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Research article

Evaluation of C–reactive protein and fibrinogen in comparison to CEA and CA72–4 as diagnostic biomarkers for colorectal cancer

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ABSTRACT

Carcinoembryonic antigen (CEA) and carbohydrate antigen 72–4 (CA72–4) are commonly used markers for colorectal cancer (CRC) in clinical applications. However, low positivity rate and sensitivity limits their clinical effectiveness. In this study, we explored the potential of C–reactive protein (CRP) and fibrinogen to improve the diagnostic efficiency of traditional biomarkers of CRC. The concentrations of CRP and fibrinogen in plasma were significantly higher in CRC patients compared with benign or healthy controls. The area under the ROC curves (AUCs) showed that the diagnostic efficacy of CRP and fibrinogen was 0.745 (95% CI: 0.712–0.779) and 0.699 (95% CI: 0.663–0.734), respectively. AUC increased to 0.750 (95% CI: 0.716–0.784) when CRP and fibrinogen were combined. It also further improved to 0.889 (95% CI: 0.866–0.913) when CRP and fibrinogen were integrated with CEA and CA72–4. Moreover, this combination increased the maximum area under AUC to 0.857 (95% CI: 0.830–0.883), which effective differentiated CRC from benign disease. Overall, this study found that CRP and fibrinogen were highly expressed in the plasma of CRC patients, suggesting their potential to improve the diagnostic efficiency of traditional biomarkers of CRC.

1. Introduction

Colorectal cancer (CRC) is the most common cancer worldwide, and the leading cause of cancer–related deaths in most countries [1]. Despite significant progress in CRC diagnosis and therapy, the current diagnosis methods are not effective, leading to very poor prognosis of patients [2]. Body fluid–centered testing is an inexpensive and non–infiltrative approach, which is well suited for large–scale screening, monitoring tumor progression and conducting prognostic assessment [3]. For example, plasma carcinoembryonic antigen (CEA) and carbohydrate antigen 72–4 (CA72–4) are commonly used in laboratories as tumor markers for CRC [4]. However, these markers have not been applied in the clinic because of their unsatisfactory sensitivity and specificity. Therefore, there is a need to research and identify new methods with improved sensitivity and specificity for CRC diagnosis.

It is well known that chronic inflammation increases cancer risk and is one of the hallmarks of cancer [5,6]. Numerous studies have elucidated the link between chronic inflammation of the intestinal tract and CRC development, indicating the important role of

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inflammatory factors in the tumorigenesis of CRC [7]. This suggests that the factors associated with tumor inflammation have the potential to be valuable diagnostic biomarkers for CRC. C–reactive protein (CRP), a plasma protein synthesized by the liver, is an inflammatory reaction protein with proinflammatory properties [8]. Studies have shown that it plays central roles in the pathological process of many disease, including infections and auto–immune diseases like rheumatoid arthritis or malignancies [9]. Given that malignant carcinomas are chronic inflammation diseases, the plasma CRP contents are often elevated in cancer patients [10,11]. Fibrinogen is a soluble 340 kDa glycoprotein comprising of three polypeptide chains: alpha, beta, and gamma. It plays a significant role in the coagulation cascade and fibrinolysis. Moreover, plasma fibrinogen contents have been documented to modulate the systemic inflammation response [12]. Recent studies have revealed that circulating fibrinogen level is generally high in solid malignancies, and is commonly associated with tumor stage, invasion, and recurrence [13]. These findings suggest that both CRP and fibrinogen are inflammatory factors present in cancer patients, suggesting their potential to be exploited for routine assessment in numerous clinical laboratories [14].

The aim of the present study was to evaluate the diagnostic efficiency of single use or combined use of CRP and fibrinogen with traditional tumor markers on CRC patients to provide a more sensitive combination for CRC diagnosis. It is expected that our findings will provide a more optimized scheme to improve the diagnostic efficiency of CRC.

2. Materials and methods

2.1. Samples collection

This study involved 373 CRC patients and 505 colorectal polyp patients admitted at the Taian City Central Hospital from 3rd April 2019 to 20th March 2021. All patients were newly diagnosed with CRC and confirmed by two independent pathologists. All peripheral plasma samples were collected from 7:30 to 9:30 a.m. before the intervention at the clinical laboratory department. The blood samples of the patients were collected before they received surgery, chemotherapy, or other treatments. The demographic information of the participants including gender, age, tumor location, TNM stage and grade of differentiation is summarized in Table 1. A total of 520 healthy controls who participated in the health examination at the Health Management Center were also selected and included in the healthy control group. All healthy controls showed normal results after receiving a full package of health examination, including blood routine, urine routine, stool routine, blood clotting tests, full sets of tests for plasma biochemistry and tumor markers, chest computed tomography (CT) scan, abdominal B ultrasound, electrocardiogram (ECG), and gastrointestinal endoscopy. In addition, qualified healthy controls had no chronic disease, such as immune–deficiency disease, hypertension, or diabetes.

2.2. Tumor marker detection

The plasma CEA and CA72–4 contents were assessed quantitatively using the electro–chemiluminescence assay (ECLIA) on the Roche Cobas e601 fully automated immuno–assay platform (Roche Diagnostics GmbH, Germany). The CRP and fibrinogen contents were determined using Cobas e601 (Roche, Mannheim, Germany) and CA7000 analyzer (Sysmex Corporation, Kobe, Japan),

Table 1
Demographic and clinical characteristics of the participants.

Characteristics	CRC (n = 373)	BC (n = 505)	HC (n = 520)
Gender, male n (%)	244 (65.4)	335 (66.4)	317 (60.9)
Age, years	66.26 ± 9.07	58.83 ± 10.42	49.33 ± 10.62
Location			
Right	132		
Transverse	66		
Left	113		
Sigmoid	24		
Rectal	38		
T stage			
T1	87		
T2	140		
T3	101		
T4	45		
N stage			
N0	243		
N1	98		
N2	32		
M stage			
M0	341		
M1	32		
Differentiation			
Well	36		
Moderate	291		
Poor	46		

CRC, colorectal cancer; BC, benign control; HC, healthy control.

respectively. The original two–level quality control (QC) products, including PC TM1 and PC TM2, PC U1 and PC U2, and PC V1 and PC V2, were run alongside patient samples. The daily QC results were analyzed in accordance with the Westgard Sigma rules. The common QC rules were as follows: 1_{2s}, 1_{3s}, 2_{2s}, R_{4s}, 4_{1s}, and 10X. Patients' clinical parameters, including age, gender, pathology diagnosis, and the laboratory test results were retrieved from the medical records system.

2.3. Statistical analyses

The Mann–Whitney *U* test was used to compare differences between the CRC subjects and healthy controls or colorectal polyp patients. All statistical analyses were performed using GraphPad Prism 6.0 (San Diego, United States) software. Receiver operating characteristic (ROC) curves were utilized to assess the diagnostic abilities of the tumor biomarkers. All ROC curves were generated with SPSS v22.0 (SPSS Inc., United States) software. Multiple parameters were combined in models for ROC curve analysis. Briefly, a multinomial logistic regression analysis model was built with patient diagnosis classification as the dependent variable and CRP, fibrinogen, CEA, CA72–4 as factors using SPSS software. Subsequently, the constant terms and coefficients of the logistic regression equation were obtained. The compute variable function in SPSS was then used to calculate combined predictors. Finally, combining diagnosis ROC curve was built using combined predictors and patient diagnosis classification. The *p*–values were utilized for comparison between AUCs for single and combined parameters using MedCalc v20.1 (MedCalc Inc., Mariakerke, Belgium) software. Experimental results are presented as the mean ± standard deviation (SD), with $p < 0.05$ considered statistically significant.

3. Results

3.1. Expression levels of CRP and fibrinogen in plasma

To evaluate the potential of CRP and fibrinogen in the diagnosis of CRC, we first assessed their concentration in the plasma of 520 healthy individuals, 505 colorectal polyp patients, and 373 CRC patients. The results showed that CRP and fibrinogen were significantly elevated in the CRC group compared with benign or healthy controls (Fig. 1A and B). Furthermore, the correlation of the stratification of the population with CRP and fibrinogen levels was analyzed. The results showed that high levels of CRP and fibrinogen were significantly associated with tumor differentiation (Table 2, $p = 0.026$ and $p = 0.017$, respectively). We also assessed the expression levels of CEA and CA72–4, which the most commonly utilized CRC biomarkers in clinical applications. The results showed CEA and CA72–4 were highly expressed in CRC plasma samples compared with benign or healthy controls (Fig. 1C and D).

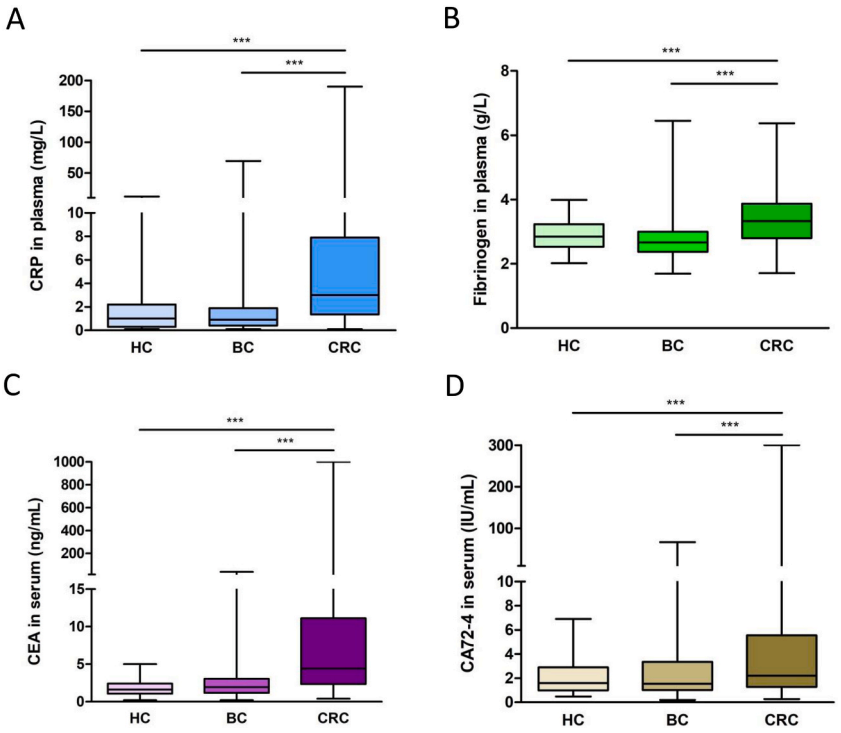

Fig. 1. The expression of CRP, fibrinogen, CEA, and CA72–4 in plasma. The expression levels of CRP (A), fibrinogen (B), CEA (C) and CA72–4 (D) in 520 healthy controls (HC), 505 benign controls (BC), and 373 CRC patients, respectively. (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, NS: not significant).

Table 2
Relationship between stratification of the population and CRP and fibrinogen levels.

Variable	Cases	CRP	*p*–value*	fibrinogen	*p*–value*
		Median with interquartile range		Median with interquartile range	
Age			0.180		0.286
<60	92	2.500 (1.225–7.025)		3.310 (2.770–3.722)	
≥60	281	3.500 (1.450–8.650)		3.330 (2.805–3.925)	
Gender			0.806		0.525
Male	244	3.350 (1.300–8.400)		3.330 (2.742–3.915)	
Female	129	2.800 (1.400–7.300)		3.300 (2.950–3.790)	
Location			0.515		0.122
Right	132	2.500 (1.200–6.725)		3.390 (2.797–3.877)	
Transverse	66	3.900 (1.800–6.400)		3.435 (2.962–3.927)	
Left	113	2.900 (1.400–7.600)		3.350 (2.830–3.860)	
Sigmoid + Rectal	62	3.500 (1.250–7.600)		3.060 (2.650–3.740)	
Differentiation			0.026*		0.017*
Well	36	3.850 (1.600–7.300)		3.145 (2.615–3.820)	
Moderate	291	2.800 (1.200–7.600)		3.320 (2.790–3.860)	
Poor	46	6.550 (1.575–24.87)		3.505 (3.072–4.175)	

p–values are based on Mann–Whitney *U* test or One-way ANOVA analysis. *$p < 0.05$ indicates significant difference.

3.2. Association between CRP, fibrinogen, CEA, CA72–4 and the tumor stage

To determine the biological relevance of the biomarkers of CRC, we analyzed the relationship between their expression levels and the TNM stages. As shown in Fig. 2, the levels of CRP, fibrinogen, CEA and CA72–4 were all positively correlated with CRC clinical M stage (Fig. 2A–D). The level of CEA was correlated with all the clinical T stage, N stage and M stage, with the highest levels observed in T4, N2 and M1, respectively (Fig. 2C). An increase in T stage and N stage was associated with higher CRP and fibrinogen levels to a certain degree (Fig. 2A and B). However, the levels of CA72–4 showed no significant differences between different T stages (Fig. 2D).

3.3. Diagnostic potential of plasma CRP and fibrinogen in CRC patients

Further, an ROC curve was generated to validate the diagnostic potential of plasma CRP and fibrinogen for CRC patients. The areas under the curve (AUCs) for the plasma CRP and fibrinogen in patients were 0.745 (95% CI: 0.712–0.779) and 0.699 (95% CI: 0.663–0.734), respectively, which were higher compared with healthy controls. The diagnostic efficiency of CRP and fibrinogen combination was also explored. The AUC this combination was 0.750 (95% CI, 0.716–0.784), indicating that plasma CRP and fibrinogen could function as non–infiltrative plasma factors for CRC (Fig. 3A). Furthermore, the AUC for CEA and CA72–4 was 0.837 (95% CI: 0.810–0.865) and 0.631 (95% CI: 0.594–0.669), respectively. When CEA and CA72–4 were combined, the AUC value improved to 0.852 (95% CI: 0.826–0.879) (Fig. 3B). To investigate the independent effect of the parameters on CRC diagnosis, multivariable logistic regression analysis was performed. The results demonstrated that old age, high CRP, fibrinogen, and CEA levels were independently predictive factors of CRC (Table 3).

3.4. The combination of CRP, fibrinogen, and traditional CRC biomarkers enhanced the diagnostic value

When CEA was combined with CRP and fibrinogen, its AUC increased from 0.837 (95% CI: 0.810–0.865) to 0.877 (95% CI: 0.853–0.901) and 0.859 (95% CI: 0.833–0.888) (Fig. 4A and B), respectively. Combining all three factors increased the AUC value to 0.880 (95% CI, 0.855–0.904) (Fig. 4C). An AUC of 0.765 (95% CI: 0.731–0.799) was obtained when CRP and fibrinogen were combined with CA72-4 (Fig. 4D–F) and 0.888 (95% CI: 0.865–0.912) and 0.872 (95% CI: 0.847–0.897), when plasma CRP or fibrinogen were combined with CEA and CA72–4, respectively (Fig. 4G and H). Notably, the greatest AUC of 0.889 (95% CI, 0.866–0.913) was attained when all four parameters were combined, which was significantly higher than the value for individual parameters (Fig. 4I, Table 4, All $p < 0.0001$).

3.5. Distinguishing CRC from benign disease

To further evaluate the diagnostic value of plasma CRP and fibrinogen for CRC and benign controls, we collected 505 plasma specimens of colorectal polyps in the benign control group. As shown in Fig. 5A, the AUCs of CRP and fibrinogen were 0.758 (95% CI: 0.726–0.790) and 0.761 (95% CI: 0.731–0.791), respectively, which was higher compared with the benign controls. When CRP and fibrinogen, the AUC reached 0.789 (95% CI: 0.758–0.819). Meanwhile, the AUCs for CEA and CA72–4 were 0.776 (95% CI: 0.747–0.806) and 0.633 (95% CI: 0.597–0.669), respectively, which increased to 0.784 (95% CI: 0.755–0.813) when the two were combined (Fig. 5B).

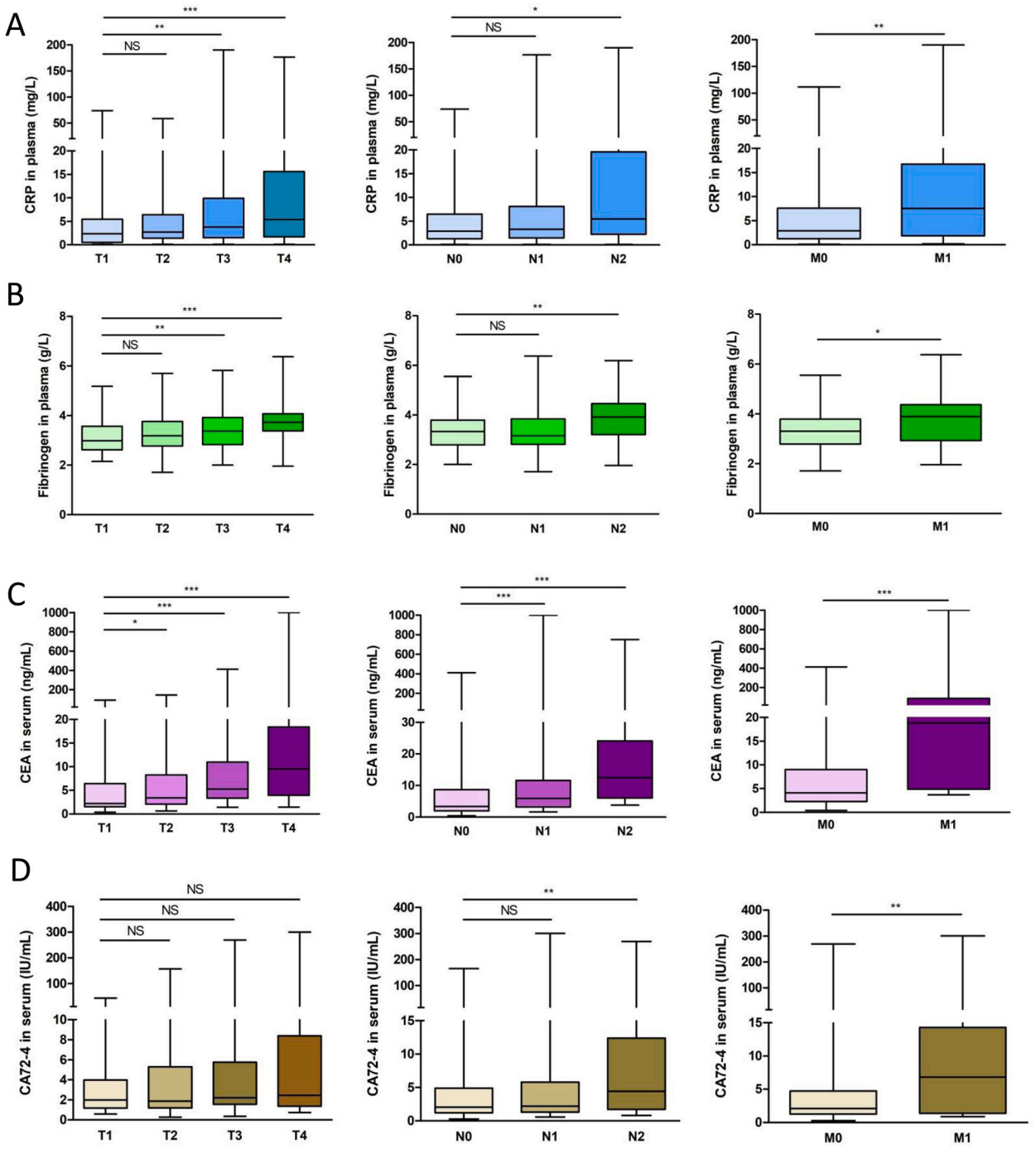

Fig. 2. Association between the plasma levels of CRP, fibrinogen, CEA, CA72–4 and tumor stage. Assessment of CRP (A), fibrinogen (B), CEA (C) and CA72–4 (D) levels derived from CRC patient plasma according to the TNM stage. (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, NS: not significant).

3.6. The diagnostic performance of combining the biomarkers to differentiate benign and CRC disease

CRP and fibrinogen significantly elevated the AUC of CEA from 0.776 (95% CI: 0.747–0.806) to 0.836 (95% CI: 0.809–0.864) and 0.838 (95% CI: 0.812–0.864), respectively (Fig. 6A and B). For combined CRP, fibrinogen, and CEA, the AUC value increased to 0.883 (95% CI, 0.826–0.880) (Fig. 6C). The integration of CRP and fibrinogen with CA72–4 resulted in a higher AUC of 0.756 (95% CI: 0.723–0.790) and 0.767 (95% CI: 0.736–0.799), respectively (Fig. 6D and E). Combining all three factors above increased the AUC value to 0.785 (95% CI, 0.742–0.817) (Fig. 6F). Moreover, when both CEA and CA72–4 were combined with CRP and fibrinogen, AUCs

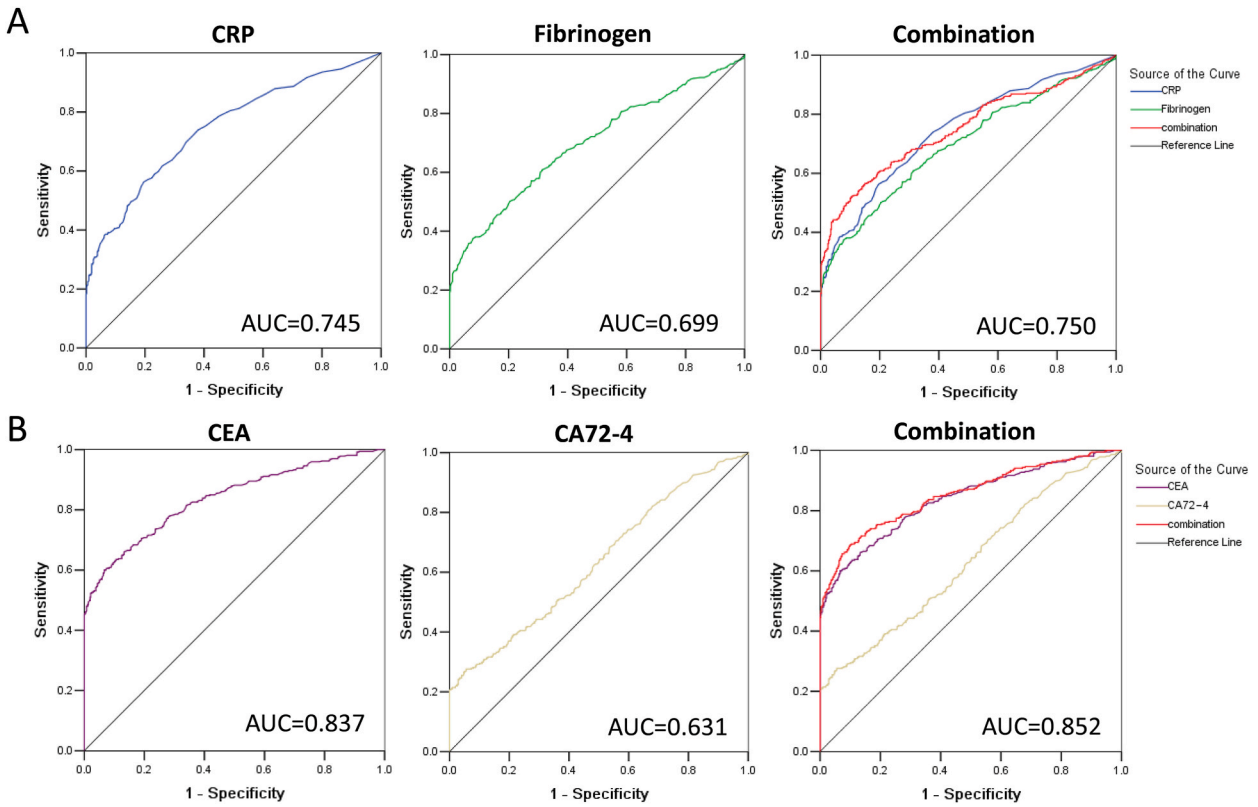

Fig. 3. Receiver–operating characteristics (ROC) curve of CRP, fibrinogen, CEA, and CA72–4 in plasma for CRC. (A) AUC for CRP, fibrinogen, and the combination of CRP and fibrinogen for CRC. (B) AUC for CEA, CA72–4, and the combination of CEA and CA72–4 for CRC.

Table 3
Multivariable logistic regression analysis for CRC diagnosis.

Variable	Modeled vs. reference	t	*p*–value
Gender	Male vs. Female	−0.171	0.864
Age	Young vs. Old	17.949	<0.001*
BMI	Low vs. High	0.345	0.730
CRP	Low vs. High	4.199	<0.001*
fibrinogen	Low vs. High	6.994	<0.001*
CEA	Low vs. High	2.371	0.018*
CA724	Low vs. High	1.766	0.077

p–values are based on D'Agostino–Pearson test; *$p < 0.05$ indicates significant difference.

of 0.841 (95% CI: 0.814–0.868) and 0.841 (95% CI: 0.815–0.867) were obtained, respectively (Fig. 6G and H). The highest AUC of 0.857 (95% CI, 0.830–0.883) was obtained for a combination of all four factors (Fig. 6I).

4. Discussion

It is well established that chronic inflammation in the tumor microenvironment is closely associated with carcinogenesis and tumor progression [15]. Numerous studies have highlighted the clinical significance of various inflammation–related markers in several types of cancer [16]. Other studies have proven that the inflammation–related biomarkers are correlated with prognosis in many solid cancers, such as rectal cancer, non–small cell lung cancer, and hepatocellular carcinoma [17–19]. However, the positivity rate and sensitivity are unsatisfactory, which limits their use in clinical practice [20]. Recent studies have revealed that diagnosis based on a combination of current tumor signatures may be practical for clinical application [21,22]. Herein, we screened routinely available biochemical laboratory parameters, and found that plasma CRP and fibrinogen may be potentially effective diagnostic markers of CRC. We also analyzed the value of the combined detection of CRP and fibrinogen with CEA and CA72–4 using 373 CRC patients, 505 colorectal polyp individuals, and 520 health donors. From the results, a more optimized combination was obtained that could improve the diagnostic efficiency of CRC.

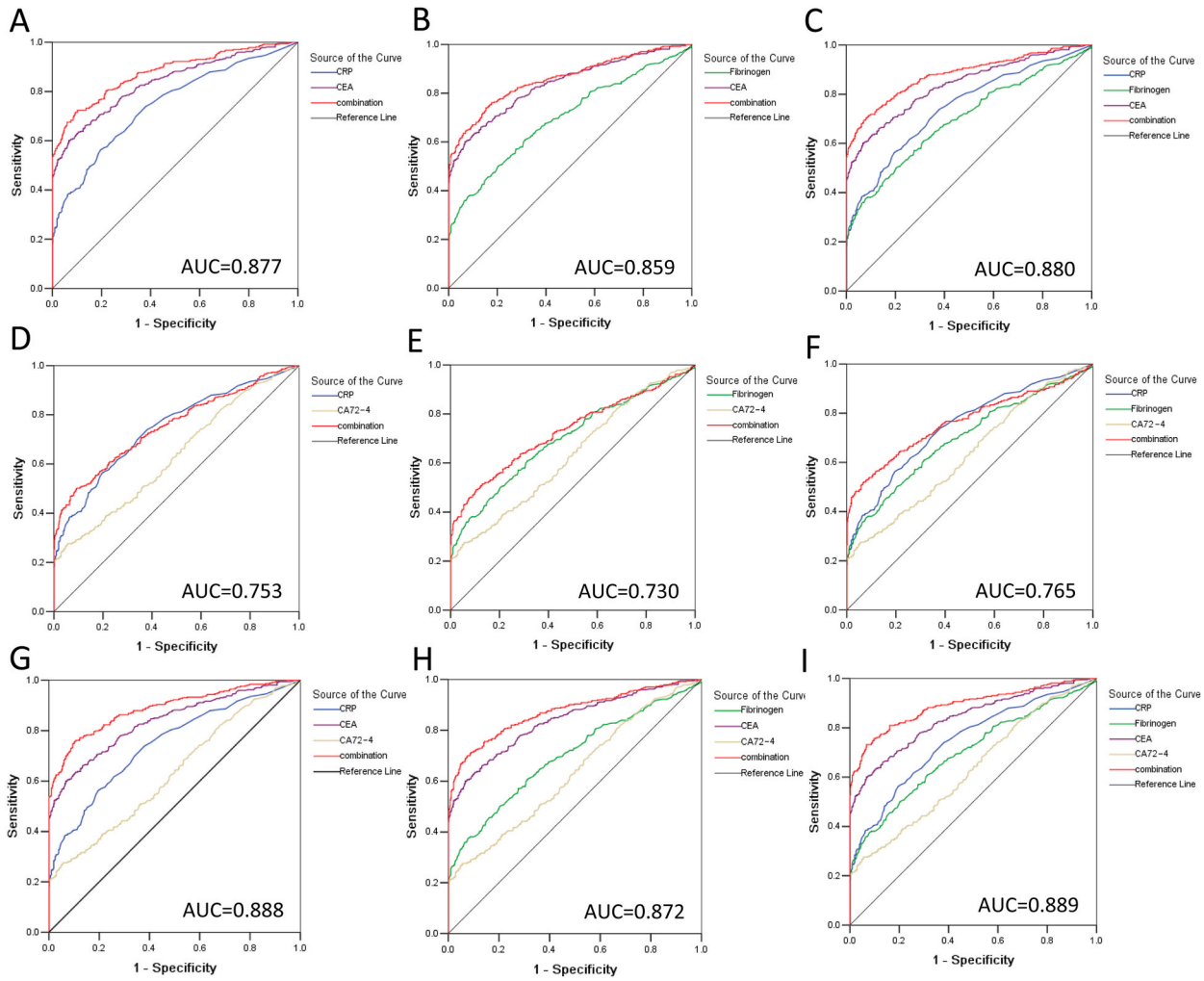

Fig. 4. Improved diagnostic value of plasma CRP and fibrinogen combined with traditional tumor markers in CRC patients. The AUCs of CEA combined with CRP (A), fibrinogen (B), and both (C). The AUCs of CA72–4 combined with CRP (D), fibrinogen (E), and both (F). The AUCs of CEA and CA72–4 combined with CRP (G), CA72–4 (H), and both (I).

Table 4
Comparison between the AUCs for CRP, fibrinogen, CEA, CA72–4 and combination of them all.

AUCs	Combination of four parameters		
	Difference between areas	95% CI	*p*–value
CRP	0.144	0.112–0.176	$^*p < 0.0001$
fibrinogen	0.191	0.157–0.225	$^*p < 0.0001$
CEA	0.0523	0.0324–0.0722	$^*p < 0.0001$
CA72–4	0.258	0.220–0.296	$^*p < 0.0001$

CI, confidence interval; *p*-values are based on pairwise comparison; $^*p < 0.05$ indicates significant difference.

As one of the highly sensitive indicators of inflammation, CRP is easily detectable in the plasma [23]. For cancer patients, given that the host body depicts a state of non–specific inflammation in the tumor microenvironment, the tumor cells release proinflammatory factors that can induce secretion into blood of CRP by hepatocytes [24]. Accumulating evidence has demonstrated that the plasma CRP level is significantly increased in the blood of patients with tumors, suggesting its potential function as a biomarker for tumor progression [9]. Moreover, the increased level is associated with tumor differentiation, metastasis, and postoperative survival rate. Wiciński et al. reported that CRP could distinguish patients with endometriosis, soft tissue sarcomas, and possibly endometrial cancer [25]. In addition, the study found that CRP possibly mediates carcinogenesis and cancer progression by activating inter alia, FcgRs/MAPK/ERK, and FcgRs/NF–κB/NLRP3 pathways [25]. Yang et al. revealed that CRP is valuable in the diagnosis of ovarian

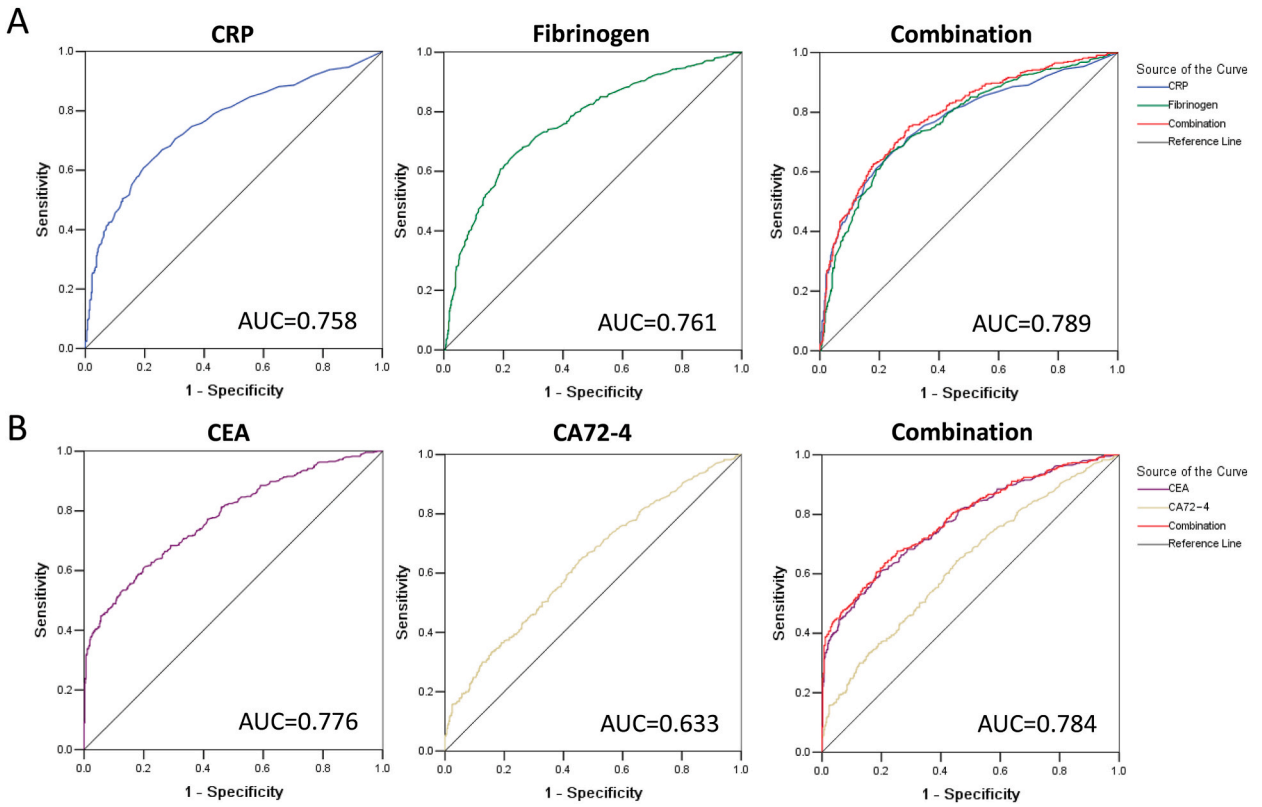

Fig. 5. Diagnostic value of CRP, fibrinogen, CEA, and CA72–4 in CRC compared to the benign controls. (A) AUC for CRP, fibrinogen, and the combination of CRP and fibrinogen in CRC. (B) AUC for CEA, CA72–4, and the combination of CEA and CA72–4.

cancer, and that combining CRP with CA125 and human epididymis secretory protein E4 (HE4) improved the diagnostic efficacy of ovarian cancer [26]. Consistent with previous findings, the present study found that combining plasma CRP with CEA or CA72–4 enhanced the AUCs from 0.836 (95% CI: 0.811–0.861) and 0.654 (95% CI: 0.619–0.688) to 0.883 (95% CI: 0.861–0.905) and 0.763 (95% CI: 0.731–0.794), respectively.

It has previously been reported that fibrinogen plays a vital role in the process of coagulation and regulation of inflammatory response [27]. The proinflammatory effect of fibrinogen may be involved in many diseases, including rheumatoid arthritis, colitis, lung fibrosis, and several types of cancer [28]. Besides, among the numerous clinical parameters, fibrinogen is a pivotal factor in individuals with cancer, which exhibits its potential as a tool for routine assessment in diverse clinical laboratories [29]. Previous studies have revealed that fibrinogen is not only involved in tumor angiogenesis and metastasis [30], but it is also associated with poor prognosis of some types of tumor, including CRC. For example, Son et al. reported that higher preoperative plasma fibrinogen levels were associated with gender, age, tumor differentiation, tumor stage, plasma CEA levels, and higher neutrophil/lymphocyte and platelet/lymphocyte ratios of CRC patients. The elevated plasma fibrinogen level was independently associated with worse disease–free survival and overall survival among patients [31]. Moreover, changes in plasma fibrinogen level induced by chemoradiotherapy (CRT) may be a promising biomarker for evaluating its therapeutic effect in rectal cancer patients. Kawai et al. found that the post–CRT fibrinogen level significantly correlated with lymphatic invasion, venous invasion, tumor size, depth of invasion, and the pathological tumor regression grading. In addition, patients with high post–CRT fibrinogen had significantly shorter disease–free survival [32]. These results proved that plasma fibrinogen also has great potential as a biomarker for the prognosis of CRC patients. Bloomston et al. identified 154 potential plasma markers for pancreatic cancer (PC) based on proteomic analysis involving a combination of two–dimensional gel electrophoresis and mass spectrometry and found that fibrinogen gamma discriminated cancer tissues from normal tissues [33]. This study has shown that combining plasma fibrinogen with CEA or CA72–4 enhanced the AUCs from 0.836 (95% CI: 0.811–0.861) and 0.654 (95% CI: 0.619–0.688) to 0.863 (95% CI: 0.839–0.883) and 0.742 (95% CI: 0.710–0.775), respectively. However, it should be noted that clinical validation of the combination using a larger sample size may be needed to demonstrate its application value in clinical practice.

This study has some limitations. Most patients in our hospital did not record the Duke's classification, and as a result, the underlying associations of the tumor markers described here with Duke's classification are still not well understood and require further investigation. Second, the sample size was small and future large–scale and well–designed prospective studies are needed to further validate the preliminary results, especially for the predictive role of CA72–4. Third, given the restraint of the broad specificity, CRP and fibrinogen may not be the ideal independent diagnostic markers for a specific disease. However, by combining them with the

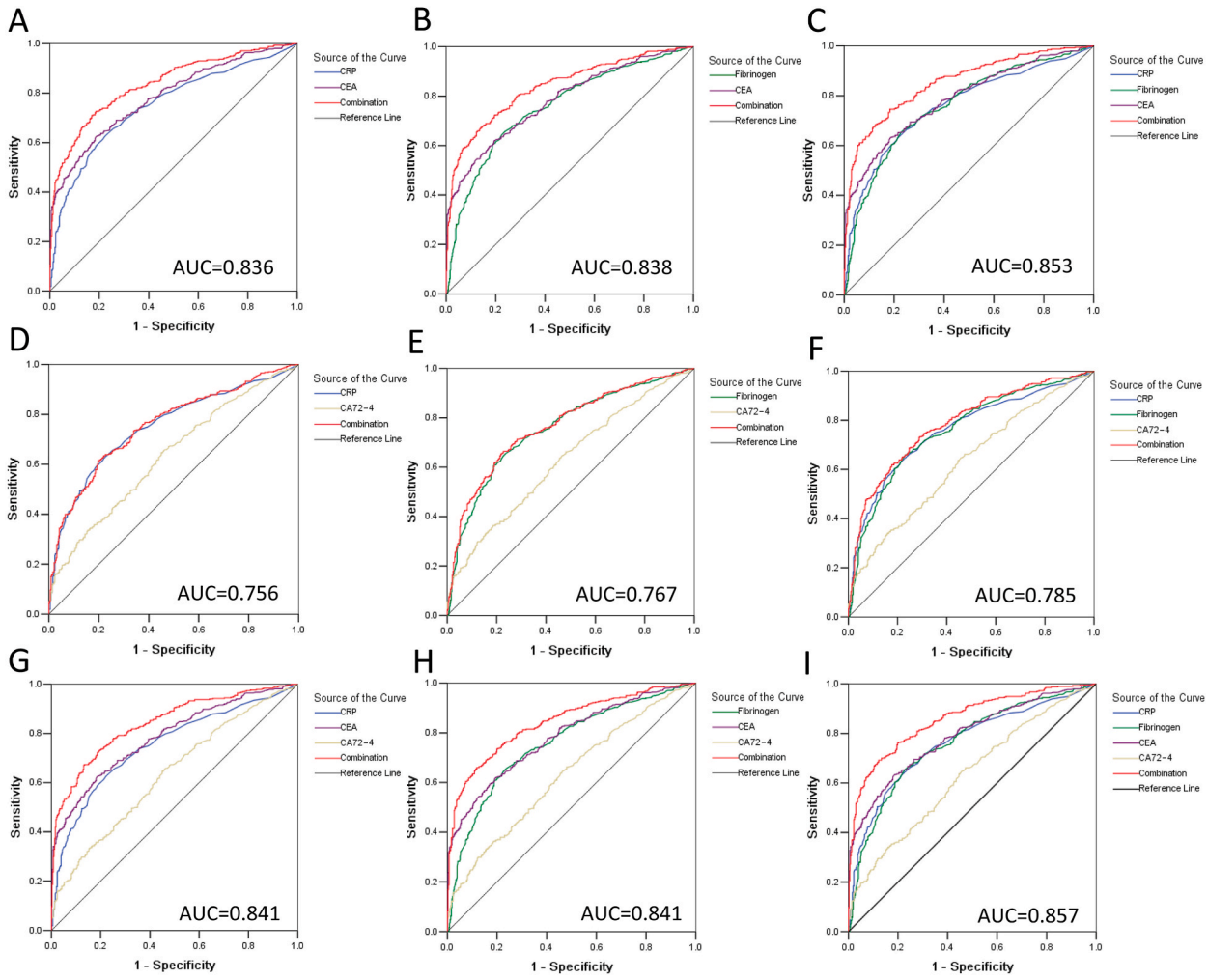

Fig. 6. Improved diagnostic value of combined biomarkers in CRC compared to the benign controls. The AUCs of CEA combined with CRP (A), fibrinogen (B), and both (C). The AUCs of CA72–4 combined with CRP (D), fibrinogen (E), and both (F). The AUCs of CEA and CA72–4 combined with CRP (G), CA72–4 (H), and both (I).

traditional tumor markers, such as CEA and CA72–4, it is possible to improve diagnostic efficiency of CRC and the positivity rate of CRC in screening the general population.

5. Conclusion

In summary, this study found that the two routinely available clinical laboratory parameters CRP and fibrinogen were highly expressed in the plasma of CRC patients, which indicates their great diagnostic potential. In addition, combining CRP and fibrinogen with the traditional tumor markers could significantly improve the diagnosis of CRC.

Ethics statement

The study was carried out in accordance with the Declaration of Helsinki. The experimental protocols were approved by the Ethics Committee of the Taian City Central Hospital (approval number: 20190303).

Declarations

Author contribution statement

Fan Bu: Performed the experiments.
Shenyun Cao: Analyzed and interpreted the data.

Xiangzhu Deng: Contributed reagents, materials, analysis tools or data.
Zhijun Zhang: Conceived and designed the experiments.
Xiaodong Feng: Conceived and designed the experiments; Wrote the paper.

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Data availability statement

Data will be made available on request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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