Research Article

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# Characteristics and survival associated with pathological complete response following neoadjuvant treatment of locally advanced gastric cancer: a multicenter analysis in a real-world setting

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## ABSTRACT

**Background :** Neoadjuvant treatment (NAT) has become the standard treatment for locally advanced gastric cancer (LAGC). A small number of patients could achieve pathological complete response (pCR) after NAT. This study was performed to determine the factors predicting pCR and recurrence, and to investigate the pattern of recurrence in patients with pCR after NAT followed by surgery.

**Methods :** We collected 488 LAGC patients who underwent surgery in three hospitals between September 2015 and October 2022. The primary endpoint was overall survival (OS) and recurrence-free survival (RFS). Logistic regression analyses were performed to identify independent variables associated with pCR and the nomogram was created.

**Result :** 80 (16.4%) patients were found with pCR and had significantly better OS and RFS than non-pCR group. The recurrence rates in the pCR and non-pCR groups were 7.5% (6 of 80) and 40.2% (164 of 408) respectively. However, the recurrence time and location had no significant difference between these two groups. Interestingly, all the 6 pCR patients who had recurrences received adjuvant therapy. Chemotherapy plus immunotherapy as NAT could significantly increase the pCR rate and prolong RFS than chemotherapy alone. Both OS and RFS were not significantly different between all patients who received adjuvant chemotherapy and observation only. Histological type and NAT regimen were independent factors to predict pCR in the nomogram.

**Conclusion** : Patients with pCR had a lower recurrence rate and better prognosis than the non-pCR group. Patients receiving chemo-immunotherapy as NAT had a higher pCR rate than those receiving chemotherapy alone.

**KEYWORDS** : Stomach Neoplasms; Neoadjuvant Therapy; Pathological complete response; Recurrence; Immunotherapy

## Introduction

Gastric cancer (GC) is the fourth most common malignant tumor and one of the leading causes of cancer-related death(1). Several countries or areas in Europe, especially Italy, Spain, and East Europe, have a much higher incidence of GC than other parts of Europe(2). Eastern Asia had high incidence

Journal of Immunology (ISSN 2995-861X)

and mortality rates for gastric cancer(3). In China, most of the GC patients present with advanced disease, and thus have a poor prognosis after radical surgery.

Surgery alone did not improve OS and DFS much in some locally advanced gastric cancer (LAGC) patients(4). Until now, several randomized trials and meta-analyses have established that preoperative therapy is the preferred treatment option for LAGC(5-8). Since then, neoadjuvant treatment (NAT) has been found to cause tumor downstaging and increase the likelihood of complete tumor resection(6, 9, 10).

The histological response of GC patients to NAT was used to predict prognosis and determine sensitivity to chemotherapy. Becker et al. proposed a four-tiered grading system based on a large number of GC patients, and tumor regression was considered as an independent prognostic factor for survival(11, 12). Lower post-neoadjuvant pathological stage (ypStage) may lead to survival benefit(13, 14). Those with no viable tumor cells in the primary tumor are considered to have a pathological complete response (pCR). Despite having a demonstrable survival benefit, pCR does not mean cure. In 2011, Fields et al. analyzed the recurrence patterns and survival time of LAGC patients with pCR after surgery in a large cohort study, and there were 27% pCR patients relapsed within 5 years(15). Moreover, the value of adjuvant therapy in patients with pCR is also unknown.

The current study was designed to figure out the potential clinical factors that could predict pCR and recurrence, evaluate the pattern and timing of recurrence in pCR patients and non-pCR patients after NAT followed by surgery for LAGC.

## MATERIALS AND METHODS

### Patient Selection

We retrospectively reviewed the clinical and pathological data of 488 LAGC patients who underwent surgery in three academic medical centers between September 2015 and October 2022. The inclusion criteria included: 1. diagnosed with LAGC or gastric/gastroesophageal junction (GEJ) cancer; 2. received chemotherapy or chemotherapy combined with immunotherapy before surgery; 3. underwent gastrectomy; 4. tumor regression grade (TRG) was estimated with postoperative pathological specimens. The exclusion criterion included a history of another malignancy within the last 5 years except for cured basal cell carcinoma of the skin and cured carcinoma in situ of the cervix. Neoadjuvant therapy was based on doublet or triplet combinations of fluoropyrimidine-based and platinum-based chemotherapy regimens. Patients who used the XELOX (Capecitabine plus Oxaliplatin) or SOX (S-1 plus Oxaliplatin) regimen received three cycles of neoadjuvant therapy, while patients who used the FOLFOX (Fluorouracil plus Leucovorin, and Oxaliplatin) or FLOT (Fluorouracil plus Leucovorin, Oxaliplatin, and Docetaxel) regimen received four cycles of neoadjuvant therapy. We evaluated the efficacy based on enhanced Computed Tomography (CT) after 2-3 cycles of treatment. Tumor responses included complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). The perioperative treatment period was 6 months. Our study was performed under the Declaration of Helsinki protocols and was approved by the local Ethics Committee. In addition, this study is fully compliant with the STROCSS criteria.

Clinicopathological data including age, gender, body mass index (BMI), tumor and lymph node status, tumor differentiation, Lauren histologic type, mis-match repair (MMR) status, Epstein-Barr virus-encoded RNA (EBER) status, and the effect of preoperative treatment, and details of the surgery were collected.

### Survival Analysis and Pathology

The overall survival (OS) was defined as the period from the date of diagnosis to death or the final follow-up date, and the recurrence-free survival (RFS) was calculated from the curative surgery to the time of recurrence or death or the final follow-up date. The failure events of the survival analysis were death for OS, and tumor recurrence or death for RFS. The censoring data referred to the failure event which have not observed and the exact survival time which was not recorded. Recurrence was defined as locoregional (at the previous site of the primary tumor and/or in regional lymph nodes within the surgical resection field) recurrence, distant (hematogenous metastases or distant lymph node metastases) recurrence, or both.

Sun Yat-sen University Cancer Center (SYSUCC) applied the National Comprehensive Cancer Network (NCCN) classification system, Nanfang Hospital and The Sixth Affiliated Hospital of Sun Yat-sen University applied American Joint Committee on Cancer (AJCC) 8th edition system to assess the TRG. NCCN and AJCC standards are similar and are both commonly used in clinical practice. pCR was defined as the absence of residual tumor cells in the resection specimen, as well as any of the resected lymph nodes.

HER2 (human epidermal growth factor receptor 2) positive was defined as any case of IHC 3+ or IHC 2+ with a positive fluorescence in situ hybridization (FISH) result, while HER2 negative is any case of IHC 0, IHC 1+, or IHC 2+ with a negative FISH result. The positive FISH results were defined as a HER2: CEP17 ratio ≥ 2.0. Histological subtypes were determined according to the Laurén classification(16). Adenocarcinomas were categorized as intestinal, diffuse, or mixed type. We combined intestinal and mixed types as non-diffuse type when analyzed. The Mismatch Repair (MMR) system includes MLH1, MSH2, MSH6 and PMS2. Mismatch-repair-deficient (dMMR)

Journal of Immunology (ISSN 2995-861X)

was defined as loss of IHC expression of at least 1 of the MMR genes. The cases that showed preserved nuclear expression of 4 MMR proteins were considered MMR proficient (pMMR).

**Statistical Analysis and Nomogram**

OS and RFS were estimated with the Kaplan-Meier method and the log-rank test. Chi-Square test or Fisher's exact test was used for comparing clinicopathological characteristics associated with pCR and non-pCR patients, recurrence and non-recurrence patients, ypN+ and ypN- patients. All P values were two-tailed, and we considered P values less than 0.05 are statistically significant. The software for data analysis in this study were IBM SPSS version 22.0 (IBM Corp., Armonk, NY) and GraphPad Prism version 8.0.2.

After deleting the missing values, the data were divided into training group and validation group according to 7:3. Based on Chi-square test results and using data from the training cohort, significant correlation factors were identified by multivariate logistic regression analysis and recruited to build the nomogram for pCR prediction. The concordance index (C-index) and area under the receiver operator characteristic (ROC) curve (AUC) were used to quantify the model's discrimination in both the training and validation groups. Finally, the net benefit of the model was assessed using decision curve analysis (DCA). The "rms" R package was used to plot the nomogram. Calibration curves were created using bootstraps with 1,000 resamples. The "rms" R package was used to analyze calibration plots. The "rmda" R package was used to perform the DCA. R (v. 4.2.2) was used for the statistical analyses.

## RESULT

**Baseline characteristics**

We retrospectively collected 488 LAGC or GEJ cancer patients who had received NAT and gastrectomy from September 2015 to October 2022 in three academic medical centers (Nanfang Hospital of Southern Medical University, The Sixth Affiliated Hospital of Sun Yat-sen University, and SYSUCC). The majority of the patients were males (69.5%). 325 patients (66.6%) were younger than 65 years old. Tumors were predominantly located in stomach (66.4%) and received chemotherapy alone (76.2%). Two hundred and fifty-three patients (51.8%) in the cohort were diagnosed with cT3, and 188 patients (38.5%) were diagnosed with cT4. After treating with NAT, 2 patients achieved complete response (CR) and 153 patients received partial response (PR) radiologically, the overall response rate (ORR) was 48.4%. In addition, 80 patients (16.4%) got pCR, and the remaining patients (n=408, 83.6%) had residual evidence of malignancy and were referred to as non-pCR. Notably, despite no residual tumor in the primary tumor, residual carcinoma was identified in the regional lymph nodes of 7 patients, who were all in the non-pCR group. There were totally 63 (78.8%) pCR patients and 347 (85.0%) non-pCR patients who had treated with adjuvant treatment. Supplementary Table 1 lists the features of the patients.

**Supplementary Table 1.** Patient and tumor characteristics

| **Characteristics** | | **All patients N=488** | **(%)** |
|---|---|---|---|
| **Age** | Median (range) | 63 (29-78) | |
| | <65 | 325 | 66.6 |
| | ≥65 | 163 | 33.4 |
| **Gender** | Male | 339 | 69.5 |
| | Female | 149 | 30.5 |
| **BMI (kg/m²)** | <18.5 | 52 | 10.7 |
| | 18.5-23.9 | 326 | 66.8 |
| | >23.9 | 110 | 22.5 |
| **Primary site** | Stomach | 324 | 66.4 |
| | EGJ | 154 | 31.6 |
| | NA | 10 | 2.0 |
| **Preoperative treatment** | Chemotherapy | 372 | 76.2 |
| | Chemotherapy plus immunotherapy | 93 | 19.1 |

Journal of Immunology (ISSN 2995-861X)

| | | | |
|---|---|---|---|
| | Chemotherapy plus targeted therapy | 5 | 1.0 |
| | Chemotherapy plus radiotherapy | 14 | 2.9 |
| | NA | 4 | 0.8 |
| **Preoperative treatment evaluation** | CR | 2 | 0.4 |
| | PR | 153 | 31.4 |
| | SD | 147 | 30.1 |
| | PD | 18 | 3.7 |
| | Non-CR/Non-PD and NA | 168 | 34.4 |
| **Clinical T stage** | 1 | 6 | 1.2 |
| | 2 | 23 | 4.7 |
| | 3 | 253 | 51.8 |
| | 4 | 188 | 38.5 |
| | NA | 18 | 3.7 |
| **Clinical N stage** | 0 | 65 | 13.3 |
| | 1 | 143 | 29.3 |
| | 2 | 175 | 35.9 |
| | 3 | 88 | 18.0 |
| | NA | 17 | 3.5 |
| **Regional LN** | ≤5 | 384 | 78.7 |
| | >5 | 100 | 20.5 |
| | NA | 4 | 0.8 |
| **TRG** | 0 | 87 | 17.8 |
| | 1 | 81 | 16.6 |
| | 2 | 245 | 50.2 |
| | 3 | 75 | 15.4 |
| **pCR** | Yes | 80 | 16.4 |
| | No | 408 | 83.6 |
| **Differentiation** | Poor | 213 | 43.6 |
| | Medium-low | 44 | 9.0 |
| | Medium | 98 | 20.1 |
| | High | 9 | 1.8 |
| | NA | 124 | 25.4 |
| **Histology** [a] | Adenocarcinoma | 400 | 82.0 |
| | Signet ring cell carcinoma | 26 | 5.3 |
| | Others | 32 | 6.6 |
| | NA | 30 | 6.1 |
| **Lauren** | Diffuse | 44 | 9.0 |
| | Intestinal | 50 | 10.2 |
| | Mixed | 19 | 3.9 |
| | NA | 375 | 76.8 |
| **MMR** | pMMR | 322 | 66.0 |
| | dMMR | 27 | 5.5 |
| | NA | 139 | 28.5 |
| **PD-L1** | <5 | 28 | 5.7 |
| | ≥5 | 35 | 7.2 |

Journal of Immunology (ISSN 2995-861X)

| | | | |
|---|---|---|---|
| | NA | 425 | 87.1 |
| **HER-2** | Positive | 25 | 5.1 |
| | Negative | 348 | 71.3 |
| | NA | 115 | 23.6 |
| **EBER** | Negative | 177 | 36.3 |
| | Positive | 14 | 2.9 |
| | NA | 297 | 60.9 |
| **Recurrence** | Yes | 170 | 34.8 |
| | No | 318 | 65.2 |
| **Status** [b] | Alive | 377 | 77.3 |
| | Dead | 111 | 22.7 |

[a] Other of histology included poorly adherent carcinoma and mixed component carcinoma.

b Dead of status only included patients who died of cancer.

pCR: pathological complete response; BMI: body mass index; EGJ: esophageal–gastric junction; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; LN: lymph node; TRG: tumor regression grade; MMR: mis-match repair; pMMR: proficiency of mismatch repair; dMMR: deficiency of mis-match repair; PD-L1: programmed cell death-ligand 1; HER-2: human epidermal growth factor receptor 2; EBER: Epstein-Barr virus-encoded RNA; NA: not available.

**Clinicopathological characteristics analysis**

We compared the basic characteristics between the pCR and non-pCR patients (Table 1). Patients who are male, with CR or PR in preoperative RECIST 1.1 evaluation, whose pathological type was adenocarcinoma, whose Lauren classification was diffuse type, and EBER-positive were more likely to achieve pCR (All P <0.05). We also found that patients with chemotherapy plus immunotherapy as NAT had a higher pCR rate (33.3%) than patients who were treated with chemotherapy alone (11.0%) (P < 0.001).

**Table1.** Clinicopathologic variables associated with pathological complete response.

| **Characteristics** | | **Non-pCR N=408 (%)** | **pCR N=80 (%)** | **P value** |
|---|---|---|---|---|
| **Age** | Median (range) | 62 (29-78) | 64.5 (29-76) | |
| | <65 | 276 (84.9) | 49 (15.1) | 0.267 |
| | ≥65 | 132 (81.0) | 31 (19.0) | |
| **Gender** | Male | 273 (80.5) | 66 (19.5) | 0.006 |
| | Female | 135 (90.6) | 14 (9.4) | |
| **BMI (kg/m²)** | <18.5 | 47 (90.4) | 5 (9.6) | 0.162 |
| | ≥18.5 | 361 (82.8) | 75 (17.2) | |
| **Primary site *** | Stomach | 279 (86.1) | 45 (13.9) | 0.055 |
| | EGJ | 122 (79.2) | 32 (20.8) | |
| **Preoperative treatment evaluation*** | CR or PR | 130 (76.9) | 39 (23.1) | 0.003 |
| | SD or PD | 158 (88.8) | 20 (11.2) | |
| **Clinical T stage*** | 1 | 5 (83.3) | 1 (16.7) | 0.842 |
| | 2 | 19 (82.6) | 4 (17.4) | |
| | 3 | 216 (85.4) | 37 (14.6) | |
| | 4 | 156 (83.0) | 32 (17.0) | |
| **Clinical N stage*** | 0 | 53 (81.5) | 12 (18.5) | 0.430 |
| | 1 | 126 (88.1) | 17 (11.9) | |
| | 2 | 144 (82.3) | 31 (17.7) | |

Journal of Immunology (ISSN 2995-861X)

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|---|---|---|---|---|
| | 3 | 72 (81.8) | 16 (18.2) | |
| **Differentiation*** | Poor differentiation | 221 (89.8) | 25 (10.2) | 0.054 |
| | Medium-high | 135 (83.3) | 27 (16.7) | |
| | differentiation | | | |
| **Histology*** | Adenocarcinoma | 343 (85.8) | 57 (14.2) | 0.018 |
| | Signet ring cell carcinoma | 26 (100.0) | 0 (0.0) | |
| | Others | 31 (96.9) | 1 (3.1) | |
| **Lauren*** | Diffuse | 40 (83.3) | 8 (16.7) | 0.036 |
| | Non-diffuse | 113 (94.2) | 7 (5.8) | |
| **MMR*** | pMMR | 300 (93.2) | 22 (6.8) | 0.130 |
| | dMMR | 23 (85.2) | 4 (14.8) | |
| **PD-L1*** | <5 | 21 (75.0) | 7 (25.0) | 0.209 |
| | ≥5 | 21 (60.0) | 14 (40.0) | |
| **HER-2*** | Positive | 23 (92.0) | 2 (8.0) | 1.000 |
| | Negative | 312 (89.7) | 36 (10.3) | |
| **EBER*** | Negative | 157 (88.7) | 20 (11.3) | <0.001 |
| | Positive | 6 (42.9) | 8 (57.1) | |

Patients with data not available were not included in the analysis. Statistically significant P values are given in bold (P<0.05). Non-diffuse of Lauren included intestinal and mixed type. Other histology included poorly adherent carcinoma and mixed component carcinoma.

pCR: pathological complete response; BMI: body mass index; EGJ: esophageal–gastric junction; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; MMR: mis-match repair; pMMR: proficiency of mismatch repair; dMMR: deficiency of mis-match repair; PD-L1: programmed cell death-ligand 1; HER-2: human epidermal growth factor receptor 2; EBER: Epstein-Barr virus-encoded RNA; NA: not available.

*Patients whose information was not available are not enrolled for analysis.

A total of 170 (34.8%) patients had recurrence after NAT and surgery. We compared the clinicopathologic variables of the recurrence group with those of the non-recurrence group (Table 2). Patients who were younger than 65 years old, whose primary site was in stomach, with TRG 2 or 3, with poor differentiation, had more than 5 positive regional lymph nodes, had neurovascular invasion, whose Lauren classification was diffuse type, and with pMMR were more likely to recur (All P<0.05). Patients with chemotherapy plus immunotherapy as NAT had a lower recurrence rate (15.1%) than patients who were treated with chemotherapy alone (40.3%) (P < 0.001)

**Table 2.** Clinicopathologic variables associated with recurrence.

| **Characteristics** | | **Non-recurrence N=318 (%)** | **Recurrence N=170 (%)** | **P value** |
|---|---|---|---|---|
| **Age** | <65 | 197 (60.6) | 128 (39.4) | 0.003 |
| | ≥65 | 121 (74.2) | 42 (25.8) | |
| **Gender** | Male | 227 (67.0) | 112 (33.0) | 0.209 |
| | Female | 91 (61.1) | 58 (38.9) | |
| **BMI (kg/m²)** | <18.5 | 37 (71.2) | 15 (28.8) | 0.338 |
| | ≥18.5 | 281 (64.4) | 155 (35.6) | |
| **Primary site*** | Stomach | 199 (61.4) | 125 (38.6) | 0.015 |

Journal of Immunology (ISSN 2995-861X)

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|---|---|---|---|---|
| | EGJ | 112 (72.7) | 42 (27.3) | |
| **Preoperative treatment evaluation*** | CR or PR | 111 (65.7) | 58 (34.3) | 0.238 |
| | SD or PD | 106 (59.6) | 72 (40.4) | |
| **Postoperative treatment** | Yes | 256 (62.4) | 154 (37.6) | 0.005 |
| | No | 61 (79.2) | 16 (20.8) | |
| **TRG** | 0 or 1 | 127 (75.6) | 41 (24.4) | <0.001 |
| | 2 or 3 | 191 (59.7) | 129 (40.3) | |
| **Postoperative Regional LN*** | ≤5 | 271 (70.6) | 113 (29.4) | <0.001 |
| | >5 | 46 (46.0) | 54 (54.0) | |
| **Differentiation*** | Poor differentiation | 138 (56.1) | 108 (43.9) | <0.001 |
| | Medium-high differentiation | 123 (75.9) | 39 (24.1) | |
| **Histology*** | Adenocarcinoma | 258 (64.5) | 142 (35.5) | 0.360 |
| | Signet ring cell carcinoma | 14 (53.8) | 12 (46.2) | |
| | Others | 23 (71.9) | 9 (28.1) | |
| **Neurovascular invasion*** | Yes | 119 (56.1) | 93 (43.9) | <0.001 |
| | No | 194 (72.7) | 73 (27.3) | |
| **Lauren** | Diffuse | 23 (47.9) | 25 (52.1) | 0.002 |
| | Non-diffuse | 88 (73.3) | 32 (26.7) | |
| **MMR*** | pMMR | 197 (61.2) | 125 (38.8) | 0.036 |
| | dMMR | 22 (81.5) | 5 (18.5) | |
| **PD-L1*** | <5 | 21 (75.0) | 7 (25.0) | 0.444 |
| | ≥5 | 29 (82.9) | 6 (17.1) | |
| **HER-2*** | Positive | 17 (68.0) | 8 (32.0) | 0.652 |
| | Negative | 221 (63.5) | 127 (36.5) | |
| **EBER*** | Negative | 118 (66.7) | 59 (33.3) | 0.360 |
| | Positive | 11 (78.6) | 3 (21.4) | |

Patients with data not available were not included in the analyses. Statistically significant P values are given in bold (P<0.05). Non-diffuse of lauren included intestinal and mixed type. Others of histology included poorly adherent carcinoma and mixed component carcinoma.

pCR: pathological complete response; BMI: body mass index; EGJ: esophageal–gastric junction; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; TRG: tumor regression grade; LN: lymph node; MMR: mis-match repair; pMMR: proficiency of mismatch repair; dMMR: deficiency of mis-match repair; PD-L1: programmed cell death-ligand 1; HER-2: human epidermal growth factor receptor 2; EBER: Epstein-Barr virus-encoded RNA; NA: not available.

* Patients whose information was not available are not enrolled for analysis.

**The relationship between recurrence and pathological complete response**

The recurrence rate was 7.5% (6 of 80 patients) and 36.5% (149 of 408 patients) respectively in the pCR group and non-pCR group (P < 0.05). However, there were no significant differences in the time and location of recurrences in these two groups. Table 3 summarizes the timing and pattern of recurrences for all patients with tumor recurrence. All the 6 pCR patients who received postoperative therapy had recurrence, while none of the 17 pCR patients without adjuvant therapy had recurrence, interestingly.

Journal of Immunology (ISSN 2995-861X)

**Table 3**. Timing and patterns of recurrence/metastasis in local advanced gastric cancer patients

| Variable | | Number (%) | | P value |
|---|---|---|---|---|
| | | Non-pCR N=164 | pCR N=6 | |
| **Time**[a] | Median | 12.1 months | 7.3 months | |
| | <2 year | 128 (78.0) | 5 (83.3) | 0.539 |
| | ≥2 years | 17 (22.0) | 1 (16.7) | |
| **Progression pattern**[a] | Local/ regional | 13 (7.9) | 2 (40.0) | 0.119 |
| | Distant | 122 (74.4) | 3 (60.0) | |
| | Both | 11 (6.7) | 0 (0.0) | |
| **Postoperative treatment** | Yes | 148 (90.2) | 6 (100) | 1.000 |
| | No | 16 (9.8) | 0 (0.0) | |

[a] A total of 19 patients were found dead and had unknown progression patterns and time.

The details of the 6 pCR patients who suffered from recurrence were listed in Supplementary Table 2. We found that they were all male patients and received adjuvant therapy, including 1 patient treated with chemotherapy plus immunotherapy as NAT and the other 5 patients only treated with neoadjuvant chemotherapy. Among them, 66.7% (4/6) patients achieved a PR after NAT, and another 2 patients achieved stable disease (SD). Among the patients (5/6) with recurrence information available, 2 patients developed locoregional recurrence, another 3 patients developed distant recurrence (including peritoneum, distant lymph nodes and bone). During the follow-up period, 3 patients died of recurrence.

**Supplemental Table 2**. Detailed information of 6 patients who got recurrence following a pathologic complete response.

| Patient ID | Gender | Clinical TNM stage | Primary position | Preoperative treatment | Preoperative therapeutic effect | Postoperative treatment | Duration of postoperative treatment (months) | Recurrence location | Time to recurrence (months) | Status at last follow-up | Survival after recurrence (months) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **01** | Male | IIIA | Gastric | Chemotherapy plus immunotherapy | PR | XELOX+PD-1 | 1.5 | NA | NA | Dead | NA |
| **02** | Male | IIB | NA | Chemotherapy | PR | Abraxane | 1.5 | Local/ regional | 24.07 | Alive | 0.73 |
| **03** | Male | IIIA | Gastric | Chemotherapy | SD | SOX | 1.5 | Local/ regional | 15.60 | Dead | 8.03 |
| **04** | Male | IIA | Gastric | Chemotherapy | PR | FOLFOX | 1.5 | Distant lymph nodes | 8.90 | Alive | 31.93 |
| **05** | Male | IA | EGJ | Chemotherapy | PR | SOX | 2.3 | Peritoneum | 3.73 | Alive | 40.00 |
| **06** | Male | IIIA | Gastric | Chemotherapy | SD | PD-1 | 0.8 | Bone | NA | Dead | NA |

XELOX includes the drugs capecitabine (Xeloda) and oxaliplatin. SOX includes the drugs S-1 and oxaliplatin. FOLFOX includes the drugs leucovorin calcium (folinic acid), fluorouracil, and oxaliplatin.
pCR: pathological complete response; EGJ: esophageal–gastric junction; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; NA: not available.

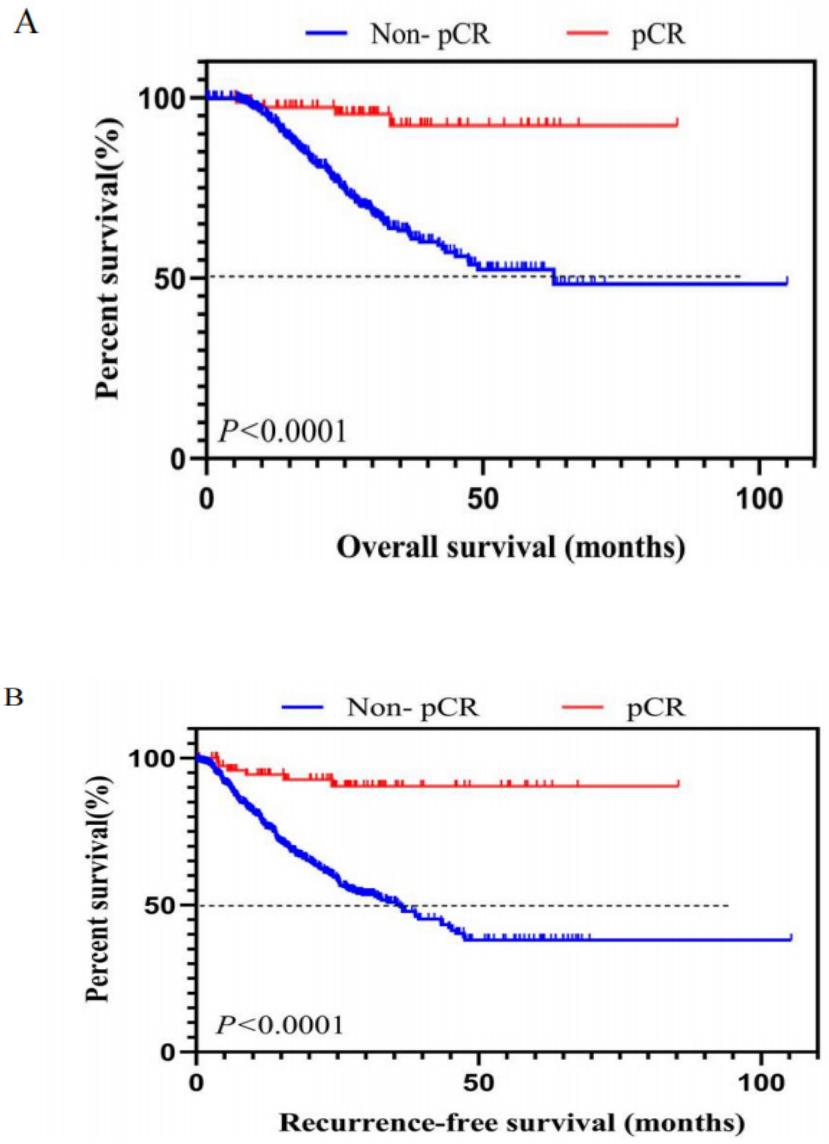
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**Survival analysis**

Furthermore, we evaluated the prognosis of pCR and non-pCR patients. LAGC patients with pCR had significantly better OS and RFS than those with non-pCR (Both P< 0.05, Fig 1A, 1B). The median OS for the whole population was not reached and median RFS was 44.7 months. The pCR patients did not reach the median OS or RFS. For the non-pCR patients, the median OS and RFS were 62.8 months and 20.9 months, respectively. After NAT, the accuracy of the lymph node (LN) ratio as a predictive index for GC patients still need to be proven. Therefore, we separated patients into 2 groups, high LN ratio (>30%) and low LN ratio (≤30%). Patients with low LN ratio achieved significant longer OS and RFS than those with high-LN ratio (Both P< 0.05, Fig 1C, 1D). In addition, patients who were treated with chemotherapy plus immunotherapy as neoadjuvant treatment had lower recurrence rate than those with chemotherapy alone (15.1% vs 40.3%). But there was no significant difference of RFS and OS between these two groups due to the small sample size (Fig 2).

Furthermore, we explored the value of postoperative therapy in patients with recurrence and found that patients with recurrence who received adjuvant therapy seem to have numerical better OS than those without (25.97 vs 24.40 months, P=0.179, Fig 3). Both OS and RFS had not significant difference between adjuvant chemotherapy group and observation group.

**Figure 1**



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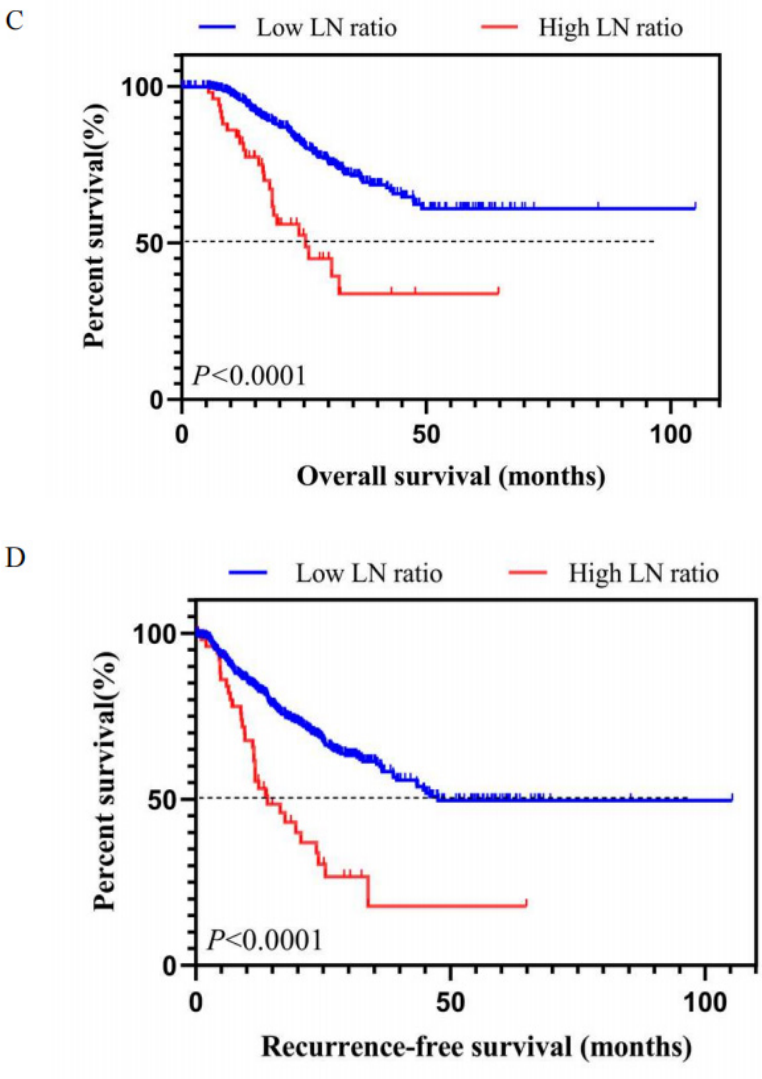



Figure 1. Kaplan–Meier estimates of overall (A) and recurrence-free (B) survival stratified by pCR vs. non-pCR. Kaplan–Meier estimates of overall (C), and recurrence-free (D) survival stratified by Low LN ratio (≤30%) vs. High LN ratio (>30%).

**sample size (Fig 2).**

Figure 2. Kaplan-Meier curves for patients with chemotherapy or chemotherapy plus immunotherapy as neoadjuvant therapies. (A) Overall survival, P=0.174; (B) Recurrence-free survival, P=0.091.

Furthermore, we explored the value of postoperative therapy in patients with recurrence and found that patients with recurrence who received adjuvant therapy seem to have numerical better OS than those without (25.97 vs 24.40 months, P=0.179, Fig 3). Both OS and RFS had not significant difference between adjuvant chemotherapy group and observation group.

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**Figure 2**

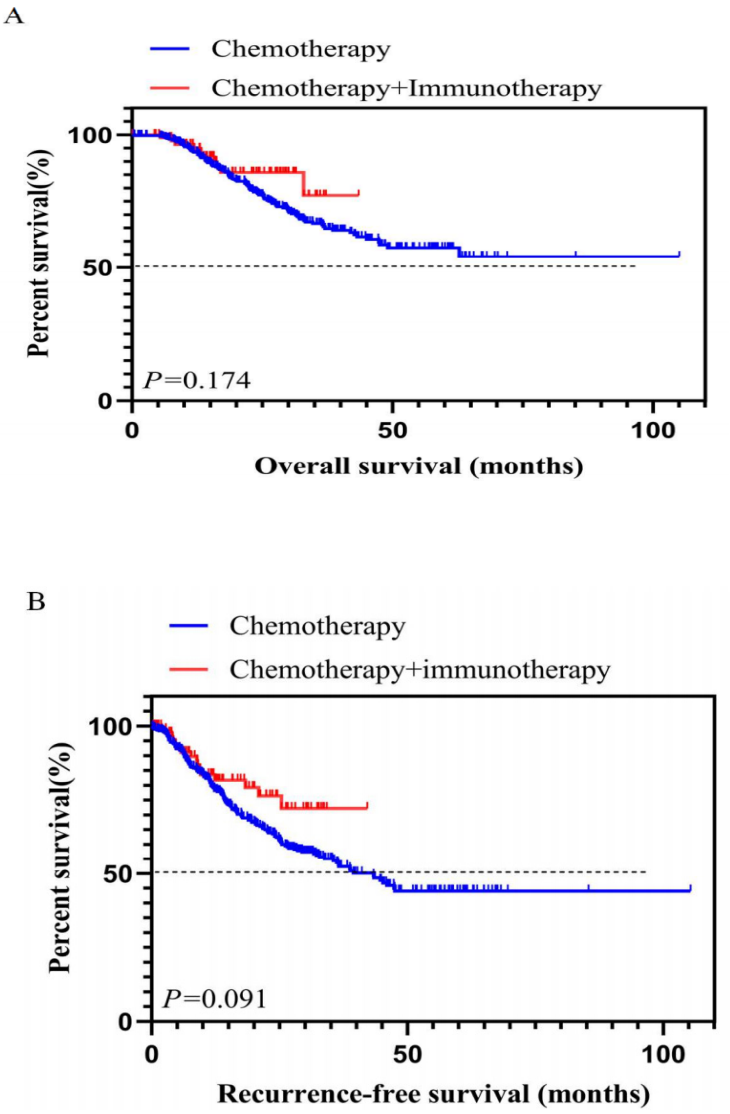
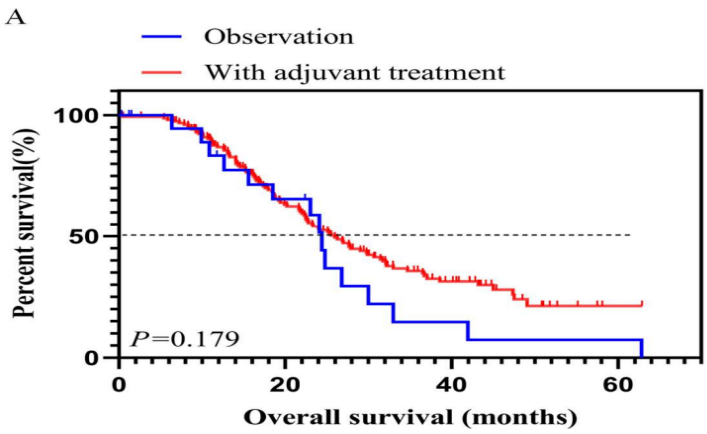



**Figure 3**



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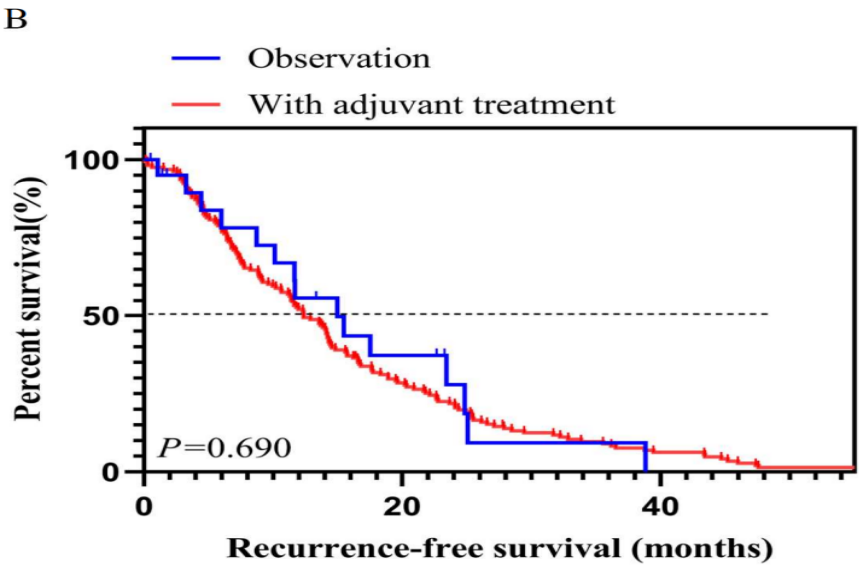



Figure 3. Kaplan-Meier curves for relapsed patients with adjuvant treatment and postoperative observation alone. (A) Overall survival, P=0.179; (B) Recurrence-free survival, P=0.690.

**TRG and 3-year RFS rate**

We further investigated the 3-year RFS rates in different TRG groups and different treatment groups. The 3-year RFS rate was 66.5% in patients with TRG 0-1, and 50.9% in patients with TRG 2-3 (P<0.001, Fig 4A). Among the patients with TRG 0-1, the 3-year RFS rate of those without systemic therapy after surgery was 81.4% and those with systemic therapy was 64.4% (P = 0.129, Fig 4B).

**Figure 4**

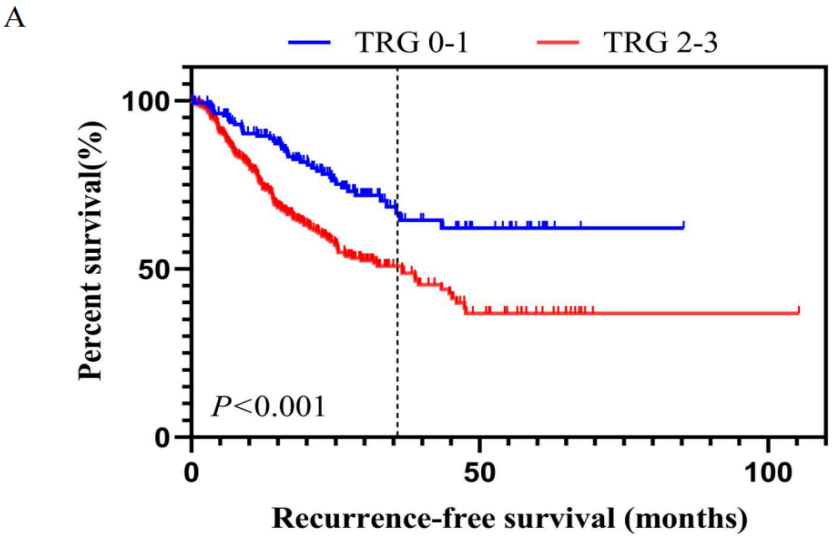
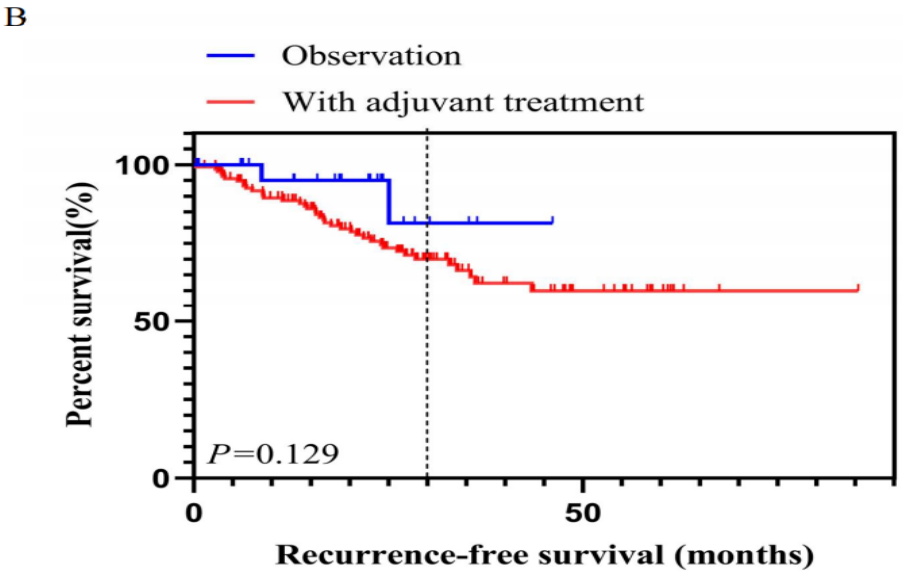



Figure 4. Recurrence-free survival (A) for patients with different TRG, P<0.001; (B) for patients with TRG 0-1 and with or without adjuvant treatment, P=0.129.

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**Nomogram construction**

Significant factors in the Chi-Square test or Fisher's exact test (we excluded EBER, Lauren type and preoperative treatment evaluation, because there were too many missing values) and NAT regimen were accessed into the multivariate logist analysis. The multivariate logist analysis showed that preoperative treatment (P < 0.001) and pathological type (P = 0.027) were independent factors for pCR (Supplementary Table 3).

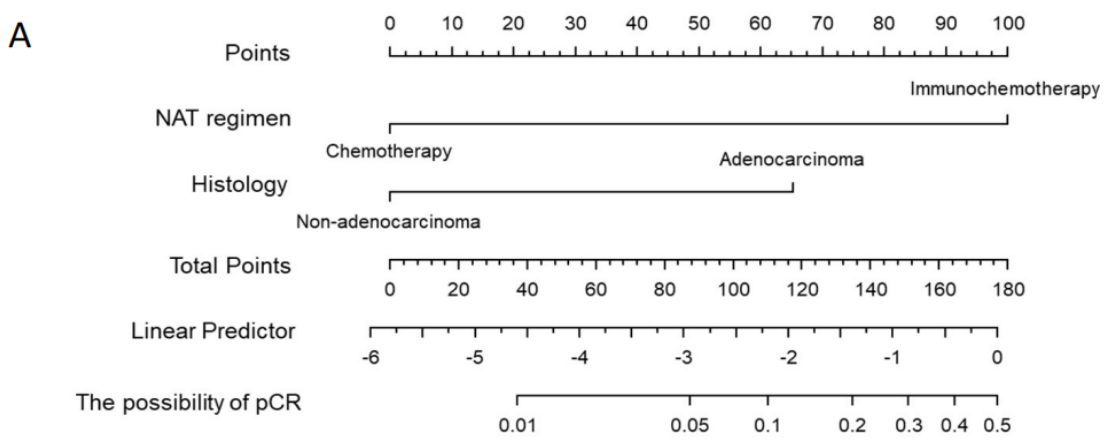
**Supplemental Table 3.** Multivariate logistic regression analysis of the significant factors of pCR in gastric cancer patients.

| Variable | Estimate | SE | Z value | P value |
|---|---|---|---|---|
| Intercept | -4.3816 | 0.7169 | -6.112 | <0.001 |
| Gender | 0.9667 | 0.6037 | 1.601 | 0.1093 |
| NAT regimen | 3.6437 | 0.5941 | 6.133 | <0.001 |
| Histological type | -2.4143 | 1.0898 | -2.215 | 0.0267 |

SE, standard error.

Next, using the multivariate analysis mentioned above as a basis, the predictive nomogram was created (Fig 5A). By using bootstrap resampling, the nomogram's C-index was determined to be 0.844 on the training set (Fig 5B), 0.820 on the validation set (Fig 5C). The calibration curves showed that the data and nomogram predictions agreed quite well (Fig 5D, E), and the pCR prediction C-index was 0.820. DCA was also used to validate the clinical utility of the model based on the net benefit (Fig 5F, G).

**Figure 5**



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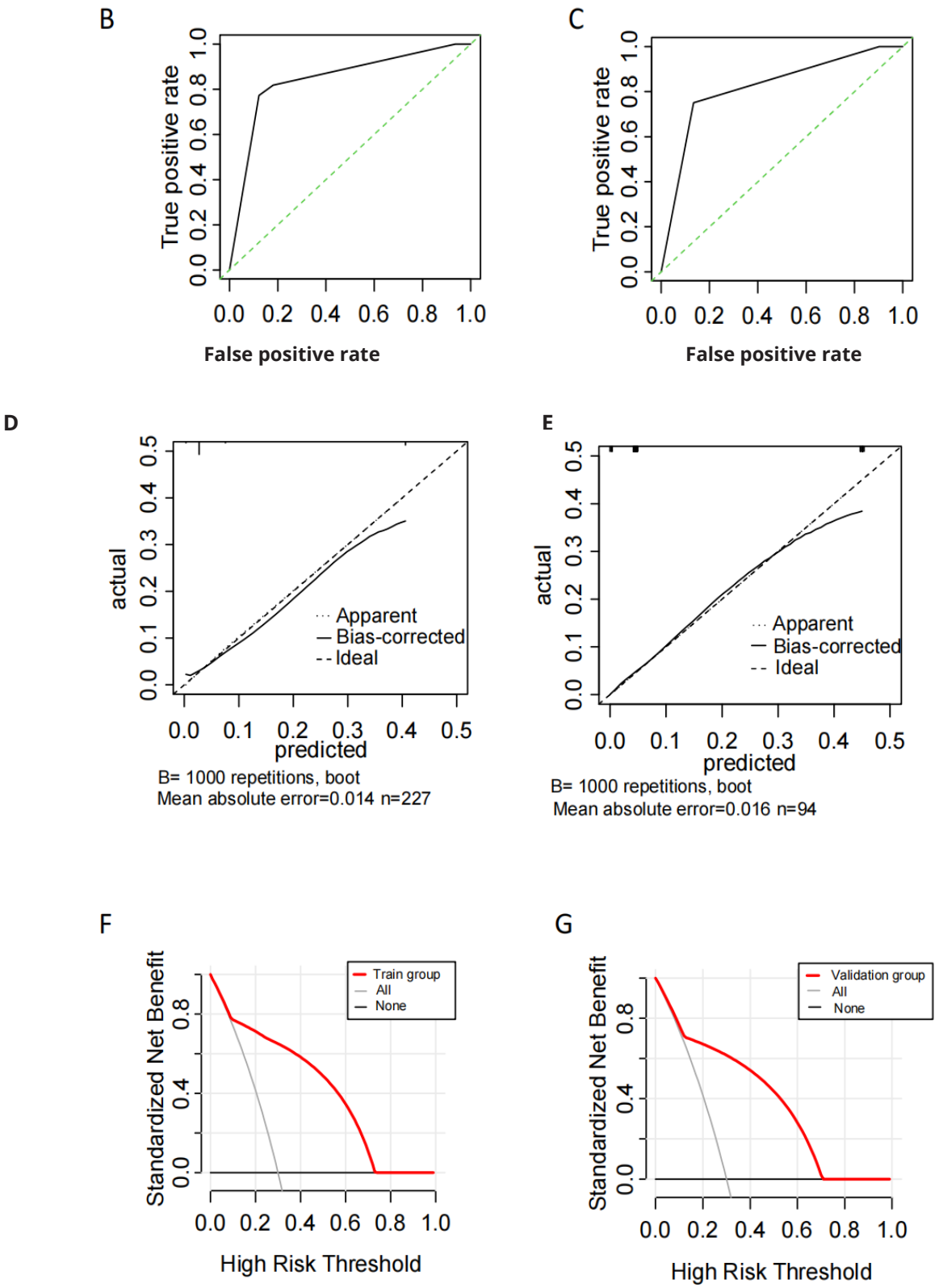



Figure 5. (A) Nomogram that can predict the possibility of pCR in gastric patients with neoadjuvant treatment. Receiver operating characteristic (ROC) curves for pCR prediction in the training (B) and internal-validation groups (C). Calibration curves in the training (D), and internal-validation (E) cohorts. Decision curve analyses in the training (F), and internal-validation group (G).

Journal of Immunology (ISSN 2995-861X)

**DISCUSSION**

In this multicenter real-world study of LAGC patients who underwent NAT and radical surgery, the median OS was not reached after a median follow-up of 30.7 months, and the recurrence rate was 34.8% in our study, better than the median OS of 12 months for patients who underwent surgery alone and the recurrence rate after radical resection was up to 80%(4). The 3-year RFS was 56.3% in our study, which was close to the RESOLVE trial (59.4%)(17). The predicted 3-, and 5-year OS rates for patients in our study were 67.2% and 58.0% respectively, higher than those in the FLOT trail(9). Therefore, NAT is recommended for patients with LAGC. Both our previous study and some of others have concluded that the pathological evaluation method (i.e. TRG) is accurate for estimating the efficacy of NAT and is strongly relevant to prognosis(18-20). Among the 488 LAGC patients who underwent NAT in the present study, we found 80 (16.4%) patients had pCR. Both OS and RFS were significantly improved in the pCR group than non-pCR group. Furthermore, the recurrence rate was significant lower in the pCR group than in the non-pCR group, 7.5% vs 36.5%. Li et al finished a meta-analysis and found that GC patients who achieved pCR after NAT could gain a better outcome than those without pCR(21). Another pool analysis concluded that pCR correlated with improved OS significantly(22). These results are consistent with ours and revealed that pCR may become the valid predictors for longer OS. However, few research has incorporated clinical traits to predict the pCR of GC patients on neoadjuvant treatment. Therefore, in this work, we established and validated a predictive nomogram based on clinicopathological features using data from three medical centers and a real-world investigation.

Firstly, we found that patients with the following factors including male, CR or PR in preoperative RECIST 1.1 evaluation, adenocarcinoma in pathological type, diffuse type in Lauren classification, and EBER-positive status were more likely to get pCR. Spoerl et al concluded that pathological combined complete and subtotal regression was higher in intestinal than in diffuse and mixed type, which is contrary to our study(23). The possible reasons may include that the majority of patients in the research of Spoerl et al were GEJ cancer instead of GC, and a high proportion of patients in our study with unknown Lauren classification.

What's more, chemotherapy plus immunotherapy as NAT may lead to lower recurrence rate and higher pCR rate than neoadjuvant chemotherapy alone. Data from phase II trials has confirmed that the addition of immunotherapy to NAT can achieve promising efficacy (17). In addition, a meta-analysis revealed that immunotherapy-based NAT for LAGC was safe and also had greater pCR and R0 resection rates(24). Our nomogram suggested that pCR was more significantly impacted by the neoadjuvant therapy regimen. In both the training (C-index = 0.844) and validation (C-index = 0.820) sets, the nomogram showed good applicability. However, larger randomized phase III trials are needed.

It is worth noting that the risk of recurrence persists even for patients with pCR after NAT. Therefore, it is crucial to comprehend the pattern and timing of recurrence in individuals who underwent surgery after receiving NAT. In all the patients with recurrence, 125 patients (73.5%) had distant metastasis, 15 patients (8.8%) had local recurrence, 11 patients (6.5%) had both local recurrence and distant metastasis, and other 19 patients (11.2%) had unknown recurrence location. There was no significant difference on the time and location of recurrence between pCR group and non-pCR group, which was consistent with other studies(15, 25). Furthermore, we found that patients with the following factors were more likely to recur, including younger than 65 years old, primary site in stomach, with TRG 2 or 3, with poor differentiation, with more than 5 positive regional lymph nodes, with neurovascular invasion, diffuse type, and pMMR Lymph node metastasis have been reported as one of the most crucial elements influencing the prognosis of GC patients(26). Because it is less affected by the number of LN examinations, LN ratio is considered as a prospective index of prognosis(27). These findings are consistent with our results, which could have significant impact on the individualized treatment of GC patients receiving NAT. For GC patients with suspected regional lymph node metastasis, a more positive preoperative systemic approach may be required before surgery.

Till now there is no prospective study to evaluate the role of adjuvant therapy for patients with pCR. Viewpoints vary from different cancers, for there is no consensus on the advantages of and indications for adjuvant chemotherapy in pCR patients(28). Spring et al concluded that no additional postoperative adjuvant chemotherapy is required for breast cancer patients who attained pCR after surgery because additional treatment does not increase efficacy(29). Dossa et al demonstrated that the use of adjuvant therapy may confer a survival benefit in the pCR population by potentially eradicating residual micrometastatic disease in rectal cancer patients(30, 31). There was a significant higher incidence of central nervous system (CNS) recurrences in pCR patients(15). Most chemotherapy drugs cannot pass through the blood-brain barrier. Therefore, the role of adjuvant therapy for GC patients with pCR after NAT and radical surgery is still controversial. Our results showed that relapsed GC patients who underwent adjuvant therapy had numerical longer median OS compared with those who did not receive adjuvant therapy, but the difference was not significant. Moreover, the 6 pCR patients who suffered from recurrence all received adjuvant therapy, while none of the 17 pCR patients who did

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not receive adjuvant therapy had recurrence. Prospective clinical trial is warranted to evaluate the role of adjuvant therapy for GC patients with pCR.

There were some inherent limitations in this study. Firstly, this study had its retrospective nature. As such, it was susceptible to both selection and treatment bias. Secondly, we acknowledged that our observations were based on a small number of total events (6 recurrences in 80 pCR patients). Finally, this is a multi-center study. Therefore, center heterogeneity is unavoidable. Due to the items of regular testing differed marginally between the pathology departments in different institutions, there were many missing values for some items, such as Lauren classification and Combined Positive Score (CPS) of PD-L1. However, to our knowledge, this is the largest sample size of gastric/ GEJ cancer patients with a pCR after NAT and radical surgery. In addition, we analyzed the possible predictors for pCR and risk factors of recurrence. The nomogram for pCR prediction of GC was first reported. The recurrence sites and time were directly compared between pCR and non-pCR patients, which is also rarely reported.

To sum up, our results suggested that pCR after NAT is associated with significant improvement of RFS and OS in LAGC patients. The addition of immunotherapy to NAT can lead to higher pCR rate and lower recurrence rates. Our nomogram accurately predicted gastric pCR after NAT, although further external validation is required. The role of adjuvant therapy for patients with pCR after surgery needs to be confirmed in prospective clinical trial.

**Authors' contributions**

Conception and design of this study were carried out by QMZ and ZLY. LMY, CS, LDD and YX collected the data. LMY and CS carried out the statistical analysis. LMY wrote the original draft. GWL, CYE and ZZW finished the investigation and methodology. All authors read and approved the final manuscript. All the authors decided to submit the manuscript for publication.

**Competing interests**

The authors declare no potential conflicts of interest.

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**Role of funder statement :** The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and the decision to submit the manuscript for publication.

**Ethics approval and consent to participate**

This study was performed in accordance with the Declaration of Helsinki protocols and was approved by the Ethics Committee from Sun Yat-sen University Cancer Center with accession N.O.: B2022-775-01. All authors had access to the study data and reviewed and approved the final manuscript.

**Availability of data and materials**

Miao-Zhen Qiu and Li-Ying Zhao had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Data Statement**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Patient consent for publication**

Not applicable.

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**ABBREVIATIONS**

**NAT**: Neoadjuvant treatment
**GC**: gastric cancer
**pCR**: pathological complete response
**OS**: overall survival
**RFS**: recurrence-free survival
**GEJ**: gastric/gastroesophageal junction
**SYSUCC**: Sun Yat-sen University Cancer Center
**TRG**: tumor regression grade
**BMI**: body mass index
**MMR**: mis-match repair
**EBER**: Epstein-Barr virus-encoded RNA
**NCCN**: National Comprehensive Cancer Network
**AJCC**: American Joint Committee on Cancer
**CR**: complete response
**PR**: partial response
**ORR**: overall response rate
**LN**: lymph node
**SD**: stable disease
**CNS**: central nervous system
**CPS**: combined positive score
**C-index**: concordance index
**ROC**: receiver operator characteristic curve
**AUC**: area under the receiver operator characteristic curve
**DCA**: decision curve analysis