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ORIGINAL RESEARCH

Pretreatment Albumin-to-Fibrinogen Ratio Independently Predicts Chemotherapy Response and Prognosis in Patients with Locally Advanced Rectal Cancer Undergoing Total Mesorectal Excision After Neoadjuvant Chemoradiotherapy

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Background: Neoadjuvant chemoradiotherapy (nCRT) followed by surgery of total mesorectal excision (TME) is currently accepted as the standard treatment for locally advanced rectal cancer (LARC). This study aimed to investigate the potential prognostic factors, including the albumin-to-fibrinogen ratio (AFR) for LARC patients.

Methods: We retrospectively recruited LARC patients (cT3-4 and/or cN1-2) who underwent nCRT followed by TME between January 2011 and January 2015. The cut-off value of pretreatment AFR for overall survival (OS) was determined by the receiver operating characteristic (ROC) curve. The potential predictive factors for prognosis in the LARC patients were assessed by the univariate and multivariate Cox's proportional hazard regression and Kaplan–Meier curve analyses.

Results: AFR was a significant predictor for OS with a cut-off value of 8.65 and an AUC of 0.882 (P<0.001). The pretreatment AFR level was the only independent risk factor for pathologic response to nCRT (HR: 2.44, 95% CI: 1.43–4.17, P=0.003), 5-year OS (HR: 3.31, 95% CI: 1.51–6.77, P=0.005) and disease-free survival (DFS) (HR: 2.73, 95% CI: 1.34–5.47, P=0.007) in LARC patients. A low pretreatment AFR level was significantly associated with a poor 5-year OS and DFS by the Log rank test (P=0.003 and 0.006, respectively).

Conclusion: Pretreatment AFR level was an independent prognostic factor in LARC patients undergoing TME after nCRT.

Keywords: locally advanced rectal cancer, total mesorectal excision, neoadjuvant chemoradiotherapy, prognosis, albumin-to-fibrinogen ratio

Introduction

Colorectal cancer (CRC), is the third most commonly diagnosed cancer and the second leading cause of cancer-related death in both sexes combined worldwide.[1] According to GLOBOCAN reports, there were over 1.8 million new CRC cases and 881,000 CRC-related deaths in 2018, accounting for almost 10% of cancer cases and deaths.[1] Rectal cancer (RC) approximately accounts for 30% of CRC and has a worse clinical prognosis.[2] To improve tumor resectability, preserve anal sphincter, and localize tumor for locally advanced rectal cancer (LARC)

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patients, neoadjuvant chemoradiotherapy (nCRT) followed by surgery of total mesorectal excision (TME) is currently accepted as the standard treatment.[3,4] The prognosis and survival rates of the LARC patients with nCRT have significantly improved.[5] However, the clinical efficacy differs significantly in different patients due to personal heterogeneity. Thus, to investigate the effective predictors and design individualized treatment for LARC patients is of great clinical meaning.

Accumulating evidence has indicated that the host factors, including the status of nutrition, inflammation, and immune system, are significantly associated with the prognosis in patients with malignancies as well as tumor characteristics.[6,7] Albumin (Alb), and fibrinogen (Fib) are two widely used inflammatory markers and they are both accepted as potential prognostic factors in various malignancies, eg, lung cancer,[8] gastric cancer,[9] and colon cancer.[10] Alb-to-Fib ratio (AFR), which is calculated based on Alb and Fib concentrations, has also been reported as a prognostic parameter in various malignancies.[11,12] However, whether AFR could serve as a predictor for treatment response and survival in LARC patients undergoing nCRT remains unclear. This study aimed to investigate potential prognostic factors (including AFR) for LARC patients.

Patients and Methods

Patients

This single-center retrospective study was approved by the Medical Institutional Ethics Committee of our hospital (approval number: KY200901103). We retrospectively recruited LARC patients (cT3-4 and/or cN1-2) who underwent nCRT followed by TME at the Department of Oncology and General Surgery, Taizhou Peoples' Hospital between January 2009 and January 2016. All enrolled patients were required to offer the signed informed consent for nCRT and operations. The inclusion criteria were as follows: (a) aged between 18 and 75 years; (b) histologically diagnosed with LARC within 12 cm from the anal verge; (c) with the imaging results of abdominal and pelvic computed tomography (CT) or PET-CT, pelvic magnetic resonance imaging (MRI); and (d) undergoing TME after nCRT. The exclusion criteria were as follows: (a) with distant metastasis; (b) combined with hepatic, kidney, or hematological disorders; (c) with autoimmune diseases, acute infections, or other malignancies; (d) with molecular targeted drugs therapy; (e) who did not finish the nCRT due to adverse reactions; and (f) with incomplete data or lost to follow-up. This study was conducted in accordance with the Declaration of Helsinki.

Treatment and Follow-Up

Before the start of nCRT, all enrolled patients received the pathological diagnosis by rectal biopsy. The nCRT protocols, surgical procedures, and follow-ups were performed according to the latest Chinese Guidelines for the diagnosis and treatment of colorectal cancer (2009, 2015). In brief, preoperative radiotherapy was administered to the area of the pelvic region (radiation dose: 45.0–50.4 Gy, 1.8–2.0 Gy per time, 5 times per week, for 25–28 times). During the radiotherapy, chemotherapy was concomitantly performed. FOLFOX or XELOX was the general chemotherapy regimen with a duration of 2–3 months and 6–12 weeks after the completion of nCRT, TME was performed as the standard surgical procedure. Based on the guidelines, the postoperative 5-year follow-up was performed every 3 months within the first 2 years, and every 6 months in the following 3 years.

Pathologic Response to nCRT

As described by previous reports by Mandard et al[13], the pathologic response to nCRT was evaluated using five tumor regression grades (TRG1–5). In brief, TRG1 (complete regression): absence of residual cancer and fibrosis; TRG2: presence of rare residual cancer cells scattered through the fibrosis; TRG3: increased number of residual cancer cells, but fibrosis predominated; TRG4: residual cancer outgrowing fibrosis; and TRG5: absence of regressive changes. A good pathologic response to nCRT was defined as TRG1-3, while a poor pathologic response was defined as TRG4-5.

Prognosis Evaluation

All the enrolled patients were followed-up until death or over a period of 5 years. Locoregional recurrence was defined as the tumor recurrence of lymphatic vessels, anastomosis, or adjacent organs. Distant metastasis was defined as the tumor spread outside the pelvic cavity. Disease-free survival (DFS) was calculated from the day of initial nCRT beginning to the disease progression (distant metastasis, or locoregional recurrence), death or the 5-year follow-up. Overall survival (OS) was calculated from the day of initial nCRT beginning to death or the 5-year follow up.

Data Collection

The demographics and clinicopathological characteristics of the enrolled patients were collected, including the age, gender, body mass index (BMI), pretreatment comorbidities (hypertension, diabetes), habits of smoking and drinking, distance from anal verge, clinical T and N stage before nCRT, lymph vascular invasion, perineural invasion, pathologic differentiation, and postoperative TNM stage. The TNM stage was verified based on the CRC TNM Staging System by the American Joint Committee on Cancer/International Union Against Cancer (7th edition). The treatment-related parameters including radiotherapy dose, operation type, operation time and estimated blood loss were also recorded. The tumor mutational status including KRAS, BRAF, and mismatch repair (MMR) were also recorded. As described in previous reports, if one or more of the four proteins (MLH1, PMS2, MSH2, and MSH6) in the tumor epithelial cell nuclei was defective, the patients were identified as defective MMR (dMMR). If all the proteins were positive, then the patients were identified as proficient MMR (pMMR).

Laboratory Tests

Fasting blood samples of all the enrolled patients were obtained on 1 day before nCRT initiation. Blood cell and biochemical analyses including hemoglobin (Hb), white blood cell (WBC), hematocrit (Hct), C-reactive protein (CRP), creatinine, urea, Alb, and Fib were detected in the laboratory of our hospital using the blood samples obtained from them. AFR was calculated as Alb (g/L) divided by Fib (g/L).

Statistical Analysis

The statistical analysis was performed with SPSS 19.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism 8.0 (GraphPad Inc., CA, USA). Categorical and quantitative data were expressed as number (n) with percentage (%) and mean levels with standard deviation (SD) as appropriate. Chi-square test, Student's *t*-test, and Mann–Whitney *U*-test were used for data analysis as appropriate. The receiver operating characteristic (ROC) curve was plotted to identify the cut-off value of the pretreatment AFR for OS. The univariate and multivariate Cox's proportional hazard regression analyses were performed to investigate the risk factors for pathologic response to nCRT, 5-year OS and DFS. The Kaplan–Meier curve analyses were performed to identify the association between the pretreatment AFR and 5-year OS and DFS. A two-sided P value <0.05 was accepted as statistically different.

Results

Patient Characteristics

The flowchart of this study is shown in Figure 1. According to the inclusion criteria, 378 patients were initially enrolled and 58 were excluded on the basis of the exclusion criteria (8 with distant metastasis, 10 combined with hepatic, kidney, or hematological disorders, 10 with autoimmune diseases, infections, or other malignancies, 5 with molecular-targeted drugs therapy, and 20 with incomplete data or lost to follow-up). As a result, 320 LARC patients who underwent TME after nCRT were included in this retrospective study. To identify the cut-off value of pretreatment AFR for OS, ROC curve analysis was conducted. As shown in Figure 2, AFR was a significant predictor for OS with a cut-off value of 8.65, an AUC of 0.882, a sensitivity of 80.68%, a specificity of 80.53% (95% CI: 0.844–0.920, P<0.001). Based on the cut-off value, the enrolled patients were categorized into two groups, the high AFR group (≥8.65, n=131) and the low AFR (<8.65, n=189) group. The detailed demographics and clinicopathological characteristics are summarized in Table 1. The median age was 54 years and male patients occupied 70.3% (225/320). The differences in clinicopathological characteristics were compared between the low and high AFR groups (Table 1). The patients in low the AFR group had a higher rate of elderly (≥65 years) patients (P=0.022), a higher Charlson Comorbidity Index (P=0.008), comorbidity of hypertension (P=0.038), and positive lymph vascular invasion (P=0.032) than those in the high AFR group. Moreover, the low AFR group was associated with a poorer (or mucinous) pathologic differentiation (P=0.021), a higher pathological TNM stage (P=0.021), and a poorer pathologic response to nCRT (TRG4-5). No statistical differences were observed with respect to gender, BMI, diabetes, habits of smoking and drinking, distance from anal verge, cT and cN stage before nCRT, perineural invasion, radiotherapy dose, operation type, operation time and estimated blood loss between the patients with high and low AFR (P>0.05). Table 2 lists the laboratory tests associated with AFR in the LARC patients. Patients in the low AFR group had a higher rate of elevated CRP level (>0.8mg/L)

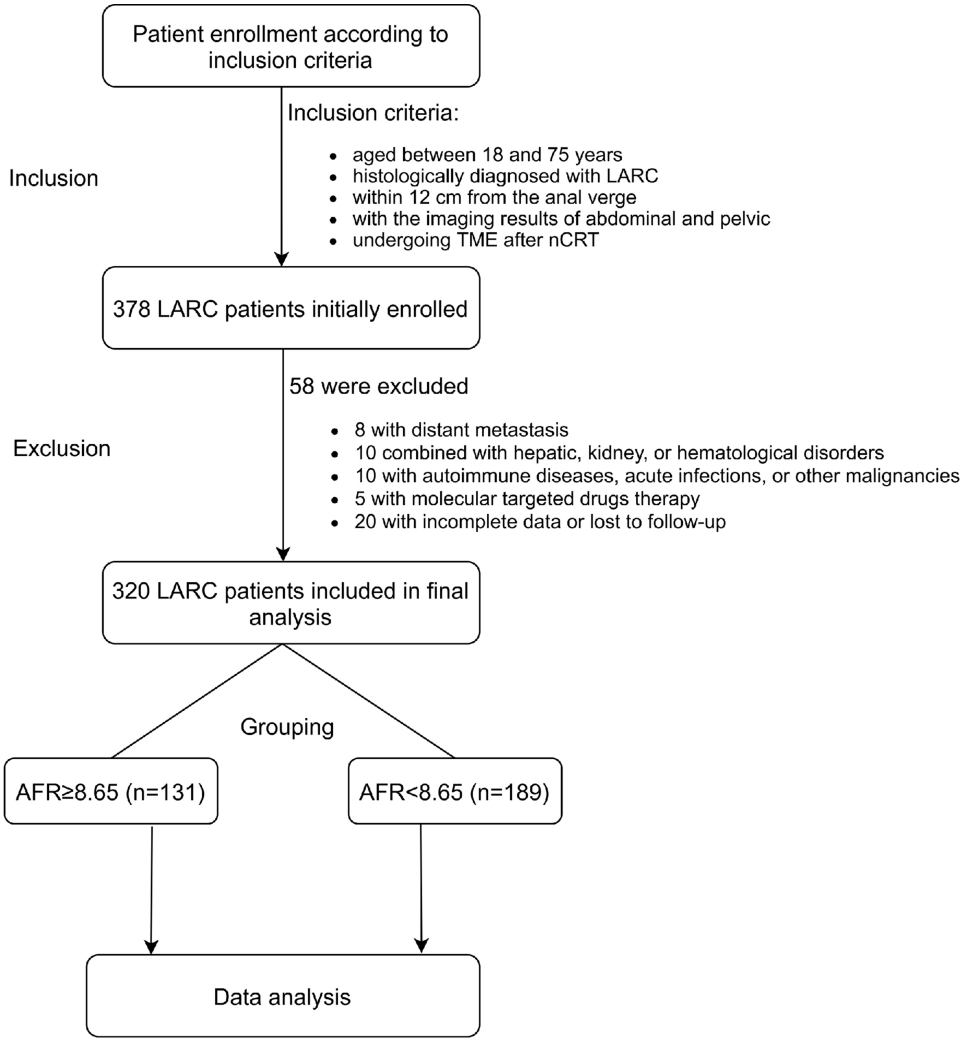

Figure 1 The flowchart of patient inclusion and exclusion.
Abbreviations: LARC, locally advanced rectal cancer; TME, total mesorectal excision; nCRT, neoadjuvant chemoradiotherapy; AFR, albumin-to-fibrinogen ratio.

in comparison with those in the high AFR group (P=0.008).

Risk Factors for Pathologic Response to nCRT, 5-Year OS and DFS

To investigate potential prognostic factors for LARC patients, we choose pathologic response to nCRT, 5-year OS and DFS as the observational endpoints. As illustrated in Table 3, lymph vascular invasion (HR: 2.15, 95% CI: 1.03–4.37, P=0.019) and pretreatment AFR (<8.65 vs ≥8.65) (HR: 2.44, 95% CI: 1.43–4.17, P=0.003) were two independent risk factors for TRG4-5 (poor pathological response) by univariate and multivariate Cox regression analyses. Moreover, lymph vascular invasion (HR: 0.46, 95% CI: 0.33–0.61, P=0.023) and pretreatment AFR (HR: 0.39, 95% CI: 0.21–0.62, P=0.009) were also risk factors for TRG1 (complete response, see Table 4). In addition, age (<65 vs ≥65) (HR: 2.42, 95% CI: 1.10–5.32, P=0.029), pathologic differentiation (well/moderate vs poor/mucinous) (HR: 2.83, 95% CI: 1.44–7.33, P=0.018) and pretreatment AFR (≥8.65 vs <8.65) (HR: 3.31, 95% CI: 1.51–6.77, P=0.005) were the three independent predictors for 5-year OS in LARC patients undergoing TME after nCRT (see Table 5). Furthermore, pretreatment AFR (≥8.65 vs <8.65) (HR: 2.73, 95% CI: 1.34–5.47, P=0.007) and CEA (<5 vs ≥5) (HR: 1.73, 95% CI: 1.12–2.66, P=0.034) were two significant factors for 5-year DFS, which is shown in Table 6.

Pretreatment AFR Associated with 5-Year OS and DFS

To further identify the association between pretreatment AFR and survival in LARC patients, Kaplan–Meier curve

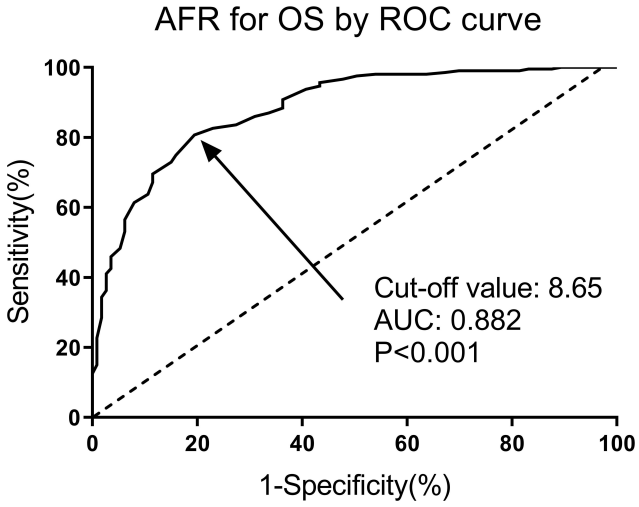

Figure 2 Predictive and cut-off value of AFR for OS in LARC patients by ROC curve. AFR was a significant predictor for OS with a cut-off value of 8.65, an AUC of 0.882, a sensitivity of 80.68%, a specificity of 80.53% (95% CI: 0.844–0.920, P<0.001).

Abbreviations: AFR, albumin-to-fibrinogen ratio; OS, overall survival; LARC, locally advanced rectal cancer; ROC, receiver operating characteristic; AUC, area under the curve, CI, confidence interval.

analyses were performed. As shown in Figure 3A and B, the results indicated that a low pretreatment AFR level was significantly associated with a poor 5-year OS and DFS by Log rank test (P=0.003 and 0.006, respectively).

Tumor Mutational Status, AFR and Oncologic Outcomes

We also evaluated the status of tumor mutational status, AFR and oncologic outcomes in 248 patients with complete mutational data. As shown in Table 7, no significant association between tumor mutational status (KRAS, BRAF, and MMR) and AFR was observed (P>0.05). In addition, the mutational status was also not significantly associated with 5-year OS (see Figure 4A–C, P>0.05).

Discussion

Our findings firstly indicated that pretreatment AFR was an independent prognostic factor for the LARC patients undergoing TME after nCRT. In this study, three observational endpoints including pathologic response to nCRT, 5-year OS and DFS were set for prognosis evaluation. Our univariate and multivariate Cox proportional hazard regression analyses revealed different risk factors for different endpoints (eg, age, pathologic differentiation, and pretreatment AFR for 5-year OS). However, our results only supported the pretreatment AFR level as the only

Table 1 Clinicopathological Variables Associated with AFR in LARC Patients

Variables	AFR		*P*-value
	≥8.65	<8.65	
Number, n (%)	131(40.9)	189(59.1)	–
Age (year), n (%)	–	–	0.022*
≥65	70(53.4)	125(66.1)	-
<65	61(46.6)	64(33.9)	-
Gender, n (%)	–	–	0.774
Male	89(67.9)	136(72.0)	–
Female	42(32.1)	53(28.0)	–
BMI (kg/m^2), n (%)	–	–	0.610
≥24.5	26(19.8)	42(22.2)	–
<24.5	105(80.1)	147(77.8)	–
Charlson Comorbidity Index	3.5±0.6	3.6±0.7	0.184
Comorbidities, n (%)	–	–	–
Hypertension	16(12.2)	40(21.2)	0.038*
Diabetes	12(9.2)	24(12.7)	0.325
Active smoker, n (%)	19(14.5)	30(15.9)	0.748
Heavy drinker, n (%)	13(9.9)	24(12.7)	0.445
Serum CEA (ng/mL), n (%)	–	–	0.222
≥5	63(48.1)	104(55.0)	–
<5	68(51.9)	85(45.0)	–
Distance from anal verge (cm), n (%)	–	–	0.471
≥5	52(39.7)	80(42.3)	–
<5	79(60.3)	109(57.7)	–
cT stage before nCRT, n (%)	–	–	0.811
cT3	53(40.5)	79(41.8)	–
cT4	78(59.5)	110(58.2)	–
cN stage before nCRT, n (%)	–	–	0.796
Negative	76(58.0)	98(51.9)	-
Positive	55(42.0)	91(48.1)	-
Lymph vascular invasion, n (%)	–	–	0.032*
Negative	112(85.5)	143(75.7)	–
Positive	19(14.5)	46(24.3)	–
Perineural invasion, n (%)	–	–	0.607
Negative	109(83.2)	153(81.0)	-
Positive	22(16.8)	36(19.0)	-
Pathologic differentiation, n (%)	–	–	0.021*
Well/moderate	114(87.0)	144(76.2)	-
Poor/mucinous	17(13.0)	45(23.8)	-

(*Continued*)

Table 1 (Continued).

Variables	AFR		*P*-value
	≥8.65	<8.65	
Pathological TNM stage, n (%)	–	–	0.021*
II	67(59.3)	72(38.1)	-
III	64(40.7)	117(61.9)	-
Chemotherapy regimens, n (%)	–	–	0.660
XELOX	73(55.7)	110(58.2)	–
FOLFOX	58(44.3)	79(41.8)	–
Radiotherapy dose (Gy), n (%)	–	–	0.381
≥50 Gy	74(56.5)	116(61.4)	–
<50 Gy	57(43.5)	73(38.6)	–
Operation type, n (%)	–	–	0.293
Laparotomy	26(19.8)	47(24.9)	–
Laparoscopic	105(80.2)	142(75.1)	–
Operation time (min)	162.1±33.8	157.3±40.1	0.263
Estimated blood loss (mL)	118.2±57.2	111.7±60.8	0.336
Pathologic response, n (%)	–	–	0.011*
TRG1-3	82(62.6)	91(48.1)	–
TRG4-5	49(37.4)	98(51.9)	–

Note: *P value<0.05.
Abbreviations: AFR, albumin-to-fibrinogen ratio; LARC, locally advanced rectal cancer; BMI, body mass index; nCRT, neoadjuvant chemoradiotherapy; CEA, carcinoembryonic antigen.

independent risk factor for pathologic response to nCRT, 5-year OS and DFS.

The specific mechanism for the prognostic role of AFR predicting cancer prognosis remains incomplete in terms of clarity. Fib, an important protein in the maintenance of hemostasis, is also widely reported to be an acute-phase protein that is involved in inflammatory responses.[14] Moreover, the synthesis of Fib can be regulated by several inflammatory cytokines, including interleukin-1 (IL-1) and IL-6.[15] There is increasing evidence that an elevated Fib level can serve as a strong predictor for unfavorable outcomes in some types of cancers, such as epithelial ovarian cancer[16] and pancreatic cancer.[17] The frequently observed elevated Fib level in patients with multiple cancers is related to unfavorable prognoses.[18,19] In cancer patients, elevated Fib expression due to the abnormally activated coagulation system can possess anti-cancer properties combined with sodium selenite.[20] In addition, Fib can regulate the growth of tumor cells by binding to various growth factors,[21] and enhance cell invasion, migration, and metastasis via epithelial–mesenchymal transition.[22] Furthermore, Fib can also participate in tumor progression by involving in angiogenesis.[23]

Table 2 Laboratory Tests Associated with AFR in LARC Patients

Variables	AFR		*P*-value
	≥8.65	<8.65	
Number, n (%)	131(40.9)	189(59.1)	–
Hb (g/L)	111.4±8.2	112.1±7.5	0.430
WBC (x10^9/L)	7.7±2.4	7.4±2.1	0.237
Hct	0.40±0.08	0.41±0.07	0.237
Creatinine(umol/L)	75.2±10.3	73.9±13.1	0.343
Urea(mmol/L)	5.8±1.5	5.9±1.3	0.526
CRP (mg/L), n (%)	–	–	0.008*
>0.8	39(29.8)	84(44.4)	–
≤0.8	92(70.2)	105(55.6)	–

Note: *P value<0.05.
Abbreviations: AFR, albumin-to-fibrinogen ratio; LAFR, locally advanced rectal cancer; Hb, hemoglobin; Alb, albumin; WBC, white blood cell; Hct, hematocrit; CRP, C-reactive protein.

Alb, a well-established nutritional biomarker, is also an acute-phase protein in response to systemic inflammation.[14] The synthesis of Alb in hepatocytes can be significantly affected by proinflammatory cytokines released by inflammatory cells or tumor tissues, eg IL-4, and IL-6, resulting in decreased Alb expression.[24] A previous study of 431 CRC patients identified that serum Alb expression was a reliable prognostic factor for overall survival.[25] A low serum Alb level usually heralds the status of malnutrition, which indicates the weakness of the immune system in patients.[26] In addition, decreased serum Alb correlates to an enhanced inflammatory response to cancers and increased release of various cancer-related cytokines involved in tumor development.[27]

AFR, which combines these two biomarkers, has attracted a lot of attention in recent decades. Recently, accumulating evidence has verified the prognostic value of AFR in various diseases, including peritonitis-induced sepsis,[28] non-small-cell lung cancer after platinum-based chemotherapy,[29] and advanced epithelial ovarian cancer.[30] In addition, some other biomarkers reflecting systematic inflammatory status, such as CRP, and neutrophil-to-lymphocyte ratio (NLR), have also shown prognostic values in malignancies.[31] It has been well established that inflammation can promote carcinogenesis and increase the risk of cancer development, including CRC.[32] Moreover, regular non-steroidal anti-inflammatory drugs are associated with a decreased risk of CRC.[33]

Table 3 Risk Factors Associated with Poor Pathological Response (TRG4-5) in LARC Patients Undergoing nCRT by Univariate and Multivariate Cox Proportional Hazards Analyses

Variables	Univariate		Multivariate	
	HR(95% CI)	*P* value	HR(95% CI)	*P* value
Pathologic differentiation (poor/mucinous vs well/moderate)	2.20(1.39–3.11)	0.037*	1.41(0.91–2.16)	0.091
Lymph vascular invasion (positive vs negative)	2.02(1.33–3.13)	0.009*	2.15(1.03–4.37)	0.019*
TNM stage (III vs II)	1.53 (1.01–2.37)	0.039*	1.21(0.71–2.05)	0.413
AFR (<8.65 vs ≥8.65)	2.78(1.79–4.32)	0.001*	2.44(1.43–4.17)	0.003*
CRP (≥0.8 vs <0.8)	1.86(1.06–3.36)	0.029*	1.03(0.64–1.63)	0.824

Note: *$P<0.05$.
Abbreviations: TRG, tumor regression grade; AFR, albumin-to-fibrinogen ratio; LARC, locally advanced rectal cancer; nCRT, neoadjuvant chemoradiotherapy; CRP, C-reactive protein; HR, hazard ratio; CI, confidence interval.

Table 4 Risk Factors Associated with Complete Response (TRG1) in LARC Patients Undergoing nCRT by Univariate and Multivariate Cox Proportional Hazards Analyses

Variables	Univariate		Multivariate	
	HR(95% CI)	*P* value	HR(95% CI)	*P* value
Pathologic differentiation (poor/mucinous vs well/moderate)	0.50(0.28–0.91)	0.027*	0.59(0.35–1.01)	0.587
Lymph vascular invasion (positive vs negative)	0.42(0.23–0.60)	0.011*	0.46(0.33–0.61)	0.023*
TNM stage (III vs II)	0.35(0.09–0.82)	0.041*	0.87(0.42–1.74)	0.713
AFR (<8.65 vs ≥8.65)	0.31(0.12–0.71)	0.005*	0.39(0.21–0.62)	0.009*

Note: *$P<0.05$.
Abbreviations: TRG, tumor regression grade; AFR, albumin-to-fibrinogen ratio; LARC, locally advanced rectal cancer; nCRT, neoadjuvant chemoradiotherapy; HR, hazard ratio; CI, confidence interval.

Table 5 Risk Factors Associated with 5-Year OS in LARC Patients by Univariate and Multivariate Cox Proportional Hazards Analyses

Variables	Univariate		Multivariate	
	HR(95% CI)	*P* value	HR(95% CI)	*P* value
Age (<65 vs ≥65)	3.31(1.46–7.41)	0.007*	2.42(1.10–5.32)	0.029*
Pathologic differentiation (well/moderate vs poor/mucinous)	3.91(1.51–9.12)	0.011*	2.83(1.44–7.33)	0.018*
Lymph vascular invasion (negative vs positive)	2.96(1.51–5.76)	0.003*	1.93(0.88–4.31)	0.098
TNM stage (II vs III)	2.43(1.47–4.17)	0.012*	1.99(0.91–4.39)	0.089
AFR (≥8.65 vs <8.65)	3.47(1.55–7.67)	0.002*	3.31(1.51–6.77)	0.005*

Note: *$P<0.05$.
Abbreviations: OS, overall survival; AFR, albumin-to-fibrinogen ratio; LARC, locally advanced rectal cancer; HR, hazard ratio; CI, confidence interval.

Table 6 Risk Factors Associated with 5-Year DFS in LARC Patients by Univariate and Multivariate Cox Proportional Hazards Analyses

Variables	Univariate		Multivariate	
	HR(95% CI)	*P* value	HR(95% CI)	*P* value
Age (<65 vs ≥65)	1.74(1.05–2.91)	0.032*	1.27(0.62–2.56)	0.473
Pathologic differentiation (well/moderate vs poor/mucinous)	2.78(1.31–5.67)	0.019*	1.69(0.76–3.69)	0.191
AFR (≥8.65 vs <8.65)	2.97(1.52–5.68)	0.001*	2.73(1.34–5.47)	0.007*
CEA (<5 vs ≥5)	2.45(1.43–4.19)	0.011*	1.73(1.12–2.66)	0.034*

Note: *$P<0.05$.
Abbreviations: DFS, disease-free survival; AFR, albumin-to-fibrinogen ratio; LARC, locally advanced rectal cancer; CEA, carcinoembryonic antigen; HR, hazard ratio; CI, confidence interval.

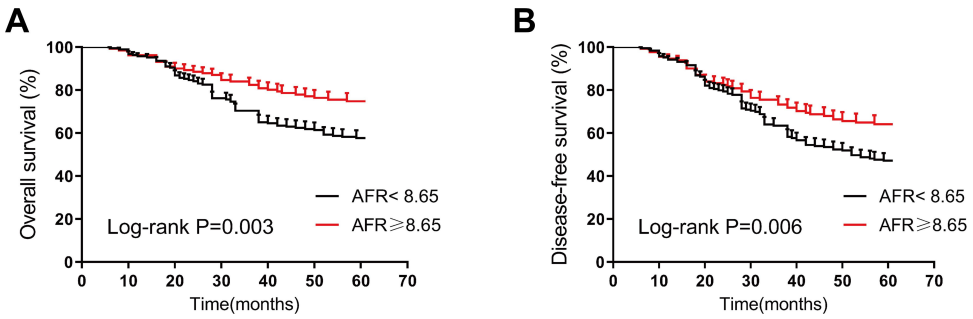

Figure 3 Overall survival (**A**) and disease-free survival (**B**) stratified by AFR in LARC patients by Kaplan–Meier curve analyses. A low pretreatment AFR (<8.65) was significantly associated with a poor overall survival (P=0.003) and disease-free survival (P=0.006) by Log rank test.
Abbreviations: AFR, albumin-to-fibrinogen ratio; LARC, locally advanced rectal cancer.

The complicated and close correlation between inflammation and tumors might be a possible explanation for the prognostic role of AFR in LARC patients. A previous study by Shen et al revealed baseline NLR (≥2.8) as a prognostic factor for LARC patients undergoing nCRT.[34] A clinical trial by Dudani et al reported that NLR and platelet-to-lymphocyte ratio (PLR) are two useful predictive and prognostic markers in LARC patients.[35] However, some other studies did not indicate a significant association between NLR, PLR and outcomes in LARC patients.[36,37] A recent meta-analysis by Jin et al indicated lymph node ratio (LNR) as an independent prognostic factor for RC patients after nCRT.[38] A multi-institutional study on 965 LARC patients undergoing nCRT indicated elevated platelet count as a negative predictive and prognostic marker.[39] To our knowledge, this study firstly highlighted AFR as an independent risk factor for both pathological response for nCRT and prognosis in LARC patients.

Table 7 KRAS, BRAF and MMR Status Associated with AFR in LARC Patients

Variables	AFR		*P*-value
	≥8.65	<8.65	
Number, n (%)	97(39.1)	151(60.9)	–
KRAS, n (%)	–	–	0.21
Wild type	63(64.9)	86(57.0)	-
Mutated	34(35.1)	65(43.0)	-
BRAF (V600E), n (%)	–	–	0.74
Wild type	91(93.8)	140(92.7)	–
Mutated	6(6.2)	11(7.3)	–
MMR, n (%)	–	–	0.29
pMMR	80(82.5)	116(76.8)	–
dMMR	17(17.5)	35(23.2)	–

Abbreviations: AFR, albumin-to-fibrinogen ratio; LAFR, locally advanced rectal cancer; MMR, mismatch repair; dMMR, defective mismatch repair; pMMR, proficient mismatch repair.

Due to the individual heterogeneity to treatment response, it is necessary for clinical practice to investigate novel predictors and generate personalized treatment strategies. The laboratory parameters added to clinicopathological characteristics (eg, TNM stage, pathologic differentiation) may have important roles in the personalized treatment determination. Among the clinicopathological and laboratory variables, AFR has some significant advantages, such as high sensitivity, wide availability, easy acquirement, and low economic cost. Pre-treatment evaluation of the AFR may have significant meanings in risk stratifications and prognosis prediction of LARC. More intensive care, frequent treatment efficacy evaluation and postoperative follow-up, and timely therapeutic strategies adjustment are suggested for patients with low AFR levels. We consider that pretreatment AFR evaluation may be beneficial for the therapeutic management and follow-up of LARC patients. However, we admit that this study has some great limitations. First, this is a single-center study with a relatively small sample size. Second, whether the modulation of pretreatment AFR level (eg Alb supplement, coagulation function improvement) can improve the prognosis of LARC patients remains unknown due to the retrospective nature of this study. Last, only pretreatment AFR was calculated and whether the AFR level at some other time points (eg after nCRT treatment, after the surgery) can also predict the prognosis in LARC patients is unclear.

Conclusions

This study indicated that pretreatment AFR level was an independent risk factor for pathologic response to nCRT,

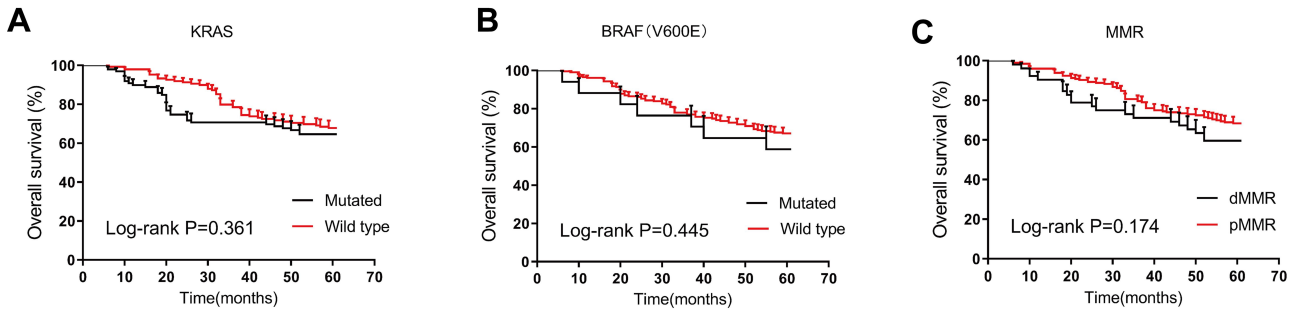

Figure 4 Overall survival stratified by KRAS (**A**), BRAF (**B**), and MMR (**C**) in LARC patients by Kaplan–Meier curve analyses. The mutational status was also not significantly associated with 5-year OS (P>0.05).

Abbreviations: LARC, locally advanced rectal cancer; OS, overall survival; MMR, mismatch repair; dMMR, defective mismatch repair; pMMR, proficient mismatch repair.

5-year OS and DFS in LARC patients undergoing TME after nCRT.

Data Sharing Statement

Please contact the corresponding author (Junxing Huang, email: dr_huangjunxing@hotmail.com) for data requests.

Ethics Approval and Consent to Participate

This study was approved by the Medical Institutional Ethics Committee of Taizhou People's Hospital. All patients included were required to offer written informed consent.

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Disclosure

All the authors declare that they have no competing interests.

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