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RESEARCH ARTICLE

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Circulating fibrinogen to pre-albumin ratio is a promising biomarker for diagnosis of colorectal cancer

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Background: Inflammation and nutrition are closely associated with initiation and progression of colorectal cancer (CRC). This study aimed to investigate the diagnostic value of the FAR (FAR = 100*Fibrinogen/Albumin) and FPR (FPR = Fibrinogen/pre-Albumin) in CRC.

Methods: Neutrophil-to-lymphocyte ratio (NLR), FPR, and FAR were calculated in 455 newly diagnosed CRC patients, 455 healthy individuals, and 455 benign controls with colorectal polyp. The diagnostic value of biomarker for CRC was evaluated by receiver operating characteristic curve (ROC). Logistic regression analysis was adopted to assess the risk factors for telling CRC apart from benign disease. Moreover, the combined biomarkers were used for discriminating between CRC and benign disease.

Results: Neutrophil-to-lymphocyte ratio, FAR, and FPR were significantly higher in CRC patients compared with the benign or healthy controls ($P < 0.05$). ROC analysis showed that the diagnostic efficacy of FAR and FPR were better than NLR for CRC. Besides, FPR, NLR, carcinoembryonic antigen (CEA), and carbohydrate antigen 19-9 (CA199) were markedly associated with differentiation of benign disease and CRC in the logistic regression analysis. And the combination of FPR, CEA, and CA199 had the maximum area under the ROC curve (AUC) in separating CRC from benign disease (AUC = 0.845, Sensitivity = 67.9%, Specificity = 85.3%, Positive Predictive Value = 83.5%, Negative Predictive Value = 70.9%).

Conclusions: Fibrinogen/pre-Albumin could be a useful CRC diagnostic biomarker, and the combination of FPR, CEA, and CA199 could significantly improve the diagnostic efficacy in discriminating CRC from the benign colorectal disease.

KEYWORDS
colorectal cancer, diagnosis, FPR, sensitivity, specificity

1 | INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers around the world, and the morbidity and mortality of CRC in China are increasing in recent years.[1,2] Unfortunately, only 40% of CRC are diagnosed at an early stage, and 5-year survival rate was merely 65% in 2012.[3] The occult blood test was usually detected for screening CRC patients until now, but its low sensitivity always resulted in missed diagnosis. Colonoscopy has been recognized as the gold standard for CRC diagnosis; however, its invasive, painful, and expensive propensity restrict the utilization for CRC patients. Besides, several serum biomarkers have been used in the early diagnosis of

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CRC, such as carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA199), and tumor-specific growth factor. Nevertheless, their clinical effectiveness for CRC early detection remains controversial.[4]

It has been widely known that cancers are closely associated with systemic inflammatory response and the nutritional status of patients. Plenty of evidence indicated that inflammation plays a vital role in the development and progression of various cancers, including CRC.[5-7] Meanwhile, malnutrition is a significant problem in cancer patients and could result in a number of clinical consequences, such as deteriorated quality of life, decreased response to treatment, and shorter survival rate.[8] Accordingly, some novel biomarkers which reflected the systemic inflammation and nutritional status were increasingly investigated in the prediction of cancer progression and prognosis, such as neutrophil-to-lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and the modified Glasgow prognostic score (mGPS).[9,10] However, there were few studies to report the diagnostic value of these inflammation-based biomarkers.

Fibrinogen (Fib), which plays a vital part in clot formation, was also observed to act as a prominent role in directly or indirectly regulating inflammatory response.[11,12] Many studies have emphasized that the preoperative plasma Fib level could independently predict prognosis of various cancers.[13-17] Furthermore, serum albumin (Alb) or pre-albumin (pAlb) level was proved to be significant low in cancer individuals comparing to healthy controls.[18,19] Hence, Fib-to-Alb ratio (FAR, 100*Fib/Alb) and Fib-to-pAlb ratio (FPR, Fib/pAlb), which could reflect both the inflammatory and nutritional state, seem to be potential diagnostic biomarkers for CRC patients.

In this study, we comprehensively analyzed the diagnostic value of FAR and FPR in CRC and explored whether biomarker combinations could improve the diagnostic efficacy in distinguishing CRC from the benign colorectal disease.

2 | MATERIALS AND METHODS

2.1 | Study population

According to the power ($1-\beta = 0.85$) and the level of significance ($\alpha < 0.05$), the minimum sample size of the cases and controls was calculated as 403 using PASS version 11.0.10. Thus, a total of 455 CRC patients newly diagnosed at the Second Affiliated Hospital of Nanchang University between Jan 2011 and Dec 2014 were enrolled in our study. The cases were confirmed by two pathologists according to the American Joint Committee on Cancer TNM staging system (7th Edition) classification system. In addition, 455 patients with colorectal polyp were included as benign controls, and sex- and age-matched healthy individuals were enrolled as healthy controls. Patients without hematological disorders, hepatic damage, autoimmune diseases, recent infection, or other malignancies were eligible for enrollment. Healthy controls were collected by physical examination, including the questionnaire, the blood routine examination, all blood biochemical indices, B-ultrasonography, and imagological examination. Ethical approval was obtained from the Second Affiliated Hospital of Nanchang University and adhered to the tenets of the Declaration of Helsinki.

2.2 | Clinical parameter and laboratory results

Patients' clinical parameter including age, sex, tumor location, TNM classification, and tumor grade were retrieved from medical records. Meanwhile, laboratory results were also collected from medical records. Clauss method was selected to detect circulating Fib using SYSMEX CA-7000 machine (Sysmex, Tokyo, Japan). Bromocresol green and immune turbidimetric methods were chosen to measure serum concentrations of Alb and pAlb using OLYMPUS AU5400 machine (Beckman Coulter, Tokyo, Japan). Electro-chemiluminescence immunoassay was used to detect serum levels of CEA and CA199 by the machine of SIEMENS ADVIA Centaur CP (Siemens, Erlangen, Germany). All peripheral blood, plasma, and serum samples were collected from 7:30 to 9:30 am in the period before the intervention. And the respective inter- and intra-batch coefficient of variance of the kits was <5%.

2.3 | Statistical analysis

The minimum sample size was calculated by PASS version 11.0.10 program (NCSS, LLC, Kaysville, UT, USA). IBM SPSS 20.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Kolmogorov-Smirnow test was selected to assess the normality of calculated parameters. The data with normal and skewed distributions were, respectively, showed as mean ± standard deviation (SD) and median (25% quartile-75% quartile). Student's *t* test was selected to assess normally distributed parameter; otherwise, Mann-Whitney *U* test was performed. The chi-square test was used for categorical variables. Receiver-operating characteristics (ROC) curve analysis was performed to identify cutoff values of these biomarkers, and the differences in the area under the curve (AUC) were analyzed using MedCalc version 15.0 (MedCalc Software, Mariakerke, Belgium). A *P*-value <0.05 was considered statistically significant.

3 | RESULTS

3.1 | Clinical characteristics of enrolled participants

The overall baseline characteristics of all the participants were summarized in Table 1. Four hundred and fifty-five CRC cases, 455 healthy controls, and 455 benign controls were recruited. The median age of the CRC patients, healthy controls, and benign controls were 58, 55, and 57, respectively. There is no statistical significance between three groups in age ($P > 0.05$). As for CRC patients, 196 (43.1%) were colon cases and 259 (56.9%) were rectal cancer patients; the numbers of patient in stage I, II, III and IV were 49 (10.8%), 164 (36.0%), 177 (38.9%), and 65 (14.3%), respectively. Of all the patients, 14 (3.1%), 370 (81.3%) and 71 (15.6%) tumors were good, median, and poor cell differentiation. The patients with T1, T2, T3, and T4 were 10 (2.2%), 55 (12.1%),

TABLE 1 The baseline characteristics of the CRC, healthy, and benign controls

Characteristics	Cases (n = 455)	Healthy (455)	Benign (455)
Age (y, M with R)	58 (24, 86)	55 (22, 91)	57 (17, 87)
Sex (male/female)	252/203	252/203	252/203
Location			
Colon	196 (43.1%)		
Rectal	259 (56.9%)		
TNM stage			
I	49 (10.8%)		
II	164 (36.0%)		
III	177 (38.9%)		
IV	65 (14.3%)		
Differentiation level			
High	14 (3.1%)		
Middle	370 (81.3%)		
Low	71 (15.6%)		
Invasion depth			
T1	10 (2.2%)		
T2	55 (12.1%)		
T3	70 (15.4%)		
T4	320 (70.3%)		
Lymph node metastasis			
N0	232 (51.0%)		
N1	151 (33.2%)		
N2	72 (15.8%)		
Neutrophil(*10^9/L)	3.45 (2.73, 4.58)[NA]	3.46 (2.79, 4.19)	3.38 (2.70, 4.24)
Lymphocyte(*10^9/L)	1.62 (1.30, 2.03)[ab]	1.95 (1.60, 2.32)	1.74 (1.35, 2.11)
Fibrinogen(g/L)	3.20 (2.66,3.72)[ab]	2.77 (1.40,2.24)	2.70 (2.28,3.14)
Albumin(g/L)	39.87 (37.23,41.86)[ab]	44.01 (42.01,45.78)	41.38 (39.30, 43.53)
pre-Albumin(mg/L)	198.60 (153.20, 242.30)[ab]	248.55 (209.43, 286.14)	266.50 (235.40, 301.90)
NLR (ratio)	2.23 (1.62, 2.90)[ab]	1.81 (1.40, 2.24)	1.94 (1.48, 2.61)
FAR (ratio)	8.04 (6.59, 9.64)[ab]	6.38 (5.37, 7.47)	6.49 (5.48, 7.71)
FPR (ratio)	16.22 (11.79, 21.87)[ab]	11.16 (8.81, 14.53)	10.00 (8.04, 12.35)
CEA (ng/mL)	3.03 (1.52, 8.00)[b]		1.38 (0.76, 2.21)
CA199 (U/mL)	15.93 (8.72, 29.51)[b]		10.06 (6.64, 16.82)

Cases, patients with CRC; FAR, 100*Fibrinogen/Albumin; FPR, Fibrinogen/pre-Albumin; Benign controls, patients with colorectal polyp; M with R, Mean with range; NA, not significant; NLR, neutrophil-to-lymphocyte ratio.

[a]$P < 0.05$: cases vs healthy controls.

[b]$P < 0.05$: cases vs benign controls.

70 (15.4%), and 320 (70.3%), respectively. Two hundred and thirty-two (51.0%) CRC patients were identified without lymph node metastasis.

Fibrinogen level, NLR, FAR, and FPR were significantly higher in CRC patients compared with healthy participants; however, Alb and pAlb were obviously low in the cases (Table 1, Figures 1 and S1A). The similar results were observed between the cases and the benign controls. Moreover, the levels of CEA and CA199 were apparently increased in CRC patients than that in benign controls. To further explore the diagnostic and predictive values of FPR, FAR, and NLR, we investigated associations between these biomarkers and TNM stage. The higher levels of FPR, FAR, and NLR were observed in I/

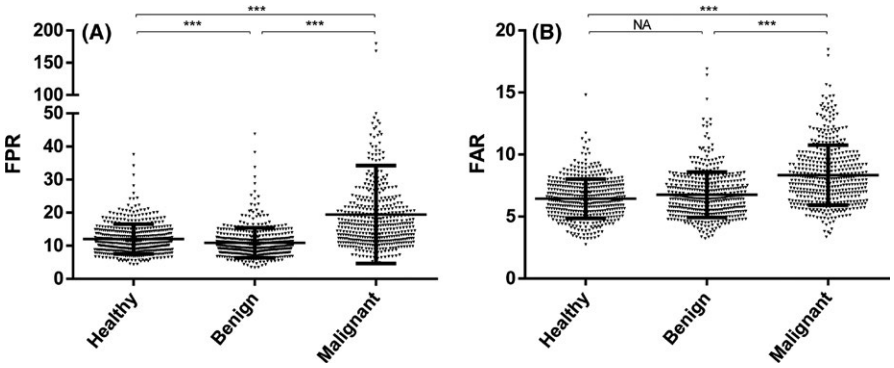

FIGURE 1 Fibrinogen/pre-Albumin (FPR) (A) and 100*Fibrinogen/Albumin (FAR) (B) level in the cases, healthy and benign controls

II and III/IV stage comparing to the controls, and the levels in stage III/IV exceed that in stage I/II patients for these three biomarkers (Figures 2 and S1B).

3.2 | Diagnostic value of FPR, FAR, and NLR

Receiver-operating characteristics analysis showed that FAR owned the highest diagnostic efficacy in discriminating cases from healthy controls, and the AUC (0.741) was close to that of FPR (0.738). The optimal cutoff values of FAR and FPR were 8.018 (sensitivity, Sen = 50.5%, specificity, Spe = 86.2%, positive predictive value (PPV) = 78.5%, negative predictive value (NPV) = 63.5%), and 15.360 (Sen = 54.1%, Spe = 81.3%, PPV = 75.4%, NPV = 63.6%), respectively. Otherwise, the optimal cutoff value, AUC, sensitivity, and specificity value of NLR were 2.217, 0.644, 51.2%, and 74.3% (Figure 3A and Table 3).

3.3 | Logistic regression analysis

Logistic regression analysis was used to evaluate the risk factors for telling CRC apart from benign disease. The risk factors found to be markedly associated with differentiation of benign disease and CRC in the regression analysis included FPR (odds ratio, OR = 5.532; 95% confidence interval, 95% CI = 3.715-8.238, $P < 0.05$), NLR (OR = 1.423, 95% CI = 1.022-1.981, $P < 0.05$), CEA (OR = 5.882, 95% CI = 4.016-8.615, $P < 0.05$), and CA199 (OR = 1.782, 95% CI = 1.258-2.524, $P < 0.05$) (Table 2).

3.4 | Distinguishing CRC from benign disease

In the cases and benign controls, the diagnostic value of FPR was better than FAR, NLR, CEA, and CA199 ($P < 0.05$), indicating FPR was the best one among these biomarkers for distinguishing CRC from benign disease. Therefore, FPR in conjunction with other biomarkers were further analyzed for combined detection. (Figure 4) As expected, the combined biomarkers resulted in enhanced diagnostic efficacy, and the combination of FPR, CEA, and CA199 had the maximum AUC in discriminating between CRC and benign disease (AUC = 0.845, Sen = 67.9%, Spe = 85.3%, PPV = 83.5%, NPV = 70.9%). Further, four biomarkers' (FPR, NLR, CEA and CA199) combination was adopted to separate CRC from benign disease, resulting in an improved efficacy. (AUC = 0.843, Sen = 83.5%, Spe = 68.8%, PPV = 74.2%, NPV = 79.1%) (Table 3).

4 | DISCUSSION

Cancer-related inflammation has been recognized as a hallmark of tumorigenesis and progression.[20] Numerous studies reported that inflammatory bowel disease could trigger choric inflammation and increase the risk of CRC.[21] On the contrary, the continuous use of low-dose anti-inflammatory drugs such as aspirin or NSAIDs could reduce the risk of CRC.[22] The measurement of the systemic inflammatory response has been extensively analyzed; however, the diagnostic roles of FAR and FPR in CRC remained unclear.

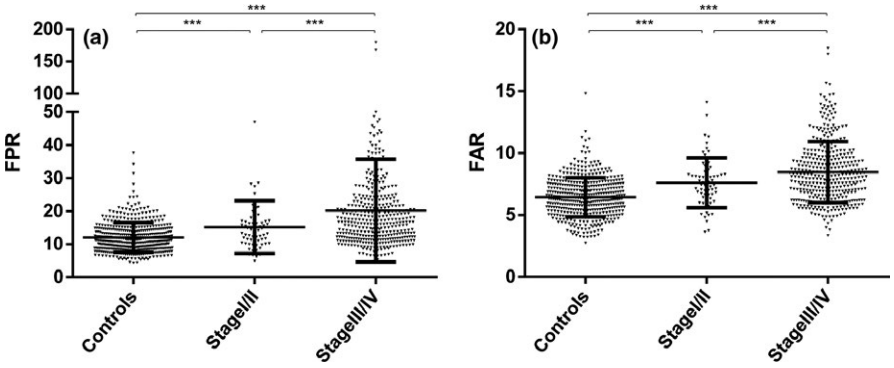

FIGURE 2 Fibrinogen/pre-Albumin (FPR) (A) and 100*Fibrinogen/Albumin (FAR) (B) level in TNM stage and healthy controls

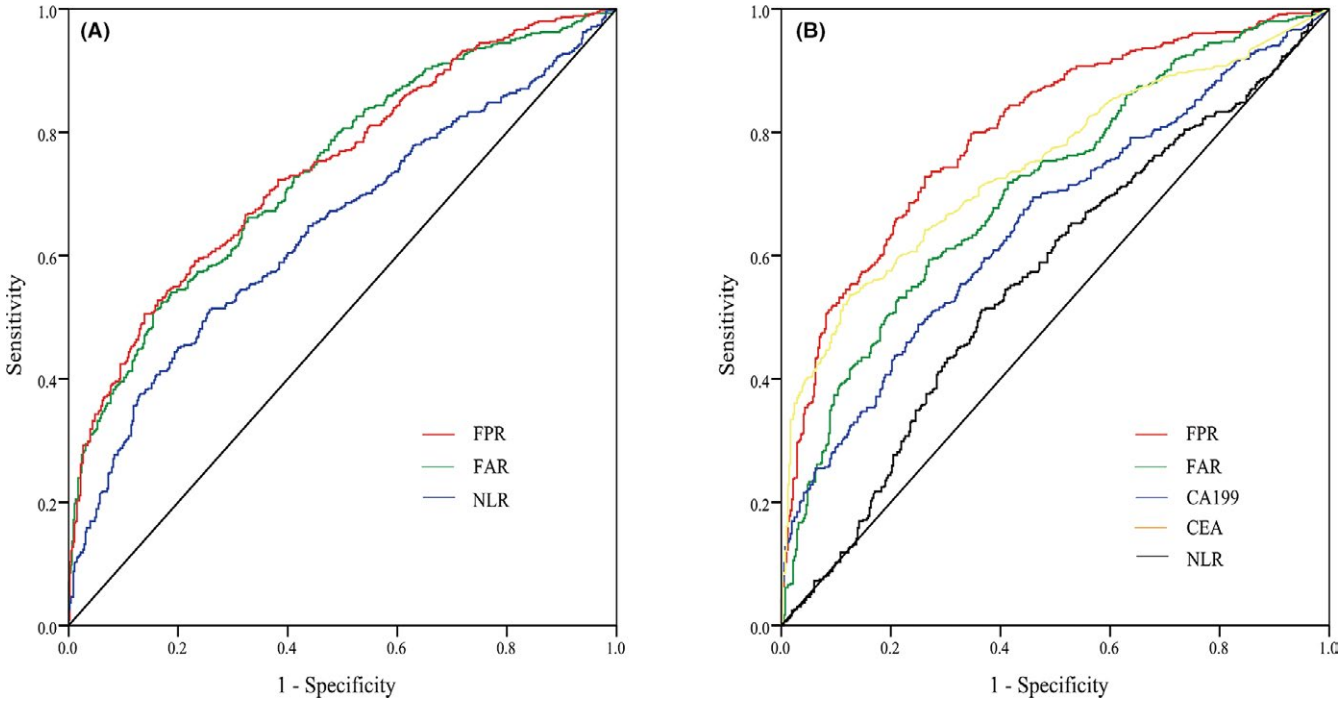

FIGURE 3 Diagnostic efficacy of inflammatory-based biomarkers in colorectal cancer (CRC). (A) Receiver-operating characteristics (ROC) curve of CRC compared with healthy controls; (B) ROC curve of CRC compared with benign controls

TABLE 2 Multiple logistic regression analysis of factors used for differentiation CRC from benign colorectal disease

Variables	β	OR (95% CI)	*P* value
FPR	1.711	5.532 (3.715-8.238)	0.000
FAR	0.192	1.211 (0.810-1.812)	0.351
NLR	0.353	1.423 (1.022-1.981)	0.037
CEA	1.772	5.882 (4.016-8.615)	0.001
CA199	0.578	1.782 (1.258-2.524)	0.000

CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 19-9; CI, confidence interval; FAR, 100*Fibrinogen/Albumin; FPR, Fibrinogen/pre-Albumin; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio.

In the present study, we firstly assessed the diagnostic value of the FAR and FPR in CRC patients. Our study demonstrates that elevated Fib level, NLR, FAR, and FPR were observed in the cases compared with the healthy or benign controls; however, Alb and pAlb were obviously low in the cases. We also found NLR, FAR, and FPR were elevated in the early tumor stage compared with healthy controls, indicating that these three parameters could act as early diagnostic markers for CRC. In addition, our results revealed that the CRC diagnostic value of FAR and FPR was superior to NLR, and the combination of FPR, CEA, and CA199 could increase the diagnostic efficacy for distinguishing CRC from benign disease. The logistic analysis revealed that FPR represented a risk factor for distinguishing CRC from the benign colorectal disease. Besides, the following reasons could explain our findings further.

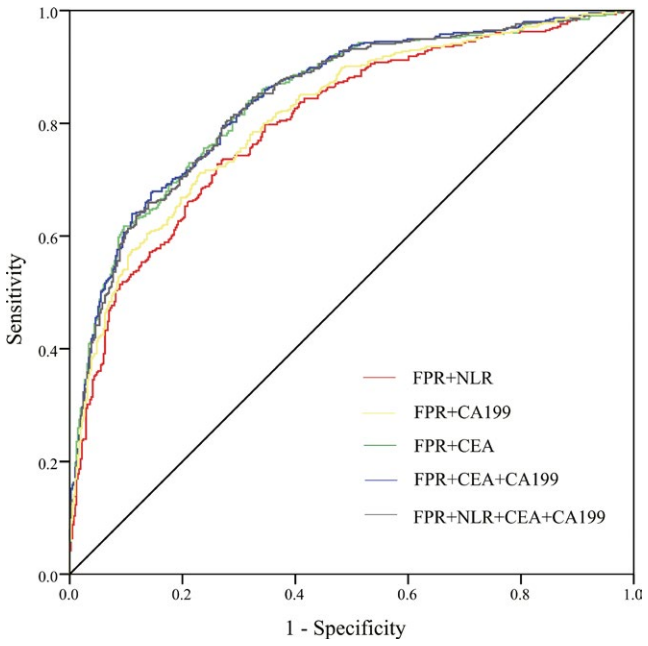

FIGURE 4 Receiver-operating characteristics (ROC) curve of combined biomarkers compared with benign controls in colorectal cancer (CRC)

On the one hand, tumor cell could stimulate hemostatic system to promote the pro-thrombotic property and to trigger the generation of Fib.[23] Malignant human and experimental animal tumor cells could express many procoagulant and fibrinolytic factors which sustained adhesion and survival of tumor cells, including Fib.[24] And then, Fib could not only facilitate adhesion among tumor cells,

TABLE 3 The diagnostic value of CRC biomarkers compared with healthy controls and benign controls

Biomarker	Cut-off value		AUC		Sen (%)		Spe (%)		PPV (%)		NPV (%)		YI	
	a	*b*	*a*	*b*	*a*	*b*	*a*	*b*	*a*	*b*	*a*	*b*	*a*	*b*
FPR	15.360	12.247	0.738	0.801	54.1	72.7	81.3	74.3	75.4	73.9	63.6	73.2	0.3538	0.4703
FAR	8.018	7.529	0.741	0.707*	50.5	59.3	86.2	72.5	78.5	68.4	63.5	64.1	0.3670	0.3187
NLR	2.217	2.218	0.644*	0.565*	51.2	51.2	74.3	64.0	66.6	58.7	60.4	56.7	0.2549	0.1516
CEA		2.780		0.746*		53.6		87.5		82.4		63.3		0.4113
CA199		16.570		0.652*		48.8		75.0		68.1		57.2		0.2379
FPR+CEA		-		0.841*		80.2		72.4		76.0		77.0		0.5260
FPR+NLR		-		0.800		73.4		73.6		73.6		73.5		0.4703
FPR+CA199		-		0.814*		71.2		76.9		77.1		71.0		0.4813
FPR+CEA+CA199		-		0.845*		67.9		85.3		83.5		70.9		0.5325
FPR+NLR+CEA+CA199		-		0.843*		83.5		68.8		74.2		79.1		0.5227

AUC, area under curve; *a*, compared with healthy controls; *b*, compared with benign controls; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 19-9; FAR, 100*Fibrinogen/Albumin; FPR, Fibrinogen/pre-Albumin; NLR, neutrophil-to-lymphocyte ratio; NPV, negative predictive value; PPV, positive predictive value; Sen, sensitivity; Spe, specificity; YI, Youden's index.
*$P < 0.05$ vs FPR.

platelets, and endothelial cells, but also regulate tumor cell proliferation and migration by interacting with multiple receptors of cancer cells.[25,26] Consequently, enhanced tumor cell escaping and impaired immunologic surveillance directly result in the onset and progression of cancer.

On the other hand, the prevalence of malnutrition is high in patients with cancer. Moreover, the common inflammatory cytokines, interleukin-6, could suppress the synthesis of nutritional protein, leading to hypoproteinemia in cancer patient.[27] Serum Alb and pre-Alb, two accepted biomarkers to assess the nutritional condition, were recognized to be significant factors to predict recovery and survival of CRC cases in some studies.[28]

Above all, it appears to be reasonable to explore the diagnostic efficacy of FPR and FAR for CRC, and that could be more convincible on account of the combined reflection of inflammation and malnutrition. However, some limitations in the current study should be addressed. The sample size in the current study was small, and our results need to be validated by prospective research in further research around the world.

5 | CONCLUSION

Fibrinogen/pre-Albumin represents a useful CRC diagnostic biomarker, and the combination of FPR, CEA, and CA199 could significantly improve the diagnostic efficacy in discriminating CRC from the benign colorectal disease.

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ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Second Affiliated Hospital of Nanchang University and adhered to the tenets of the Declaration of Helsinki.

DATA AVAILABILITY

Readers can access the data supporting the conclusions of the study by contacting with author through Email.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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