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# Predicting Pathological Complete Response to Neoadjuvant Immunotherapy in Gastric Adenocarcinoma: A Nomogram Based on Serum Tumor Markers and Inflammatory Indices

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## Abstract

# Background

Although neoadjuvant immunotherapy improves tumor regression in gastric cancer, many patients lack optimal pathological responses. This study aimed to identify independent predictors of pathological complete response (pCR) following neoadjuvant immunotherapy in gastric adenocarcinoma and to develop a predictive model incorporating tumor markers and inflammatory indices.

# Methods

We retrospectively analyzed 288 gastric cancer patients receiving neoadjuvant therapy (2021–2024). Pretreatment inflammatory indices (NLR, LMR, PLR, SII) and their dynamic changes were calculated. After multiple imputation for missing data, LASSO regression and multivariate logistic regression were performed to identify independent predictors of pCR following immunotherapy. A nomogram was constructed and internally validated using bootstrap resampling (1000 replicates) with AUC, calibration curves, and decision curve analysis (DCA).

# Results

A total of 146 patients received neoadjuvant immunotherapy and 142 received chemotherapy. The immunotherapy group exhibited a significantly higher pCR rate (22.6% vs. 9.2%, P = 0.002). Multivariate analysis revealed that CEA > 1.85 ng/mL (OR = 0.17), NLR > 2 (OR = 0.17), Delta-LMR > 0.5 (OR = 0.05), and Depth of invasion T4 (OR = 0.14) were independent predictors of pCR following immunotherapy. A nomogram incorporating these factors achieved a bootstrap-corrected AUC of 0.798 (95% CI: 0.748–0.896) with favorable calibration and clinical utility.

# Conclusions

Neoadjuvant immunotherapy achieved a significantly higher pCR rate than chemotherapy. Elevated NLR, CEA, Delta-LMR, and Depth of invasion T4 were independent risk factors for pCR failure. The nomogram based on these predictors showed favorable discrimination and accuracy, which potentially aid clinicians in identifying potential responders and guiding personalized treatment strategies.

## Introduction

Global cancer statistics[1] from 2022 show that gastric cancer ranks fifth in both new incidence and cancer-related mortality worldwide. In China, it remains the third leading cause of cancer-related death[2]. The prevention and treatment of gastric cancer in China still faces substantial challenges. Most patients are diagnosed at an advanced stage with a 5-year survival rate below 30% for advanced disease,

whereas early-stage patients have a 5-year survival rate exceeding 90%[2]. Currently, the treatment of gastric cancer is centered on surgery complemented by multidisciplinary comprehensive therapy. Neoadjuvant therapy has become an important treatment approach recommended by domestic and international guidelines, as it can achieve tumor downstaging, improve R0 resection rates, and eliminate micro-metastases[3, 4]. Despite continuous therapeutic advances, long-term survival in gastric cancer remains unsatisfactory, and more effective treatment strategies and predictive tools are urgently needed.

In recent years, immune checkpoint inhibitors have achieved remarkable progress in the neoadjuvant treatment of gastric cancer. *NEOSUMMIT-01* [5] study demonstrated that adding toripalimab to neoadjuvant chemotherapy significantly improved the pathological complete response (pCR) rate, and subsequent 3-year follow-up[6] showed that neoadjuvant chemoimmunotherapy improved 3-year event-free survival (EFS) and overall survival (OS). Although the significant EFS benefit of neoadjuvant immunotherapy has been confirmed only in the *MATTERHORN*[7], and *ASTRUM-006*[8] studies (Phase III), the substantial pCR benefit has been supported by multiple studies[5–14]. Moreover, a series of studies have found that gastric cancer patients achieving pCR have better EFS and OS than those who do not[12, 15–19], indicating that pCR is not only a direct reflection of neoadjuvant efficacy but also a recognized surrogate prognostic marker. However, even in the era of neoadjuvant immunotherapy, a considerable proportion of patients still fail to achieve ideal pathological regression. Therefore, accurately identifying patients who may benefit from immunotherapy before treatment has become a critical clinical issue.

In the exploration of predictive biomarkers, tumor markers have received extensive attention. Carcinoembryonic antigen (CEA), carbohydrate antigen 19 – 9 (CA19-9), and carbohydrate antigen 724 (CA724) have been widely used for dynamic monitoring of gastric cancer progression and for evaluating clinical efficacy and prognosis[2]. Numerous studies[20–24] have shown that scoring systems combining CEA, CA19-9, and CA72-4 enhance predictive accuracy for progression-free survival (PFS) or pathological response in gastric cancer patients. However, the sensitivity and specificity of combined tumor markers remain limited, making it difficult to meet the clinical need for precise risk stratification.

Growing evidence[25–27] indicates that systemic inflammatory response also plays an important role in the development, progression, and immunotherapy response of gastric cancer. Peripheral blood inflammatory indices such as neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) have attracted considerable attention due to their simple detection and low cost. Previous studies have shown that baseline NLR and LMR are significantly associated with progression-free and overall survival in gastric cancer patients receiving immunotherapy[28]; NLR is a strong predictor of major pathological response (MPR) in advanced gastric cancer patients receiving immunochemotherapy[29]; and patients with low NLR and PLR had a higher pCR rate (33.8%), whereas those with elevated indices had the lowest pCR rate (10.7%)[30].

Given the independent prognostic value of these two biomarker categories in oncology, some researchers have combined traditional tumor markers with blood inflammatory indices to systematically

evaluate their predictive performance for survival and regression after neoadjuvant therapy in gastric cancer. *Yu et al.*[29] constructed a nomogram incorporating CEA, CA19-9, NLR, and SII to predict MPR, achieving excellent discrimination (AUC = 0.848). *Bi et al.*[30] found that a ≥ 70% decline in CEA levels and a pretreatment NLR below 2.5 served as independent prognostic indicators for achieving pCR after neoadjuvant chemotherapy by a retrospective cohort of 215 patients with advanced gastric cancer. Based on these studies, we raise the following scientific question: Can the combination of tumor markers and blood inflammatory indices effectively predict pCR after neoadjuvant immunotherapy in gastric cancer?

Therefore, our study aims to comprehensively explore biomarkers associated with neoadjuvant immunotherapy in gastric cancer patients and develop a clinically accessible predictive model integrating multidimensional serological indicators, providing a simple, cost-effective, and generalizable tool for pCR prediction to assist clinicians in accurately identifying potential beneficiaries and formulating individualized treatment plans, thereby improving patient survival outcomes.

## Materials and methods

# Data Collection

Our study retrospectively enrolled 288 gastric cancer patients who received neoadjuvant therapy and radical gastrectomy at Zhongshan Hospital of Fudan University, from 2021 to 2024 (142 received neoadjuvant chemotherapy, 146 received neoadjuvant immunotherapy). Criteria for inclusion included the following: (1) gastric adenocarcinoma by endoscopy or postoperative pathology; (2) receipt of neoadjuvant therapy before surgery; (3) availability of complete routine blood test and serum tumor marker results at initial diagnosis and within 2 weeks before surgery. Criteria for exclusion included the following: (1) carcinoma in situ; (2) previous history of other primary malignancies; (3) presence of acute infection, autoimmune disease, or hematological disorders before surgery; (4) severely missing clinical data. Demographic, clinical, and pathological information, including sex, age, tumor markers (CEA, CA19-9, CA724), complete blood cell counts, tumor type, size, differentiation, lymph node metastasis, and distant metastasis, were collected through the hospital electronic medical record system. Management of all patients was based on international guidelines, and TNM staging was assessed according to the 8th edition of the American Joint Committee on Cancer (AJCC) criteria.

## Data Processing

Pretreatment blood inflammatory indices were calculated from complete blood counts, including neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and their dynamic changes (Delta-NLR, Delta-PLR, Delta-LMR, Delta-SII). Calculation formulas were: NLR = neutrophil count / lymphocyte count; LMR = lymphocyte count / monocyte count; PLR = platelet count / lymphocyte count; SII = platelet count ×

neutrophil count / lymphocyte count; Delta-NLR = post-treatment NLR / pretreatment NLR; Delta-LMR = post-treatment LMR / pretreatment LMR; Delta-PLR = post-treatment PLR / pretreatment PLR; Delta-SII = post-treatment SII / pretreatment SII. Cutoff values for blood inflammatory indices and their changes, as well as tumor markers, were determined by ROC curves and Youden's index. And patients were categorized into normal (or low) and elevated groups (NLR: 2; LMR: 4.5; PLR: 138; SII: 483; Delta-NLR: 0.56; Delta-LMR: 0.45; Delta-PLR: 0.68; Delta-SII: 0.42; CEA: 1.85 ng/mL; CA19-9: 13.1 U/mL; CA724: 1.9 U/mL). For missing variables (1%–20%) in the neoadjuvant immunotherapy group, multiple imputation by chained equations (MICE) was performed with 20 imputations (m = 20) and 80 iterations, and convergence was confirmed by trace plots.

# Statistical Analysis

Continuous variables were expressed as “mean ± standard deviation” and compared using independent-sample t-test or Mann–Whitney U test. Categorical and ordinal variables were expressed as “n (%)” and compared using $\chi^2$ test or Fisher's exact test. For the entire cohort (n = 288), preliminary baseline analysis was conducted between the chemotherapy and immunotherapy groups, and variables with $P < 0.10$ were directly included in a multivariate logistic regression model to compare the effect of treatment on pCR rate after adjustment to confirm the efficacy advantage of neoadjuvant immunotherapy. The immunotherapy group (n = 146) was separately divided into non-pCR and pCR subgroups for preliminary comparison. After multiple imputation for missing data in the immunotherapy group (m = 20), least absolute shrinkage and selection operator (LASSO) regression was independently performed on each of the 20 imputed datasets. Five-fold cross-validation (nfolds = 5) was applied to lambda, and the lambda.1se criterion combined with a selection frequency threshold of 0.5 was used to identify non-zero coefficient variables based on minimizing binomial deviance. The selected non-zero coefficient variables were then included in multivariate logistic regression to further identify independent factors for pCR after neoadjuvant immunotherapy, and a nomogram was constructed based on these independent factors. Finally, bootstrap resampling with 1000 replicates was performed to calculate the bootstrap-corrected AUC and AUC optimism to evaluate predictive performance and stability. And calibration curves and decision curves were plotted to assess model accuracy and clinical utility. Model goodness-of-fit was evaluated by the Le Cessie–van Houwelingen test and Brier score. All statistical analyses were performed using R software (version 4.6.0, http://www.r-project.org/). Multiple imputation was performed using the mice package, and LASSO regression was performed using the glmnet package. $P < 0.05$ was considered statistically significant. Notably, to avoid multicollinearity, variables including Blood cell counts, Pathology, and Meta organ were not included in LASSO regression analysis.

## Results

# Comparison of basic clinical characteristics and efficacy assessment between the chemotherapy and immunotherapy groups

The clinicopathological characteristics of the neoadjuvant chemotherapy and neoadjuvant immunotherapy groups are presented in Table 1. A total of 142 patients received neoadjuvant chemotherapy and 146 received neoadjuvant immunotherapy. Although there were no significant differences in Sex or Age distribution between the two groups, Age composition approached statistical significance (P = 0.076). Tumor markers (CEA, CA19-9, CA724), Blood cell counts, and blood inflammatory indices showed no significant differences between the chemotherapy and immunotherapy groups. TNM stage differed significantly between the two groups (P = 0.038). Although the overall distribution of Pathology was not significantly different (P = 0.059), the derived variable (Mucinous/signet-ring) showed significant difference (P = 0.031). Lauren classification, EBER, and CPS showed no significant differences, but mismatch repair (MMR) protein showed a significant difference (P = 0.002). Notably, the pCR rate in the neoadjuvant immunotherapy group was significantly higher than that in the chemotherapy group (22.6% vs. 9.2%, P = 0.002), suggesting that immunotherapy confers superior pathological response in the neoadjuvant setting.

Table 1
Comparison of basic clinical characteristics between the Chemotherapy and Immunotherapy groups.

| **Factors** | | **Chemotherapy** | **Immunotherapy** | **P-value** |
|---|---|---|---|---|
| | | **N = 142** | **N = 146** | |
| Sex | Male | 43 (30%) | 34 (23%) | 0.186 |
| | Female | 99 (70%) | 112 (77%) | |
| Age (years) | < 65 | 73 (51%) | 59 (40%) | 0.076 |
| | ≥ 65 | 69 (49%) | 87 (60%) | |
| CEA | Normal | 34 (24%) | 45 (31%) | 0.235 |
| | Elevated | 107 (76%) | 101 (69%) | |
| | NAs | 1 | 0 | |
| CA19-9 | Normal | 79 (60%) | 83 (62%) | 0.802 |
| | Elevated | 53 (40%) | 51 (38%) | |
| | NAs | 10 | 12 | |
| CA724 | Normal | 23 (21%) | 31 (26%) | 0.352 |
| | Elevated | 87 (79%) | 86 (74%) | |
| | NA | 32 | 29 | |
| Blood cell count | Neutrophil | 3.6 (1.3) | 3.8 (1.5) | 0.287 |
| | Lymphocyte | 1.5 (0.5) | 1.6 (0.6) | 0.617 |
| | Monocyte | 0.5 (0.2) | 0.5 (0.2) | 0.683 |
| | Platelet | 257.0 (269.5) | 254.8 (91.5) | 0.080 |
| NLR | Low | 89 (63%) | 91 (62%) | > 0.999 |
| | Elevated | 53 (37%) | 55 (38%) | |
| LMR | Low | 27 (19%) | 31 (21%) | 0.662 |
| | Elevated | 115 (81%) | 115 (79%) | |
| PLR | Low | 91 (64%) | 96 (66%) | 0.805 |
| | Elevated | 51 (36%) | 50 (34%) | |

CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen; NLR, the rate of neutrophils to lymphocytes; LMR, the rate of lymphocytes to monocytes; PLR, the rate of platelets to lymphocytes; SII, systemic immune-inflammation index; Mucinous/signet-ring, mucinous or signet-ring cell composition in pathology.

| Factors | | Chemotherapy N = 142 | Immunotherapy N = 146 | P-value |
|---|---|---|---|---|
| SII | Low | 78 (55%) | 93 (64%) | 0.150 |
| | Elevated | 64 (45%) | 53 (36%) | |
| TNM stage | I | 9 (6.3%) | 12 (8.2%) | 0.038 |
| | II | 52 (37%) | 60 (41%) | |
| | III | 66 (46%) | 46 (32%) | |
| | IV | 15 (11%) | 28 (19%) | |
| Pathology | Traditional | 98 (69%) | 117 (80%) | 0.059 |
| | Mucinous | 3 (2.1%) | 5 (3.4%) | |
| | Signet-ring | 9 (6.3%) | 3 (2.1%) | |
| | Mixed | 32 (23%) | 21 (14%) | |
| Mucinous/signet-ring | Positive | 44 (31%) | 29 (20%) | 0.031 |
| | Negative | 98 (69%) | 117 (80%) | |
| Differentiation | Middle-low | 104 (76%) | 104 (72%) | 0.499 |
| | Middle-high | 33 (24%) | 40 (28%) | |
| | NA | 5 | 2 | |
| Lauren classification | Diffused | 34 (25%) | 22 (16%) | 0.170 |
| | Mixed | 54 (40%) | 56 (41%) | |
| | Intestinal | 48 (35%) | 58 (43%) | |
| | NA | 6 | 10 | |
| MMR | pMMR | 136 (98%) | 125 (88%) | 0.002 |
| | dMMR | 3 (2.2%) | 17 (12%) | |
| | NA | 3 | 4 | |
| EBER | Negative | 132 (99%) | 134 (97%) | 0.684 |
| | Positive | 2 (1.5%) | 4 (2.9%) | |

CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen; NLR, the rate of neutrophils to lymphocytes; LMR, the rate of lymphocytes to monocytes; PLR, the rate of platelets to lymphocytes; SII, systemic immune-inflammation index; Mucinous/signet-ring, mucinous or signet-ring cell composition in pathology.

| Factors | | Chemotherapy N = 142 | Immunotherapy N = 146 | P-value |
|---|---|---|---|---|
| | NA | 8 | 8 | |
| CPS | Negative | 16 (23%) | 20 (17%) | 0.347 |
| | Positive | 54 (77%) | 96 (83%) | |
| | NA | 72 | 30 | |
| Response | non-pCR | 129 (91%) | 113 (77%) | 0.002 |
| | pCR | 13 (9.2%) | 33 (23%) | |

CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen; NLR, the rate of neutrophils to lymphocytes; LMR, the rate of lymphocytes to monocytes; PLR, the rate of platelets to lymphocytes; SII, systemic immune-inflammation index; Mucinous/signet-ring, mucinous or signet-ring cell composition in pathology.

To adjust for imbalances in the above factors and clarify the independent efficacy of immunotherapy, Therapy and variables with $P < 0.10$ from Table 1. (Age, TNM stage, Mucinous/signet-ring, MMR) were included in a multivariate logistic regression model, with results shown in Table 2. The results showed that Therapy was an independent factor for pCR after neoadjuvant therapy in gastric adenocarcinoma, with neoadjuvant immunotherapy significantly increasing pCR rate (OR = 3.05, 95% CI: 1.39–7.16, P = 0.007), further confirming the significant benefit of immunotherapy in achieving pCR.

Table 2
Multivariate logistic regression analysis for pCR in all patients (n = 288).

| Factors | | Beta | OR(95%CI) | Wald | P-value |
|---|---|---|---|---|---|
| Therapy | Chemo | 1.0 (reference) | 1.0 (reference) | | |
| | Immuno | 1.14 | 3.05 (1.39–7.16) | 2.69 | 0.007 |
| Age (years) | < 65 | 1.0 (reference) | 1.0 (reference) | | 0.973 |
| | ≥ 65 | -0.02 | 0.99 (0.47–2.09) | -0.03 | |
| TNM stage | I | 1.0 (reference) | 1.0 (reference) | | |
| | II | -1.51 | 0.22 (0.07–0.68) | -2.67 | 0.008 |
| | III | -1.58 | 0.21 (0.07–0.66) | -2.70 | 0.007 |
| | IV | -1.69 | 0.19 (0.05–0.71) | -2.42 | 0.016 |
| Mucinous/signet-ring | Positive | 1.0 (reference) | 1.0 (reference) | | |
| | Negative | 1.42 | 4.11 (1.35–17.98) | 2.21 | 0.027 |
| MMR | dMMR | 1.0 (reference) | 1.0 (reference) | | |
| | pMMR | -0.50 | 0.61 (0.22–1.93) | -0.90 | 0.369 |

Therapy, neoadjuvant therapy schedule (Chemo, neoadjuvant chemotherapy; Immuno, neoadjuvant immunotherapy); Mucinous/signet-ring, mucinous or signet-ring cell composition in pathology.

# Comparison of basic clinical characteristics between the non-pCR and pCR subgroups in immunotherapy group

To explore factors influencing pCR benefit from neoadjuvant immunotherapy, immunotherapy patients were divided into the non-pCR (N = 113) and pCR (N = 33) subgroups based on pCR. Comparison of clinicopathological characteristics between the two subgroups is presented in Table 3. Sex and Age showed no significant differences. Among major tumor markers, the proportion of patients with elevated baseline CEA was significantly higher in the non-pCR subgroup (P = 0.001), while CA19-9 and CA724 showed no significant differences. Regarding hematological parameters, the proportion of patients with elevated baseline NLR was significantly higher in the non-pCR subgroup (P = 0.008). The proportions of patients with elevated Delta-LMR and Delta-SII also showed significant differences between the two subgroups (Delta-LMR P = 0.015; Delta-SII P = 0.041). Additionally, TNM stage, Depth of invasion, and Lymph node meta showed significant intergroup differences (TNM stage P < 0.001; Depth of invasion P < 0.001; Lymph node meta P = 0.029). Although Distant meta showed no statistical difference, the derived variable based on liver metastasis (Meta organ) showed significant difference between groups (P = 0.035), suggesting that patients with liver metastasis may be more likely to achieve pCR from neoadjuvant immunotherapy compared to other metastatic sites. We further classified immunotherapy

regimens into different categories and found that different PD-1 combination regimens have potential statistical significance (P = 0.059), suggesting that choice of chemotherapeutic agents may affect the efficacy of immunotherapy combinations. Overall, the statistical differences in CEA, NLR, Delta-LMR, and Delta-SII between non-pCR and pCR subgroups suggest their potential predictive value for pCR.

Table 3
Comparison of the non-pCR and pCR subgroups in immunotherapy group (n = 146).

| Factors | | non-pCR N = 113 | pCR N = 33 | P-value |
|---|---|---|---|---|
| Sex | Male | 27 (24%) | 7 (21%) | 0.819 |
| | Female | 86 (76%) | 26 (79%) | |
| Age (years) | < 65 | 46 (41%) | 13 (39%) | > 0.999 |
| | ≥ 65 | 67 (59%) | 20 (61%) | |
| CEA | Normal | 27 (24%) | 18 (55%) | 0.001 |
| | Elevated | 86 (76%) | 15 (45%) | |
| CA19-9 | Normal | 59 (58%) | 24 (75%) | 0.097 |
| | Elevated | 43 (42%) | 8 (25%) | |
| | NAs | 11 | 1 | |
| CA724 | Normal | 21 (23%) | 10 (42%) | 0.072 |
| | Elevated | 72 (77%) | 14 (58%) | |
| | NA | 20 | 9 | |
| Blood cell count | Neutrophil | 3.8 (1.6) | 3.8 (1.3) | 0.461 |
| | Lymphocyte | 1.6 (0.6) | 1.5 (0.5) | 0.963 |
| | Monocyte | 0.5 (0.2) | 0.5 (0.1) | 0.957 |
| | Platelet | 257.4 (95.3) | 245.8 (77.7) | 0.772 |
| NLR | Low | 64 (57%) | 27 (82%) | 0.008 |
| | Elevated | 49 (43%) | 6 (18%) | |
| LMR | Low | 27 (24%) | 4 (12%) | 0.225 |

CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen; Delta-NLR, the change of NLR before and after neoadjuvant therapy (NLR, the rate of neutrophils to lymphocytes). Delta-LMR, the change of LMR before and after neoadjuvant therapy (LMR, the rate of lymphocytes to monocytes). Delta-PLR, the change of PLR before and after neoadjuvant therapy (PLR, the rate of platelets to lymphocytes). Delta-SII, the change of SII before and after neoadjuvant therapy.(SII, systemic immune-inflammation index) Meta organ, distant metastasis based on specific organ (M0: no distant organ metastasis; Mh: only hepatic distant metastasis; M1: non-hepatic distant metastasis or multiple site metastasis); Mucinous/signet-ring, mucinous or signet-ring cell composition in pathology; Immunotherapy, neoadjuvant immunotherapy schedule (PD1, PD1 inhibitor monotherapy; PD1 + CCNSA, PD1 inhibitor combined with cell cycle non-specific agent; PD1 + CCSA, PD1 inhibitor combined with cell cycle specific agent; PD1 + CTLA4, PD1 inhibitor combined with CTLA4 inhibitor or dual immune checkpoint inhibitor).

| Factors | | non-pCR<br>N = 113 | pCR<br>N = 33 | P-value |
|---|---|---|---|---|
| | Elevated | 86 (76%) | 29 (88%) | |
| PLR | Low | 71 (63%) | 25 (76%) | 0.213 |
| | Elevated | 42 (37%) | 8 (24%) | |
| SII | Low | 68 (60%) | 25 (76%) | 0.149 |
| | Elevated | 45 (40%) | 8 (24%) | |
| Delta-NLR | Low | 26 (23%) | 12 (36%) | 0.175 |
| | Elevated | 87 (77%) | 21 (64%) | |
| Delta-LMR | Low | 3 (2.7%) | 5 (15%) | 0.015 |
| | Elevated | 110 (97%) | 28 (85%) | |
| Delta-PLR | Low | 44 (39%) | 17 (52%) | 0.231 |
| | Elevated | 69 (61%) | 16 (48%) | |
| Delta-SII | Low | 38 (34%) | 18 (55%) | 0.041 |
| | Elevated | 75 (66%) | 15 (45%) | |
| TNM stage | I | 3 (2.7%) | 9 (27%) | < 0.001 |
| | II | 47 (42%) | 13 (39%) | |
| | III | 40 (35%) | 6 (18%) | |
| | IV | 23 (20%) | 5 (15%) | |
| Pathology | Traditional | 86 (76%) | 31 (94%) | 0.188 |
| | Mucinous | 5 (4.4%) | 0 (0%) | |
| | Signet-ring | 3 (2.7%) | 0 (0%) | |
| | Mixed | 19 (17%) | 2 (6.1%) | |

CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen; Delta-NLR, the change of NLR before and after neoadjuvant therapy (NLR, the rate of neutrophils to lymphocytes). Delta-LMR, the change of LMR before and after neoadjuvant therapy (LMR, the rate of lymphocytes to monocytes). Delta-PLR, the change of PLR before and after neoadjuvant therapy (PLR, the rate of platelets to lymphocytes). Delta-SII, the change of SII before and after neoadjuvant therapy.(SII, systemic immune-inflammation index) Meta organ, distant metastasis based on specific organ (M0: no distant organ metastasis; Mh: only hepatic distant metastasis; M1: non-hepatic distant metastasis or multiple site metastasis); Mucinous/signet-ring, mucinous or signet-ring cell composition in pathology; Immunotherapy, neoadjuvant immunotherapy schedule (PD1, PD1 inhibitor monotherapy; PD1 + CCNSA, PD1 inhibitor combined with cell cycle non-specific agent; PD1 + CCSA, PD1 inhibitor combined with cell cycle specific agent; PD1 + CTLA4, PD1 inhibitor combined with CTLA4 inhibitor or dual immune checkpoint inhibitor).

| Factors | | non-pCR<br>N = 113 | pCR<br>N = 33 | P-value |
|---|---|---|---|---|
| Mucinous/signet-ring | Positive | 27 (24%) | 2 (6.1%) | 0.025 |
| | Negative | 86 (76%) | 31 (94%) | |
| Differentiation | Middle-low | 81 (73%) | 23 (70%) | 0.825 |
| | Middle-high | 30 (27%) | 10 (30%) | |
| | NA | 2 | 0 | |
| Lauren classification | Diffused | 18 (17%) | 4 (15%) | 0.315 |
| | Mixed | 48 (44%) | 8 (30%) | |
| | Intestinal | 43 (39%) | 15 (56%) | |
| | NA | 4 | 6 | |
| MMR | pMMR | 102 (90%) | 23 (79%) | 0.825 |
| | dMMR | 11 (9.7%) | 6 (21%) | |
| | NA | 0 | 4 | |
| EBER | Negative | 110 (98%) | 24 (92%) | 0.161 |
| | Positive | 2 (1.8%) | 2 (7.7%) | |
| | NA | 1 | 7 | |
| CPS | Negative | 16 (19%) | 4 (13%) | 0.588 |
| | Positive | 70 (81%) | 26 (87%) | |
| | NA | 27 | 3 | |
| Depth of invasion | T2 | 8 (7.1%) | 11 (33%) | < 0.001 |
| | T3 | 35 (31%) | 13 (39%) | |
| | T4 | 70 (62%) | 9 (27%) | |

CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen; Delta-NLR, the change of NLR before and after neoadjuvant therapy (NLR, the rate of neutrophils to lymphocytes). Delta-LMR, the change of LMR before and after neoadjuvant therapy (LMR, the rate of lymphocytes to monocytes). Delta-PLR, the change of PLR before and after neoadjuvant therapy (PLR, the rate of platelets to lymphocytes). Delta-SII, the change of SII before and after neoadjuvant therapy.(SII, systemic immune-inflammation index) Meta organ, distant metastasis based on specific organ (M0: no distant organ metastasis; Mh: only hepatic distant metastasis; M1: non-hepatic distant metastasis or multiple site metastasis); Mucinous/signet-ring, mucinous or signet-ring cell composition in pathology; Immunotherapy, neoadjuvant immunotherapy schedule (PD1, PD1 inhibitor monotherapy; PD1 + CCNSA, PD1 inhibitor combined with cell cycle non-specific agent; PD1 + CCSA, PD1 inhibitor combined with cell cycle specific agent; PD1 + CTLA4, PD1 inhibitor combined with CTLA4 inhibitor or dual immune checkpoint inhibitor).

| Factors | | non-pCR<br>N = 113 | pCR<br>N = 33 | P-value |
|---|---|---|---|---|
| Lymph node meta | N0 | 56 (50%) | 9 (27%) | 0.029 |
| | N1-3 | 56 (50%) | 24 (73%) | |
| Distant meta | M0 | 90 (80%) | 28 (85%) | 0.620 |
| | M1 | 23 (20%) | 5 (15%) | |
| Meta organ | M0 | 90 (80%) | 28 (85%) | 0.035 |
| | Mh | 9 (8.0%) | 5 (15%) | |
| | M1 | 14 (12%) | 0 (0%) | |
| Immunotherapy | PD1 | 5 (4.4%) | 3 (9.1%) | 0.059 |
| | PD1 + CCNSA | 79 (70%) | 27 (82%) | |
| | PD1 + CCSA | 27 (24%) | 2 (6.1%) | |
| | PD1 + CTLA4 | 2 (1.8%) | 1 (3.0%) | |

CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen; Delta-NLR, the change of NLR before and after neoadjuvant therapy (NLR, the rate of neutrophils to lymphocytes). Delta-LMR, the change of LMR before and after neoadjuvant therapy (LMR, the rate of lymphocytes to monocytes). Delta-PLR, the change of PLR before and after neoadjuvant therapy (PLR, the rate of platelets to lymphocytes). Delta-SII, the change of SII before and after neoadjuvant therapy.(SII, systemic immune-inflammation index) Meta organ, distant metastasis based on specific organ (M0: no distant organ metastasis; Mh: only hepatic distant metastasis; M1: non-hepatic distant metastasis or multiple site metastasis); Mucinous/signet-ring, mucinous or signet-ring cell composition in pathology; Immunotherapy, neoadjuvant immunotherapy schedule (PD1, PD1 inhibitor monotherapy; PD1 + CCNSA, PD1 inhibitor combined with cell cycle non-specific agent; PD1 + CCSA, PD1 inhibitor combined with cell cycle specific agent; PD1 + CTLA4, PD1 inhibitor combined with CTLA4 inhibitor or dual immune checkpoint inhibitor).

## Multiple imputation and LASSO regression analysis in immunotherapy group

To further explore factors influencing pCR benefit from neoadjuvant immunotherapy, we first applied multiple imputation by chained equations (MICE) to handle missing values in immunotherapy group, generating 20 complete datasets. LASSO regression was performed on each dataset with five-fold cross-validation (nfolds = 5), and the lambda.1se criterion was used to select non-zero coefficient variables (Fig. 1.A/B). Subsequently, the selection frequency of each variable across the 20 datasets was calculated (Fig. 1.C), and a frequency threshold of 0.5 was applied to identify stable predictors. Ultimately, six stable predictors were identified through multiple imputation and LASSO regression, including CEA, Depth of invasion, NLR, Delta-LMR, Immunotherapy, and Lymph node meta.

## Multivariate logistic regression analysis and construction of the nomogram for pCR in immunotherapy group

To identify independent factors for pCR benefit from neoadjuvant immunotherapy, the six stable variables selected by LASSO regression were included in a multivariate logistic regression model, with results shown in Table 4. The analysis revealed that CEA (OR = 0.17, 95%CI:0.05–0.53, P = 0.003), NLR (OR = 0.17, 95%CI:0.04–0.56, P = 0.007), and Delta-LMR (OR = 0.05, 95%CI:0.01–0.36, P = 0.006) were independent factors influencing pCR after neoadjuvant immunotherapy in gastric adenocarcinoma. Elevated CEA (> 1.85 ng/mL), elevated NLR (> 2), and elevated Delta-LMR (> 0.5) were independent unfavorable factors for achieving pCR. Regarding Depth of invasion, compared with T2 stage, T4 stage patients had significantly lower odds of achieving pCR (OR = 0.14, 95% CI: 0.03–0.53, P = 0.004), while T3 stage showed a negative trend without significance (OR = 0.55, 95% CI: 0.14–2.16, P = 0.386). In addition, Immunotherapy and Lymph node meta showed no significant differences. Based on the multivariate regression results, CEA, NLR, Delta-LMR, and Depth of invasion were used to construct a nomogram for predicting pCR rate after neoadjuvant immunotherapy in gastric adenocarcinoma, with shown in Fig. 2.

Table 4
Multivariate logistic regression analysis for pCR in immunotherapy group (n = 146).

| Factors | | Beta | OR(95%CI) | Wald | P-value |
|---|---|---|---|---|---|
| Intercept | - | 4.10 | 60.3 (3.49-1381.38) | 2.73 | 0.006 |
| CEA | Normal | 1.0 (reference) | 1.0 (reference) | | |
| | Elevated | -1.79 | 0.17 (0.05–0.53) | -2.96 | 0.003 |
| NLR | Normal | 1.0 (reference) | 1.0 (reference) | | |
| | Elevated | -1.77 | 0.17 (0.04–0.56) | -2.69 | 0.007 |
| Delta-LMR | Normal | 1.0 (reference) | 1.0 (reference) | | |
| | Elevated | -3.02 | 0.05 (0.01–0.36) | -2.76 | 0.006 |
| Lymph node meta | N0 | 1.0 (reference) | 1.0 (reference) | | |
| | N1-3 | -0.79 | 0.45 (0.15–1.30) | -1.44 | 0.150 |
| Depth of invasion | T2 | 1.0 (reference) | 1.0 (reference) | | 0.038 |
| | T3 | -0.60 | 0.55 (0.14–2.16) | -1.87 | 0.386 |
| | T4 | -2.00 | 0.14 (0.03–0.53) | -2.83 | 0.004 |
| Immunotherapy | PD1 | 1.0 (reference) | 1.0 (reference) | | |
| | PD1 + CCNSA | 0.84 | 2.30 (0.35–17.88) | 0.85 | 0.397 |
| | PD1 + CCSA | -1.60 | 0.20 (0.01–2.22) | -1.26 | 0.206 |
| | PD1 + CTLA4 | 2.63 | 13.92 (0.37–379.14) | 1.57 | 0.115 |

CEA, carcinoembryonic antigen; NLR, the rate of neutrophils to lymphocytes; Delta-LMR, the change of LMR before and after neoadjuvant therapy (LMR, the rate of lymphocytes to monocytes). Immunotherapy, neoadjuvant immunotherapy schedule (PD1, PD1 inhibitor monotherapy; PD1 + CCNSA, PD1 inhibitor combined with cell cycle non-specific agent; PD1 + CCSA, PD1 inhibitor combined with cell cycle specific agent; PD1 + CTLA4, PD1 inhibitor combined with CTLA4 inhibitor or dual immune checkpoint inhibitor).

# Internal validation of the nomogram for pCR prediction

To evaluate the discrimination and clinical utility of the pCR prediction nomogram, bootstrap resampling with 1000 replicates was performed to calculate the AUC, and ROC curves, calibration curves, and decision curves (DCA) were plotted, as shown in Fig. 3. The original ROC curve of the prediction model (Fig. 3.A) showed an original AUC of 0.828 (95% CI: 0.753–0.902), with a bootstrap-corrected AUC of 0.798 (95% CI: 0.748–0.896) and an optimism of 0.03, indicating good discriminatory ability. The

calibration curve (Fig. 3.B) showed good agreement between the apparent curve and the bias-corrected curve, both close to the 45° reference line. The Brier score was 0.127, and the Le Cessie–van Houwelingen test yielded Z = 0.55, P = 0.581, indicating no significant lack of fit or systematic bias. The DCA (Fig. 3.C) showed that the nomogram model (Model) was far from both extreme strategies (All, None), with an optimal threshold range of 3%–75%, a mean net benefit of 0.086, and a maximum net benefit of 0.207, demonstrating strong clinical applicability. Taken together, the AUC, calibration curve, and DCA indicate that the nomogram based on CEA, NLR, Delta-LMR, and Depth of invasion has good accuracy and practical value for predicting pCR rate after neoadjuvant immunotherapy in gastric adenocarcinoma.

# Discussion

This study aimed to predict pathological complete response (pCR) after neoadjuvant immunotherapy in gastric adenocarcinoma based on tumor markers and blood inflammatory indices. By modeling 146 gastric adenocarcinoma patients receiving neoadjuvant immunotherapy using LASSO regression combined with logistic regression, and validating via bootstrap cross-validation (R = 1000), we found that serum CEA, NLR, Delta-LMR, and Depth of invasion could effectively predict pCR rate after neoadjuvant immunotherapy. The convenient detection and high diagnostic efficiency of this model may help clinicians estimate pCR status in advance and make individualized treatment decisions.

Currently, extensive research has focused on tumor markers and blood inflammatory indices, but evidence regarding the efficacy benefit of immunotherapy in the neoadjuvant setting and its predictive factors remains insufficient. *Li et al.*[31] retrospectively analyzed 67 locally advanced gastric cancer patients and found that the pCR rate in the neoadjuvant immunotherapy group (chemotherapy combined with PD-1/PD-L1 inhibitors) was significantly higher than that in conventional chemotherapy (25.7% vs. 6.2%, P = 0.032), consistent with our findings (22.6% vs. 9.2%, P = 0.002). *Bi et al.*[30] retrospectively analyzed 215 gastric cancer patients receiving neoadjuvant chemotherapy and found that patients with low baseline NLR and PLR had a higher pCR rate compared to those with elevated baseline NLR and PLR (33.8% vs. 10.7%, P < 0.001), and post-treatment CEA decline ≥ 70% and baseline NLR < 2.5 were independent predictors of pCR. Compared with *Bi et al.*'s study on neoadjuvant chemotherapy, our study independently validated the predictive role of CEA and NLR for pCR in the neoadjuvant immunotherapy context, expanding the application scenarios of these biomarkers. *Yu et al.*[29] found that CEA < 1.765 ng/mL (OR = 0.26), CA19-9 < 18.390 U/mL (OR = 0.148), NLR < 2.422 (OR = 0.265), and SII < 597.483 (OR = 0.194) were independent predictors of major pathological response (MPR) based on 113 locally advanced gastric cancer patients receiving neoadjuvant immunotherapy. Our multivariate logistic regression showed that CEA < 1.85 ng/mL (OR = 0.17, P = 0.003) and NLR < 2 (OR = 0.17, P = 0.007) were independent favorable factors for pCR, highly consistent with *Yu et al.*'s findings.

Moreover, multiple studies have demonstrated the predictive value of LMR for tumor regression in solid tumors. In colorectal cancer, *Shi et al.*[32] reported that LMR was an independent predictor of pCR after neoadjuvant chemoradiotherapy (NCRT) in locally advanced rectal cancer. *Zhao et al.*[33] found in locally

advanced esophageal squamous cell carcinoma receiving neoadjuvant chemoradiotherapy that pretreatment LMR was an independent predictor of pCR (OR = 5.093, P = 0.004). In lung cancer receiving neoadjuvant chemotherapy combined with immunotherapy, *Peng et al.*[34] found that low baseline LMR was an independent predictor of objective response rate (ORR) (OR = 0.21, P = 0.04). Our study is the first to introduce the dynamic indicator Delta-LMR in the context of neoadjuvant immunotherapy for gastric adenocarcinoma, and multivariate regression analysis found it independently associated with pCR (P = 0.006), filling a gap in evidence for this biomarker in gastric cancer immunotherapy.

Regarding tumor markers, *Zhang et al.*[23] constructed a nomogram prognostic model based on dynamic changes in CA72-4, CEA, and CA125 before and after neoadjuvant chemotherapy, which showed superior discrimination compared to TNM stage (AUC: 0.827 vs. 0.678, P < 0.001). *Yu et al.*[29] constructed a nomogram for predicting major pathological response (MPR) after neoadjuvant immunotherapy in gastric cancer based on five predictors (pre-treatment tumor bed diameter, CEA, CA19-9, NLR, SII), which demonstrated good discrimination (AUC = 0.848, 95% CI: 0.773–0.923) and good calibration (Hosmer–Lemeshow test: $\chi^2$=4.705, P = 0.789), indicating that combining tumor markers and blood inflammatory indices with clinicopathological features has good predictive value for tumor regression and survival prognosis in gastric cancer patients. Accordingly, our pCR prediction nomogram based on CEA, NLR, Delta-LMR, and Depth of invasion also demonstrated stable discrimination (bootstrap-corrected AUC = 0.798) and good calibration (Le Cessie–van Houwelingen test: Z = 0.55, P = 0.584), and DCA indicated strong clinical utility.

Notably, Delta-SII showed significant differences between the non-pCR and pCR subgroups (P = 0.041), but LASSO cross-validation indicated insufficient stability, suggesting that it may be susceptible to perioperative factors as a derived composite formula and may have high heterogeneity in clinical practice. Similarly, EBER also showed insufficient stability in selection frequency statistics across the 20 datasets, because of the low EBER positivity rate in our cohorts. In addition, Lymph node meta showed significant differences in the non-pCR/pCR subgroup analysis of immunotherapy group (P = 0.029) and was identified as a stable predictor by LASSO regression. But after inclusion in multivariate analysis, it showed a negative trend with no significant (OR = 0.45, P = 0.15), suggesting that Lymph node meta may have a negative effect on pCR, but its independence may be weakened by pathological collinearity with Depth of invasion. This collinearity suggests that in the neoadjuvant immunotherapy context, the degree of local invasion may play a more important role in determining primary tumor regression than regional lymph node invasion, for systemic immunosuppressive patterns dominated by T4 infiltration. On the other hand, lymph nodes and the primary tumor have relatively independent anatomical microenvironments, and this spatiotemporal heterogeneity further diminishes the weight of lymph node metastasis in assessing primary tumor regression. In the final multivariate logistic regression, T3 stage relative to T2 did not significantly affect pCR attainment (OR = 0.55, P = 0.386), but T4 stage was significantly associated with reduced pCR rate (OR = 0.14, P = 0.004), suggesting a possible threshold effect of Depth of invasion on immunotherapy response. Although T3 stage tumors have invaded the subserosa, the local immune microenvironment may retain partial activity. Once tumors penetrate the serosa (T4 stage), extensive peritoneal dissemination and malignant ascites may induce strong

immunosuppression, counteracting the antitumor effect of PD-1 inhibitors. However, the non-significant result for T3 stage in our study may also be limited by sample size, preventing the trend from reaching significance.

Nevertheless, this study has several limitations. First, this is a single-center retrospective study. Although bootstrap internal validation was performed and a low AUC optimism (0.030) was observed, the sample size is relatively limited, and overfitting and selection bias cannot be completely excluded. Second, our nomogram did not incorporate biomarkers recommended by guidelines[35, 36] for predicting immunotherapy efficacy, and our study showed that PD-L1 combined positive score (CPS), DNA mismatch repair (MMR) protein, and Epstein–Barr virus-encoded small RNA (EBER) showed no differences between the non-pCR and pCR subgroups, contradicting guideline recommendations. This may be attributable to low biomarker positivity rates and insufficient sample size. Furthermore, this study included patients receiving neoadjuvant immunotherapy but did not account for internal heterogeneity arising from different immunotherapy combination regimens, nor did it conduct parallel comparative analyses with neoadjuvant chemotherapy patients, all of which limit the generalizability of our findings. Therefore, prospective, multicenter studies with independent external cohorts, incorporating molecular biomarkers and stratified analyses by treatment regimen, are needed to further validate the model's effectiveness and clarify its clinical applicability.

# Conclusion

This study confirms that the pathological complete response (pCR) rate after neoadjuvant immunotherapy was significantly higher than that after neoadjuvant chemotherapy in gastric adenocarcinoma. Based on pCR status, we identified four independent predictors (CEA, NLR, Delta-LMR, Depth of invasion) through LASSO regression and multivariate logistic regression. Bootstrap internal validation indicated that the pCR nomogram based on these predictors had stable discrimination and a broad risk tolerance range. This model may assist clinicians in identifying patients who are sensitive to neoadjuvant immunotherapy and likely to achieve pCR, enabling early optimal individualized treatment decisions and advancing precision practice in neoadjuvant immunotherapy for gastric cancer.

# Declarations

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**Conflicts of Interest**

None to declare.

**Author Contributions**

Jiajun He, and Heng Zhang participated in Study concepts and design. Pengju Zheng and Li'ang Xu participated in Data acquisition and analysis. Hanzhang Ji and Shangui Huang participated in preparing figures 1-2, tables 1-4. Jiajun He wrote the main manuscript text. All authors reviewed the manuscript.

**Data Availability**

The data supporting the findings of this study cannot be made publicly available because of patient privacy considerations and institutional restrictions. The data generated and/or analysed during the current study may be available from the corresponding author upon reasonable request.

**Ethics approval**

This study is conducted in accordance with the principles of the Declaration of Helsinki and the Declaration of Istanbul. The research has been approved by the Ethics Committee of Zhongshan Hospital (Ethics approval number: B2026-501).

**Consent to participate**

Informed consent was obtained from all individual patients included in the study.

**Consent for publication**

Not applicable.

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# Figures

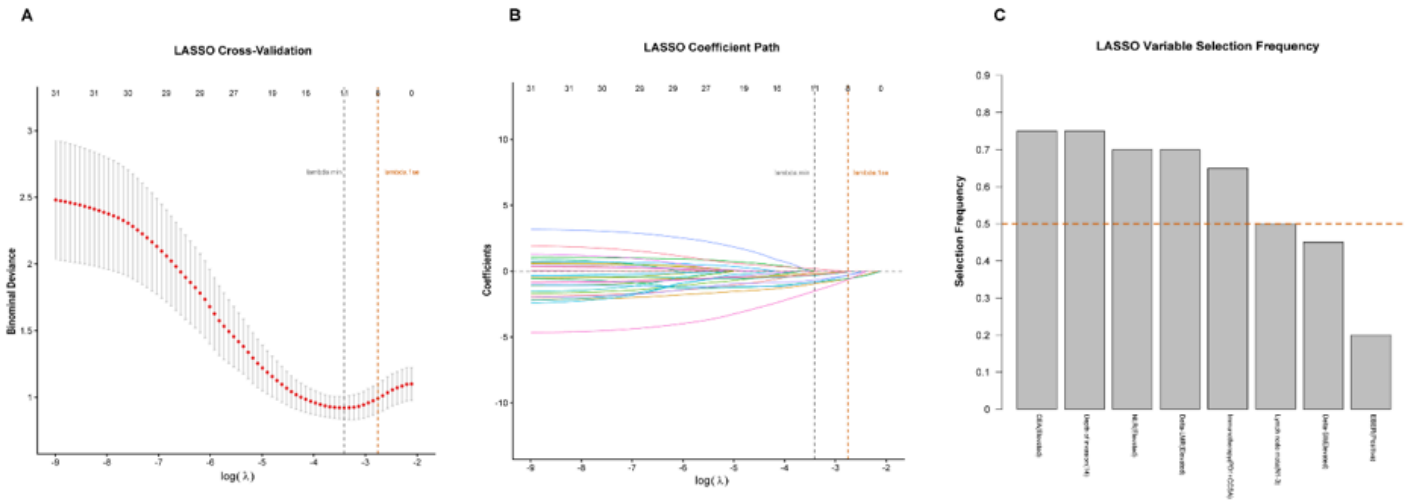
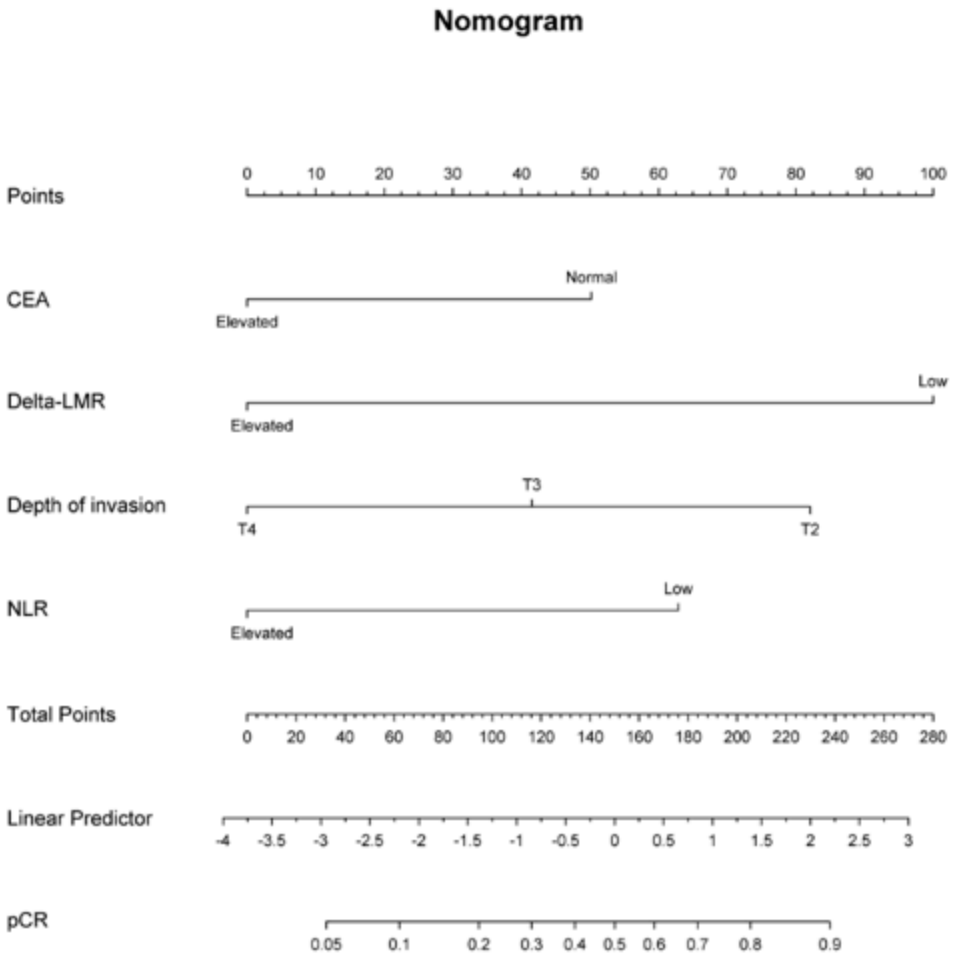



**Figure 1**

**LASSO regression analysis for pCR with multiple imputation method in immunotherapy group (n=146).** (A) LASSO cross-validation from the first imputed dataset; (B) LASSO coefficient path from the first imputed dataset; (C) LASSO variable selection frequency for the 20 imputed dataset (Threshold = 0.5).




## Figure 2

**Nomogram to predict pCR in immunotherapy group (n=146).** Nomogram generation for predicting pCR integrated with CEA, Delta-LMR, Depth of invasion, and NLR.

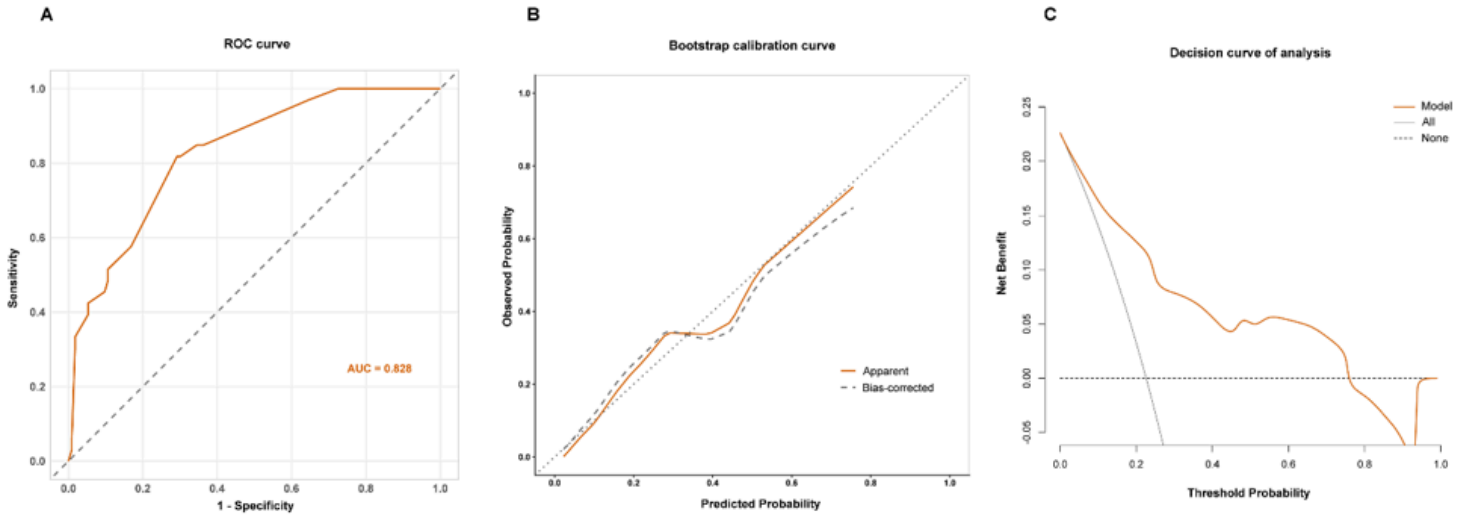



**Figure 3**

**Bootstrap cross-validation for the nomogram (resampling = 1000).** (A) the receiver operating characteristic (ROC) curve for the nomogram validation (AUC=0.828, 95%CI: 0.753-0.902), internal validation via 1000 bootstrap resamples revealed bootstrap-corrected AUC was 0.798 (95%CI: 0.748-0.896) with an optimism of 0.03; (B) Bootstrap calibration curve of the nomogram with the bootstrap method (Le Cessie–van Houwelingen test Z=0.55, P=0.581; Bier score: 0.127); (C) Decision curve analysis (DCA) of the nomogram with the bootstrap method (the optimal threshold range: 3%-75%; the mean net benefit: 0.086; the maximal net benefit: 0.207).

# Supplementary Files

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