RESEARCH ARTICLE

Feasibility of CYFRA 21-1 as a serum biomarker for the detection of colorectal adenoma and advanced colorectal adenoma in people over the age of 45

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Background: Colon adenoma (CA) is a premalignant lesion of colorectal cancer, and its early removal is closely associated with more prolonged survival in the general population. In this study, we aimed to evaluate the relationship between diverse biologic markers and a newly diagnosed CA and to predict the clinical possibility of cytokeratin-19 soluble in serum fragment (CYFRA 21-1) as a screening tool in asymptomatic adults aged over 45 years.

Methods: Four hundred and seventy-nine patients with a histologically confirmed CA or benign colon polyp (BCP), 76 patients with only benign colorectal diseases and 223 negative controls with no CA or BCP detected on colonofibroscopy were investigated. Multiple tumor markers and biochemical markers were simultaneously checked by radioimmunoassay and enzyme immunoassay.

Results: The CYFRA 21-1 alone showed significant stepwise contrastive potential among the three groups ($P < .001$). Based on the receiver operating characteristic (ROC) analysis, Area under the curve (AUC) for CYFRA 21-1, with a value of 0.732 (95% confidence interval, 0.656–0.809, $P < .001$) for differentiating between negative controls and patients with advanced colon adenoma, was comparatively the highest among all analyzed factors. The sensitivity of CYFRA 21-1 was significantly higher than that of the other tumor markers in the diagnosis of CA and advanced CA, respectively ($P < .001$).

Conclusions: Considering the results of our study, CYFRA 21-1 showed a significant diagnostic performance and significant stepwise comparative potential in differentiating patients with CA from benign controls. CYFRA 21-1 could be a simple and effective screening test for the diagnosis of CA.

KEYWORDS

benign polyp, colon adenoma, colonofibroscopy, colorectal cancer, CYFRA 21-1

1 | INTRODUCTION

Colorectal cancer (CRC) is the most prevalent cancer of the gastrointestinal tract worldwide. The incidence of CRC has increased over the past several decades because of western dietary habits and systematized healthcare program based on endoscopy in South Korea.¹ Colorectal cancer is projected to be the third most common cancer

among the estimated new cases (134 490/1 685 210, 8.0%) and estimated deaths (49 730/595 690, 8.3%) in both males and females in USA.²

A colon adenoma (CA) is a primitive premalignant lesion of CRC and it could be detected by a CRC screening program. Effective management of CA can reduce the possibility of CRC occurrence and can secure good quality of life.

There are various CA or CRC screening tests, and they include fecal-occult blood testing (FOBT) or exfoliated DNA, double-contrast barium enema (DCBE), endoscopic assessment such as flexible colonofibroscopy (CFS), computed tomographic colonography (CTC), and multiple tumor markers (MTM) including carcinoembryonic antigen (CEA), cancer antigen 19-9 (CA19-9), and cytokeratin-19 soluble in serum fragment (CYFRA 21-1).³⁻⁵ The usual screening assessment of CRC mainly consists of a few different methods, and among them, FOBT with CFS combination including MTM is usually applied to the healthcare program in South Korea. Because DCBE is less effective, its preparation is more complicated than the other methods and its application gives a radiation burden to the patients, it is seldom used. Although CFS has a distinctive advantage of simultaneously examining and managing treatment of diverse polyp lesions including CA, in the patients aged under 50 years in Western countries, it should not be generally recommended because it may have an intricate preparation process, with inaccurate results, and perforation or bleeding during the procedure. Although CTC offers the possibility of replacing endoscopic procedure, the possibility of unnecessary irradiation should not be overlooked especially in younger people and its result is not always satisfactory.⁶

The MTM approach provides a simple analytical tool not only to diagnose CRC but also to be used for a broaden population checking program.^{4,5} In CRC, CEA is the most important marker to evaluate staging before treatment and to detect disease recurrence.⁷ However, because of poor sensitivity and specificity in managing early stage CRC, CEA cannot be routinely recommended for screening.⁸ Although CA19-9 is known to play a role in evaluating disease recurrence and predicting prognosis of patients with advanced stage CRC, its role as a screening test has not been systematically investigated.⁸⁻¹⁰

Cytokeratin-19 soluble in serum fragment is known as one of the cytokeratin tumor markers, like tissue polypeptide antigen (TPA) and tissue polypeptide specific antigen (TPS).^{11,12} To the best of our knowledge, there are few reports investigating the clinical utility with respect to CRC or CA screening with these MTM. Other factors like thyroid-stimulating hormone (TSH), high-sensitivity C-reactive protein (hsCRP), cholesterol levels (triglyceride (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C)) have been reported as being possibly associated with CA or CRC development and they were included in this study.¹³⁻¹⁵

The aim of this study was to evaluate the diagnostic importance of the abovementioned diverse biologic markers and especially of CYFRA 21-1 to early diagnose a benign colon polyp (BCP) or CA and the possibility to be used as a screening tool.

2 | MATERIALS AND METHODS

2.1 | Patients

A total of 778 subjects aged over 45 years who underwent an annual healthcare program and screening colonoscopy at our health screening center, between 2012 and 2015 were enrolled in this study. For this study, we received approval from the Institutional Review

Board of Dankook University Hospital. Colonoscopies and routine blood check-ups were conducted by well-trained endoscopists and experienced technicians, respectively. Exclusion criteria included: (i) cancer diagnosis within the last 3 years (n=6), (ii) history of known benign bowel disease such as irritable bowel syndrome or inflammatory bowel disease (n=22), (iii) no histopathologic report (n=9), (iv) presumptive lower GI bleeding (n=2), and (v) poor bowel preparation (n=49). Benign colorectal diseases included as part of benign controls were non-specific colitis or proctitis, hemorrhoids, diverticulitis, and melanosis coli. Finally, among 479 patients with histologically confirmed CA or BCP, 76 patients with only benign colorectal diseases and 223 with negative controls with no CA or BCP detected on colonofibroscopy were investigated in the current study.

2.2 | Screening colonofibroscopy and CA classification

Bowel preparation was performed with polyethylene glycol lavage and 2.5 liters of water. Patients with poor bowel preparation were excluded from this study. During colonoscopy procedures, sedatives were used occasionally for reducing anxiety or if patients wanted sedation. The polyp location and number recorded before their removal was analyzed. A diagnosis of CA and the grades of dysplasia were defined according to the criteria of the World Health Organization.¹⁶ Dysplasia was classified as low-grade dysplasia or high-grade dysplasia, based on the degree of cytologic atypia and the presence of any architectural abnormality in the gland. The classification of CA was categorized as non-advanced and advanced adenoma. Advanced colon adenoma (ACA) was defined as polyps with villous features, serrated type, high-grade dysplasia, more than three low-grade adenomas except for BCP.^{17,18} In this study, we categorized the total enrolled subjects into six separate groups and analyzed the different groups according to each statistical analysis; negative controls (subjects without any large bowel diseases), benign controls (negative controls plus patients with benign colorectal diseases), patients with only BCPs, patients with CA (regardless of BCP existence), patients with ACA (among patients with CA) and patients with total colon polyps (CA plus BCP).

2.3 | Radioimmunoassay for CYFRA 21-1, CA19-9, and TSH

Among the tumor markers, serum CYFRA 21-1 (iZotope, Budapest, Hungary) and CA 19-9 (iZotope) were measured by a solid-phase immunoradiometric assay based on the two-site sandwich method. Measurements of TSH (Cisbio Assays, Codolet, France) were performed by the same method.

2.4 | Enzyme immunoassay for CEA, AFP, hsCRP, TG, LDL-C, and HDL-C

Blood samples were collected to determine the serum level for AFP, CEA, LDL-C, HDL-C, TG, and hs-CRP assay. Measurements of AFP

and CEA were performed on the fully automated Roche system using the cobas e platform (Roche Diagnostics, Penzberg, Germany). hs-CRP, HDL-C, and LDL-C levels in each sample were also measured on the fully automated Roche system using the cobas c platform (Roche Diagnostics). All of these automated assays took 18 minutes for detection of each analyte, and they were analyzed according to the manufacturer's method sheets. The test principle for CEA and AFP was the sandwich principle, i.e., the electrochemiluminescence immunoassay for use on cobas e immunoassay analyzers. The principle of homogeneous enzymatic colorimetric test was used for LDL-C and HDL-C, which has been described elsewhere.^{19,20} TG was tested by using the enzymatic colorimetric method²¹ and hs-CRP was assessed by the particle enhanced immunoturbidimetric method, in which human CRP agglutinates with latex particles coated with monoclonal anti-CRP antibodies. The precipitate was determined turbidimetrically^{22,23} on cobas c analyzers.

2.5 | Statistics

Total estimated data were expressed as mean $\pm$ SD, and *P* values of less than .05 were considered statistically significant. Statistical analysis was performed using SPSS (version 23.0; SPSS, Chicago, IL, USA). The difference in distribution of colon polyps and adenoma and the diagnostic performance of CA or ACA were evaluated by chi-square test. The correlational relationship between MTM and biochemical parameters was evaluated by Pearson's rank correlation with adjustment. Receiver operating characteristic (ROC) curves were plotted for CYFRA 21-1, CEA, CA 19-9, AFP, and hsCRP to assess their diagnostic performances in differentiating negative or benign controls from patients with ACA or CA. By analyzing the ROC curves, the modified cutoff values were calculated to evaluate sensitivity results of MTM.

Evaluation of the significant relationship among the three groups (benign controls, patients with only BCP, and patients with CA) was performed by one-way ANOVA with Bonferroni's and Dunnett's three multiple comparison tests.

3 | RESULTS

3.1 | Patient characteristics

Overall characteristics of the enrolled patients and control groups are shown in Table 1. There were a higher number of men than women among the total enrolled subjects and patients with CA (*P*<.001). In patients with BCP and patients with CA, the presence of BCP and CA was dominant in the rectosigmoid colon (*P*<.001) (Table 1). But in case of BCP, the distribution in the sigmoid colon and the rectum was more or less different (149 vs 108), while in case of adenomas, the number of sites of sigmoid CA was higher than the number of sites of rectal CA (136 vs 32), and this result was noted in patients with ACA (33 vs 8).

3.2 | Correlational relationship between multiple tumor markers and biochemical parameters in patients with colon adenoma

According to Table 2 which demonstrates the relationship between MTM and some chemical parameters possibly associated with CA, in case of CYFRA 21-1, there was a weak correlational relationship with hsCRP (*r*=.266, *P*<.001), and in case of CEA, there was a weak correlation with CA 19-9 (*r*=.342, *P*<.001) and TG (*r*=.166, *P*=.004). However, there is no significant relationship between the number of CA or BCP and MTM (not shown).

TABLE 1 Enrolled subjects characteristics

Age (range)	49.8 $\pm$ 5.1 (45-71 years)
Sex (Male: Female)	593: 185
Enrolled subjects classification (M:F, %)	
Negative controls	223 (139:84, 28.7)
Patients with benign colorectal diseases	76 (54:22, 9.8)
Patients with only benign polyps	188 (149:39, 24.2)
Patients with colon adenoma	291 (251:40, 37.3)
Patients with only advanced colon adenoma (among patients with colon adenoma)	59 (54:5)
Colon adenoma distribution (382 sites, %)	
Cecum and Ascending colon	83 (21.7)
Transverse colon	78 (20.4)
Descending colon	53 (13.8)
Sigmoid colon and Rectum	168* (44.1)
Benign polyps distribution (407 sites, %)	
Cecum and Ascending colon	64 (15.7)
Transverse colon	45 (11.1)
Descending colon	41 (10.1)
Sigmoid colon and Rectum	257* (63.1)

**P*<.001.

TABLE 2 Correlative relationship between MTM and biochemical parameters in patients with colon adenoma

	CA19-9	TSH	CYFRA 21-1	TG	LDL-C	HDL-C	AFP	CEA	hsCRP
CA19-9									
<i>r</i>	1	-.03	-.049	-.006	-.030	.080	-.039	.342	-.058
<i>P</i> value	.	.61	.41	.92	.61	.17	.29	<.001	.33
CEA									
<i>r</i>	.342	-.074	.091	.166	-.019	-.073	.060	1	.023
<i>P</i> value	<.001	.21	.12	.004	.75	.22	.31	.	.70
AFP									
<i>r</i>	-.039	-.024	.036	.068	.144	.049	1	.060	-.055
<i>P</i> value	.51	.69	.55	.25	.01	.41	.	.31	.35
CYFRA 21-1									
<i>r</i>	-.049	-.486	1	.031	-.054	-.025	.036	.091	.266
<i>P</i> value	.40	.41	.	.59	.36	.68	.55	.12	<.001

MTM; multiple tumor markers; TSH, thyroid-stimulating hormone; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CEA, carcinoembryonic antigen; AFP, A-fetoprotein; CA19-9, cancer antigen 19-9; hsCRP, high-sensitivity C-reactive protein; *r*, Pearson's correlation coefficient.

Bold lettering indicates statistically significant values.

3.3 | Analysis of ROC curves and sensitivity/specificity of multiple tumor markers in patients with colon adenoma and advanced colon adenoma

To compare the capability of the MTM and hsCRP to discriminate between negative controls and patients with CA and ACA and between benign controls and patients with CA and ACA, respectively, the receiver operating characteristic (ROC) curves were analyzed (Table 3, Figure 1 and 2). For example, in case of comparison between negative controls and patients with ACA, the area under the curve (AUC) for CYFRA 21-1, with a value of 0.732 (95% confidence interval (CI), 0.656-0.809) was higher than that for the other three tumor markers and hsCRP. AUCs for CEA, CA 19-9, AFP, and hsCRP were 0.628, 0.489, 0.552, and 0.637, respectively (Table 3, Figure 1C). In all analytical cases including differentiation between negative or benign controls and patients with total colon polyps, CA and ACA, the ROC analysis suggested that CYFRA 21-1 was superior to the other tumor markers (Figures 1 and 2). Sensitivity of CYFRA 21-1 for CA and ACA with adjusted cutoff values estimated from the ROC analysis was

22.3% and 30.5%, respectively (cutoff value: 1.02 and 1.03 ng/mL). Sensitivity of CYFRA 21-1 was significantly higher than that of the other parameters (Table 4).

3.4 | ANOVA with post hoc tests among benign controls, patients with a benign colon polyp, and patients with colon adenoma

To evaluate the relationship between benign controls, patients with BCP, and patients with CA, ANOVA with post hoc tests was performed (Table 5). In our analysis, benign controls were younger than patients with a CA. Subjects with colon adenoma had a higher hsCRP level than benign controls and patients with only BCP. With respect to CEA, benign controls showed a significantly lower value than patients with CA. CYFRA 21-1 alone showed significant step-wise comparative potential among the three groups ($P < .001$). There was no significant comparative result between benign controls and patients with BCP or CA in the other tumor markers and biochemical factors.

Marker	Negative controls vs advanced colon adenoma		Benign controls vs advanced colon adenoma	
	AUC on ROC (95% CI)	<i>P</i> value	AUC on ROC (95% CI)	<i>P</i> value
CA 19-9	0.489 (0.406-0.572)	.796	0.494 (0.413-0.576)	.576
CYFRA 21-1	0.732 (0.656-0.809)	<.001	0.707 (0.628-0.786)	<.001
AFP	0.552 (0.473-0.628)	.219	0.548 (0.472-0.624)	.244
CEA	0.628 (0.542-0.714)	.003	0.623 (0.583-0.708)	.003
hsCRP	0.637 (0.559-0.715)	.001	0.610 (0.532-0.689)	.007

CEA, carcinoembryonic antigen; AFP, A-fetoprotein; CA19-9, cancer antigen 19-9; hsCRP, high-sensitivity C-reactive protein.

Bold lettering indicates statistically significant values ($P < .05$).

TABLE 3 Analysis of Receiver operating Characteristic (ROC) curves between negative controls and patients with advanced colon adenoma and between benign controls and patients with advanced colon adenoma

FIGURE 1 Diagnostic performances of multiple tumor markers and hsCRP for discriminating between negative controls and polyp diseases. (A) Receiver operating characteristic (ROC) curves for differentiating negative controls from patients with total polyps. The areas under the ROC curves (AUC) for CA19-9, CYFRA 21-1, AFP, CEA, and hsCRP were 0.48, 0.68^a, 0.53, 0.59^a, and 0.58^b, respectively (^a $P < .001$, ^b $P = .001$). (B) ROC curves for differentiating negative controls from patients with colon adenoma. AUC for CA19-9, CYFRA 21-1, AFP, CEA, and hsCRP were 0.48, 0.71^a, 0.53, 0.60^a, and 0.60^a, respectively (^a $P < .001$). (C) ROC curves for differentiating negative controls from patients with advanced adenoma. AUC for CA19-9, CYFRA 21-1^a, AFP, CEA, and hsCRP were 0.49, 0.73^a, 0.55, 0.63^b, and 0.64^c, respectively (^a $P < .001$, ^b $P < .01$, ^c $P = .001$)

FIGURE 2 Diagnostic performances of multiple tumor markers and hsCRP for discriminating between benign controls and polyp diseases. (A) ROC curves for differentiating benign controls from patients with total polyps. AUC for CA19-9, CYFRA 21-1, AFP, CEA, and hsCRP were 0.49, 0.65^a, 0.52, 0.58^a, and 0.55^b, respectively (^a $P < .001$, ^b $P < .05$). (B) ROC curves for differentiating benign controls from patients with colon adenoma. AUC for CA19-9, CYFRA 21-1, AFP, CEA, and hsCRP were 0.49, 0.68^a, 0.52, 0.59^a, and 0.57^b, respectively (^a $P < .001$, ^b $P < .01$). (C) ROC curves for differentiating benign controls from patients with advanced adenoma. AUC for CA19-9, CYFRA 21-1^a, AFP, CEA, and hsCRP were 0.49, 0.71^a, 0.55, 0.62^b, and 0.61^b, respectively (^a $P < .001$, ^b $P < .01$)

TABLE 4 Sensitivity Results of CEA, CA19-9, AFP, and CYFRA 21-1 in patients with colon adenoma and advanced colon adenoma

	CEA	CA 19-9	AFP	CYFRA 21-1
Colon adenoma diagnosis (Sensitivity, %)	8.9% (26/291)	4.1% (12/291)	3.4% (10/291)	22.3% [*] (65/291)
Adjusted cutoff value (ng/mL or U/mL)	4.41	25.95	6.57	1.02
Advanced adenoma diagnosis (Sensitivity, %)	11.8% (1/59)	3.3% (2/59)	1.7% (1/59)	30.5% [*] (18/59)
Adjusted cutoff value (ng/mL or U/mL)	4.41	25.95	6.57	1.03

CEA, carcinoembryonic antigen; AFP, A-fetoprotein; CA19-9, cancer antigen 19-9.

^{*} $P < .001$.

4 | DISCUSSION

In the current study, the efficacy of MTM in differentiating between the benign control group and patients with CA or ACA was evaluated. The important finding of our study suggests that CYFRA 21-1 has a

more significant discriminative ability than the other biological markers with respect to screening population over the age of 45 years with no past medical history. In addition, CYFRA 21-1 showed significantly different sequential values from benign controls to patients with ACA.

TABLE 5 Comparative relationship of multiple tumor markers and biochemical parameters between benign controls, patients with only benign colon polyps and patients with colon adenomas

	Benign controls (1)	Patients with benign colon polyps (2)	Patients with colon adenoma (3)	ANOVA* Scheffe's test or Dunnett T3 test (1, 2, 3)
Age	49.0±4.5	49.6±5.1	50.8±5.4	P<.001 1-3
CA19-9	10.2±8.9	9.9±8.0	9.8±7.8	P=.827
TSH	2.65±2.38	2.17±1.66	2.37±2.27	P=.55
CYFRA 21-1	0.48±0.29	0.62±0.40	0.73±0.49	P<.001 1-2, 2-3, 1-3
TG	123.5±103.6	127.0±75.7	136.8±98.0	P=.223
LDL-C	134.8±34.3	134.7±38.3	131.2±34.5	P=.396
HDL-C	57.0±14.8	54.2±15.0	54.8±14.4	P=.076
AFP	3.10±2.0	3.23±2.53	3.07±1.55	P=.654
CEA	1.93±1.3	2.37±1.91	2.39±1.68	P=.001 1-2, 1-3
hsCRP	0.09±0.12	0.09±0.11	0.13±0.18	P=.004 1-3

TSH, thyroid-stimulating hormone; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CEA, carcinoembryonic antigen; AFP, A-fetoprotein; CA19-9, cancer antigen 19-9; hsCRP, high-sensitivity C-reactive protein.

Bold lettering indicates statistically significant values ($P<.01$).

*ANOVA with post hoc tests, each pair of digits showed that two groups' comparison was significantly different at $P<.017$.

Cytokeratin is one of the structural proteins found in the intracytoplasmic cytoskeleton of epithelial tissue.²⁴ Until now, twenty different cytokeratin members have been discovered. Because cytokeratin plays a role in maintaining normal cell environment as a filamentous structure, it is released following cell death and its soluble fragment can be detected in the serum.²⁵ Hence, CYFRA 21-1 assay is used to specifically detect the soluble fragment of cytokeratin 19 in blood specimens with two monoclonal antibodies.²⁶ CYFRA 21-1 has been reported to monitor the post treatment process in patients with non-small cell lung cancer (NSCLC), to predict the poor prognosis of early stage NSCLC, to exhibit diagnostic usefulness in predicting bladder cancer, and to show good monitoring of breast cancer patients after chemotherapy, on comparing with an assay which combines CEA and CA 15-3.²⁷⁻³⁰

Like our research, there are few established reports that investigated the unique capacity of tumor markers to discriminate between benign disease and premalignant lesion. Chu et al.³¹ demonstrated that based on the ROC analysis, CYFRA 21-1 (AUC=0.726) showed the highest statistical power to differentiate between benign pulmonary lesion and lung cancer in patients with pulmonary masses that needed to be evaluated, among MTM including squamous cell carcinoma antigen (SCC), CEA, and NSE (AUC=0.601, 0.646, and 0.602, respectively). As mentioned above, CYFRA 21-1 above the adjusted cutoff value reflects the calibration potential to even differentiate controls with BCP and patients with CA and ACA in our study. Hence, it can be suggested that CYFRA 21-1 could indicate the neoplastic burden induced through carcinogenesis in benign cells. In addition, keratin 19 is one of the chiefly premalignant keratins in the colonic epithelium and it has been reported that its expression level could be affected by altering the diet and

anatomical intervention in the normal colon mucosa or adenoma tissue.³² Hence, considering this information, CYFRA 21-1 can reflect the sophisticated change in the colonic cellular environment, such that it could be a biologic marker that detects not only colon cancer but also a premalignant lesion, on comparing with other tumor markers and cytokines.

In the field of CRC, among multiple serum tumor markers, CEA has been generally utilized for monitoring after neoadjuvant or palliative diverse medical treatment, post operative follow-up after curative surgery, and detection of recurrence.^{7,33,34} But, when it comes to screening of CRC or CA, its efficacy has not been proved, and rather, it is controversial.³⁵ On the other hand, according to the results of this study, CYFRA 21-1 could become one of the potential screening tools to evaluate ACA regarded as premalignant lesion possibly progressing to colon cancer in asymptomatic individuals. In addition, CYFRA 21-1 has been found to be less affected by age, sex, smoking, and pregnancy,³⁶ and its elevated level is less often detected in benign liver diseases and renal failure; hence, high specificity of CYFRA 21-1 has been reported for NSCLC.^{37,38}

Inflammation has been known to be attributed to the process of development of CA or adenocarcinoma.¹⁵ Hence, hsCRP quantifying the degree of inflammation, albeit non-specific, was evaluated as one of the clinical parameters in our study. As we had predicted, hsCRP showed a relatively considerable calibration ability to evaluate patients with colon polyps or adenoma among the enrolled subjects, although its ability was lower than that of CYFRA 21-1, based on the ROC analysis. Of course, the application of hsCRP alone in a screening program for CRC is not enough, but a new approach combined with serum tumor markers or FOBT could be useful for estimating its unique efficacy as a screening tool. Although CFS has been recognized

as one of the important tools in screening of colorectal cancer, because its practical accessibility is not easy due to high costs in some countries and uncomfortable preparation such as large amount of consumption of polyethylene glycol solution, evaluation of a more simple and convenient method such as a serum tumor marker in CRC screening is thought to be a valuable clinical study. Because workmanship during CFS could inevitably be variable according to the individual's skills and experience, an abnormally elevated CYFRA 21-1 with other markers such as hsCRP before the endoscopic procedure could draw the physician's attention to the screening procedure, which could make the CRC screening program more effective. Recently, Wong et al.³⁹ demonstrated that the sensitivity of FOBT in detecting CRC and premalignant lesions ranged from 7.2% to 23.2% with different cutoff values, which were not considerably different from our result (CYFRA 21-1: 22.3%, CA and 30.5%, ACA). Considering this result, CYFRA 21-1 could be one of the multiple modalities or supportive methods in the field of colon adenoma or colorectal adenocarcinoma screening.

The current study had several limitations. Each life habit, other clinical parameters such as BMI and socioeconomic status were not included. Because of the criteria of a single center study and age requirement (more than 45 years), the sample size in our study was not large, but because healthcare programs are different at each medical center, a large-scale multicenter study that includes our MTM combination including CYFRA 21-1 is difficult but it is warranted to evaluate the comparison of MTM in detecting not only CA but also other premalignant conditions.

5 | CONCLUSION

Our study demonstrates that CYFRA 21-1 showed significant diagnostic performance in differentiating patients with CA from asymptomatic adults aged over 45 years, compared to the multiple investigated biomarkers. In addition, hsCRP might offer the possibility of being useful as a supportive screening tool in the diagnosis of colorectal neoplasm. Large-scale researches are required to establish the clinical utility of CYFRA 21-1 in CA detection or screening of malignancies including CRC.

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