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

Siyi Lu1,*
Zhenzhen Liu1,*
Xin Zhou1
Bingyan Wang1
Fei Li1
Yanpeng Ma1
Wendong Wang1
Junren Ma1
Yuxia Wang2
Hao Wang2
Wei Fu1

1Department of General Surgery, Peking University Third Hospital, Beijing 100191, People’s Republic of China; 2Department of Radiotherapy, Peking University Third Hospital, Beijing 100191, People’s Republic of China

*These authors contributed equally to this work

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. 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 status17 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 capcitabine dose during the whole period of radiotherapy (RT) 1650 mg/m² 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
(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 $\leq5$ 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 (Continued).

| Variables       | Total Number (%) |
|-----------------|------------------|
| Number of patients |                  |
| 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, compared 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

| 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            | 76 (61.8)        |
| ≤5cm            | 47 (38.2)        |
| T category      |                  |
| ypT0-2          | 87 (70.7)        |
| ypT3-4          | 36 (29.3)        |
| 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) |
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
(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                     |                    |                     |         |
| Male                       | 52 (74.3)          | 15 (68.2)           | 0.575   |
| Female                     | 18 (25.7)          | 7 (31.8)            |         |
| Age, years [median (95% CI)] | 60 (57–63)         | 63 (57–67)          | 0.339   |
| CEA ≤ 5 ng/mL              | 63 (90)            | 14 (63.6)           | 0.01    |
| CEA > 5 ng/mL              | 7 (10)             | 8 (36.4)            |         |
| Site                       |                    |                     |         |
| Low                        | 21 (30)            | 5 (22.7)            | 0.509   |
| Mid-high                   | 49 (70)            | 17 (77.3)           |         |
| Length >5 cm               | 31 (44.3)          | 16 (72.7)           | 0.02    |
| ≤5 cm                      | 39 (55.7)          | 6 (27.3)            |         |
| T category ypT0-2          | 47 (67.1)          | 5 (22.7)            | <0.001  |
| ypT3-4                     | 23 (32.9)          | 17 (77.3)           |         |
| ypN status                 |                    |                     |         |
| Negative                   | 51 (72.9)          | 11 (50)             | 0.046   |
| Positive                   | 19 (27.1)          | 11 (50)             |         |
| Histology                  |                    |                     |         |
| Well differentiation       | 3 (4.8)            | 1 (4.5)             | 0.125   |
| Moderate differentiation   | 56 (88.9)          | 16 (72.7)           |         |
| Poor differentiation       | 4 (6.3)            | 5 (22.7)            |         |
| LVI                        |                    |                     |         |
| Positive                   | 4 (5.7)            | 3 (13.6)            | 0.446   |
| Negative                   | 66 (94.3)          | 19 (86.4)           |         |
| PNI                        |                    |                     |         |
| Positive                   | 7 (10)             | 7 (31.8)            | 0.032   |
| Negative                   | 63 (90)            | 15 (68.2)           |         |
| Tumor deposits             |                    |                     |         |
| Positive                   | 13 (18.6)          | 5 (22.7)            | 0.904   |
| Negative                   | 57 (81.4)          | 17 (77.3)           |         |
| TRG                        |                    |                     |         |
| 0–1                        | 47 (67.1)          | 7 (31.8)            | 0.003   |
| 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) | 123.6 (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. 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. Approximately 40% of LARC patients displayed ypT3-4 or ypN+ disease after NCRT. TNM staging system is widely used to stratify high-risk LARC patients. 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. 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. Among 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
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. 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. In addition, FIB can promote tumor cell adhesion, cell proliferation, and cell migration through incorporation with vascular endothelial growth factor and fibroblast growth factor. 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. Moreover, inflammation and malnutrition could further suppress ALB synthesis. In addition, cancer-associated malnutrition leads to impaired immune function, which decreases treatment efficacy, and increases morbidity and mortality. 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.

NCRT could affect the systemic inflammatory response and reduce levels of the peripheral leukocyte. The capability of leukocyte-based inflammation markers might be limited to prognosis prediction of LARC patients after radical resection. 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,
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. 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. Currently,
Table 4 Binary Logistic Regression Model for TRG in LARC Patients

| Variables               | 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 (1.004–4.959) | 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 result 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.

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Disclosure
The authors declare no conflicts of interest for this work.

References
1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
2. Chen W, Sun K, Zheng R, et al. Cancer incidence and mortality in China, 2014. Chin J Cancer Res. 2018;30(4):1–12. doi:10.21147/j.issn.1000-9604.2018.01.01
3. Yang J, Lin Y, Huang Y, et al. Genome landscapes of rectal cancer before and after preoperative chemoradiotherapy. Theranostics. 2019;9(23):6856–6866. doi:10.7150/thno.37794
4. Howlader NNA, Krapcho M, Miller D, et al., eds. SEER Cancer Statistics Review. Bethesda, MD: National Cancer Institute; 1975–2016.
5. Tie J, Cohen JD, Wang Y, et al. Serial circulating tumour DNA analysis during multimodality treatment of locally advanced rectal cancer: a prospective biomarker study. Gut. 2019;68(4):663–671. doi:10.1136/gutjnl-2017-315852
6. Kane C, Glynne-Jones R. Should we favour the use of 5x5 preoperative radiation in rectal cancer. Cancer Treat Rev. 2019;81:101908. doi:10.1016/j.ctrv.2019.101908
7. Collette L, Bosset JF, den Dulk M, et al. Patients with curative resection of cT3–4 rectal cancer after preoperative radiotherapy or chemoradiotherapy: does anybody benefit from adjuvant fluorouracil-based chemoradiotherapy? A trial of the European Organisation for Research and Treatment of Cancer Radiation Oncology Group. J Clin Oncol. 2007;25(28):4379–4386.
8. Fokas E, Liersch T, Fietkau R, et al. Tumor regression grading after preoperative chemoradiotherapy for locally advanced rectal carcinoma revisited: updated results of the CAO/ARO/AIO-94 trial. J Clin Oncol. 2014;32(15):1554–1562. doi:10.1200/JCO.2013.54.3769
9. Chen QG, Zhang L, Sun F, et al. Elevated FPR confers to radiochemoresistance and predicts clinical efficacy and outcome of metastatic colorectal cancer patients. Aging. 2019;11(6):1716–1732. doi:10.18632/aging.101864
10. Zhu J, Tan Z, Hollis-Hansen K, Zhang Y, Yu C, Li Y. Epidemiological trends in colorectal cancer in China: an ecological study. Dig Dis Sci. 2017;62(1):235–243. doi:10.1007/s10620-016-4362-4
11. Zhang L, Zhang J, Wang Y, et al. Potential prognostic factors for predicting the chemotherapeutic outcomes and prognosis of patients with metastatic colorectal cancer. J Clin Lab Anal. 2019;33(8):e22958. doi:10.1002/jcla.22958
12. Izkowitz SH, Yio X. Inflammation and cancer IV. Colorectal cancer in inflammatory bowel disease: the role of inflammation. Am J Physiol Gastrointest Liver Physiol. 2004;287(1):G7–G17. doi:10.1152/ajpgi.00579.2004
13. Terzî J, Grivennikov S, Karin E, Karin M. Inflammation and colon cancer. Gastroenterology. 2010;138(6):2101–2114. doi:10.1053/j.gastro.2010.01.058
14. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002;420(6917):860–867.
15. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature. 2004;442(7106):344–446. doi:10.1038/nature04985
16. Barato A, Abe Vicente Cavagnari M, Silva Fucuta P, Manousakis Forones N. Association between nutrition status and survival in elderly patients with colorectal cancer. Nutrition Clin Pract. 2017;32(5):658–663. doi:10.1177/0884531617706894
17. Gupta D, Lis CG. Pretreatment serum albumin as a predictor of cancer survival: a systematic review of the epidemiological literature. Nutr J. 2010;9(1):69.
18. Wang YY, Liu ZZ, Xu D, Liu M, Wang K, Xing BC. Fibrinogen–Albumin Ratio Index (FARI): A More Promising Inflammation-Based Prognostic Marker for Patients Undergoing Hepatectomy for Colorectal Liver Metastases. Ann Surg Oncol. 2019;26(11):3682–3692. doi:10.1245/s10434-019-07586-3
19. Galdiero MR, Marone G, Mantovani A. Cancer Inflammation and Cytokines. Cold Spring Harb Perspect Biol. 2018;10(8):a028662.
20. Ojerholm E, Smith A, Hwang WT, et al. Neutrophil-to-lymphocyte ratio as a bladder cancer biomarker: assessing prognostic and predictive value in SWOG 8710. Cancer. 2017;123(5):794–801. doi:10.1002/cncr.30422
21. Chan JC, Chan DL, Diakos CI, et al. The Lymphocyte-to-Monocyte Ratio is a Superior Predictor of Overall Survival in Comparison to Established Biomarkers of Resectable Colorectal Cancer. Ann Surg. 2017;265(3):539–546. doi:10.1097/SLA.0000000000001743
22. Krenn-Pilko S, Langsenlehner U, Thurner EM, et al. The elevated preoperative platelet-to-lymphocyte ratio predicts poor prognosis in breast cancer patients. Br J Cancer. 2014;110(10):2524–2530. doi:10.1038/bjc.2014.163
23. Hu B, Yang XR, Xu Y, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res. 2014;20(23):6212–6222. doi:10.1158/1158-8341.CCR-14-0442
24. Hsueh SW, Liu KH, Hung CY, et al. Significance of the Glasgow Prognostic Score in Predicting the Postoperative Outcome of Patients with Stage III Gastric Cancer. J Clin Med. 2019;8(9):1448. doi:10.3390/jcm8091448
25. Perisanidis C, Pyarri A, Cohen EE, et al. Prognostic role of pretreatment plasma fibrinogen in patients with solid tumors: A systematic review and meta-analysis. Cancer Treat Rev. 2015;41(10):960–970. doi:10.1016/j.ctrv.2015.10.002
26. Smith CA, Kachnic LA. Evolving Treatment Paradigm in the Treatment of Locally Advanced Rectal Cancer. J National Comprehens Cancer Network. 2018;16(7):909–915. doi:10.6004/jnccn.2018.7032
27. Cho IR, Park JC, Park CH, et al. Pre-treatment neutrophil to lymphocyte ratio as a prognostic marker to predict chemotherapeutic response and survival outcomes in metastatic advanced gastric cancer. Gastric Cancer. 2014;17(4):703–710. doi:10.1007/s10120-013-0330-2
28. You X, Zhou Q, Song J, Gan L, Chen J, Shen H. Preoperative albumin-to-fibrinogen ratio predicts severe postoperative complications in elderly gastric cancer subjects after radical laparoscopic gastrectomy. BMC Cancer. 2019;19(1):931. doi:10.1186/s12885-019-1463-4
29. Wu M, Pan Y, Jia Z, et al. Preoperative Plasma Fibrinogen and Serum Albumin Score Is An Independent Prognostic Factor for Resectable Stage II-III Gastric Cancer. Dis Markers. 2019;2019:9060845. doi:10.1155/2019/9060845
30. Li SQ, Jiang YH, Lin J, et al. Albumin-to-fibrinogen ratio as a promising biomarker to predict clinical outcome of non-small cell lung cancer individuals. Cancer Med. 2018;7(4):1231–1231. doi:10.1002/cam4.1428
Lu et al

31. Sun F, Tan YA, Gao QF, et al. Circulating fibrinogen to pre-albumin ratio is a promising biomarker for diagnosis of colorectal cancer. J Clin Lab Anal. 2019;33(1):e22635. doi:10.1002/jcla.22635

32. Xu W-Y, Zhang -H-H, Xiong J-P, et al. Prognostic significance of the fibrinogen-to-albumin ratio in gallbladder cancer patients. World J Gastroenterol. 2018;24(29):3281. doi:10.3748/wjg.v24.i29.3281

33. Wang Y, Chen W, Hu C, et al. Albumin and fibrinogen combined prognostic grade predicts prognosis of patients with prostate cancer. J Cancer. 2017;8(19):3992. doi:10.7150/jca.21061

34. Hwang J-T, Chung JK, Rob EY, et al. Prognostic influence of preoperative fibrinogen to albumin ratio for breast cancer. J Breast Cancer. 2017;20(3):254–263. doi:10.4048/jbc.2017.20.3.254

35. Xu Q, Yan Y, Gu S, et al. A Novel Inflammation-Based Prognostic Score: the Fibrinogen/Albumin Ratio Predicts Prognoses of Patients after Curative Resection for Hepatocellular Carcinoma. J Immunol Res. 2018:4925498. doi:10.1155/2018/4925498

36. Vecchio FM, Valentini V, Minsky BD, et al. The relationship of pathologic tumor regression grade (TRG) and outcomes after preoperative therapy in rectal cancer. Int J Radiat Oncol Biol Phys. 2005;62(3):752–760. doi:10.1016/j.ijrobp.2004.11.017

37. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol. 2010;17(6):1471–1474. doi:10.1245/s10434-010-0985-4

38. Kim SH, Chang HJ, Kim DY, et al. What Is the Ideal Tumor Regression Grading System in Rectal Cancer Patients after Preoperative Chemoradiotherapy? Cancer Res Treatment. 2016;48(3):998–1009. doi:10.4134/crt.2015.254

39. Fokas E, Strobel P, Fietkau R, et al. Tumor Regression Grading After Preoperative Chemoradiotherapy as a Prognostic Factor and Individual-Level Surrogate for Disease-Free Survival in Rectal Cancer. J Natl Cancer Inst. 2017;109(12):12. doi:10.1093/jnci/djx095

40. Hardiman KM, Ulitzn PJ, Kuczick RD, et al. Intra-tumor genetic heterogeneity in rectal cancer. Lab Invest. 2016;96(1):4–15. doi:10.1038/labinvest.2015.131

41. Glynn-Jones R, Wyrwicz L, Tiret E, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29(Suppl 4):iv263. doi:10.1093/annonc/mdy161

42. Simpson-Haidaris P, Rybarczyk B. Tumors and fibrinogen: the role of fibrinogen as an extracellular matrix protein. Ann N Y Acad Sci. 2001;936(1):406–425. doi:10.1111/j.1749-6632.2001.tb03525.x

43. Sahni A, Simpson-Haidaris P, Sahni S, Vadav G, Francis C. Fibrinogen synthesized by cancer cells augments the proliferative effect of fibroblast growth factor-2 (FGF-2). J Thrombosis Haemostasis. 2008;6(1):176–183. doi:10.1111/j.1538-7836.2007.02808.x

44. Sahni A, Khorana AA, Baggs RB, Peng H, Francis CW. FGF-2 binding to fibrin (ogen) is required for augmented angiogenesis. Blood. 2006;107(1):126–131. doi:10.1182/blood-2005-06-2460

45. Yeun JY, Kaysen GA. Factors influencing serum albumin in dialysis patients. Am J Kidney Dis. 1998;32(6):S118–S125. doi:10.1016/S0272-6386(98)70174-X

46. Van Cutsem E, Arends J. The causes and consequences of cancer-associated malnutrition. Eur J Oncol Nurs. 2005;9:S51–S63. doi:10.1016/j.ejon.2005.09.007

47. Chen J-H, Zhai E-T, Yuan Y-J, et al. Systemic immune-inflammation index for predicting prognosis of colorectal cancer. World J Gastroenterol. 2017;23(34):6261. doi:10.3748/wjg.v23.i34.6261

48. Meng X, Chang Q, Liu Y, et al. Determinant roles of gender and age on SII, PLR, NLR, LMR and MLR and their reference intervals defining in Henan, China: A posteriori and big-data-based. J Clin Lab Anal. 2018;32(2):e22228. doi:10.1002/jcla.22228

49. Zhou Z-Q, Pang S, Yu X-C, et al. Predictive values of postoperative and dynamic changes of inflammation indexes in survival of patients with resected colorectal cancer. Current Med Sci. 2018;38(5):798–808. doi:10.1007/s11596-018-1946-6

50. Ryan J, Warrier S, Lynch AC, Heriot AG. Assessing pathological complete response to neoadjuvant chemoradiotherapy in locally advanced rectal cancer: a systematic review. Colorectal Dis. 2015;17(10):849–861. doi:10.1111/codi.13081

51. Trakarnsanga A, Gönen M, Shia J, et al. Comparison of tumor regression grade systems for locally advanced rectal cancer after multimodality treatment. JNCI. 2014;106(10):. doi:10.1093/jnci/dju248

52. Dhadda A, Dickinson P, Zaitoun A, Gandhi N, Bessell E. Prognostic importance of Mandurum tumour regression grade following pre-operative chemo/radiotherapy for locally advanced rectal cancer. Eur J Cancer. 2011;47(8):1318–1145. doi:10.1016/j.ejca.2010.12.006

53. Peng Y-F, Yu W-D, Pan H-D, et al. Tumor regression grades: potential outcome predictor of locally advanced rectal adenocarcinoma after preoperative radiotherapy. World J Gastroenterol. 2015;21(6):1851. doi:10.3748/wjg.v21.i6.1851

54. Dreyer SB, Powell AG, McSorley ST, et al. The Pretreatment Systemic Inflammatory Response is an Important Determinant of Poor Pathologic Response for Patients Undergoing Neoadjuvant Therapy for Rectal Cancer. Ann Surg Oncol. 2017;24(5):1295–1303. doi:10.1245/s10434-016-5684-3

55. Lee YJ, Kim WR, Han J, et al. Prognostic impact of immunonutritional status changes during preoperative chemoradiation in patients with rectal cancer. Ann Coloproctol. 2016;32(6):208. doi:10.3393/ac.2016.32.6.208

56. Sun F, Peng HX, Gao QF, et al. Preoperative circulating FPR and CCF score are promising biomarkers for predicting clinical outcome of stage II-III colorectal cancer patients. Cancer Manag Res. 2018;10:2151–2161. doi:10.2147/CMAR.S167398

57. Gao QF, Qiu JC, Huang XH, et al. The predictive and prognostic role of a novel ADS score in esophageal squamous cell carcinoma patients undergoing esophagectomy. Cancer Cell Int. 2018;18:153. doi:10.1186/s12935-018-0648-2