

Preoperative circulating FPR and CCF score are promising biomarkers for predicting clinical outcome of stage II–III colorectal cancer patients

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Introduction: Inflammation and nutrition are considered as two important causes leading to the progression and poor survival of colorectal cancer (CRC). The objective of this study is to investigate the prognostic significance of preoperative albumin-to-fibrinogen ratio (AFR), fibrinogen-to-pre-albumin ratio (FPR), fibrinogen (Fib), albumin (Alb), and pre-albumin (pre-Alb) in CRC individuals.

Materials and methods: In this study, 3 years' follow-up was carried out in 702 stage I–III resected CRC patients diagnosed between January 2008 and December 2013. The optimal cutoff points and prognostic values of AFR, FPR, Fib, Alb, pre-Alb, and a novel carcinoembryonic antigen (CEA)-carbohydrate antigen 19-9 (CA199)-FPR (CCF) score were assessed by X-tile software, Kaplan–Meier curve, and Cox regression model. We established the CRC prognostic nomogram, and its predictive efficacy was determined by Harrell's concordance index (c-index).

Results: Our results showed that high FPR was obviously correlated with poor survival of CRC patients. The prognostic predictive efficacy of CCF score was superior to FPR, CEA, CA199, CEA-CA199 (CCI), and CEA-FPR (CFI) score. Moreover, stage II–III patients harboring high FPR or elevated CCF (score ≥ 1) could benefit from adjuvant chemotherapy, rather than those with low FPR or CCF (score = 0). Additionally, the c-index (0.728) of the nomogram containing CCF score was significantly higher than that (0.626) without it ($p < 0.01$).

Conclusion: These findings illustrated that FPR and CCF score were promising biomarkers to predict the prognosis of CRC and to classify the stage II–III patients who could benefit from the adjuvant chemotherapy.

Keywords: inflammation, colorectal cancer, FPR, CCF score, survival

Introduction

Colorectal cancer (CRC) is one of the most common malignancies and a leading cause in the last decade of cancer-related death worldwide;^{1,2} it is also the fifth most common cancer and the fifth leading cause of death in China.³ Although substantial progress had been achieved in decades, ~60% of CRC individuals were diagnosed with node or distant metastasis and the 5 years' survival rate was merely 65% from 2006 to 2012.⁴ Thus, novel, effective, stable, and economical biomarkers may help to improve diagnostic and predictive efficacy of the disease.

It was reported that an estimated 15% of the cancer-related death was attributed to chronic inflammation,⁵ and accumulating evidence indicated that inflammation was one of the most crucial causes facilitating onset and metastasis of CRC.⁶ Recent studies have found vital roles of inflammation-induced genetic alternation, immune cells, cytokines, and other mediators in each step of colonic tumorigenesis and progression.^{7–10} Moreover,

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the continuous use of low-dose nonsteroidal anti-inflammatory drugs was associated with a decreased risk of CRC.^{11,12}

Systematic chronic inflammation could contribute to both abnormal peripheral immune cell count and aberrant concentrations of circulating albumin (Alb) and pre-albumin (pre-Alb) as well as fibrinogen (Fib). Our previous study indicated that preoperative neutrophil-to-lymphocyte ratio was an independent prognostic factor for poor recurrence-free survival and overall survival (OS) in CRC.¹³ Several studies showed that elevated pretreatment plasma Fib was associated with short progression-free survival in various malignancies, including CRC.^{14,15} Moreover, Alb and pre-Alb were observed to be significantly lower in cancer individuals in comparison with the healthy controls.^{16,17} Hence, we hypothesized that the two new biomarkers, Alb-to-Fib ratio (AFR) and Fib-to-pre-Alb ratio (FPR), might reflect the severity of systemic inflammation and predict the survival of CRC individuals.

In this study, we measured the preoperative circulating levels of Fib, Alb, pre-Alb, carcinoembryonic antigen (CEA), and carbohydrate antigen 19-9 (CA199) and performed 3 years' follow-up to evaluate potential prognostic roles of them in 702 stage I–III surgically resected CRC individuals. Furthermore, we established and compared the prognostic efficacy of CEA-CA199-FPR (CCF), CEA-CA199 (CCI), and CEA-FPR (CFI) scores. Finally, we evaluated the roles of FPR, CEA, CA199, and CCF in predicting clinical efficacy of adjuvant chemotherapy among stage II–III CRC patients.

Materials and methods

Population

In our study, 702 stage I–III CRC individuals were included. All of them were first diagnosed, and pathologically confirmed according to the seventh edition of TNM/The Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) classification, and were without hematologic, hepatic, autoimmune diseases, recent infection, or other malignancies, and were from the Second Affiliated Hospital of Nanchang University and Nanjing First Hospital between January 2008 and December 2013. All the enrolled patients had only radical resection performed, without preoperative neoadjuvant radiochemotherapy, and the clinical characteristics and follow-up data were obtained from each patient. To compare the difference of FPR in recurrent/distant metastatic CRC patients and in the progression-free patients, the controls were randomly selected to match the recurrent or distant metastatic cases with gender and age in the ratio of 1:1, and all of them were from the progression-free patients in the follow-up period. Written informed consents were signed by each eligible patient, and the study was approved

by the institutional ethic commissions of the Second Affiliated Hospital of Nanchang University and Nanjing First Hospital.

Data collection and laboratory detection

We collected clinical baseline characteristics of all the patients from medical records. All preoperative sodium citrate anticoagulant peripheral blood and serum samples were collected at 7:30–9:30 am in the period before the intervention. Clauss method was selected to detect circulating Fib using SYSMEX CA-7000 machine (Sysmex, Tokyo, Japan), and inter- and intrabatch coefficients of variation (CVs) of the kit were <4.41% and 3.66%, respectively. Bromocresol green and immune turbidimetric methods were used to measure serum Alb and pre-Alb using OLYMPUS AU5400 machine (Beckman Coulter, Tokyo, Japan), and the inter- and intrabatch CVs of the kits were <3.17% and 1.83%, and 3.09% and 2.76%, respectively. Electrochemiluminescence immunoassay was used to detect CEA and CA199 by a machine from Siemens ADVIA Centaur CP (Siemens, Erlangen, Germany), and the respective inter- and intrabatch CVs of the kits were <3.32% and 3.25%, and 3.48% and 3.26%.

Follow-up

We performed 3 years of follow-up regularly, by means of telephone, email, and medical record, every 3 months for the first 2 years and every 6 months in the third year. The deadline of the follow-up was December 2016. OS was the end point of the study, and it was calculated from the time of surgical resection to death or the deadline.

Construction of novel prognostic score

To further investigate the prognostic values of FPR, CEA, and CA199, we established and compared the CCI, CFI, and CCF scores. The CCI score was composed of CEA and CA199, and the patient with both CEA >5 ng/mL and CA199 >37 U/mL was given a score of 2, and patients with only one or neither of these abnormalities were allocated a score of 1 or 0, respectively. Similarly, the patient with both elevated CEA (>5 ng/mL) and FPR (>18.3) was allocated a CFI score of 2, and patients with only one or neither of these elevated levels were allocated a score of 1 or 0, respectively. Additionally, CCF score consisted of preoperative FPR, CEA, and CA199, and patients with either none, one, two, or three elevated levels of them (CEA>5ng/ml, CA199>37U/ml, FPR>18.3) were considered as 0, 1, 2, and 3 score, respectively.

Statistics

The optimal cutoff points of FPR, AFR, Fib, and Alb were determined by X-tile software version 3.6.1 (Yale University,

New Haven, CT, USA), and were based on 3 years' OS. Chi-square test or Fisher's exact test were used to compare the categorical variable in the groups, and Mann–Whitney *U* or Student's *t*-test were selected to examine the difference in continuous variables. The sample power was evaluated using PASS version 11.0.10 program (NCSS, California, USA). The difference in survival rate was calculated using Kaplan–Meier curve with log-rank test, and the independent prognostic predictor was identified by Cox proportional hazards model. The predicted efficacy of the prognostic predictors was assessed by time-dependent receiver operating characteristics (ROC) analysis. We established a 3 years' OS nomogram using R 3.3.2 software (Institute for Statistics and Mathematics, Vienna, Austria), and the predictive accuracy was evaluated by Harrell's concordance index (c-index). A *p*-value <0.05 was recognized as statistical significance, and all the statistical analyses were conducted using IBM SPSS 20.0 software (IBM Corporation, Armonk, NY, USA).

Results

Baseline characteristics of patients

The baseline characteristics of CRC patients in the present study are summarized in [Table S1](#). A total of 702 patients were recruited in our study, and the powers of the sample size were 0.99 for FPR, 0.89 for AFR, 0.93 for Fib, 0.98 for pre-Alb, and 0.85 for Alb. The majority of included patients were stage II (44%) and stage III (43%) cases, and proportions of the cases with T1–T2 and T3–T4 depth were 15.2% and 84.8%, respectively. Lymph-node metastasis was observed in 302 patients, and 89.3% of the patients were G1–G2 grade cases. Moreover, 66.1% of the eligible patients received adjuvant chemotherapy. Three hundred twenty-three (62.0%), 152 (29.2%), and 46 (8.8%) patients were allocated CCI score 0, 1, and 2, respectively. Two hundred twenty-eight (43.6%),

209 (40.0%), and 86 (16.4%) patients harbored CFI 0, 1, and 2 score, respectively. The respective numbers of patients with CCF score 0, 1, 2, and 3 were 210 (40.3%), 190 (36.5%), 97 (18.6%), and 24 (4.6%). Up to follow-up deadline, 123 patients had died and 128 patients had confirmed recurrence or distant metastasis in our study.

Correlation of FPR, AFR, Fib, Alb, and pre-Alb with clinical characteristics

Using X-tile software, we found that the optimal cutoff points based on OS were 3.8 g/L for Fib, 33.3 g/L for Alb, 187.4 mg/L for pre-Alb, 18.3 for FPR, and 9.2 for AFR ([Figure 1](#) and [Figure S1](#)). The relationships between the biomarkers and clinical characteristics are described in [Table 1](#). All of the biomarkers were closely associated with age >60 years, large tumor size, and poor OS. FPR, AFR, and Fib were significantly associated with tumor size, depth of invasion, and node metastasis. Furthermore, circulating FPR in patients with stage III–IV, T3–T4 depth, N1–N2 metastasis, and tumor size >5cm was higher than in those with stage I–II, T1–T2 depth, N0 metastasis, and tumor size ≤5cm, respectively ([Figure 2](#), [Table S2](#)). Besides, we compared the difference in circulating FPR in 128 randomly selected nonrecurrent/metastatic patients and 128 recurrent/metastatic patients. Intriguingly, FPR in recurrent patients was significantly higher than that of nonrecurrent/metastatic patients (*p*<0.05).

Prognostic roles of FPR, AFR, Fib, Alb, and pre-Alb in CRC

In the present study, the Kaplan–Meier curve with log-rank test and Cox proportion regression model were selected to investigate the prognostic roles of the baseline characteristics and FPR, AFR, Fib, Alb, and pre-Alb in CRC. As shown in [Figure 3](#), FPR (>18.3), AFR (≤9.2), Fib (>3.8 g/L), Alb

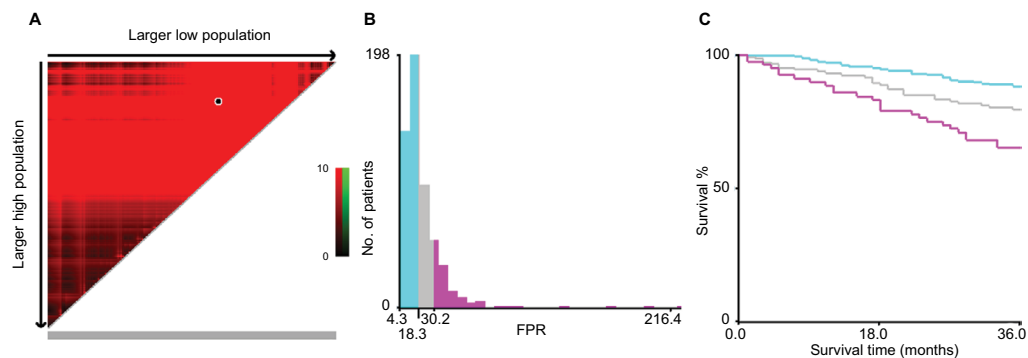


Figure 1 The optimal cutoff value of preoperative circulating FPR in 702 CRC patients using X-tile software.

Notes: The data are represented graphically in a right-triangular grid where the point represents the data from a given set of divisions (A). The plots showed the χ^2 log-rank values produced, dividing them into three groups by the cutoff points 18.3 and 30.2. The optimal cutoff point, 18.3, was determined by locating the brightest pixel on the X-tile plot. The distribution of number of patients is shown on the histogram (B) and the corresponding populations are displayed on the Kaplan–Meier curve (C). Larger low population= larger population with low FPR level; larger high population= larger population with high FPR level.

Abbreviations: CRC, colorectal cancer; FPR, fibrinogen-to-pre-albumin ratio.

Table 1 Correlations of preoperative circulating Fib, Alb, pre-Alb, AFR, and FPR with clinicopathologic characteristics in 702 CRC patients

Characteristics	Patients grouped by FPR level (n=555)			p-value*			Patients grouped by AFR level (n=680)			p-value*			Patients grouped by Fib level (n=682)			p-value*			Patients grouped by Alb level (n=700)			p-value*			Patients grouped by pre-Alb level (n=566)			p-value*		
	>18.3	≤18.3		>9.2	≤9.2		>3.8	≤3.8		>3.8	≤3.8		>33.3	≤33.3		>187.4	≤187.4		>33.3	≤33.3		>187.4	≤187.4		>187.4	≤187.4		>187.4	≤187.4	
Gender	141	209	Male	345	81	0.477	108	319	0.092	398	41	0.304	202	156	0.001	86	122		230	31		206	156		202	156		0.304		
	89	116	Female	217	37		50	205		239	31		86	122		230	31		239	31		206	156		202	156				
Age (years)	148	173	≤60	270	39	<0.001	59	250	0.003	290	14	<0.001	150	107	0.001	239	14		239	14		206	156		202	156		<0.001		
	82	152	>60	292	79		99	274		329	58		138	171		329	58		329	58		206	156		202	156				
Smoking	39	63	Yes	90	28	0.505	30	88	0.060	112	8	0.187	62	41	0.039	112	8		112	8		206	156		202	156		0.187		
	191	262	No	472	90		128	436		516	64		226	237		516	64		516	64		206	156		202	156				
Drinking	25	34	Yes	47	15	0.890	18	44	0.158	60	3	0.189	34	26	0.413	60	3		60	3		206	156		202	156		0.189		
	205	291	No	515	103		140	480		568	69		254	252		568	69		568	69		206	156		202	156				
Hypertension	41	60	Yes	117	20	0.911	32	106	0.379	123	19	0.215	59	46	0.236	123	19		123	19		206	156		202	156		0.215		
	189	265	No	445	98		126	418		505	53		229	232		505	53		505	53		206	156		202	156				
Diabetes	19	15	Yes	34	12	0.105	17	30	0.109	41	10	0.031	15	22	0.234	41	10		41	10		206	156		202	156		0.031		
	211	310	No	528	106		141	494		587	62		273	256		587	62		587	62		206	156		202	156				
Chemotherapy	152	214	Yes	366	87	1.000	118	335	0.085	421	43	0.237	190	182	0.930	421	43		421	43		206	156		202	156		0.237		
	78	111	No	196	31		40	189		207	29		98	96		207	29		207	29		206	156		202	156				
Tumor grade	209	286	G1–G2	500	109	0.332	141	470	0.323	101	66	0.687	254	250	0.591	101	66		101	66		206	156		202	156		0.687		
	21	39	G3–G4	62	9		17	54		527	6		34	28		527	6		527	6		206	156		202	156				
Tumor stage	15	60	I	83	7	<0.001	10	80	0.013	86	5	0.007	54	21	<0.001	86	5		86	5		206	156		202	156		0.007		
	102	142	II	247	49		68	229		272	36		122	130		272	36		272	36		206	156		202	156				
	113	123	III	232	62		80	215		270	31		112	127		270	31		270	31		206	156		202	156				
Depth of invasion	15	73	T1–T2	99	7	<0.001	10	96	0.001	101	6	<0.001	63	25	<0.001	101	6		101	6		206	156		202	156		0.086		
	215	252	T3–T4	463	111		148	428		527	66		225	253		527	66		527	66		206	156		202	156				
Lymph node status	117	202	N0	330	56	0.009	78	309	0.032	358	41	<0.001	176	151	0.107	358	41		358	41		206	156		202	156		1.000		
	113	123	N1–N2	232	62		80	215		270	31		112	127		270	31		270	31		206	156		202	156				
Tumor size (cm)	111	251	≤5	391	40	<0.001	61	371	<0.001	411	30	<0.001	219	148	<0.001	411	30		411	30		206	156		202	156		<0.001		
	119	74	>5	171	78		97	153		217	42		69	130		217	42		217	42		206	156		202	156				
CA199 (U/mL)	174	270	≤37	443	88	0.006	120	411	0.592	495	43	0.761	243	207	0.009	495	43		495	43		206	156		202	156		<0.001		
	40	37	>37	73	18		24	68		83	10		28	50		83	10		83	10		206	156		202	156				
CEA (ng/mL)	16	18	NA	46	12	0.002	14	45	0.002	50	19		17	21	<0.001	50	19		50	19		206	156		202	156		<0.001		
	128	228	≤5	355	62		87	330		393	31	0.182	155			393	31		393	31		206	156		202	156				
	86	81	>5	163	44		57	151		187	22		67	102		187	22		187	22		206	156		202	156				
OS	16	16	NA	44	12		14	43		48	19		15	21	<0.001	48	19		48	19		206	156		202	156		0.009		
	176	290	Alive	477	87	<0.001	118	448	0.005	526	51	0.002	258	217	<0.001	526	51		526	51		206	156		202	156		0.009		
	54	35	Dead	85	31		40	76		102	21		30	61		102	21		102	21		206	156		202	156				

Notes: *Difference between groups was tested by chi-square test. p-value <0.05 shown in bold.

Abbreviations: AFR, albumin-to-fibrinogen ratio; Alb, albumin; CA199, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CRC, colorectal cancer; Fib, fibrinogen; FPR, fibrinogen-to-pre-albumin ratio; NA, not available; OS, overall survival.

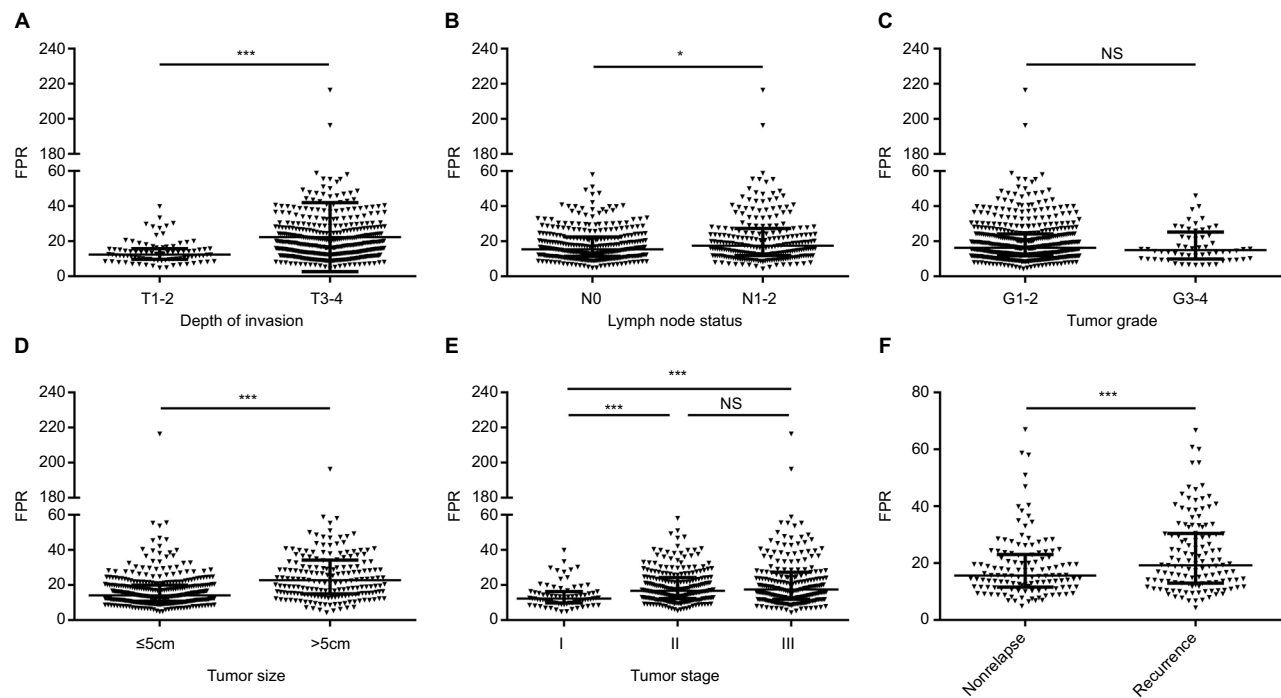


Figure 2 The correlation of FPR with clinical characteristics and comparison of FPR in nonrelapse and recurrent CRC patients.

Notes: (A) FPR with depth of invasion; (B) FPR with lymph node; (C) FPR with tumor grade; (D) FPR with tumor size; (E) FPR with tumor stage; (F) comparison of FPR in nonrelapse and recurrent CRC patients. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Abbreviations: CRC, colorectal cancer; FPR, fibrinogen-to-pre-albumin ratio; NS, no significance.

(≤ 33.3 g/L), and pre-Alb (≤ 187.4 mg/L) were negatively associated with 3 years' OS in the Kaplan–Meier curve. G3–G4 differentiation (crude hazard ratio [HR]=1.867, 95% CI=1.145–3.046; adjusted HR=1.718, 95% CI=1.052–2.805), stage III (crude HR=3.834, 95% CI=1.567–9.381; adjusted HR=3.368, 95% CI=1.370–8.280), T3–T4 depth (crude HR=3.792, 95% CI=1.669–8.614; adjusted HR=2.792, 95% CI=1.208–6.452), lymph-node metastasis (crude HR=1.934, 95% CI=1.354–2.762; adjusted HR=1.888, 95% CI=1.322–2.698), large tumor size (> 5 cm) (crude HR=1.979, 95% CI=1.389–2.819; adjusted HR=1.905, 95% CI=1.336–2.715), high CEA (> 5 ng/mL; crude HR=2.961, 95% CI=2.019–4.342; adjusted HR=2.719, 95% CI=1.850–3.996), and CA199 (> 37 U/mL; crude HR=2.916, 95% CI=1.934–4.398; adjusted HR=2.605, 95% CI=1.683–4.033) were significantly correlated with poor OS (Table 2).

Circulating elevated FPR (crude HR=2.398, 95% CI=1.567–3.669; adjusted HR=1.940, 95% CI=1.236–3.046) was significantly associated with an increased death risk from CRC, whereas high Alb (crude HR=0.504, 95% CI=0.315–0.806; adjusted HR=0.564, 95% CI=0.349–0.912) and pre-Alb (crude HR=0.444, 95% CI=0.287–0.687; adjusted HR=0.520, 95% CI=0.329–0.823) were significantly associated with decreased death risk from the disease.

However, no correlations were observed between AFR, Fib, and OS (Table 2).

Analysis of time-dependent ROC

Time-dependent ROC was used to compare the prognostic efficacy of each biomarker in our study. The areas under the ROC (AUCs) of FPR, Alb, and pre-Alb were larger than for the other biomarkers in the first few months (Figure 3I). Comparatively, AUC of FPR stayed at the higher level compared to Alb and pre-Alb, in the following months. In addition, CEA had the largest AUC in the last 24 months.

Prognostic values of CCI, CFI, and CCF scores

To further investigate the prognostic values of FPR, CEA, and CA199, we established and assessed the prognostic roles of CCI, CFI, and CCF scores. The higher CCI (crude HR=2.495 and adjusted HR=2.289 for score 1; crude HR=5.926 and adjusted HR=5.612 for score 2), CFI (crude HR=3.021 and adjusted HR=2.748 for score 1; crude HR=6.957 and adjusted HR=5.904 for score 2), and CCF (crude HR=2.770 and adjusted HR=2.578 for score 1; crude HR=5.902 and adjusted HR=4.753 for score 2; crude HR=12.082 and adjusted HR=11.518 for score 3) were significantly associated with reduced survival of the CRC patients (Figure 4 and Table S3).

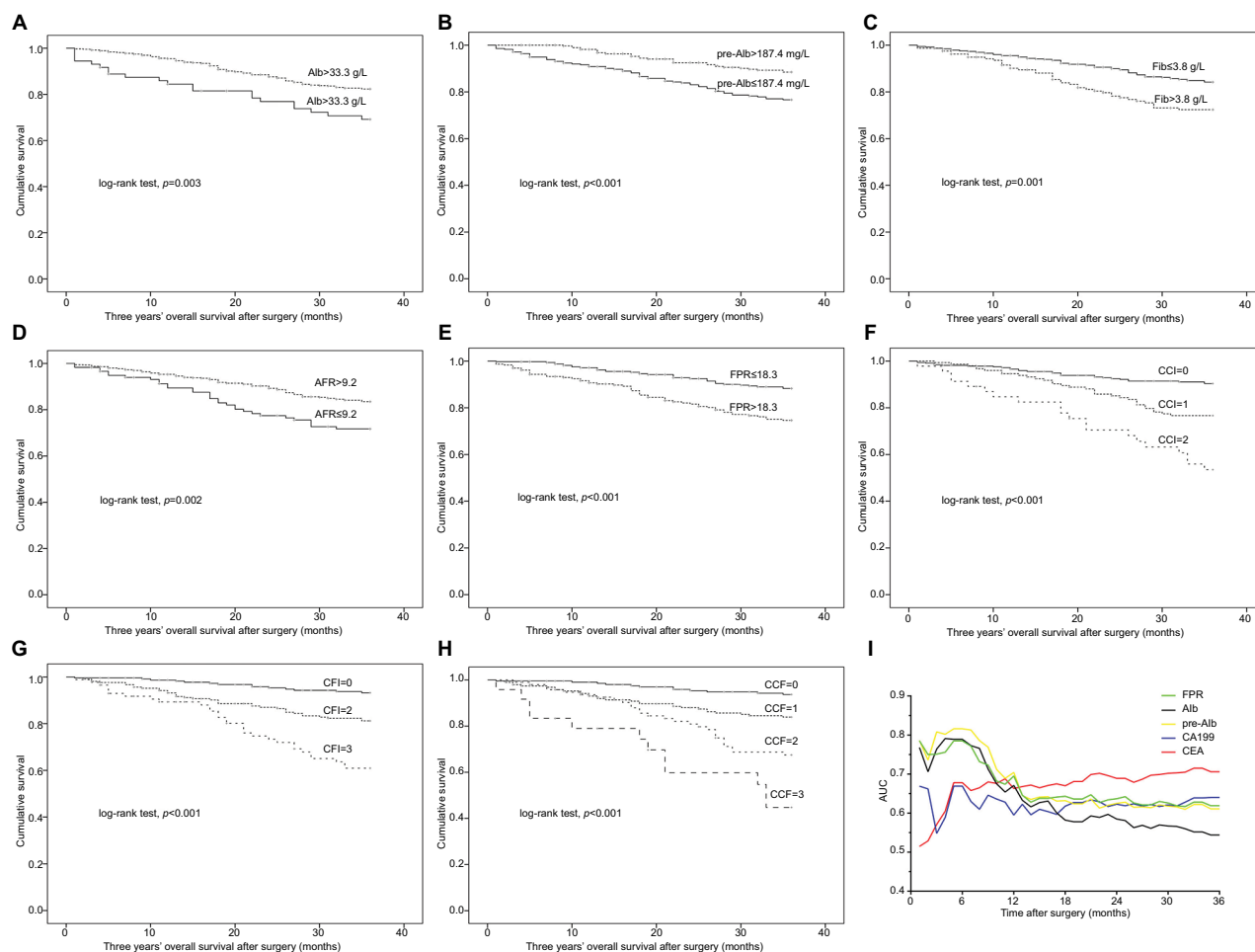


Figure 3 Kaplan–Meier curves of FPR, AFR, Fib, Alb, and pre-Alb for 3 years' OS in 702 CRC patients.

Notes: (A) Alb; (B) pre-Alb; (C) Fib; (D) AFR; (E) FPR; (F) CCI; (G) CFI; (H) CCF. Time-dependent receiver operating characteristic analysis of preoperative circulating FPR, Alb, pre-Alb, CA199, and CEA for clinical outcome of 702 CRC patients (I).

Abbreviations: AFR, albumin-to-fibrinogen ratio; Alb, albumin; pre-Alb, pre-albumin; CA199, carbohydrate antigen 19-9; CCF, CEA-CA199-FPR; CCI, CEA-CA199; CEA, carcinoembryonic antigen; CFI, CEA-FPR; CRC, colorectal cancer; Fib, fibrinogen; FPR, fibrinogen-to-pre-albumin ratio; HR, hazard ratio; OS, overall survival.

Predictive roles of FPR, CEA, CA199, and CCF in chemotherapy

To investigate the predictive roles of FPR, CEA, CA199, and CCF in adjuvant chemotherapy, we compared the survival difference of surgical stage II–III CRC patients with or without treatment of chemotherapy in each high or low FPR, CEA, CA199, and CCF subgroup. We found that OS of the patients with adjuvant chemotherapy was significantly longer than in those without it, only in CCF ≥ 1 score ($p < 0.05$, adjusted HR=0.494, 95% CI=0.303–0.806) and high FPR ($p < 0.05$, adjusted HR=0.420, 95% CI=0.241–0.731) subgroups. However, no survival difference was observed in the low FPR and CCF score subgroups, or in all subgroups stratified by CEA and CA199 (Figure 5 and Figure S2).

Assessment of the constructed nomograms

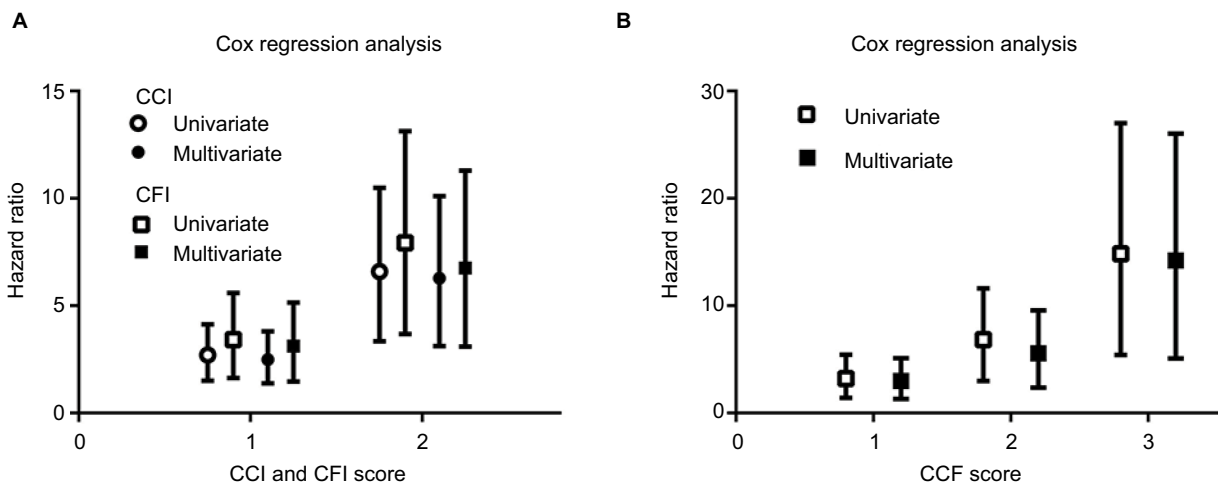
The pivotal clinical pathologic characteristics, FPR, and CCF scores were selected to construct prognostic nomograms to predict 3 years' OS of CRC and the predicted accuracy was evaluated by Harrell's c-index. The nomograms are listed in Figure 6 and Figure S3; c-indexes of the nomograms with or without CCF score were 0.728 (0.677–0.777) and 0.626 (0.568–0.684), and c-indexes of those with or without FPR were 0.722 (0.667–0.777) and 0.706 (0.648–0.764), respectively. Moreover, the significant difference between c-indexes of the nomogram with or without CCF score was observed between them ($p < 0.01$).

Table 2 Univariate and multivariate analyses of prognostic factors for 3-year overall survival by Cox regression model

Variables	Overall survival			
	Univariate cox regression		Multivariate cox regression	
	Crude HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Sex (female)	0.880 (0.606–1.277)	0.501	–	–
Age (>60 years)	1.223 (0.851–2.805)	0.277	–	–
Alcohol (yes)	1.186 (0.654–2.152)	0.575	–	–
Tobacco (yes)	0.995 (0.622–1.591)	0.982	–	–
Hypertension (yes)	0.878 (0.558–1.382)	0.575	–	–
Diabetes (yes)	1.115 (0.584–2.130)	0.741	–	–
Chemotherapy (yes)	0.882 (0.611–1.274)	0.504	–	–
Tumor grade (G3–G4)	1.867 (1.145–3.046)	0.012	1.718 (1.052–2.805)	0.030
Tumor stage (III)	3.834 (1.567–9.381)	0.003	3.368 (1.370–8.280)	0.008
Depth of invasion (T3–T4)	3.792 (1.669–8.614)	0.001	2.792 (1.208–6.452)	0.016
lymph node (N1–N3)	1.934 (1.354–2.762)	<0.001	1.888 (1.322–2.698)	<0.001
Tumor size (>5 cm)	1.979 (1.389–2.819)	<0.001	1.905 (1.336–2.715)	0.001
CEA (>5 ng/mL)	2.961 (2.019–4.342)	<0.001	2.719 (1.850–3.996)	<0.001
CA199 (>37 U/mL)	2.916 (1.934–4.398)	<0.001	2.605 (1.683–4.033)	<0.001
Fib (>3.8 mg/dL)	1.913 (1.304–2.806)	0.001	1.450 (0.961–2.188)	0.077
Alb (>33.3 g/L)	0.504 (0.315–0.806)	0.004	0.564 (0.349–0.912)	0.020
pre-Alb (>187.4 mg/L)	0.444 (0.287–0.687)	<0.001	0.520 (0.329–0.823)	0.005
AFR (>9.2)	0.531 (0.352–0.801)	0.003	0.709 (0.455–1.107)	0.130
FPR (>18.3)	2.398 (1.567–3.669)	<0.001	1.940 (1.236–3.046)	0.004

Notes: Adjusted HR (95%) was adjusted by sex, age, alcohol, tobacco, hypertension, diabetes, chemotherapy, tumor size, tumor grade, and tumor stage. The endash represent that these variables were not included in the multivariate cox regression. p-value <0.05 shown in bold.

Abbreviations: AFR, albumin/fibrinogen ratio; Alb, albumin; pre-Alb, pre-albumin; CA199, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; Fib, fibrinogen; FPR, fibrinogen-to-pre-albumin ratio; HR, hazard ratio.

**Figure 4** The HRs of CCI, CFI, and CCF scores in CRC patients.

Notes: (A) The crude and adjusted HRs of CCI and CFI score; (B) The crude and adjusted HRs of CCF score.

Abbreviations: CCF, CEA-CA199-FPR; CCI, CEA-CA199; CA199, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CFI, CEA-FPR; CRC, colorectal cancer; HR, hazard ratio; FPR, fibrinogen-to-pre-albumin ratio.

Discussion

Systemic inflammation is one of the important hallmarks of CRC.⁷ CRC cells, cancer stem cells, chronic inflammatory mediators, and inflammation-related cells, such as cancer-associated fibroblasts and endothelial cells, as well as tumor-associated macrophages form a favorable microenvironment to promote carcinogenesis of colorectal epithelial cells and to create a pre-metastatic niche in secondary organs or tissue sites for subsequent metastasis.^{18–20}

Circulating Fib, Alb, and pre-Alb were the main inflammatory biomarkers, and hyperfibrinogenemia and hypoalbuminemia were commonly observed in CRC patients.^{21,22} However, the prognostic and predictive roles of AFR and FPR in surgically resected CRC remained unknown.

We conducted this prospective study to investigate the association of preoperative AFR, FPR, Fib, Alb, pre-Alb, CEA, and CA199 with 3 years' OS in 702 I–III surgically resected CRC individuals. Our results showed that low AFR, Alb, pre-Alb,

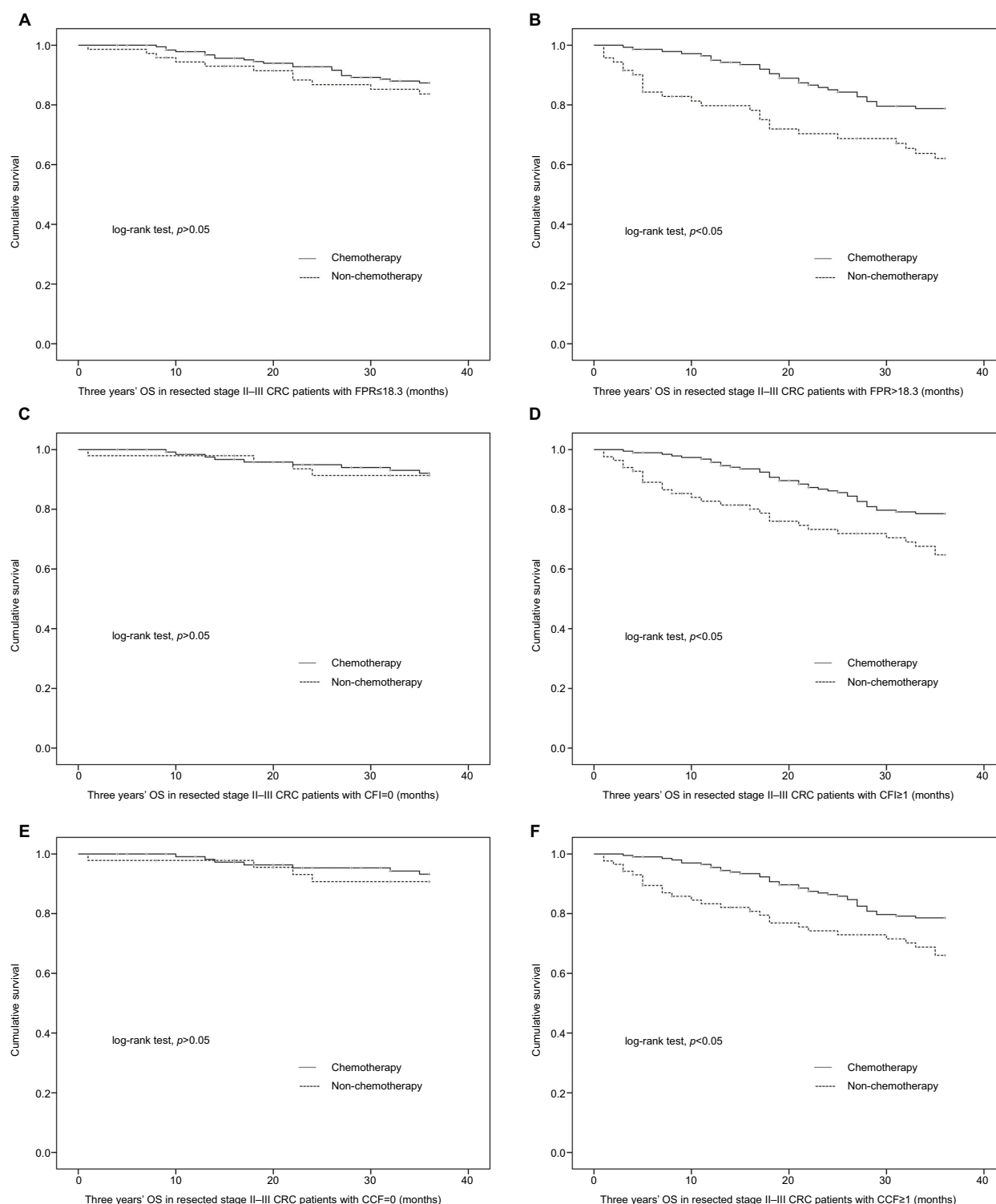


Figure 5 Kaplan-Meier curves of stage II–III CRC patients with or without treatment of chemotherapy in each subgroup stratified by FPR, CFI, and CCF. **Notes:** (A) FPR ≤ 18.3; (B) FPR > 18.3; (C) CFI = 0; (D) CFI ≥ 1; (E) CCF = 0; (F) CCF ≥ 1.

Abbreviations: CCF, CEA-CA199-FPR; CFI, CEA-FPR; CRC, colorectal cancer; FPR, fibrinogen-to-pre-albumin ratio; OS, overall survival.

and elevated Fib level were only associated with T3–T4 invasion and tumor size. However, elevated FPR was significantly associated with TNM stage, invasion depth, node metastasis, and tumor size. These results indicated that FPR was superior

to these biomarkers to in evaluating CRC progression and the tumor burden. Furthermore, low Alb and pre-Alb, and high FPR were significantly associated with poor survival of CRC, and the predicted efficacy of FPR was significantly higher than the

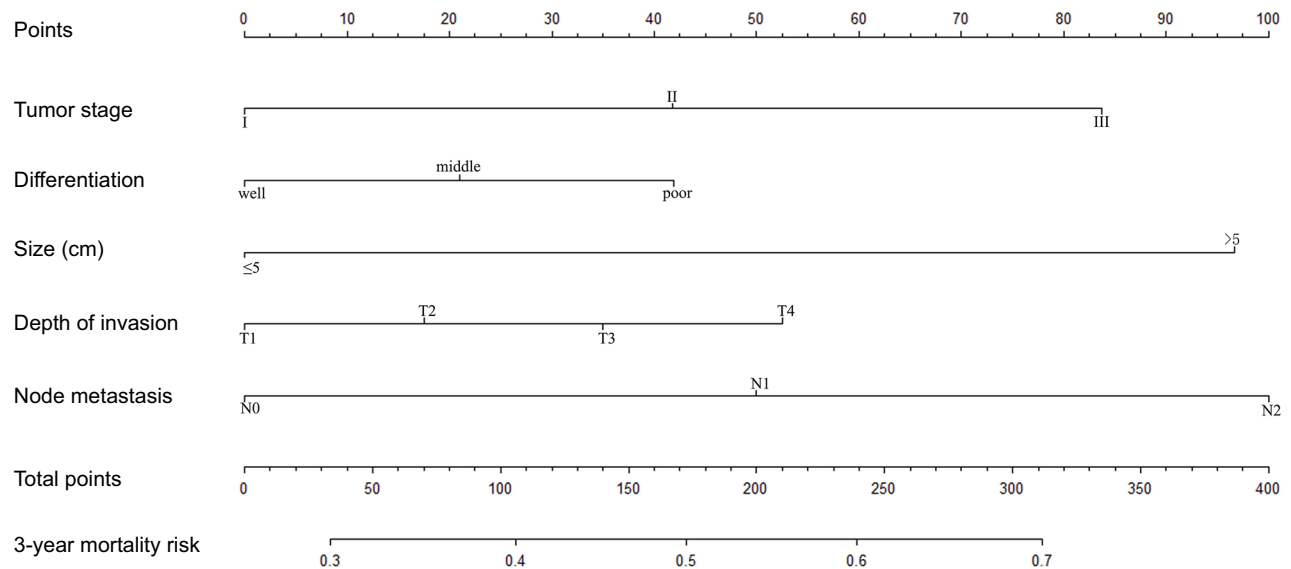
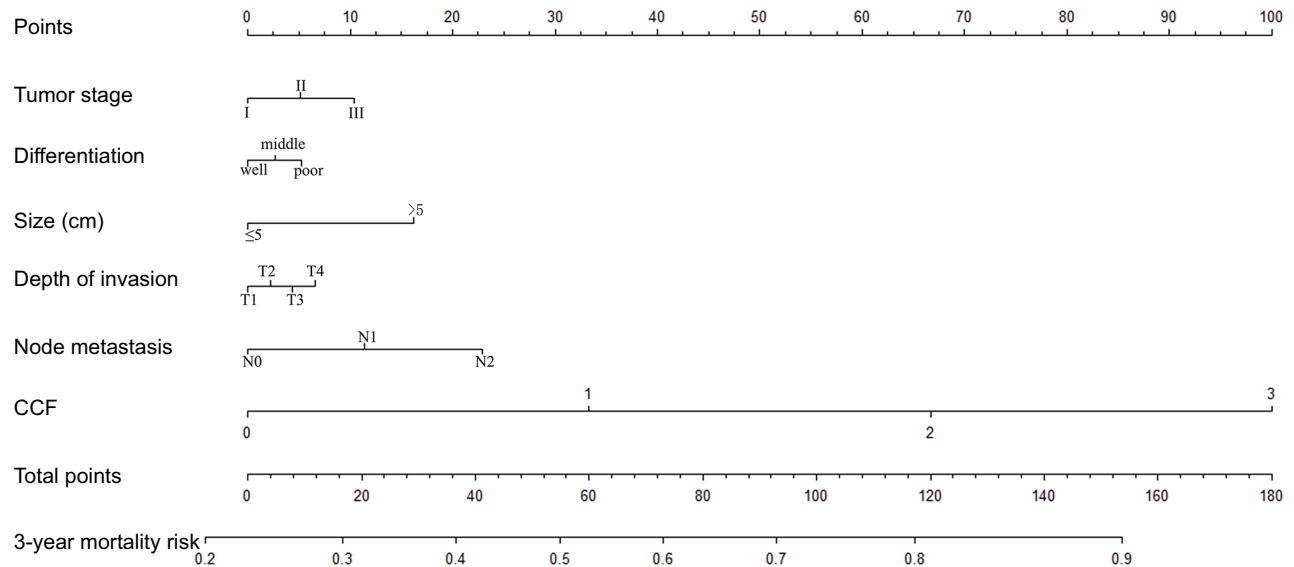
A**B**

Figure 6 Prognostic nomograms with or without CCF score for predicting 3-year OS in CRC patients.

Notes: (A) Nomogram without CCF; (B) Nomogram including CCF.

Abbreviations: CCF, CEA-CA199-FPR; CRC, colorectal cancer; FPR, fibrinogen-to-pre-albumin ratio; OS, overall survival.

others, demonstrating that it was an effective and independent prognostic factor to predict the prognosis of CRC.

In addition to the single inflammatory biomarker, the emerging novel prognostic scores have been proposed to evaluate the progression and survival of CRC. Glasgow prognostic score (GPS) and modified GPS showed good performance in predicting clinical outcome of CRC.^{23,24} Depending on FPR, CEA, and CA199, three novel CFI,

CCI, and CCF scores were first established in our study, and they were obviously associated with the survival of CRC; however, the measured HRs of CCI and CFI score were less than CCF score, suggesting that the two scores were inferior to CCF to predict survival of CRC. Moreover, no significant survival difference of stage II–III CRC patients with or without adjuvant chemotherapy was observed in any subgroup stratified by CEA and CA199, whereas the

cases that harbored high FPR and CCF score could benefit from adjuvant chemotherapy, illustrating that FPR and CCF score were useful biomarkers to precisely distinguish eligible patients who could benefit from the treatment. The c-index of the nomogram containing FPR or CCF was significantly higher than the nomogram without them, suggesting that FPR and CCF could improve predicted accuracy of the prognostic nomogram.

Notably, Fib is not only an important factor in the blood coagulation cascade but also a main acute phase reaction protein in chronic inflammation. Tumor cells could interact with all parts of the hemostatic system to stimulate prothrombotic properties and to trigger the production of Fib by liver and by itself,²⁵ contributing to the high level of Fib. Meanwhile, Fib was considered as a mediator of cancer cell proliferation;²⁶ it sustained the adhesion and survival of cancer cell emboli in the vasculature of target organs to promote metastasis,²⁷ and it could protect cancer cells escaping elimination by natural killer cells by means of formation of a shielding cover around them.²⁸ Moreover, the common inflammatory cytokine, interleukin-6, was reported to suppress the synthesis of Alb and pre-Alb, leading to hypoproteinemia in CRC patients.²⁹ Consequently, poor nutritional status and impaired immunologic surveillance of the patient directly affected clinical outcome of the disease.^{29,30} Thus, these factors might have accounted for the findings in the present study.

Our study is the first to evaluate the prognostic roles of AFR, FPR, and CCF score in survival of CRC patients. The established nomogram containing CCF was an easy-to-use system for accurately estimating 3 years' survival of CRC patients after surgery. However, some limitations in the current study should be addressed. First, the diverse postoperative chemotherapy regimens might lead to the heterogeneous outcome of the patients. Secondly, only 3 years' OS was included in our study, and we did not obtain the complete recurrence data and 5 years' of OS, so our study can not comprehensively reflect survival of the patients. Thirdly, no validated cohort was included to verify the findings in our study.

Conclusion

In summary, our data have revealed that FPR and CCF score are reliable, economical, and practical biomarkers to precisely distinguish eligible patients for treatment with adjuvant chemotherapy and to predict the prognosis of CRC. Further, multicenter and large sample size design studies are warranted to validate our results.

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Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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