PLR, Platelet to Lymphocyte Ratio; SII, Systemic Immune-Inflammation Index; ROC, Receiver Operating Characteristic; Time-ROC, Time-dependent Receiver Operating Characteristic.

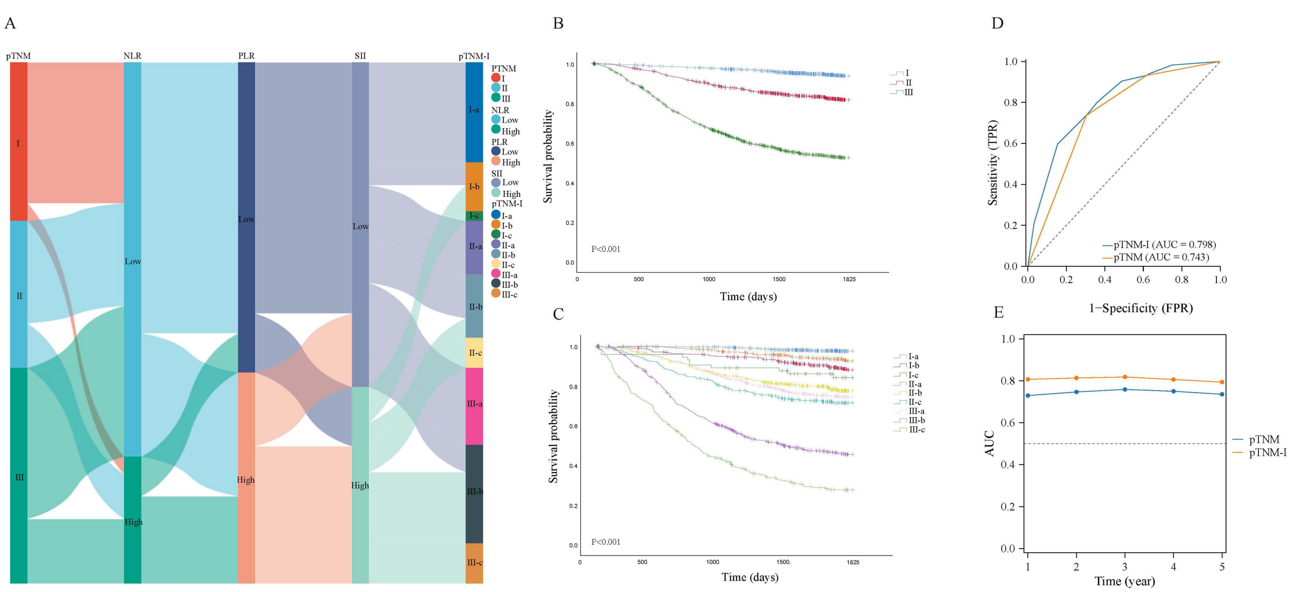


**Figure 6** Comparison of the prognostic value between pTNM staging and pTNM-I staging. (**A**) The composition of pTNM-I staging. (**B**) The impact of traditional pTNM staging on prognosis. (**C**) The impact of pTNM-I staging on prognosis. (**D**) Comparison of the performance between pTNM staging and pTNM-I staging. (**E**) Comparison of the dynamic performance between pTNM staging and pTNM-I staging.

**Abbreviations**: NLR, Neutrophil to Lymphocyte Ratio; PLR, Platelet to Lymphocyte Ratio; SII, Systemic Immune-Inflammation Index; ROC, Receiver Operating Characteristic; Time-ROC, Time-dependent Receiver Operating Characteristic.

**Table 2** Association Between pTNM Staging and Clinicopathological Characteristics

| **Characteristics** | **I-a (N=777)** | **I-b (N=382)** | **I-c (N=73)** | **II-a (N=416)** | **II-b (N=494)** | **II-c (N=233)** | **III-a (N=599)** | **III-b (N=763)** | **III-c N=312)** | ***P* value** |
|---|---|---|---|---|---|---|---|---|---|---|
| Sex | | | | | | | | | | **0.020** |
| Male | 582(14.37%) | 259(6.40%) | 51(1.26%) | 317(7.83%) | 337(8.32%) | 175(4.32%) | 452(11.16%) | 540(13.34%) | 225(5.56%) | |
| Female | 195(4.82%) | 123(3.04%) | 22(0.54%) | 99(2.45%) | 157(3.88%) | 58(1.43%) | 147(3.63%) | 223(5.51%) | 87(2.15%) | |
| Age (Mean±SD) | 57.09±9.50 | 56.95±9.85 | 57.21±10.60 | 58.18±9.31 | 59.25±9.78 | 59.93±10.82 | 58.18±10.14 | 58.14±10.58 | 59.29±10.87 | NA |
| CEA (Mean±SD) | 2.50±5.10 | 2.75±7.54 | 2.28±2.53 | 4.82±23.86 | 4.80±21.10 | 6.22±25.34 | 6.83±24.15 | 12.43±64.93 | 12.51±50.21 | NA |
| CA 19–9 (Mean±SD) | 12.17±38.06 | 13.05±30.61 | 10.72±10.56 | 22.68±84.50 | 21.10±56.53 | 28.31±95.29 | 59.00±166.15 | 58.14±161.54 | 77.65±201.14 | NA |
| Tumor location | | | | | | | | | | **<0.001** |
| Upper | 51(1.26%) | 35(0.86%) | 6(0.15%) | 60(1.48%) | 57(1.41%) | 29(0.72%) | 74(1.83%) | 89(2.20%) | 38(0.94%) | |
| Middle | 78(1.93%) | 52(1.28%) | 7(0.17%) | 67(1.65%) | 81(2.00%) | 36(0.89%) | 96(2.37%) | 137(3.38%) | 58(1.43%) | |
| Lower | 647(15.98%) | 295(7.29%) | 59(1.46%) | 286(7.06%) | 350(8.64%) | 164(4.05%) | 415(10.25%) | 511(12.62%) | 200(4.94%) | |
| Total | 1(0.02%) | 0(0%) | 1(0.02%) | 3(0.07%) | 6(0.15%) | 4(0.10%) | 14(0.35%) | 26(0.64%) | 16(0.40%) | |
| pTNM | | | | | | | | | | **<0.001** |
| I | 777(19.19%) | 382(9.43%) | 73(1.80%) | 0(0%) | 0(0%) | 0(0%) | 0(0%) | 0(0%) | 0(0%) | |
| II | 0(0%) | 0(0%) | 0(0%) | 416(10.27%) | 494(12.20%) | 233(5.75%) | 0(0%) | 0(0%) | 0(0%) | |
| III | 0(0%) | 0(0%) | 0(0%) | 0(0%) | 0(0%) | 0(0%) | 599(14.79%) | 763(18.84%) | 312(7.71%) | |
| Tumor size (mm) | | | | | | | | | | **<0.001** |
| ≤50 | 709(17.51%) | 345(8.52%) | 66(1.63%) | 304(7.51%) | 304(7.51%) | 129(3.19%) | 304(7.51%) | 323(7.98%) | 87(2.15%) | |
| >50 | 68(1.68%) | 37(0.91%) | 7(0.17%) | 112(2.77%) | 190(4.69%) | 104(2.57%) | 295(7.29%) | 440(10.87%) | 225(5.56%) | |

**Note**: $P < 0.005$ in bold.

**Abbreviations**: NA, No statistical significance; pTNM-I, pTNM-inflammation; CEA, carcinoembryonic antigen; CA 19–9, carbohydrate antigen 19–9; SD, standard deviation.

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**Table 3** Univariate and Multivariate Analysis of Factors Influencing Patient Prognosis

| Characteristics | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| | Hazard Ratio (95% CI) | *P* value | Hazard Ratio (95% CI) | P value |
| Sex | | | | |
| Male | Reference | | | |
| Female | 0.931 (0.810–1.070) | 0.315 | | |
| Age | 1.025 (1.018–1.031) | **< 0.001** | 1.020 (1.014–1.026) | **< 0.001** |
| CEA | 1.002 (1.001–1.003) | **< 0.001** | 1.001 (1.000–1.002) | 0.088 |
| CA 19-9 | 1.002 (1.001–1.002) | **< 0.001** | 1.001 (1.000–1.001) | **0.002** |
| Tumor location | | | | |
| Lower | Reference | | Reference | |
| Upper | 1.633 (1.366–1.954) | **< 0.001** | 1.355 (1.132–1.622) | **< 0.001** |
| Middle | 1.412 (1.197–1.665) | **< 0.001** | 1.173 (0.994–1.384) | 0.060 |
| Total | 4.113 (3.039–5.567) | **< 0.001** | 1.882 (1.381–2.566) | **< 0.001** |
| Tumor size | | | | |
| ≤50 | Reference | | Reference | |
| >50 | 2.846 (2.513–3.222) | **< 0.001** | 1.282 (1.123–1.463) | **< 0.001** |
| pTNM-I | 1.565 (1.512–1.619) | **< 0.001** | 1.514 (1.461–1.570) | **< 0.001** |

**Note**: $P < 0.005$ in bold.
**Abbreviations**: pTNM-I, pTNM-inflammation; CEA, carcinoembryonic antigen; CA 19–9, carbohydrate antigen 19–9; SD, standard deviation.

progression of tumors but also in the microscopic inflammatory microenvironment. We also found that the predictive abilities of different inflammatory indices vary among overall or stage I–III GC patients. Considering the differences in sensitivity, we did not select the optimal inflammatory index to construct the pTNM-I staging system; instead, we chose a comprehensive combination of inflammatory markers. The reason for this approach is that the AUC values of these inflammatory markers are all above 0.6, indicating that they possess certain predictive value. Furthermore, the combination of inflammatory markers provides more comprehensive inflammatory information. Similar studies have confirmed the application of combined inflammatory indices, such as the combination of NLR and the prognostic nutritional index,[18] and the integrated index of fibrinogen and NLR.[19] Additionally, considering the application significance of inflammatory indices for GC patients at different stages,[20,21] under the background of heterogeneous prognosis in GC, the comprehensive inflammatory indices will further reveal prognostic differences among patients in the same stage. Our results also found that the nine-class prognostic categorization of pTNM-I is statistically significant. This also suggests that the prognosis of patients with the same pTNM stage still remains uncertain.

Considering the application value of pTNM-I, we conducted a comprehensive comparison with pTNM staging, and the results consistently showed that pTNM-I staging has superior predictive capability compared to the traditional pTNM staging. Kotaro et al predicted the prognosis of 1166 GC patients based on nutrition, inflammation, and pTNM staging, and found that nutrition and inflammation could enhance the predictive ability of pTNM staging.[22] We provided a larger sample size to minimize the occurrence of random statistical phenomena. It is important that the optimal prognostic scoring system should be objective, reliable, easy to assess, and consistent.[23] Next-generation sequencing, single-cell analysis, and spatial transcriptomics are advanced techniques that can provide a more detailed assessment of tumor microenvironment changes,[24–26] but conventional blood tests often offer a more convenient assessment method. Moreover, these blood tests are routine examinations that patients must undergo upon admission.

We further considered that certain treatment approaches, such as neoadjuvant and immunotherapy, may affect a patient's peripheral immune status. Therefore, we only analyzed the results of the first blood examination upon admission. This also indicates that these blood test results may more accurately reflect the current inflammatory status of the patients. Similar results have been validated in a high-volume center with over 1000 GC cases.[27] This fully supports our research findings. In conclusion, rapid and accurate assessment provides a solid foundation for the application of pTNM-I staging.

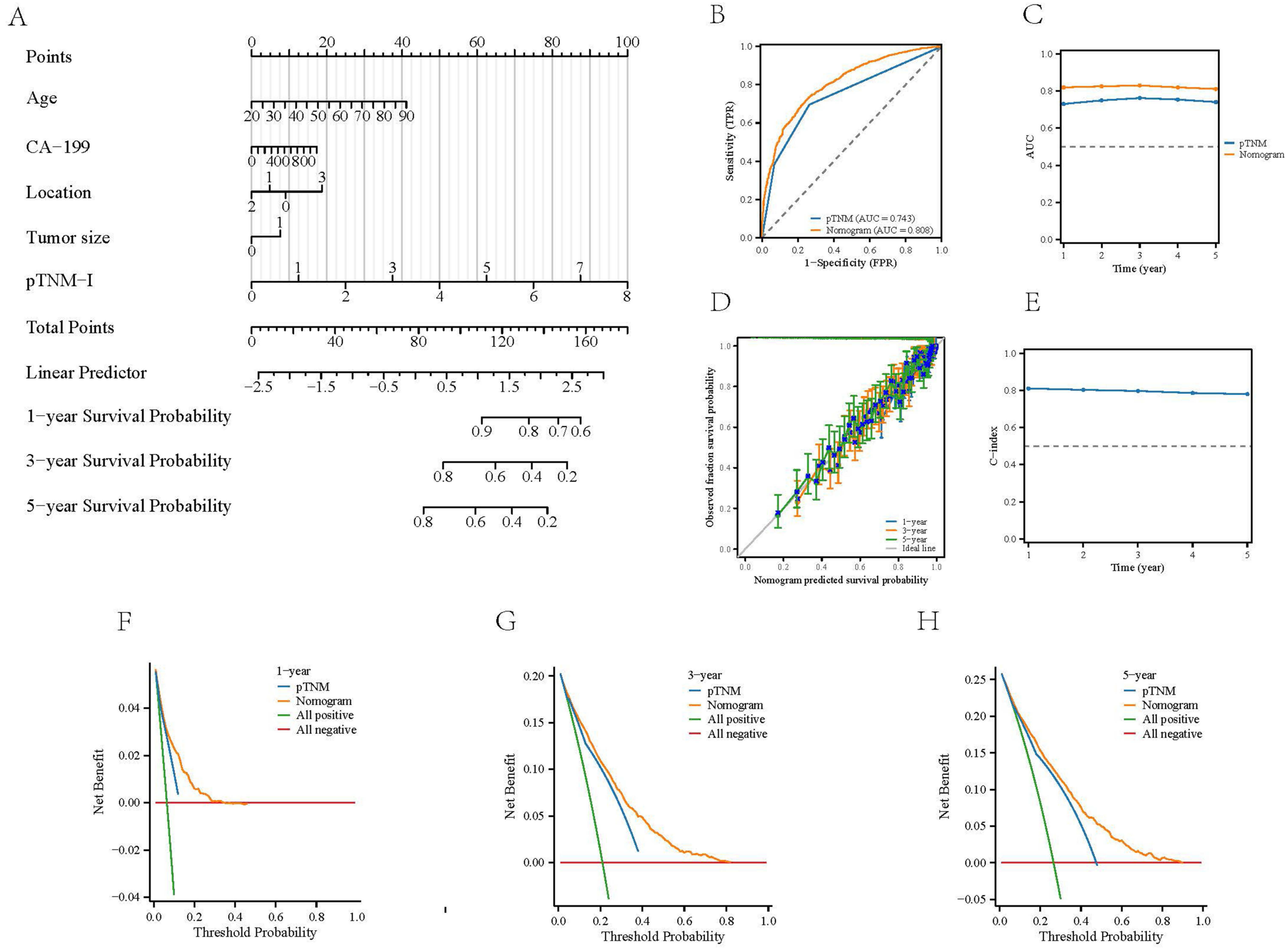


**Figure 7** Nomogram for predicting patient prognosis. (**A**) Construction of the nomogram. (**B**) Comparison of the performance between the nomogram and traditional pTNM staging. (**C**) Comparison of the dynamic performance between the nomogram and traditional pTNM staging. (**D**) Calibration plot of the nomogram. (**E**) Dynamic change in the C-index of the nomogram. (**F**) DCA curve for predicting 1-year patient prognosis. (**G**) DCA curve for predicting 3-year patient prognosis. (**H**) DCA curve for predicting 5-year patient prognosis.
**Abbreviations**: ROC, Receiver Operating Characteristic; Time-ROC, Time-dependent Receiver Operating Characteristic; DCA, Decision Curve Analysis.

In the multivariate Cox regression analysis, pTNM-I staging was identified as an independent prognostic factor associated with patient outcomes, and the Kaplan-Meier survival curves also demonstrated that pTNM-I staging provided detailed prognostic stratification. This indicates that the basic parameters constituted by NLR, PLR, and SII play a crucial role, including neutrophils, platelets, and lymphocytes. Lymphocytes are fundamental components of both innate and adaptive immunity and serve as the essential basis for immune surveillance and immune editing cells.[28] The infiltration of lymphocytes has been associated with improved prognosis, including anti-tumor activity and inhibition of angiogenesis.[29] Neutrophils are typical inflammatory cells that can secrete cytokines and effector molecules, thereby increasing the invasiveness of tumors. In meta-analyses, elevated NLR has been correlated with poor prognosis in cancer patients.[30] Platelets can reflect the adverse state of tumors, such as immunothrombosis, participating in microvascular thrombosis and promoting tumor metastasis.[31] Recent large-scale meta-analyses have also shown that elevated PLR is associated with unfavorable outcomes in cancer patients.[32] Additionally, the chi-square test revealed that pTNM-I was strongly associated with the aggressive behavior of tumors. Therefore, these studies may explain why pTNM-I can comprehensively assess prognosis and also highlight the important value of peripheral inflammatory markers.

In clinical practice, pTNM staging provides crucial information for the follow-up and treatment decision-making of GC. Compared to the seventh edition of pTNM staging, the improvements in the eighth edition of pTNM staging have further enhanced the ability to differentiate the prognosis of GC patients.[33] Galon et al proposed the pTNM-immunology staging in colorectal cancer,[34,35] which not only improves prognostic accuracy but also effectively predicts postoperative recurrence in colorectal cancer patients in prospective study.[36] In GC, inflammatory markers can effectively predict postoperative recurrence,[37] but there is a lack of detailed integration of pTNM staging with inflammatory markers. Moreover, immunotherapy holds significant value for GC, as inflammation is often an essential component of the immune response. Shen et al accurately predicted the prognosis of GC patients receiving immunotherapy based on inflammation indices.[38] Ding et al used SII to predict the prognosis of GC patients receiving anti-PD-1 therapy.[39] In our study, SII has significant value in predicting the prognosis of GC patients. As a comprehensive inflammatory index, SII has also demonstrated excellent predictive potential in multiple cancers.[9–11] These results suggest that under the highly heterogeneous biological behavior of GC, pTNM-I demonstrates inspiring potential, and we have significantly improved the prediction accuracy of GC. Therefore, in the future, it is anticipated that large-scale prospective studies will be conducted on the immunotherapy and recurrence prediction of GC based on pTNM-I, in order to enhance treatment decisions for GC. These insightful suggestions provide additional insights into the adaptability and robustness of the pTNM-I system in various clinical scenarios.

Finally, based on the pTNM-I staging system, we constructed a nomogram to predict patient prognosis. Moreover, the nomogram demonstrated superior predictive performance compared to the traditional pTNM staging system. We also applied a series of statistical analyses to validate the predictive ability of the nomogram, including DCA, ROC curves, time-dependent ROC analysis, calibration plots, and the c-index. This indicates that the nomogram, constructed based on pTNM-I and clinical pathological characteristics, will provide more robust predictive capabilities. It offers a more detailed discrimination and risk stratification for pTNM staging.

This study has certain advantages. Firstly, we proposed the pTNM-I staging system for the first time, providing a supplementary role to the traditional pTNM staging system. Secondly, we applied a relatively large sample size, and compared to small-sample studies, our statistical results are more reliable. However, this study still has some limitations. Firstly, this study is a single-center study based on an Asian population, and the applicability of the research results to different regions remains to be determined. Secondly, we only assessed the prognosis of patients through preoperative inflammatory indices, whereas the significance of the dynamic changes in inflammatory indices before and after surgery for patient prognosis remains unknown.

## Conclusion

In conclusion, we integrated multiple inflammatory markers with pTNM staging to construct the pTNM-I staging system. This system, in addition to having a more powerful predictive capability, provides more detailed prognostic stratification information through its nine-classification system compared to the traditional three-class pTNM staging. We also developed a nomogram based on pTNM-I staging and clinical pathological characteristics. Therefore, the pTNM-I staging system, as a simple, economical, and routine prognostic tool, has certain application value in predicting patient outcomes.

## Data Sharing Statement

All available data are from the case information management system of Harbin medical university cancer hospital.

## Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of Harbin Medical University Cancer Hospital. All study participants or their legal guardians provided informed written consent for personal and medical data collection prior to study enrollment. All programs followed were according to the ethical standards of the Human Subjects Responsibility Committee (institutions and countries), as well as the 1964 Helsinki Declaration and subsequent editions.

## Consent for Publication

All authors have been informed of the manuscript and have given their consent to publication.

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## Author Contributions

Zhanshuo Liu and Hao Liu designed the study, analyzed and interpreted the data, and drafted the manuscript. Zhanshuo Liu,Yue Zhang and Yuhang Yang analyzed and interpreted the data. Zhanshuo Liu, Yue Zhang, and Yuhang Yang conducted statistical analysis. Hongyu Gao revised the manuscript. The authors read and approved the final manuscript.

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## Disclosure

The authors report no conflicts of interest in this work.

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