ORIGINAL RESEARCH

# Preoperative Fibrinogen-Albumin Ratio Index (FARI) is a Reliable Prognosis and Chemoradiotherapy Sensitivity Predictor in Locally Advanced Rectal Cancer Patients Undergoing Radical Surgery Following Neoadjuvant Chemoradiotherapy

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**Background:** Inflammatory response and nutritional status are associated with cancer development and progression. The purpose of this study was to explore whether the preoperative fibrinogen-albumin ratio index (FARI) is related to prognosis and chemoradiotherapy outcome of radical surgery after neoadjuvant chemoradiotherapy (NCRT) in patients with locally advanced rectal cancer (LARC).

**Methods:** In total, 123 patients with LARC who underwent radical surgery after NCRT between June 2012 and December 2018 were collected in this study. Time-dependent receiver operating characteristic (ROC) curve analysis was made to evaluate the ability of the markers for forecasting prognosis. The correlation between FARI and clinicopathological parameters was analyzed. The Kaplan–Meier survival analysis, univariate and multivariate analysis based on Cox proportional hazards models, and subgroup analysis were performed to evaluate overall survival (OS) and disease-free survival (DFS). A nomogram was constructed to evaluate the predictive role of FARI in DFS.

**Results:** The ROC curve analysis showed that the ability of FARI on DFS prediction was superior to those of other inflammatory markers and carcinoembryonic antigen (CEA) (P<0.05). Based on the Youden's index, the optimal cut-off value of FARI was 8.8%. High FARI patients (>8.8%) showed a poor response to NCRT and a decreased DFS rate (P<0.05). In addition, multivariate analysis revealed that FARI (HR=3.098, P=0.033), neutrophil-to-lymphocyte ratio (NLR), and postoperative T stage were independent prognostic factors for DFS in TNM stage III LARC patients. However, FARI failed to distinguish patients with poor OS. Harrell's concordance index (C-index) of the nomogram containing FARI (0.807) was obviously higher than that without it (0.732) among LARC patients who underwent radical surgery after NCRT. Moreover, multivariate analysis revealed FARI (OR=3.044, P=0.012) as an independent predictor for response to NCRT.

**Conclusion:** Among LARC patients who underwent radical surgery after NCRT, preoperative FARI is an independent prognostic factor for DFS and an independent predictor for response to NCRT.

**Keywords:** rectal cancer, fibrinogen-albumin ratio index, prognosis, tumor regression grade

## Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide and the second leading cause of cancer-related deaths.[1] The incidence of CRC ranks

third in China, and the fatality rate ranks fifth.[2] Approximately 30% of all CRC are rectal cancer.[3–5] Locally advanced rectal cancer (LARC) is defined as either clinical stage T3/4 or node-positive disease.[6,7] The standard treatment for LARC is neoadjuvant chemoradiotherapy (NCRT) followed by total mesorectal excision (TME).[7,8] Although patients with LARC generally receive radical resection and postoperative adjuvant therapy, long-term oncological outcome in LARC patients are far from satisfactory.[9,10] TNM staging is a significant prognostic factor for CRC patients, but it could not further stratify the same TNM stage LARC patients with a high risk of recurrence.[11] Therefore, it is essential to identify effective biomarkers to predict progression and prognosis and to precisely stratify LARC patients with high risk of relapse in return for making them receive an optimal therapeutic regimen.

Recently, numerous studies have demonstrated that the systemic inflammation response and nutritional status are extremely important hallmarks of malignancies.[9,12,13] Proinflammatory chemokines and cytokines could promote tumor occurrence, development, and metastasis, destroy immune systems, and increase tumor resistance to NCRT.[13–15] Simultaneously, malnutrition could lead to a poorer response to NCRT, which results in poor prognosis.[9,16,17] Several biomarkers of systemic inflammatory and nutritional status, such as the lymphocyte-to-monocyte ratio (LMR), the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), the systemic immune-inflammation index (SII, based on platelet, lymphocyte, and neutrophil counts), C-reactive protein, albumin, the Glasgow prognostic score (GPS), and fibrinogen already served as prognostic indexes in different kinds of cancers.[18–25] Some of these biomarkers could also be used as predictors for radiotherapy/chemoradiotherapy efficacy in different types of cancers. NCRT, is recommended as standard treatment for LARC patients.[17,26] However, NCRT could influence the levels of circulating erythrocyte, neutrophil, lymphocyte, monocyte and platelet, and C-reactive protein.[18,27] Thus, the true state of inflammatory response in LARC patients after NCRT may fail to be reflected, the capability of the above leukocyte-based inflammatory biomarkers to predict the prognosis of LARC patients after radical resection may be limited.[18] It is widely known that serum albumin (ALB) is an important acute-phase protein reflecting not only the inflammatory state but also the nutritional status[17] and that fibrinogen (FIB), as an essential acute-phase protein, plays

a significant regulatory role in both the systemic inflammatory response and cancer progression, including proliferation, angiogenesis and metastasis of tumor cells.[25] Moreover, many studies have revealed that FIB levels and ALB levels are both correlated with prognosis in different types of cancer patients. More importantly, the fibrinogen-albumin ratio index (FARI) has been proposed as a low-cost and widely used marker to predict cancer prognosis. Several studies have demonstrated that FARI is a good predictor of prognosis in gastric tumor,[28,29] non-small cell lung tumor,[30] CRC,[9,11,18,31] gallbladder tumor,[32] prostate tumor,[33] breast tumor,[34] and hepatocellular tumor.[35] Thus, FARI might be an effective prognostic indicator for cancer.

However, few studies have reported about the role of FARI in prognosis and the prediction of response for NCRT in LARC patients undergoing radical surgery following NCRT. Hence, this study aimed to explore the correlations between FARI and survival, and between FARI and chemoradiotherapy response in LARC patients who underwent radical surgery.

## Methods
### Patients
In this retrospective study, 123 consecutively LARC (TNM stage II or stage III) patients from Peking University Third Hospital between March 2012 and December 2018 were enrolled and followed up. Ethical approval was obtained from the ethics committee of Peking University Third Hospital and adhered to the tenets of the Declaration of Helsinki. Written informed consents were signed by each eligible patient. The inclusion criteria included: 1) all patients were diagnosed with primary adenocarcinoma through histopathologic diagnosis; 2) patients were identified as LARC and treated with NCRT followed by curative TME; 3) patients received complete resection without positive tumor margins; and 4) patients possessed complete inpatient data, including preoperative complete blood counts and follow-up data. The exclusion criteria were as follows: 1) patients received anti-immunosuppressive or anti-inflammatory treatments; 2) patients with autoimmune disease, hematological disease and acute infection; 3) patients with other cancers besides rectal adenocarcinoma; and 4) patients undergoing emergency surgery for obstruction or perforation of the rectum.

## Treatment and Follow-Up

All patients underwent abdominal and pelvic magnetic resonance imaging (MRI), chest, abdominal and pelvic computed tomography (CT), colonoscopy biopsy and tumor marker test. The decision to administer NCRT or conduct radical resection was made by a multidisciplinary team, which was consisted of surgeons, oncologists, pathologists, and radiologists. Radiation doses ranged from 45 to 50 Gy given across 25 fractions. Radiation was given according to the institutional protocols. The oral capecitabine dose during the whole period of radiotherapy (RT) 1650 mg/m$^2$ per daily. Eight to 9 weeks after the end of NCRT, the LARC patients underwent curative TME, which was conducted by 4 experienced colorectal surgeons at Peking University Third Hospital. Patients were followed-up at 1 and 3 months after surgery, and every 6 months thereafter. Abdominal and pelvic contrast-enhanced CT or MRI scans, and carcinoembryonic antigen (CEA) level were routinely performed every 6 months for 2 years and then once every year for a total of 3 years at each follow-up. Colonoscopy was conducted within 1 year after surgery and then repeated in every 2–3 years. The presence of new lesions revealed by biopsy or imaging was deemed as tumor recurrence. Appropriate treatment such as repeated surgery, systemic chemotherapy, radiofrequency ablation, or RT were performed for patients with tumor recurrence. Overall survival (OS) was defined as the period from TME to death from disease, and disease-free survival (DFS) was defined as the period from TME to tumor recurrence.

## Hematological Examinations and Definition of Inflammatory Markers

Hematological examinations included blood routine examination, liver function tests, coagulation tests and CEA measurement. All blood specimens were tested in the laboratory of our hospital within two weeks before the operation. Inflammatory markers were defined as follows: NLR = (the ratio of neutrophil count to lymphocyte count); LMR = (the ratio of lymphocyte count to monocyte count); PLR = (the ratio of platelet count to lymphocyte count); SII = (platelet count) × NLR; FARI = (the ratio of fibrinogen to albumin) × 100%.

## Pathological Assessment and Definition

Tumor staging, tumor regression grade (TRG) and histology were assessed in this study. All pathological specimens were evaluated by two experienced pathologists based on the seventh AJCC TNM staging system. The AJCC-TRG system has been found to be better than any other TRG system because it had more accurate DFS prediction of rectal cancer, so this grading system was adopted in our center.[36–39] The AJCC-TRG definitions were as follows: TRG0, no tumor cells remained; TRG1, single tumor cell or small groups of tumor cells remained; TRG2, residual cancer with desmoplastic response; and TRG3, minimal evidence of tumor response.[37] In this study, TRG0-1 was defined as a good response, while TRG2-3 was defined as a poor response.

## Statistical Analysis

The differences in continuous variables and categorical variables was calculated by the independent sample *t* test and the chi-square test or Fisher's test. The area under the curve (AUC) was obtained by receiver operating characteristic (ROC) curve analysis, and the optimal cut-off value of the preoperative inflammatory markers for DFS was determined by Youden's index. Factors influencing tumor response were analyzed by binary logistic regression models, while factors that influenced DFS and OS were assessed by Cox proportional hazards model, which was established by univariate and multivariate analyses. Potential risk factors ($P < 0.1$) were adopted for multivariate analysis with the backward stepwise method following the result of univariate analysis. The Kaplan-Meier survival analysis were adopted in this study and p value was calculated by the Log-rank test. According to the Cox regression results, a prognostic nomogram for predicting the DFS of stage III LARC patients was established, and the predictive accuracy was calculated by Harrell's concordance index (C-index) and calibration. The time-dependent ROC curve and survival nomogram were constructed by the "survivalROC" and 'rms' packages, respectively, in R version 3.5.2. All statistical analyses were carried out by SPSS Statistics 19.0 (IBM Corporation, Armonk, NY, USA). A P value <0.05 was recognized as statistically significant.

## Results
### Patient Characteristics

According to the inclusion and exclusion criteria, 123 patients were eventually enrolled in the study. The detailed flow chart of the patient selection process is shown in Figure 1. The baseline clinicopathological characteristics of the patients are described in Table 1. Among the 123 eligible patients, male
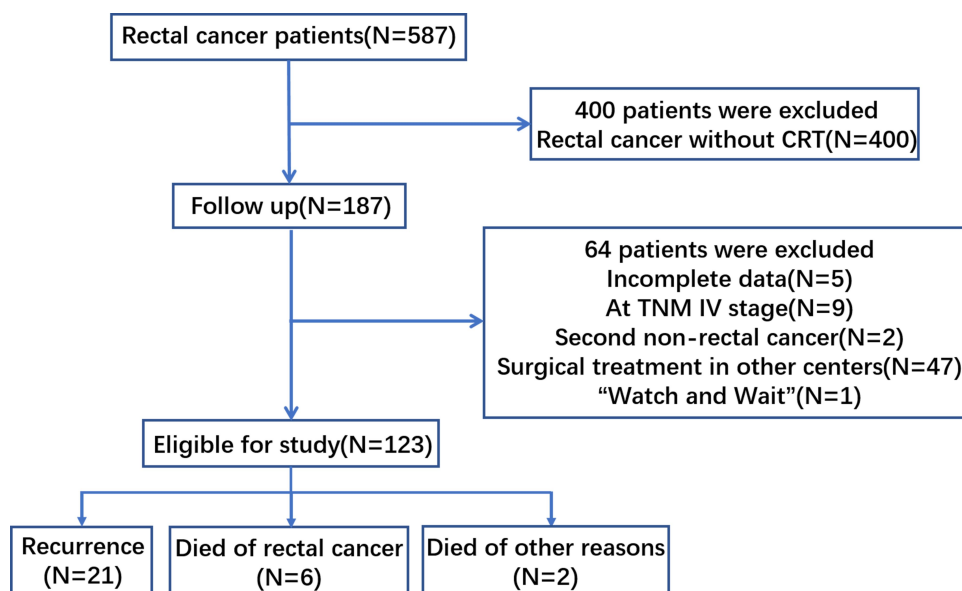
**Figure 1** Flow chart of eligible cases selection.

(71.5%) made up the majority, and sixty (range 22–82) was the median age. Forty (32.5%) patients had tumors located at the lower rectum, while the remaining 83 (67.5%) patients had tumors located at mid-high rectum. Fifty-three (43.1%) patients showed tumor length >5 cm, while 70 (56.9%) showed tumor length ≤5 cm. Seventy-six (61.8%) patients achieved ypT0-2 after NCRT, and 87 (70.7%) achieved N0 after NCRT. A total of 6 (5.3%) tumors showed well-differentiated adenocarcinoma histology, and 108 (94.7%) tumors showed moderately or poorly differentiated histology. Tumor deposits, lymphovascular invasion (LVI) and perineural invasion (PNI) were found in 20 (16.3%), 8 (6.5%) and 17 (13.8%) patients, respectively. The four-tier AJCC-TRG results were as follows: TRG0 (n=21, 17.1%), TRG1 (n=53, 43.1%), TRG2 (n=37, 30.1%), and TRG3 (n=12, 9.7%). The median levels of LMR, PLR, SII, NLR, and FARI were 2.1 (95% CI 1.9–2.3), 288.6 (95% CI 266.8–312.7), 976.5 (95% CI 875.7–1095.3), 5.0 (95% CI 4.6–5.5), and 7.7% (95% CI 7.4–8.1%), respectively.

## Survival Analysis Based on Clinical and Postoperative TNM Staging

The median follow-up time was 31 months (range 6–87 months). Local recurrence and/or distant metastasis occurred in 21 (16.4%) patients among the 123 eligible patients, and eight patients died at the last follow-up, of which 6, 1, and 1 patients died of cancer, cerebral hemorrhage and heart disease, respectively. Regarding DFS, both clinical and postoperative TNM stage III patients exhibited a lower DFS rate than TNM stage II patients (Figure 2A and C, both P<0.001). Although both clinical and postoperative TNM stage failed to distinguish patients with poor OS rates, TNM stage III patients had a worse OS tendency than TNM stage II patients (Figure 2B and D, P=0.152 and P=0.104).

## Assessment of the Capability of Systemic Inflammation Markers on Prediction of DFS and OS

To assess the capability of the markers to predict survival, time-dependent ROC curve analysis was conducted. The AUC of FARI in DFS was continuously superior to that of LMR, PLR, SII, NLR and CEA at any time point after the operation, as shown in Figure 3A. Additionally, the AUCs of FARI on 12-, 36-, and 60-month DFS prediction were 0.751, 0.801, and 0.691, respectively. Furthermore, according to ROC curve analysis, FARI had a high sensitivity for predicting the DFS rate (AUC=0.737, P=0.001), which was superior to those of NLR (AUC=0.594, P=0.175), LMR (AUC=0.514, P=0.845), PLR (AUC=0.528, P=0.692) and SII (AUC=0.553, P=0.448). However, the AUCs of FARI and the other markers in predicting the OS rate were unstable, as shown in Figure 3B.

## Optimal Cut-off Value of the Systemic Inflammation Markers in Survival Analysis

According to our data, the optimal cut-off values of the systemic inflammatory markers for DFS were determined

**Table 1** Patient Characteristics

| Variables | Total Number (%) |
|---|---|
| Gender | |
|   Male | 88 (71.5) |
|   Female | 35 (28.5) |
| Age, years | |
|   [median (95% CI)] | 60 (58–63) |
| CEA | |
|   ≤ 5 ng/mL | 106 (86.2) |
|   > 5 ng/mL | 17 (13.8) |
| Site | |
|   Low | 40 (32.5) |
|   Mid-high | 83 (67.5) |
| Length | |
|   >5cm | 53 (43.1) |
|   ≤5cm | 70 (56.9) |
| T category | |
|   ypT0-2 | 76 (61.8) |
|   ypT3-4 | 47 (38.2) |
| ypN status | |
|   Negative | 87 (70.7) |
|   Positive | 36 (29.3) |
| Histology | |
|   Well differentiation | 6 (5.3) |
|   Moderate differentiation | 95 (83.3) |
|   Poor differentiation | 13 (11.4) |
| LVI | |
|   Positive | 8 (6.5) |
|   Negative | 115 (93.5) |
| PNI | |
|   Positive | 17 (13.8) |
|   Negative | 106 (86.2) |
| Tumor deposits | |
|   Positive | 20 (16.3) |
|   Negative | 103 (83.7) |
| TRG | |
|   0–1 | 73 (59.3) |
|   2–3 | 50 (40.7) |
| NLR | |
|   [Median (95% CI)] | 5.0 (4.6–5.5) |
| LMR | |
|   [Median (95% CI)] | 2.1 (1.9–2.3) |
| PLR | |
|   [Median (95% CI)] | 288.6 (266.8–312.7) |

(*Continued*)

**Table 1** (Continued).

| Variables | Total Number (%) |
|---|---|
| SII | |
|   [Median (95% CI)] | 976.5 (875.7–1095.3) |
| FARI, % | |
|   [Median (95% CI)] | 7.7 (7.4–8.1) |

**Abbreviations:** CI, confidence interval; CEA, carcinoembryonic antigen; PNI, perineural invasion; LVI, lymphovascular invasion; TRG, tumor regression grade; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune–inflammation index; FARI, fibrinogen-albumin ratio index.

by Youden's test. The optimal cut-off value for FARI was 8.8%. Patients were dichotomized into low FARI group (≤8.8%) and high FARI group (>8.8%) by reference to the cut-off value. The optimal cut-off values for LMR, PLR, SII and NLR were 1.6, 218, 895 and 4, respectively. Likewise, based on their respective optimal cut-off values, patients were dichotomized into low and high groups. According to the cut-off value of FARI, patients in the high FARI group had a poorer DFS rate than patients in the low FARI group (Figure 4A, P<0.001). However, FARI could not distinguish patients with poor OS (Figure 4B, P=0.254). Since LARC patients are classified into stage II and stage III by reference to the TNM staging system, we wanted to know whether FARI can predict DFS in patients with different TNM stages. We found that although there was no significant difference in DFS between stage II patients in the high FARI group and those in the low FARI group, compare to the low FARI group, high FARI group had a poor DFS tendency (Figure 4C, P=0.075). Owing to no death events occurring in stage II patients, the OS rate could not be compared between high FARI and low FARI groups. Interestingly, stage III patients with high FARI level had a poorer DFS rate than patients with low FARI level (Figure 4D, P<0.001). However, no significant difference in the OS rate was found between stage III patients with high FARI level and those with low FARI level (Figure 4E, P=0.291).

## Relationship Between FARI and Clinicopathological Parameters in Clinical TNM Stage III Patients

Since FARI could distinguish TNM stage III patients with a poor DFS rate, we next analyzed the relationship between FARI and clinicopathological parameters in
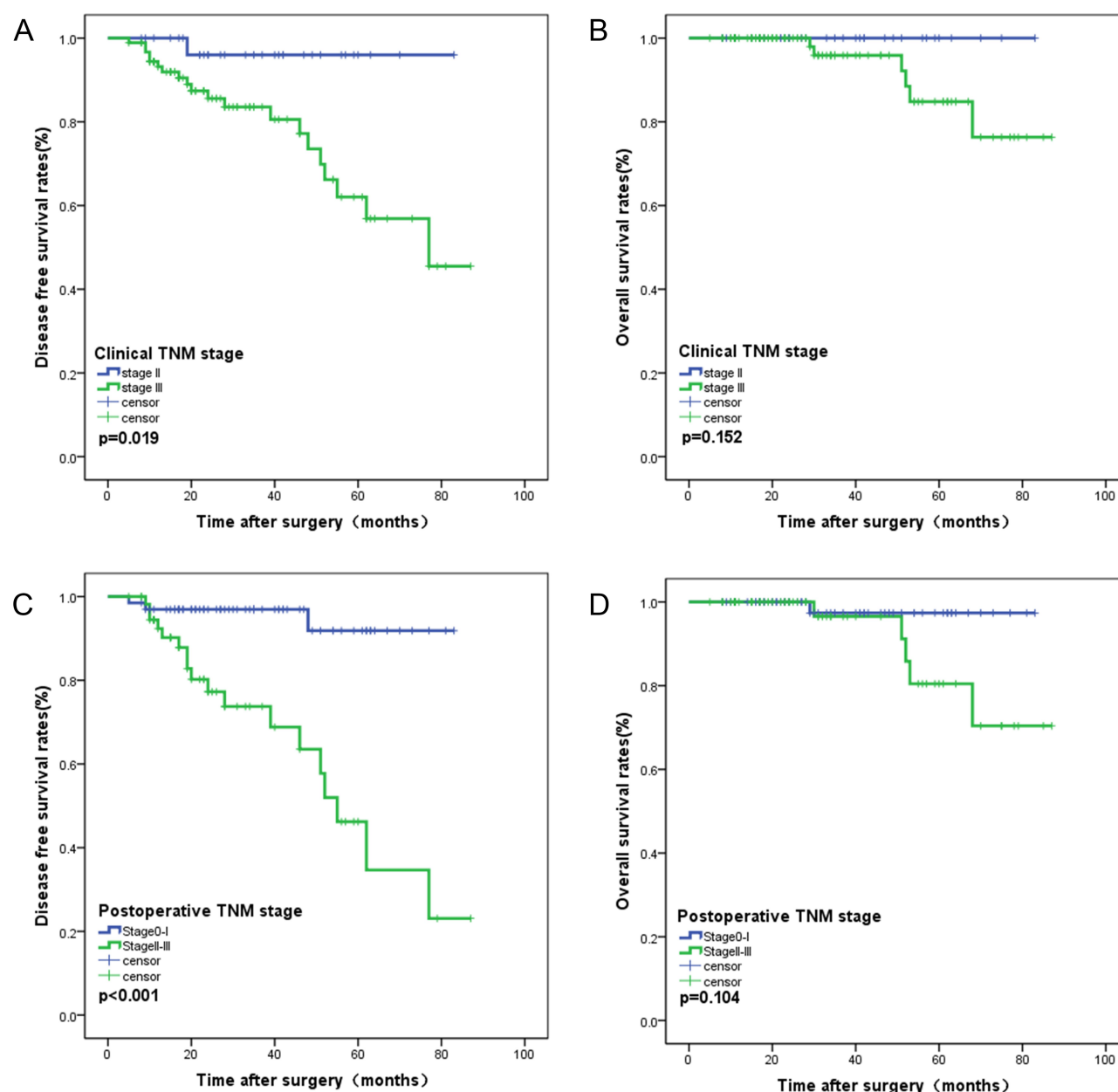
**Figure 2** Survival analysis based on clinical and postoperative TNM staging. (**A**) Kaplan–Meier analysis for DFS rate based on preoperative TNM stage. (**B**) Kaplan–Meier analysis for OS rate based on preoperative TNM stage. (**C**) Kaplan–Meier analysis for DFS rate based on postoperative TNM stage. (**D**) Kaplan–Meier analysis for OS rate based on postoperative TNM stage.

clinical TNM stage III patients. Overall, seventy (76%) patients belonged to the low FARI group, and 22 (24%) patients belonged to the high FARI group. The patients' characteristics according to the FARI level are shown in Table 2. High FARI levels were significantly associated with elevated CEA levels (P=0.01), longer tumor lengths (P=0.02), a higher postoperative T stage (P<0.001), positive lymph node status (P=0.046), positive PNI (P=0.032) and higher SII (P=0.028). The FARI level was not significantly correlated with the remaining

characteristics, such as age, sex, tumor site, histology, LVI, PLR, and tumor deposits (P>0.05).

## Cox Proportional Hazards Models for DFS and the Nomogram for DFS

Based on Cox proportional hazards models, we adopted P value < 0.1 as a significant difference. Univariable analysis showed that DFS was associated with the CEA level (P=0.05), tumor length (P=0.015), postoperative T stage
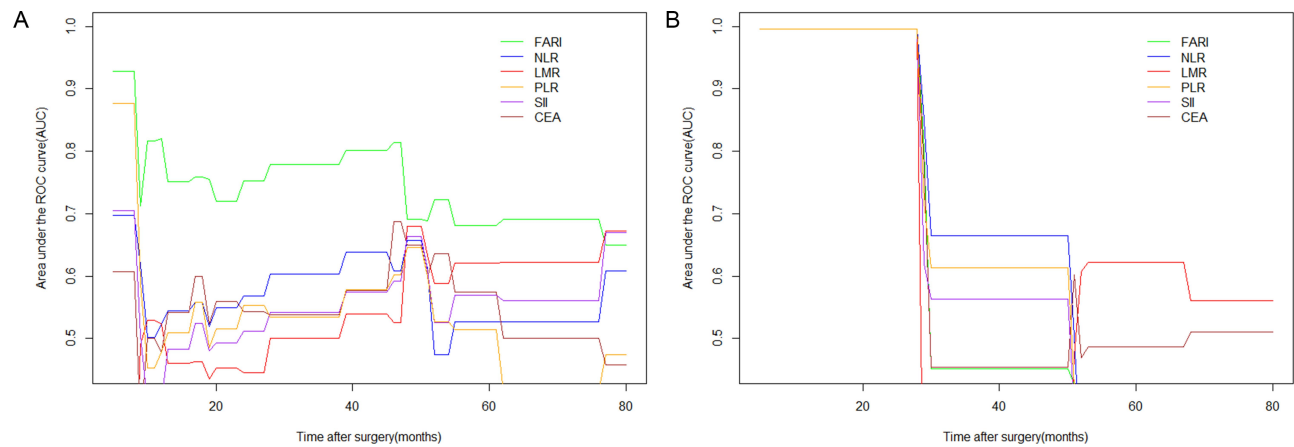
**Figure 3** Systemic inflammation markers on prediction of DFS and OS. (**A**)Time-dependent ROC curve analysis to compare the ability of FARI, NLR, LMR, PLR, SII, and CEA in predicting DFS. (**B**) Time-dependent ROC curve analysis to compare the ability of FARI, NLR, LMR, PLR, SII, and CEA in predicting OS.
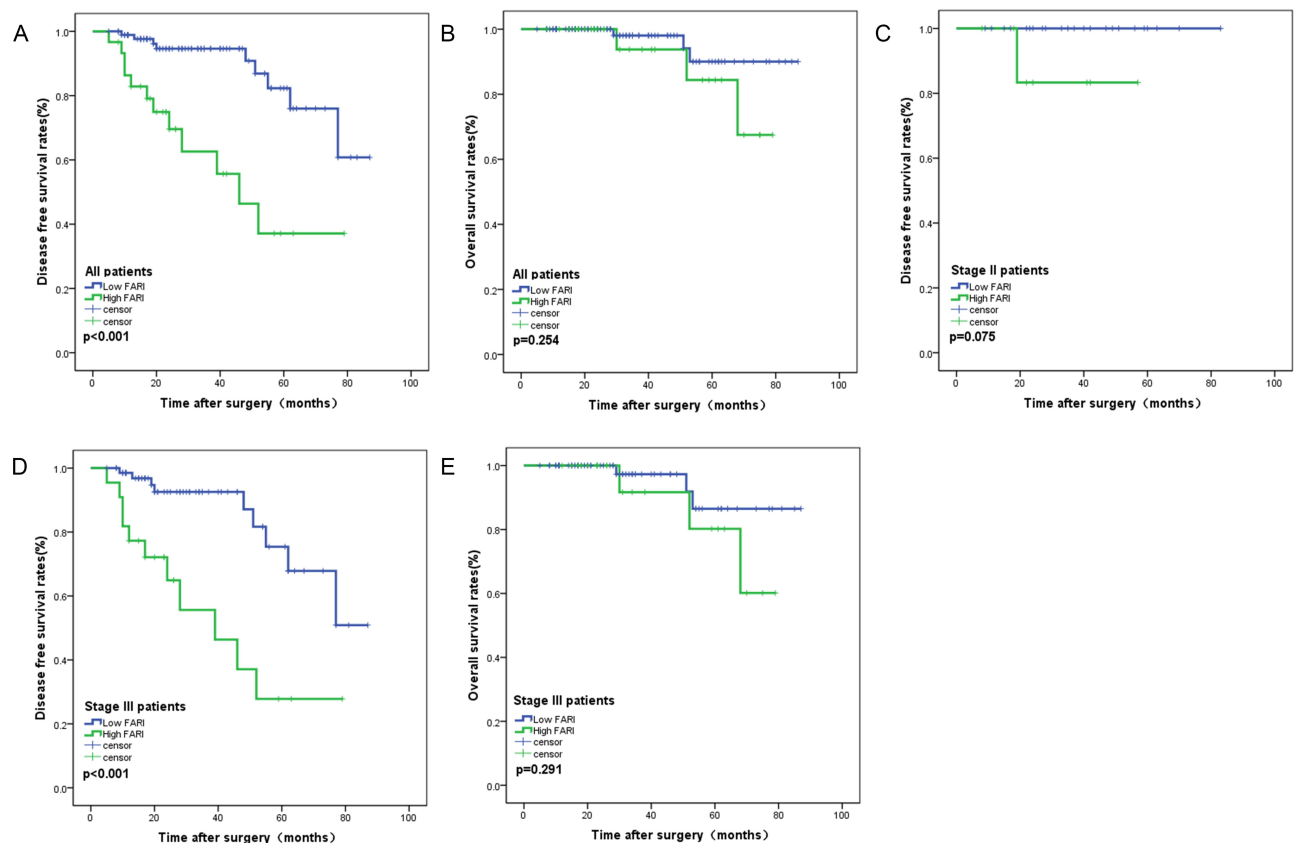


**Figure 4** Survival analysis between high FARI group and low FARI group. (**A**) Kaplan–Meier analysis for DFS rate between high FARI group and low FARI group among LARC patients (p <0.001). (**B**) Kaplan–Meier analysis for OS rate between high FARI group and low FARI group among LARC patients (p = 0.239). (**C**) Kaplan–Meier analysis for DFS rate between high FARI group and low FARI group among stage II LARC patients (p=0.075). (**D**) Kaplan–Meier analysis for DFS rate between high FARI group and low FARI group among stage III LARC patients (p<0.001). (**E**) Kaplan–Meier analysis for OS rate between high FARI group and low FARI group among stage III LARC patients (p=0.291).

(P<0.001), lymph node status (P=0.006), LVI (P=0.034), PNI (P=0.001), tumor deposits (P=0.001), NLR (P=0.033), and FARI level (P=0.001). All of the above parameters were evaluated by multivariable analysis for DFS. Among these

factors, FARI (HR=3.098, P=0.033), ypT (HR=5.562, P=0.018) and NLR (HR=2.882, P=0.032) remained associated with DFS, as shown in Table 3. Thus, the results suggest that among LARC patients who underwent radical

**Table 2** Characteristics of Patients According to Preoperative FARI Level

| Variables | Low FARI Group (%) | High FARI Group (%) | p value |
|---|---|---|---|
| Gender | | | 0.575 |
| Male | 52 (74.3) | 15 (68.2) | |
| Female | 18 (25.7) | 7 (31.8) | |
| Age, years [median (95% CI)] | 60 (57–63) | 63 (57–67) | 0.339 |
| CEA | | | 0.01 |
| ≤ 5 ng/mL | 63 (90) | 14 (63.6) | |
| > 5 ng/mL | 7 (10) | 8 (36.4) | |
| Site | | | 0.509 |
| Low | 21 (30) | 5 (22.7) | |
| Mid-high | 49 (70) | 17 (77.3) | |
| Length | | | 0.02 |
| >5 cm | 31 (44.3) | 16 (72.7) | |
| ≤5 cm | 39 (55.7) | 6 (27.3) | |
| T category | | | <0.001 |
| ypT0-2 | 47 (67.1) | 5 (22.7) | |
| ypT3-4 | 23 (32.9) | 17 (77.3) | |
| ypN status | | | 0.046 |
| Negative | 51 (72.9) | 11 (50) | |
| Positive | 19 (27.1) | 11 (50) | |
| Histology | | | 0.125 |
| Well differentiation | 3 (4.8) | 1 (4.5) | |
| Moderate differentiation | 56 (88.9) | 16 (72.7) | |
| Poor differentiation | 4 (6.3) | 5 (22.7) | |
| LVI | | | 0.446 |
| Positive | 4 (5.7) | 3 (13.6) | |
| Negative | 66 (94.3) | 19 (86.4) | |
| PNI | | | 0.032 |
| Positive | 7 (10) | 7 (31.8) | |
| Negative | 63 (90) | 15 (68.2) | |
| Tumor deposits | | | 0.904 |
| Positive | 13 (18.6) | 5 (22.7) | |
| Negative | 57 (81.4) | 17 (77.3) | |
| TRG | | | 0.003 |
| 0–1 | 47 (67.1) | 7 (31.8) | |
| 2–3 | 23 (32.9) | 15 (68.2) | |
| NLR [median (95% CI)] | 4.8 (4.2–5.5) | 5.5 (4.7–6.5) | 0.316 |
| LMR [median (95% CI)] | 2.2 (1.9–2.4) | 2.0 (1.7–2.4) | 0.441 |

(*Continued*)

**Table 2** (Continued).

| Variables | Low FARI Group (%) | High FARI Group (%) | p value |
|---|---|---|---|
| PLR [median (95% CI)] | 269.6 (241.5–300.8) | 331.5 (265.8–410.6) | 0.07 |
| SII [median (95% CI)] | 895.5 (765.4–1037.6) | 1236.8 (943.1–1545.0) | 0.028 |
| FARI, % [median(CI)] | 6.9 (6.6–7.1) | 10.5 (10.0–11.1) | <0.001 |

**Abbreviations:** CI, confidence interval; CEA, carcinoembryonic antigen; LVI, lymphovascular invasion; PNI, perineural invasion; TRG, tumor regression grade; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune–inflammation index; FARI, fibrinogen-albumin ratio index.

surgery after NCRT, preoperative FARI could be an independent prognostic factor for DFS. To further explore the predictive performance of FARI for DFS, a nomogram for the prediction of 3-year DFS was developed, as shown in Figure 5A and B. The C-indexes of nomograms including or excluding FARI were 0.807 and 0.732, respectively, which indicated that the nomogram including FARI has better predictive performance than that without it. The calibration curve for the prognostic nomogram including FARI for the 3-year DFS predicted probability is shown in Figure 5C and D.

## The Relationship Between FARI and Response to NCRT

Tumor response was defined by AJCC-TRG as mentioned above. According to survival analysis, TRG could not distinguish the patients with a poor OS or DFS rates among all LARC patients (Figure 6A and B, P=0.132 and P=0.499). Similar results were obtained in the survival analysis of stage II and stage III patients (Figure 6C–E; P=0.182, P=0.174 and P=0.623, respectively). We further performed subgroup DFS and OS analyses of TRG based on the FARI level. High FARI group was significantly associated with poor DFS and OS rates among good response group (Figure 6F and G, P<0.001 and P=0.039). However, FARI failed to distinguish patients with poor DFS and OS rates in the poor response group (Figure 6H and I, P=0.159 and P=0.398). Next, we wanted to identify which parameters impact TRG by univariate and multivariable analyses. All preoperative parameters (including systemic inflammatory markers) were included in the binary univariate analysis. We set P value < 0.1 as a significant difference. We found that tumor site

**Table 3** Cox Proportional Hazards Model for DFS in Preoperative Stage III Rectal Cancer Patients

| Variables | DFS | | | |
|---|---|---|---|---|
| | Univariable | | Multivariable | |
| | HR (95% CI) | P value | HR (95% CI) | P value |
| Gender (male vs female) | 0.502 (0.165–1.526) | 0.224 | – | – |
| Age, years | 0.992 (0.955–1.029) | 0.657 | – | – |
| CEA, ng/mL (>5 vs ≤5) | 2.673 (1.002–7.135) | 0.05 | – | – |
| Tumor site (low vs mid-high) | 1.012 (0.363–2.820) | 0.981 | - | - |
| Length (>5 vs ≤5) | 3.968 (1.301–12.107) | 0.015 | 2.959 (0.758–11.559) | 0.119 |
| ypT (T3-4 vs T0-2) | 10.903 (3.175–37.443) | <0.001 | 5.562 (1.340–23.096) | 0.018 |
| ypN (N+ vs N0) | 3.666 (1.456–9.235) | 0.006 | - | - |
| LVI (+ vs -) | 3.888 (1.104–13.690) | 0.034 | - | - |
| PNI (+ vs -) | 4.477 (1.787–11.218) | 0.001 | - | - |
| Tumor deposits (+ vs -) | 4.201 (1.735–10.169) | 0.001 | 2.447 (0.868–6.894) | 0.09 |
| NLR (≤4 vs >4) | 2.723 (1.085–6.832) | 0.033 | 2.882 (1.096–7.578) | 0.032 |
| LMR (>1.65 vs ≤1.65) | 1.946 (0.649–5.837) | 0.235 | - | - |
| PLR (≤218 vs >218) | 2.061 (0.855–4.966) | 0.107 | - | - |
| SII (≤895 vs >895) | 3.597 (1.197–10.815) | 0.023 | - | - |
| FARI (>8.8% vs ≤8.8%) | 4.535 (1.875–10.965) | 0.001 | 3.098 (1.095–8.768) | 0.033 |

**Abbreviations:** HR, hazard ratio; CI, confidence interval; CEA, carcinoembryonic antigen; LVI, lymphovascular invasion; PNI, perineural invasion; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune–inflammation index; FARI, fibrinogen-albumin ratio index.

(P=0.065) and FARI level (P=0.015) were correlated to TRG, as shown in Table 4. The two parameters were evaluated by multivariable analysis for TRG. We found that tumor site (OR=2.215, P=0.049) and FARI (OR=3.044, P=0.012) remained associated with TRG, as shown in Table 4. Thus, the results suggested that among LARC patients who underwent radical surgery after NCRT, preoperative FARI could be an independent predictor for response to NCRT.

## Discussion

Rectal cancer is a sort of molecular heterogeneous disease that leads to diverse therapeutic responses.[40] Currently, preoperative NCRT is commonly used as the standard regimen for LARC patients. Approximately 50–60% of patients are downstaged after NCRT, and 10–30% achieve pathological complete response.[7] Approximately 40% of LARC patients displayed ypT3-4 or ypN+ disease after NCRT.[41] TNM staging system is widely used to stratify high-risk LARC patients.[37] In our study, both clinical and postoperative TNM stage could well predict DFS in LARC patients. Although we did not find similar results for the OS prediction based on TNM stage, there was still a tendency for a high TNM stage to be correlated with a lower OS. The TNM staging system does not function well for LARC patients in the same TNM stage.[11]

Therefore, it is essential to establish new universal biomarkers to easily stratify LARC patients with high risk of relapse. Recently, FARI have served as great predictor of prognosis in many kinds of cancer.[9,11,18,28–31,35] Our present study also found that among LARC patients who underwent radical surgery after NCRT, preoperative FARI could distinguish patients with poor DFS rates. In addition, the predictive capability of preoperative FARI in DFS surpassed that of LMR, PLR, SII, NLR, and CEA. However, FARI could not distinguish patients with a poor OS rate, which might be due to relatively small sample or the different kinds of tumors. In detail, based on subgroup analysis for TNM stage III LARC patients, FARI could distinguish patients with poor DFS rates. Moreover, a high FARI level was significantly positively associated with higher CEA level, longer tumor length, deeper invasion, presence of lymph node metastasis and presence of PNI. These factors were highly correlated with poor prognosis. Preoperative FARI could be an independent prognostic factor for DFS among TNM stage III LARC patients were confirmed by the univariate and multivariate analyses. Among these prognostic factors, FARI (HR=3.098, P=0.033), ypT (HR=5.562, P=0.018) and NLR (HR=2.882, P=0.032) were correlated with DFS (Table 3). In further validating the predictive performance of FARI for DFS, the C-indexes of nomograms including or
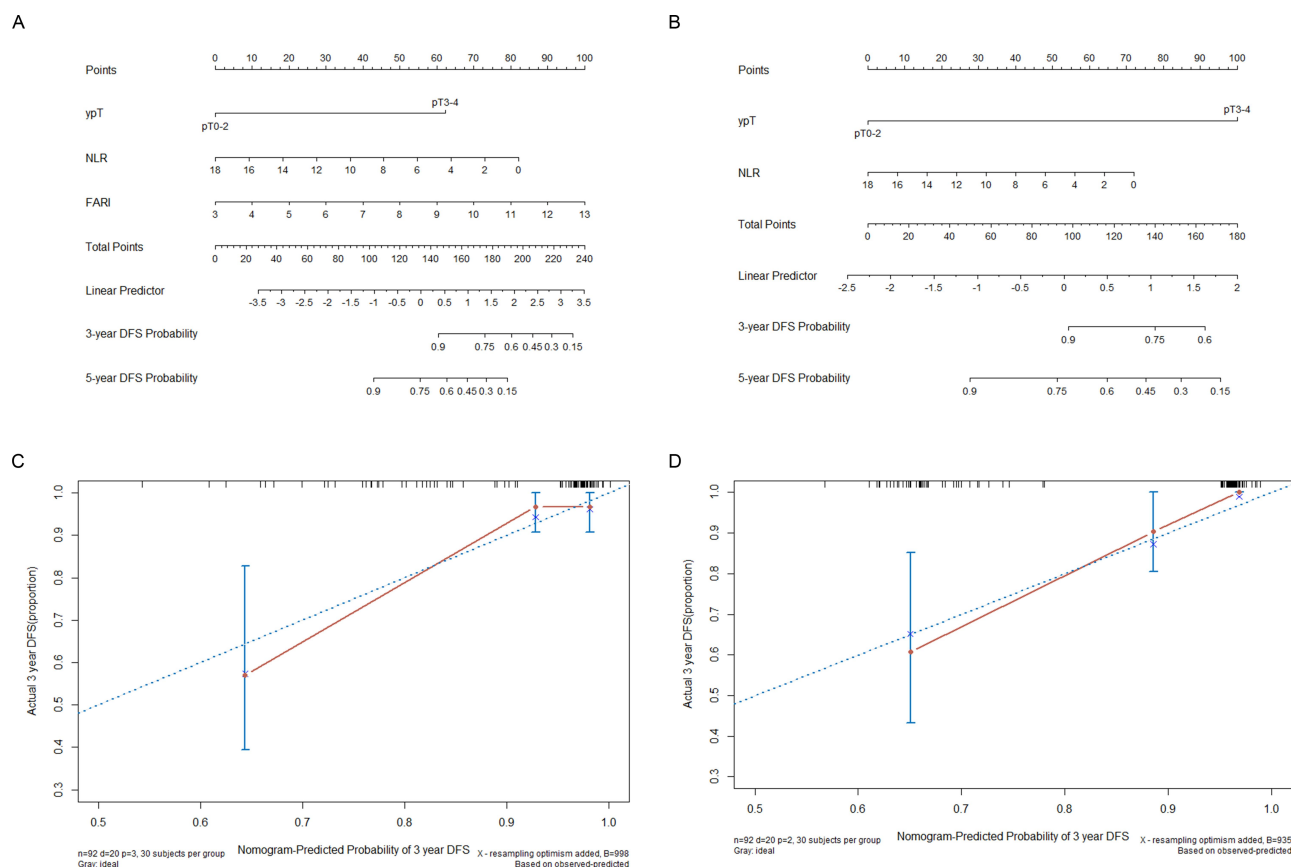
**Figure 5** Prognostic nomograms with or without FARI for predicting survival of LARC patient. (**A**) Nomogram including FARI for predicting 3-year DFS. (**B**) Nomogram without FARI for predicting 3-year DFS. (**C**) Calibration of the nomogram including FARI for 3-year DFS predicted probability. (**D**) Calibration of the nomogram excluding FARI for 3-year DFS predicted probability. The diagonal blue line represents a perfect prediction model. The red line represents the performance of the nomogram, and a closer fit to the diagonal blue line represents a better prediction.

excluding FARI were 0.807 and 0.732, respectively, which indicated that the nomogram including FARI has a better predictive performance than the one without it. Hence, among LARC patients who underwent radical surgery after NCRT, preoperative FARI could be an independent prognostic factor for DFS.

The FIB-ALB score, which is deemed as an indicator of systemic inflammation and nutritional status, has recently been used to evaluate the prognosis of various kinds of cancers.[29] FIB, as an acute-phase protein, was primarily generated by the liver. Inflammatory disorders or infection could greatly enhance the production of FIB. Moreover, malignant tumor cells can partially produce FIB, which participates in the formation of extracellular matrix.[42,43] In addition, FIB can promote tumor cell adhesion, cell proliferation, and cell migration through incorporation with vascular endothelial growth factor and fibroblast growth factor-2.[43,44] This may be the explanation of high FARI level correlated with a poor prognosis of cancer. ALB, which is produced by the liver, may not only

reflect the state of nutrition but also be involved in systemic inflammation.[29] Moreover, inflammation and malnutrition could further suppress ALB synthesis.[45] In addition, cancer-associated malnutrition leads to impaired immune function, which decreases treatment efficacy, and increases morbidity and mortality.[46] ALB, as an important part of the systemic inflammatory response, promotes IL-1, IL-6, TNF-α, and acute-phase reactant release. Thus, ALB could affect the progression of cancer.[13,15,17]

NCRT could affect the systemic inflammatory response and reduce levels of the peripheral leukocyte.[18,27] The capability of leukocyte-based inflammation markers might be limited to prognosis prediction of LARC patients after radical resection.[18] FIB and ALB are both relatively stable proteins; thus, preoperative FARI is a more stable inflammation-based prognostic marker. Among these inflammatory and nutritional status prognostic factors, NLR (HR=2.882, P=0.032) and FARI (HR=3.098, P=0.033) were associated with DFS (Table 3), while LMR and PLR were not correlated with tumor prognosis. Moreover,
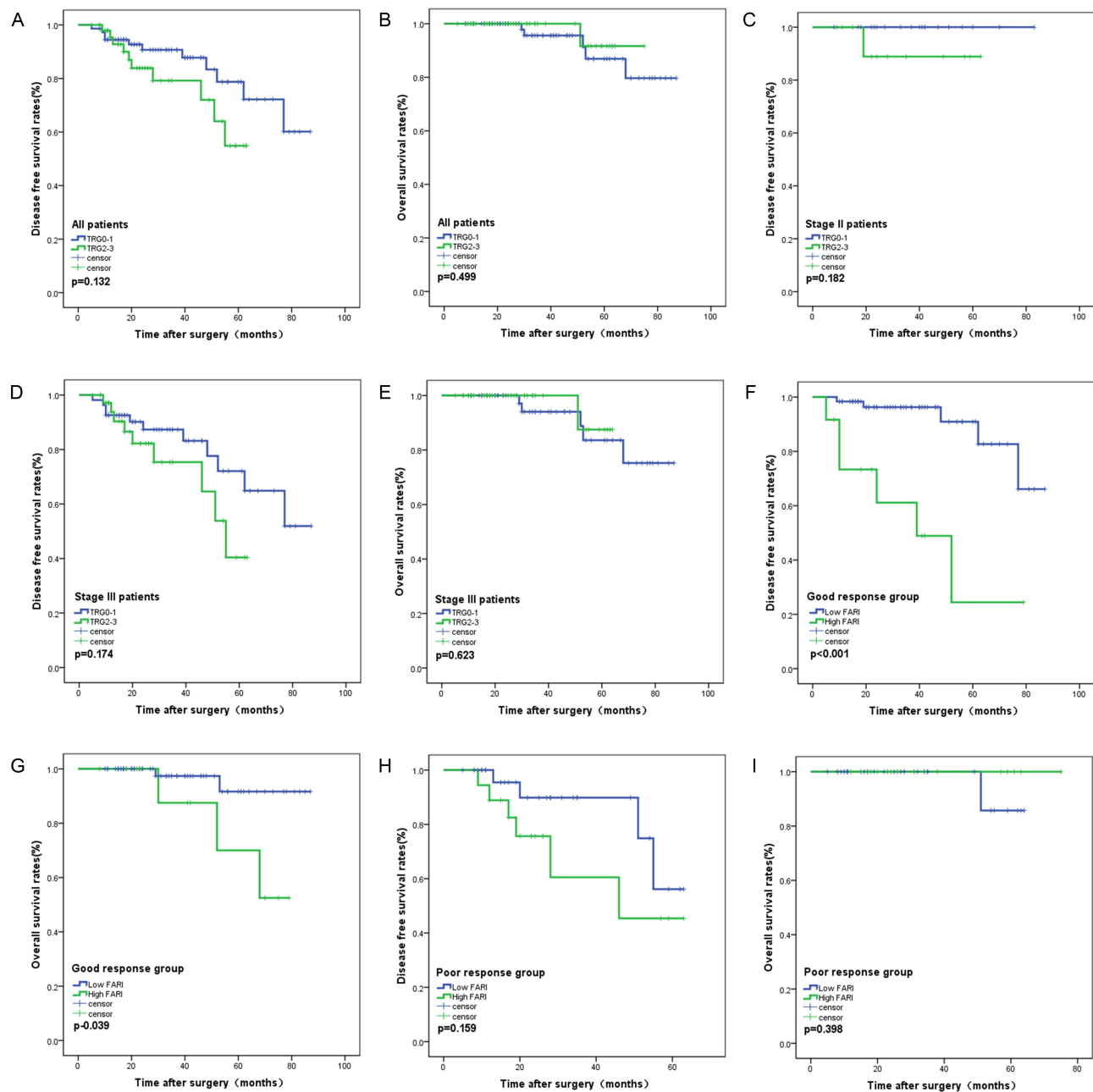
**Figure 6** The relationship between FARI and response to NCRT. (**A**) Kaplan–Meier analysis for DFS rate between good response group and poor response group among LARC patients (p=0.132). (**B**) Kaplan–Meier analysis for OS rate between good response group and poor response group among LARC patients (p=0.499). (**C**) Kaplan–Meier analysis for DFS rate between good response group and poor response group among stage II LARC patients (p=0.182). (**D**) Kaplan–Meier analysis for DFS rate between good response group and poor response group among stage III LARC patients (p=0.174). (**E**) Kaplan–Meier analysis for OS rate between good response group and poor response group among stage III LARC patients (p=0.623).(**F**) Kaplan–Meier analysis for DFS rate between high FARI group and low FARI group among good response LARC patients (p<0.001). (**G**) Kaplan–Meier analysis for OS rate between high FARI group and low FARI group among good response LARC patients (p=0.039). (**H**) Kaplan–Meier analysis for DFS rate between high FARI group and low FARI group among poor response LARC patients (p=0.159). (**I**) Kaplan–Meier analysis for OS rate between high FARI group and low FARI group among poor response LARC patients (p=0.398).

a recent study showed that NLR, LMR, PLR and SII were not stable in predicting the prognosis of cancer, which indicated that the prognostic role of these inflammatory markers in cancer needs further research.[47–49] In addition, the time-ROC curve from our data analysis showed that the predictive capability of preoperative FARI on DFS was surpassed that of LMR, PLR, SII, NLR, and CEA. This result suggested that FARI is a more stable inflammation-based prognosis factor in LARC patients who underwent radical surgery after NCRT.

Previous studies have shown that only 10–30% of LARC patients appears complete response.[40,50] Currently,

**Table 4** Binary Logistic Regression Model for TRG in LARC Patients

| Variables | TRG | | | |
|---|---|---|---|---|
| | Univariable | | Multivariable | |
| | OR (95% CI) | p value | OR (95% CI) | p value |
| Gender (male vs female) | 0.814 (0.364–1.823) | 0.618 | – | – |
| Age, years | 1.007 (0.977–1.038) | 0.643 | – | – |
| CEA, ng/mL (>5 vs ≤5) | 2.357 (0.831–6.687) | 0.107 | – | – |
| Site (low vs mid-high) | 2.058 (0.956–4.433) | 0.065 | 2.215 (1.003–4.895) | 0.049 |
| Length (>5 vs ≤5) | 1.401 (0.677–2.896) | 0.363 | - | - |
| NLR (≤4 vs >4) | 1.071 (0.513–2.238) | 0.854 | - | - |
| LMR (>1.65 vs ≤1.65) | 1.509 (0.693–3.289) | 0.300 | - | - |
| PLR (>218 vs ≤218) | 0.635 (0.287–1.404) | 0.262 | - | - |
| SII (>895 vs ≤895) | 1.047 (0.503–2.178) | 0.903 | - | - |
| FARI (>8.8% vs ≤8.8%) | 2.859 (1.226–6.667) | 0.015 | 3.044 (1.281–7.230) | 0.012 |

**Abbreviations:** TRG, tumor regression grade; OR, odds ratio; CI, confidence interval; CEA, carcinoembryonic antigen; PNI, perineural invasion; LVI, lymphovascular invasion; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune–inflammation index; FARI, fibrinogen-albumin ratio index.

TRG is commonly used to evaluate tumor responses to NCRT, and TRG has also been demonstrated as an independent prognostic factor for DFS in LARC patients.[7,8,39,51–53] In addition, TRG was also correlated to the systemic inflammatory response and nutritional status.[54,55] Therefore, we further explored the relationship between FARI and response to NCRT. According to the survival analysis, TRG could not distinguish the patients with poor OS or DFS rates among all LARC patients (Figure 6A and B, P=0.132 and P=0.499). We considered that the follow-up time of LARC patients in our study was short, our research population was special, and our study population sample was small, which might explain this inconsistency phenomenon. Interestingly, high FARI level was significantly correlated with poor DFS and OS rates in the good response group (Figure 6F and G, P<0.001 and P=0.039). However, FARI failed to distinguish patients with poor DFS and OS rates in the poor response group (Figure 6H and I, P=0.159 and P=0.398). We found that FARI (OR=3.044, P=0.012) remained associated with TRG (Table 4), while LMR, PLR, SII, NLR, and CEA were failed to predict TRG. Thus, the results suggested that among LARC patients who underwent radical surgery after NCRT, preoperative FARI could be an independent and relatively stable predictor for response to NCRT.

In our study, the cut-off value of FARI was 8.8%, and in other studies, it ranged from 6% to 11%.[9,11,18,28–31,35] The differences in the cut-off value of FARI among different studies might results from different research

patients. These findings suggest that the universal cut-off value of FARI needs further validation among LARC patients who underwent radical surgery after NCRT in the future. Recently, some researchers found that fibrinogen-to-pre-albumin ratio (FPR) could predict the prognosis of CRC and classify stage II–III patients who could benefit from the adjuvant chemotherapy.[56] Some researchers found that albumin (Alb) to fibrinogen (Fib) ratio (AFR) and a novel AFR–Alb-derived neutrophil/lymphocyte ratio (dNLR) score (ADS) was a prospective biomarker to predict clinical efficacy of NCRT and clinical prognosis of esophageal squamous cell carcinoma patients undergoing esophagectomy.[57] In our future study, we will explore the role of FPR or ADS score in prognosis and the prediction of response for NCRT among LARC patients.

However, some limitations exist in this study. First, our research population was relatively small sample size and external validation was lacked in our study, further investigation was required. Second, the follow-up time of this study was insufficient, and more meaningful results may be obtained through extending the follow-up time, which may be the reason why FARI failed to predict OS.

## Conclusion

In summary, our findings demonstrated that preoperative FARI is a simple, economical, and practical index and that among LARC patients who underwent radical surgery after NCRT, preoperative FARI could be not only an independent prognostic factor for DFS but also an independent predictor for response to NCRT. We hope that this

promising marker will serve as a common biomarker for planning tailored treatment for patients with LARC.

## Disclosure

The authors declare no conflicts of interest for this work.

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