ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2023 January 28; 29(4): 582-765

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

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NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Andrzej S Tarnawski

EDITORIAL BOARD MEMBERS

http://www.wjgnet.com/1007-9327/editorialboard.htm

PUBLICATION DATE

January 28, 2023

INSTRUCTIONS TO AUTHORS

https://www.wjgnet.com/bpg/gerinfo/204

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https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS

https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION

https://www.f6publishing.com

E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Gastroenterology

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World J Gastroenterol 2023 January 28; 29(4): 706-730

DOI: 10.3748/wjg.v29.i4.706

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Retrospective Study

Diagnostic and economic value of carcinoembryonic antigen, carbohydrate antigen 19-9, and carbohydrate antigen 72-4 in gastrointestinal cancers

Hai-Ning Liu, Can Yao, Xiao-Fan Wang, Ning-Ping Zhang, Yan-Jie Chen, Dong Pan, Guo-Ping Zhao, Xi-Zhong Shen, Hao Wu, Tao-Tao Liu

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Dauyey K, Kazakhstan; Grossi U, Italy

Received: September 18, 2022
Peer-review started: September 18, 2022
First decision: November 15, 2022
Revised: November 28, 2022
Accepted: December 21, 2022
Article in press: December 21, 2022
Published online: January 28, 2023

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Abstract

BACKGROUND

The diagnostic and economic value of carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9) and CA72-4 for gastrointestinal malignant tumors lacked evaluation in a larger scale.

AIM

To reassess the diagnostic and economic value of the three tumor biomarkers.

METHODS

A retrospective analysis of all 32857 subjects who underwent CEA, CA19-9, CA72-4, gastroscopy and colonoscopy from October 2006 to May 2018 was conducted. Then, we assessed the discrimination and clinical usefulness. Total cost, cost per capita and cost-effectiveness ratios were used to evaluate the economic value of two schemes (gastrointestinal endoscopy for all people without blood tests *vs* both gastroscopy and colonoscopy when blood tests were positive).

RESULTS

The analysis of 32857 subjects showed that CEA was a qualified biomarker for colorectal cancer (CRC), while the diagnostic efficiencies of CA72-4 were catastrophic for all gastrointestinal cancers (GICs). Regarding early diagnosis, only CEA could be used for early CRC. The combination of biomarkers didn't greatly increase the area under the curve. The economic indicators of CEA were superior to those of CA19-9, CA72-4 and any combination. At the threshold of 1.8 μg/L to 10.4 μg/L, all four indicators of CEA were lower than those in the scheme that conducted gastrointestinal endoscopy only. Subgroup analysis implied that the health checkup of CEA for people above 65 years old was economically valuable.

CONCLUSION

CEA had qualified diagnostic value for CRC and superior economic value for GICs, especially for elderly health checkup subjects. CA72-4 was not suitable as a diagnostic biomarker.

Key Words: Diagnostic test; Economic analysis; Cost-effectiveness analysis; Decision curve analysis

Core Tip: This is a retrospective study to reassess the diagnostic and economic value of traditional tumor biomarkers carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9) and CA72-4 for gastrointestinal malignant tumors in a large sample with novel indicators. Instead of increasing the diagnostic value, CA72-4 should be removed from the list of the health checkup items to avoid the waste of social medical resources for CEA were superior to those of CA19-9, CA72-4 or any other combinations in which it could be applied for early colorectal cancer and a health checkup of CEA for people above 65 years old was economically valuable.

Citation: Liu HN, Yao C, Wang XF, Zhang NP, Chen YJ, Pan D, Zhao GP, Shen XZ, Wu H, Liu TT. Diagnostic and economic value of carcinoembryonic antigen, carbohydrate antigen 19-9, and carbohydrate antigen 72-4 in gastrointestinal cancers. *World J Gastroenterol* 2023; 29(4): 706-730
URL: https://www.wjgnet.com/1007-9327/full/v29/i4/706.htm
DOI: https://dx.doi.org/10.3748/wjg.v29.i4.706

INTRODUCTION

Blood carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) are widely used as classic diagnostic markers for malignant tumors, and they are recommended by several clinical guidelines for gastrointestinal cancer (GIC) screening[1-3]. Following the introduction of the CEA and CA19-9 assessment, in 1990, blood CA72-4 was proposed as a diagnostic biomarker for gastric cancer (GC)[4]. Subsequent studies showed that CA72-4 could be used to diagnose GC and colorectal cancer (CRC)[5,6]. These studies reported sensitivities of 19%-47% in GC and 25%-43% in CRC at the cut-off value of 6 kU/L[7-13]. The clinical guidelines published by the European Group on Tumor Markers (EGTM) in 2003 suggested that CA72-4 could be a potential biomarker for CRC[14].

Based on these previous studies, blood CA72-4 began to be widely used as a tumor biomarker since 2010 in China. Nevertheless, after large-scale clinical application, we noticed, empirically, an extremely high false positive rate of CA72-4 for diagnosis. A positive result would lead the subject to undergo further examinations, including gastroscopy, colonoscopy, chest computed tomography (CT), abdominal CT, and even positron emission tomography-CT (PET-CT). The blood test with a low positive predictive value (PPV) not only brings unnecessary anxiety, invasive examinations, and extra costs to the subjects but also leads to the waste of medical resources and increases the social medical burden.

The massive data and real-world diagnostic cohorts make it possible to further explore the diagnostic and economic value of biomarkers. Through a real-world diagnostic cohort, we comprehensively analyzed the differences in the levels of CEA, CA19-9, and CA72-4 and their diagnostic and economic value in gastrointestinal tumors. Four indicators were used to comprehensively evaluate the economic value, namely, the total cost and the average cost per person for each positive patient diagnosed and their corresponding cost-effectiveness ratios. We evaluated whether age and health checkup could help us make useful recommendations for thresholds of tumor biomarkers and medical insurance policies.

Table 1 The six schemes and examination prices in economic analysis

Item	Description
Schemes	Scheme 1 Gastrointestinal endoscopy for all people without blood tests
	Scheme 2 Both of gastroscopy and colonoscopy when blood tests were positive
	Scheme 3 Gastroscopy first when blood tests were positive, and then colonoscopy when the result of gastroscopy was negative
	Scheme 4 Colonoscopy first when blood tests were positive, and then gastroscopy when the result of colonoscopy was negative
	Scheme 5 Only gastroscopy when blood tests were positive
	Scheme 6 Only colonoscopy when blood tests were positive
Examination prices	CEA, $4.64; CA19-9, $7.25; CA72-4, $7.25
	Gastroscopy & biopsy, $87.99
	Colonoscopy, $57.98; biopsy after colonoscopy, $32.62

The prices of gastroscopy and colonoscopy did not include that of intravenous anesthesia. The costs of all examinations were from Zhongshan Hospital in 2019. All costs were converted to United States dollars. CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; CA72-4: Carbohydrate antigen 72-4.

MATERIALS AND METHODS

Study population

We retrospectively analyzed all patients from October 2006 to May 2018. The inclusion criteria included: (1) Patients from the medical examination center, outpatient department or inpatient department of Zhongshan Hospital of Fudan University; and (2) patients had completed all five examinations, namely, CEA, CA19-9, CA72-4, gastroscopy and colonoscopy, within half a year. The exclusion criteria were as follows: (1) Duplicate patients; and (2) patients who had accepted anti-tumor therapies such as radiotherapy, chemotherapy or surgery.

Data extraction

All data were abstracted from our hospital information system (HIS). They included general information (*e.g.*, age, sex, medical record number, whether health checkup, past history), the concentrations of each of the three tumor biomarkers, reports of auxiliary examinations (*e.g.*, endoscopy, pathology, ultrasonography, CT, magnetic resonance, PET-CT, electrocardiogram), and the medical records of outpatients and inpatients. The generation time of these data was also provided.

The concentrations of serum CEA, CA19-9, and CA72-4 were measured with an electrochemiluminescence immunoassay (Elecsys2010, Roche Diagnostics, indianapolis, IN, United States). The traditional cut-off values for CEA, CA19-9, and CA72-4 were 5 μg/L, 37 kU/L, and 6 kU/L, respectively.

According to the regular practice of our hospital, pathological biopsy was taken when gastroscopy was performed, while colon biopsy was not necessary taken unless some lesions were found by colonoscopy. The diagnosis of GIC depends on the gold standard of pathology, and other gastrointestinal diseases are diagnosed by endoscopy and pathology. Other malignant tumors were comprehensively judged based on the medical history, pathology and imaging exams that we could collect. TNM staging of cancers was based on the American Joint Committee on Cancer Staging or case data at that time.

Economic analysis

According to the type of test and the order of endoscopy procedures, we assumed six schemes (Table 1). Four economic indicators combined with the proportion of endoscopies and the missed diagnosis rate was used to evaluate the economic value of tumor biomarkers. The four economic indicators were the total cost and cost per capita of correctly diagnosing one case of GIC and the cost-effectiveness ratio of the above two indicators. The cost-effectiveness ratio was the total cost or cost per capita divided by sensitivity. We assumed that the missed diagnosis rate and misdiagnosis of endoscopy plus necessary pathological examination for gastrointestinal malignancies were all 0.

The costs of blood tests, endoscopy and pathological examination were the cost of these procedures at Zhongshan Hospital in 2019 (Table 1). All costs were converted to United States dollars.

Considering the preliminary results, further analyses were performed on Scheme 1 (gastrointestinal endoscopy for all people without blood tests) and Scheme 2 (both gastroscopy and colonoscopy when blood tests were positive). We also calculated 9 conditions when CEA and CA19-9 were combined. They

Table 2 The clinical characteristics of subjects with and without gastric cancer, colorectal cancer and gastrointestinal cancers

	Age median (quartile)	*P* value	Male, *n* (%)	Female, *n* (%)	*P* value
Gastric cancer	61 (51, 68)	< 0.001	268 (68.4)	124 (31.6)	0.084
Non-gastric cancer	48 (42, 56)		20831 (64.2)	11634 (35.8)	
Colorectal cancer	62 (55, 70)	< 0.001	522 (58.5)	370 (41.5)	< 0.001
Non-colorectal cancer	48 (42, 55)		20577 (64.4)	11388 (35.6)	
Gastrointestinal cancer	62 (53, 69)	< 0.001	816 (62.4)	491 (37.6)	0.170
Non-gastrointestinal cancer	48 (42, 55)		20283 (64.3)	11267 (35.7)	

The *P* value was calculated with the Wilcoxon test for age and chi-square test for sex. The bold font indicates that the *P* value was less than 0.05.

were parallel (any positive was considered positive), serial (all positive was considered positive), and the formula under the traditional cut-off value (the coefficients of CEA and CA19-9 were calculated according to the logistic regression), the minimum total cost, and the minimum total cost-effectiveness ratio.

Subgroup analysis (age, health checkup/active consultation) was utilized to analyze the economic value of the three biomarkers under the traditional threshold, with a view to drawing some medical insurance recommendations.

Statistical analysis

The statistical analyses were performed using R software 3.3.5 (R Foundation for Statistical Computing, Vienna, Austria). The level of significance was set at $P < 0.05$. All tests were two-sided.

Student's *t*-test or Wilcoxon test was used to assess the differences in continuous variables, as appropriate. The chi-square test was used for counting variables. Correlations between two variables were calculated by Pearson correlation analysis or Spearman correlation analysis. The influences of age and sex on the biomarker levels were analyzed with the regression coefficient of linear regression. Categorical regression analysis was utilized to calculate the regression coefficient quantification of each stage of GC and CRC.

The diagnostic value was evaluated by means of the area under the curve (AUC) values of the receiver operating characteristics (ROC) curve, as well as the diagnostic odds ratio (DOR), sensitivity, specificity, Youden index (sensitivity + specificity-1), accuracy, predicted value and likelihood ratio on the traditional and best cut-off values. The best cut-off value referred to the threshold when the Youden index was the largest. When multiple diagnostic biomarkers were combined, logistic regression was used to calculate the formula coefficients. We used Delong's test to compare AUC.

Decision curve analysis (DCA) was performed to determine the clinical usefulness of the radiomics nomogram by quantifying the net benefits at different threshold probabilities. The clinical net benefit was defined as the true positive rate (sensitivity) minus the false positive rate (misdiagnosis rate) and was then weighted by the relative damage of the positive rate and the negative rate.

RESULTS

Clinical characteristics

According to the inclusion criteria, we screened a total of 32857 subjects aged 15 to 97 years in the HIS, including 21099 males and 11758 females. There were 24045 subjects who underwent health checkup and 8812 subjects with an active consultation (Figure 1). The ages and sexes of the subjects with GC, CRC, and GIC were significantly different from those of the subjects without the disease (Table 2).

The constituent ratios of the diseases detected by gastroscopy, colonoscopy and pathological examination are displayed in Table 3. Among them, there were 392 GC cases, 892 CRC cases and 1307 GIC cases.

Serum levels of tumor biomarkers

The concentrations of the three biomarkers were skewed (Figure 2). The correlations between the pairwise biomarkers are shown in Table 4. We found that there were significant correlations between CEA and CA19-9 in all subjects and various GICs, and the correlation coefficients were all exceed 0.245.

The median values for CEA, CA19-9, and CA72-4 Level were 1.67 μg/L, 8.50 kU/L and 1.60 kU/L, respectively. The expression levels of the biomarkers for the diseases that had more than 30 cases are shown in Table 5. The concentrations of the three biomarkers in patients with several malignant tumors were significantly different from those without malignant tumors (Figure 3). The CEA level increased

Table 3 The number and proportions of diseases in the gastroscopy, colonoscopy and pathological examination groups

Examination	Disease	No.	%
Gastroscope (without pathological examination)	Esophagitis	2887	8.8%
	Esophageal erosion	88	0.3%
	Esophageal ulcer	30	0.1%
	Esophageal protuberant lesion	491	1.5%
	Esophageal non-protuberant lesion	77	0.2%
	Barrett's esophagus	66	0.2%
	Bile reflux	1344	4.1%
	Gastric atrophy	45	0.1%
	Gastric erosion	12457	37.9%
	Gastric hemorrhage	1117	3.4%
	Gastric ulcer	1088	3.3%
	Gastric protuberant lesion	3329	10.1%
	Gastric non-protuberant lesion	225	0.7%
	Duodenitis	1473	4.5%
	Duodenal erosion	26	0.1%
	Duodenal ulcer	1548	4.7%
	Duodenal protuberant lesion	666	2.0%
	Duodenal non-protuberant lesion	31	0.1%
Colonoscopy (without pathological examination)	Colorectitis	653	2.0%
	Colorectal erosion	29	0.1%
	Colorectal ulcer	99	0.3%
	Colorectal protuberant lesion	7312	22.3%
	Colorectal non-protuberant lesion	36	0.1%
Pathological examination	Esophageal mucositis	398	1.2%
	Esophageal dysplasia	44	0.1%
	Esophageal adenoma	1	< 0.1%
	Esophageal hyperplastic polyp	2	< 0.1%
	Esophageal glandular hyperplasia	4	< 0.1%
	Chronic atrophic gastritis	1809	5.5%
	Gastric dysplasia	308	0.9%
	Gastric adenoma	13	< 0.1%
	Gastric hyperplastic polyps	117	0.4%
	Gastric glandular hyperplasia	761	2.3%
	Gastric juvenile polyps	1	< 0.1%
	Duodenal mucositis	276	0.8%
	Duodenal dysplasia	24	0.1%
	Duodenal adenoma	12	< 0.1%
	Duodenal hyperplastic polyps	10	< 0.1%
	Duodenal gland hyperplasia	31	0.1%
	Colorectal mucositis	2206	6.7%
	Colorectal high-grade intraepithelial neoplasia	330	1.0%

	Colorectal low-grade intraepithelial neoplasia	3364	10.2%
	Colorectal adenoma	3707	11.3%
	Colorectal hyperplastic polyps	1037	3.2%
	Colorectal inflammatory polyps	13	< 0.1%
	Colorectal gland hyperplasia	567	1.7%
	Colorectal juvenile polyps	3	< 0.1%
	Peutz-Jeghers polyps	5	< 0.1%
	Familial polyposis coli	3	< 0.1%
	Esophageal cancer	57	0.2%
	Gastric cancer	392	1.2%
	Duodenal cancer	25	0.1%
	Small intestine cancer	4	< 0.1%
	Colorectal cancer	892	2.7%
	Liver cancer	127	0.4%
	Pancreatic cancer	47	0.1%
	Gallbladder cancer	20	0.1%
	Bile duct cancer & ampulla cancer	10	< 0.1%
	Lung cancer	129	0.4%
	Breast cancer	55	0.2%
	Ovarian cancer	57	0.2%
	Uterine malignancy	28	0.1%
	Kidney cancer	37	0.1%
	Prostate cancer	28	0.1%
	Bladder Cancer	17	0.1%
	Leukemia	1	< 0.1%
	Lymphoma	29	0.1%
	Other malignant tumors	15	< 0.1%

Table 4 Correlation analysis of biomarker levels

	Correlation coefficient			*P* value		
	CEA and CA19-9	CEA and CA72-4	CA19-9 and CA724-4	CEA and CA19-9	CEA and CA72-4	CA19-9 and CA724-4
Whole	0.245	-0.005	-0.046	< 0.001	0.359	< 0.001
Gastric cancer	0.291	0.048	0.022	< 0.001	0.342	0.657
Colorectal cancer	0.385	0.2	0.169	< 0.001	< 0.001	< 0.001
Gastrointestinal cancer	0.354	0.164	0.134	< 0.001	< 0.001	< 0.001

P values and correlation coefficients were calculated with Pearson correlation analysis or Spearman correlation analysis. The bold font indicates that the *P* value was less than 0.05. CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; CA72-4: Carbohydrate antigen 72-4.

but did not exceed 0.3 μg/L in esophageal erosion, gastric erosion, gastric ulcer, chronic atrophic gastritis, and colorectal adenoma.

The influences of age and sex on the biomarker levels are presented in Table 6. Due to the fact that the patients with malignant tumors were elder, the age baselines of the patients with and without tumors were no equal. Moreover, the sex baseline of the CRC patients was not the same. The correlation coefficients of age and sex were both less than 0.25, indicating small influences. The regression coefficients

Table 5 The biomarker levels, comparisons between subjects with and without diseases and area under the curves of carcinoembryonic antigen, carbohydrate antigen 19-9, and carbohydrate antigen 72-4

Disease	No.	CEA			CA19-9			CA72-4		
		Median (quartile) (μg/L)	*P* value	AUC	Median (quartile) (kU/L)	*P* value	AUC	Median (quartile) (kU/L)	*P* value	AUC
Whole	32857	1.67 (1.13, 2.41)	-	-	8.50 (5.60, 13.50)	-	-	1.60 (1.05, 3.20)	-	-
Esophagitis	3137	1.88 (1.29, 2.72)	< 0.001	0.566	8.60 (5.70, 13.50)	0.439	0.504	1.60 (1.10, 3.40)	0.001	0.518
Esophageal erosion	109	1.84 (1.40, 2.90)	0.007	0.575	8.30 (5.00, 15.00)	0.938	0.498	1.50 (1.10, 3.20)	0.644	0.487
Esophageal ulcer	30	1.73 (0.90, 2.29)	0.818	0.488	7.90 (5.73, 10.38)	0.166	0.573	1.59 (1.10, 3.95)	0.572	0.470
Barrett's esophagus	66	1.91 (1.21, 3.01)	0.095	0.559	8.95 (6.25, 12.70)	0.565	0.520	1.95 (1.10, 3.98)	0.306	0.536
Bile reflux	1344	1.65 (1.07, 2.43)	0.435	0.506	8.90 (5.60, 14.73)	0.121	0.512	1.60 (1.10, 3.30)	0.130	0.512
Gastric erosion	13094	1.78 (1.22, 2.57)	< 0.001	0.555	8.60 (5.70, 13.70)	0.006	0.509	1.60 (1.00, 3.20)	0.748	0.499
Gastric ulcer	1091	1.98 (1.41, 2.98)	< 0.001	0.598	8.40 (5.50, 14.40)	0.646	0.496	1.60 (1.00, 3.20)	0.789	0.498
Gastric hemorrhage	1125	1.68 (1.12, 2.46)	0.492	0.506	8.70 (5.80, 14.50)	0.092	0.515	1.60 (1.10, 3.40)	0.331	0.509
Chronic atrophic gastritis	1839	1.90 (1.32, 2.89)	< 0.001	0.578	9.20 (6.00, 14.90)	< 0.001	0.535	1.70 (1.10, 3.40)	< 0.001	0.528
Gastric xanthoma	100	1.65 (1.13, 2.41)	0.935	0.498	10.35 (6.45, 15.18)	0.072	0.552	1.80 (1.20, 3.43)	0.111	0.546
Gastrointestinal stromal tumor	48	1.56 (1.09, 2.69)	0.903	0.505	7.80 (5.78, 13.41)	0.614	0.521	1.50 (1.10, 2.23)	0.683	0.517
Gastric hyperplastic polyps	117	1.71 (1.14, 2.89)	0.282	0.529	11.20 (7.00, 22.72)	< 0.001	0.612	1.70 (1.10, 2.40)	0.964	0.501
Gastric glandular hyperplasia	761	1.57 (1.09, 2.29)	0.050	0.521	9.50 (6.00, 15.00)	< 0.001	0.543	1.70 (1.10, 3.80)	0.010	0.527
Colorectitis	2592	1.83 (1.25, 2.70)	< 0.001	0.552	8.70 (5.70, 14.30)	0.014	0.515	1.60 (1.10, 3.40)	0.034	0.513
Colorectal erosion	167	1.72 (1.17, 2.73)	0.198	0.529	8.80 (5.95, 13.90)	0.495	0.515	1.60 (1.00, 3.10)	0.788	0.494
Colorectal ulcer	107	1.54 (1.03, 2.61)	0.658	0.512	9.10 (6.30, 16.90)	0.069	0.551	1.70 (1.09, 2.80)	0.859	0.495
Colorectal hemorrhage	36	1.57 (1.12, 3.14)	0.799	0.488	9.05 (5.73, 13.75)	0.550	0.529	1.25 (0.90, 1.95)	0.061	0.590
Colorectal cyst	41	1.53 (0.93, 2.70)	0.455	0.534	9.20 (6.50, 13.70)	0.321	0.545	1.40 (1.10, 2.40)	0.353	0.542
Colorectal adenoma	3707	1.91 (1.29, 2.84)	< 0.001	0.578	9.04 (6.00, 14.70)	< 0.001	0.532	1.60 (1.10, 3.30)	0.010	0.513
Colorectal hyperplastic polyps	1037	1.88 (1.31, 2.75)	< 0.001	0.565	8.70 (5.90, 13.70)	0.065	0.517	1.60 (1.00, 3.20)	0.379	0.492
Colorectal gland hyperplasia	567	1.87 (1.35, 2.62)	< 0.001	0.560	8.30 (5.45, 13.45)	0.308	0.512	1.50 (1.10, 3.30)	0.687	0.505
Esophageal cancer	57	2.34 (1.30, 3.78)	< 0.001	0.645	9.40 (6.40, 20.00)	0.114	0.560	2.00 (1.20, 4.20)	0.073	0.568
Gastric cancer	392	2.15 (1.35, 4.13)	< 0.001	0.625	10.30 (5.70, 20.23)	< 0.001	0.577	2.00 (1.10, 5.70)	< 0.001	0.570
Colorectal cancer	892	3.25 (1.78, 11.55)	< 0.001	0.736	13.30 (7.10, 33.45)	< 0.001	0.649	2.30 (1.20, 5.90)	< 0.001	0.598
Liver cancer	127	4.27 (2.15, 7.46)	< 0.001	0.786	17.30 (7.40, 39.15)	< 0.001	0.674	1.60 (1.15, 3.75)	0.070	0.547
Pancreatic cancer	47	3.20 (1.98, 9.63)	< 0.001	0.771	99.60 (16.95, 307.15)	< 0.001	0.830	3.10 (1.35, 9.60)	< 0.001	0.680
Lung cancer	129	4.25 (2.15, 16.67)	< 0.001	0.787	12.10 (8.20, 25.50)	< 0.001	0.668	3.40 (1.40, 9.00)	< 0.001	0.660
Breast cancer	55	2.39 (1.44, 6.06)	< 0.001	0.654	15.60 (8.30, 27.20)	< 0.001	0.693	2.10 (1.20, 4.70)	0.022	0.589
Ovarian cancer	57	1.78 (1.08, 5.63)	0.228	0.546	21.85 (8.50, 130.50)	< 0.001	0.718	6.40 (1.50, 17.70)	< 0.001	0.698

Thyroid cancer	74	1.71 (1.06, 2.48)	0.936	0.497	9.90 (6.80, 15.28)	0.067	0.562	1.70 (1.03, 3.08)	0.874	0.495
Kidney cancer	37	2.37 (1.16, 3.70)	0.015	0.615	10.60 (7.70, 17.46)	0.039	0.598	2.20 (1.40, 5.20)	0.050	0.593
Malignant tumors (except thyroid cancer)	1955	2.65 (1.49, 6.70)	< 0.001	0.692	12.00 (6.80, 28.30)	< 0.001	0.636	2.20 (1.20, 5.90)	< 0.001	0.589

The bold font of the *P* value indicates that the *P* value was less than 0.05 in the Wilcoxon test. The bold font of the area under the curve (AUC) indicates that the AUC value was greater than 0.7. CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; CA72-4: Carbohydrate antigen 72-4; AUC: Area under the curve.

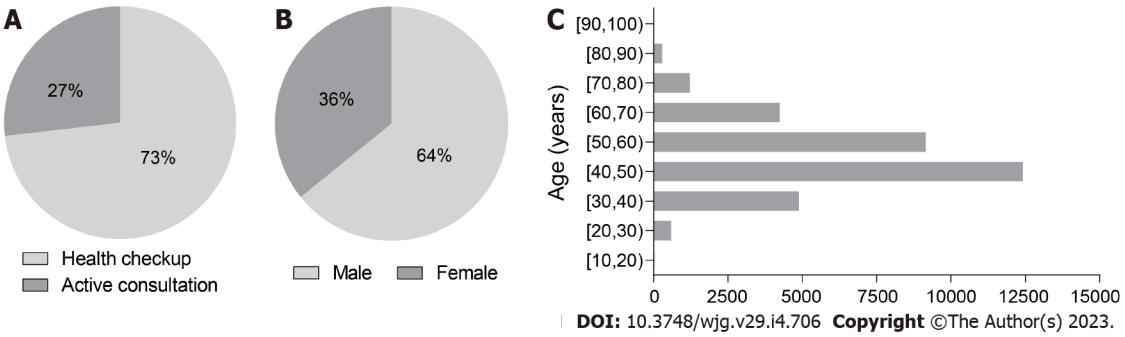

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Figure 1 Fan charts and bar plots of the clinical characteristic. A-C: There were 24045 subjects who underwent health checkup and 8812 subjects with an active consultation.

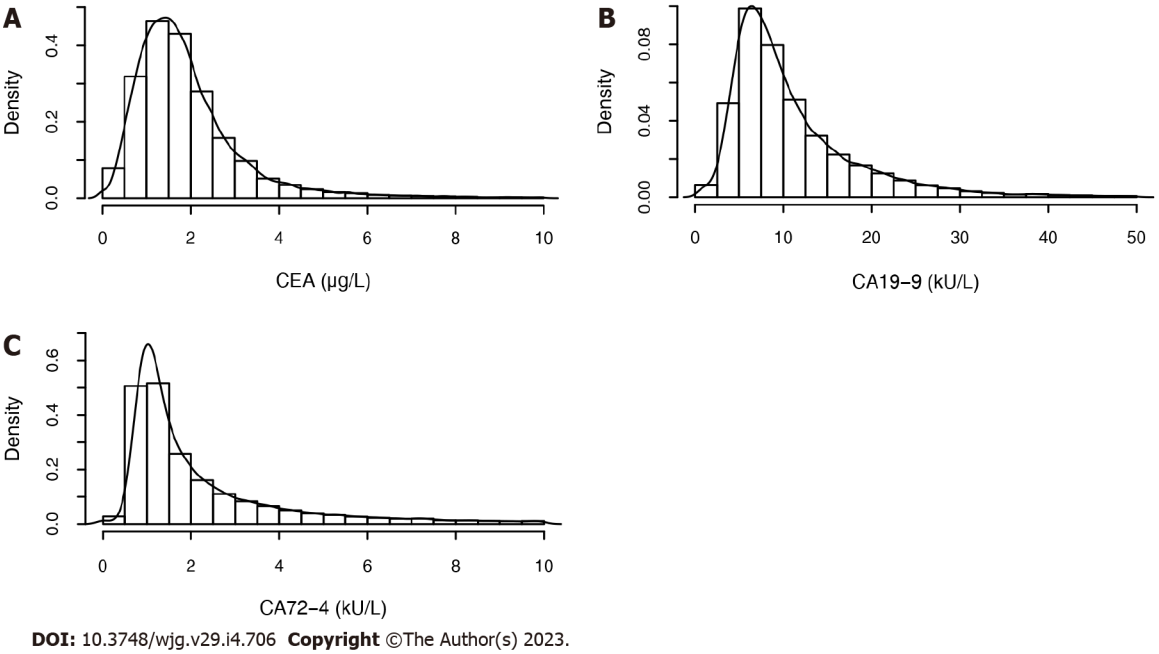

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Figure 2 Histograms of carcinoembryonic antigen, carbohydrate antigen 19-9, and carbohydrate antigen 72-4. A: Carcinoembryonic antigen; B: Carbohydrate antigen 19-9; C: Carbohydrate antigen 72-4. CEA: Carcinoembryonic antigen; CA 19-9: Carbohydrate antigen 19-9; CA 72-4: Carbohydrate antigen 72-4.

were used to calculate the effect of age on the biomarker levels. CEA, CA19-9, and CA72-4 increased by 0.41, 2.69, and 0.69, respectively, for the subjects without malignant tumors for every 10-year increase.

The biomarker levels in different malignant tumor stages are shown in Table 7 and Figure 4.

Diagnostic accuracies of tumor biomarkers

The AUCs of the three biomarkers in various benign and malignant diseases are displayed in Table 5, and the ROC curves are shown in Figure 5. An AUC above 0.7 was of moderate diagnostic value, and an AUC above 0.9 was of high diagnostic value. We found that even though the biomarker levels of several

Table 6 Correlation analysis and linear regression analysis of biomarker levels and clinical characteristics

		Age			Gender		
		***P* value**	**Correlation coefficient**	**Regression coefficient**	***P* value**	**Correlation coefficient**	**Regression coefficient**
CEA	Whole	< 0.001	0.227	0.176	< 0.001	0.236	0.004
	With malignant tumors	< 0.001	0.231	0.263	< 0.001	0.144	-2.965
	Without malignant tumors	< 0.001	0.195	0.041	< 0.001	0.248	0.472
CA19-9	Whole	< 0.001	0.135	1.076	< 0.001	-0.070	-1.400
	With malignant tumors	< 0.001	0.111	1.898	0.356	-0.021	-
	Without malignant tumors	< 0.001	0.113	0.269	< 0.001	-0.071	-2.482
CA72-4	Whole	< 0.001	0.084	0.076	< 0.001	-0.043	-0.927
	With malignant tumors	0.064	0.042	-	0.814	-0.005	-
	Without malignant tumors	< 0.001	0.069	0.052	< 0.001	-0.044	-0.773

The bold font indicates that the *P* value was less than 0.05. CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; CA72-4: Carbohydrate antigen 72-4.

diseases were significantly different, the diagnostic values of these biomarkers were not high enough. The AUC of the CEA level reached 0.7 for CRC, liver cancer, pancreatic cancer and lung cancer, while those of the CA19-9 Level reached 0.830 for pancreatic cancer and 0.7 for ovarian cancer. There was no disease in which the AUC of CA72-4 reached 0.7.

We show the diagnostic value of GC, CRC and gastrointestinal malignant tumors (the DOR, sensitivity, specificity, Youden index, accuracy, predictive value, likelihood ratio under the traditional and the best threshold) in Table 8. Furthermore, we provide several criteria for evaluating their diagnostic efficiencies as the qualified standards: positive likelihood ratio, negative likelihood ratio and DOR should be > 5.0, < 0.2 and > 10.0, respectively. Generally, there is no ideal biomarker for GC. In this study, CEA was better than CA19-9 and CA72-4. The positive likelihood ratio and DOR of CEA and CA19-9 were qualified for CRC and GIC, while those of CA72-4 were not qualified for GC, CRC or GIC.

The AUCs of diverse subgroups, including age, health checkup/active consultation and malignant tumor stage, are shown in Table 9. We defined an AUC greater than 0.7 as the qualified line. Then, the AUCs of CEA, CA19-9, and CA72-4 in the health checkup population were all unqualified. If we looked at the stages alone, CEA for stage-IV GC, CA19-9 for stage-IV CRC and CEA for stage-II-IV CRC were qualified. However, neither CEA nor CA199 can diagnose early GICs.

The DCA curves of the three biomarkers are presented in Figure 6. The DCA curve showed that under the traditional threshold and the best threshold, the clinical benefits of CEA were higher than those of CA19-9, while the clinical benefits of CA72-4 were the lowest.

Four panels were conducted with the combination of the three biomarkers. We selected the panel with the highest AUC and compared it with the single biomarker with the highest AUC (Table 10). The combination of biomarkers in the CRC and gastrointestinal malignant tumors significantly increased the AUC (Delong's test, P < 0.05) by less than 0.3, while that in GC did not. Therefore, the combination of the three biomarkers could not greatly improve the diagnostic value.

Economic analysis of tumor biomarkers with endoscopies

We analyzed the four economic indicators of the six schemes with changes in the serum levels of the three biomarkers, as shown in Figure 7. For gastroscopy only, the total cost and cost-effectiveness ratio of correctly diagnosing one case of GIC were unacceptably high. For colonoscopy only, various cost indicators were reduced within a certain range of biomarker levels. The four economic indicators of CEA in Scheme 6 (only colonoscopy conducted when blood tests were positive) were lower than those in other schemes because the diagnostic efficiencies of CEA for CRC were high, and the prevalence rate of CRC was higher than that of GC in this study. If both gastroscopy and colonoscopy were conducted, the influence of the order of gastroscopy on the four economic indicators was small. Therefore, in the follow-up study, we only calculated the economic indicators in Scheme 2 (both gastroscopy and colonoscopy when blood tests were positive) compared to those in Scheme 1 (both gastroscopy and colonoscopy for all people without blood tests).

Table 7 The biomarker levels and categorical regression analysis of each stage of gastric cancer and colorectal cancer

		Gastric cancer		Colorectal cancer	
		Median (quartile)	Quatization	Median (quartile)	Quatization
CEA (μg/L)	CIS	1.74 (1.45, 2.18)	-0.983	2.04 (1.17, 2.32)	-1.695
	Stage I	1.78 (1.29, 2.79)	-0.983	2.30 (1.45, 4.10)	-1.252
	Stage II	2.16 (1.07, 4.03)	-0.835	3.42 (2.13, 9.26)	-0.680
	Stage III	2.37 (1.31, 5.78)	-0.176	3.28 (2.00, 8.21)	-0.680
	Stage IV	3.79 (1.76, 29.1)	1.346	10.1 (2.57, 57.4)	1.168
CA19-9 (kU/L)	CIS	8.60 (5.05, 12.7)	-1.138	8.66 (6.18, 13.2)	-0.963
	Stage I	9.25 (5.88, 14.4)	-1.138	9.50 (6.20, 14.1)	-0.963
	Stage II	7.73 (5.53, 16.8)	-1.138	12.4 (7.38, 28.8)	-0.812
	Stage III	12.2 (5.63, 37.7)	0.842	13.1 (7.33, 23.0)	-0.790
	Stage IV	11.8 (5.08, 28.7)	0.903	28.9 (10.5, 216.4)	1.192
CA72-4 (kU/L)	CIS	1.50 (0.90, 3.50)	-1.203	1.50 (1.00, 2.03)	-1.550
	Stage I	1.80 (1.20, 4.33)	-0.977	1.70 (1.10, 3.20)	-1.060
	Stage II	1.90 (1.18, 4.30)	-0.789	2.10 (1.20, 3.81)	-0.818
	Stage III	2.10 (1.30, 4.63)	-0.164	1.95 (1.10, 4.21)	-0.679
	Stage IV	4.10 (1.00, 12.0)	1.340	4.75 (1.50, 15.2)	1.182

CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; CA72-4: Carbohydrate antigen 72-4; CIS: Carcinoma *in situ*.

Table 8 Diagnostic efficiencies of gastric cancer, colorectal cancer and gastrointestinal cancers at the traditional and best cut-off values

		Gastric cancer			Colorectal cancer			Gastrointestinal cancers		
		CEA	CA19-9	CA72-4	CEA	CA19-9	CA72-4	CEA	CA19-9	CA72-4
	AUC	0.625	0.577	0.570	0.736	0.649	0.598	0.705	0.627	0.590
Traditional cut-off value	Cut-off value	5.0	37.0	6.0	5.0	37.0	6.0	5.0	37.0	6.0
	DOR	6.083	5.089	2.220	14.854	11.895	2.376	12.459	10.367	2.337
	Sensitivity	0.227	0.140	0.240	0.377	0.241	0.249	0.323	0.210	0.243
	Specificity	0.954	0.969	0.876	0.961	0.974	0.878	0.963	0.975	0.879
	Youden index	0.181	0.109	0.115	0.338	0.215	0.127	0.286	0.185	0.122
	Accuracy	0.945	0.959	0.868	0.945	0.954	0.861	0.938	0.945	0.854
	PPV	0.056	0.052	0.023	0.212	0.204	0.054	0.266	0.261	0.077
	NPV	0.990	0.989	0.990	0.982	0.979	0.977	0.972	0.968	0.966
	PLR	4.927	4.516	1.927	9.640	9.269	2.034	8.759	8.400	2.012
	NLR	0.810	0.888	0.868	0.649	0.779	0.856	0.703	0.810	0.861
Best cut-off value	Cut-off value	2.6	16.3	3.8	2.8	20.7	2.0	2.5	19.6	3.4
	DOR	2.687	2.233	2.038	6.345	4.825	1.933	4.419	3.872	2.068
	Sensitivity	0.423	0.324	0.349	0.558	0.361	0.566	0.556	0.339	0.375
	Specificity	0.785	0.823	0.791	0.834	0.895	0.597	0.779	0.883	0.775
	Youden index	0.209	0.147	0.141	0.392	0.256	0.163	0.335	0.222	0.150
	Accuracy	0.781	0.817	0.786	0.827	0.881	0.596	0.770	0.861	0.759
	PPV	0.023	0.022	0.020	0.086	0.088	0.038	0.094	0.107	0.065

	NPV	0.991	0.990	0.990	0.985	0.980	0.980	0.977	0.970	0.968
	PLR	1.972	1.833	1.675	3.363	3.445	1.405	2.519	2.900	1.667
	NLR	0.734	0.821	0.822	0.530	0.714	0.727	0.570	0.749	0.806

The best cut-off value referred to the threshold when the Youden index was the largest. CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; CA72-4: Carbohydrate antigen 72-4; AUC: Area under the curve; DOR: Diagnostic odds ratio; PPV: Positive predictive value; NPV: Negative predictive value; PLR: Positive likelihood ratio; NLR: Negative likelihood ratio.

Table 9 Subgroup analysis of area under the curve for gastric cancer, colorectal cancer and gastrointestinal cancers

	Gastric cancer			Colorectal cancer			Gastrointestinal cancer		
	CEA	CA19-9	CA72-4	CEA	CA19-9	CA72-4	CEA	CA19-9	CA72-4
Whole	0.625	0.577	0.570	0.736	0.649	0.598	0.705	0.627	0.590
≥ 60 years	0.585	0.521	0.544	0.701	0.614	0.577	0.675	0.592	0.572
< 60 years	0.578	0.571	0.570	0.683	0.616	0.593	0.648	0.598	0.583
HC	0.570	0.570	0.525	0.584	0.539	0.514	0.584	0.554	0.526
AC	0.595	0.544	0.547	0.724	0.637	0.577	0.696	0.615	0.571
CIS	0.551	0.478	0.542	0.540	0.536	0.526	-	-	-
Stage I	0.554	0.525	0.565	0.675	0.546	0.512	-	-	-
Stage II	0.603	0.489	0.591	0.781	0.657	0.578	-	-	-
Stage III	0.658	0.645	0.603	0.770	0.642	0.565	-	-	-
Stage IV	0.739	0.614	0.634	0.810	0.778	0.698	-	-	-

The bold font indicates that the area under the curve value was more than 0.7. CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; CA72-4: Carbohydrate antigen 72-4; HC: Health checkup; AC: Active consultation; CIS: Carcinoma *in situ*.

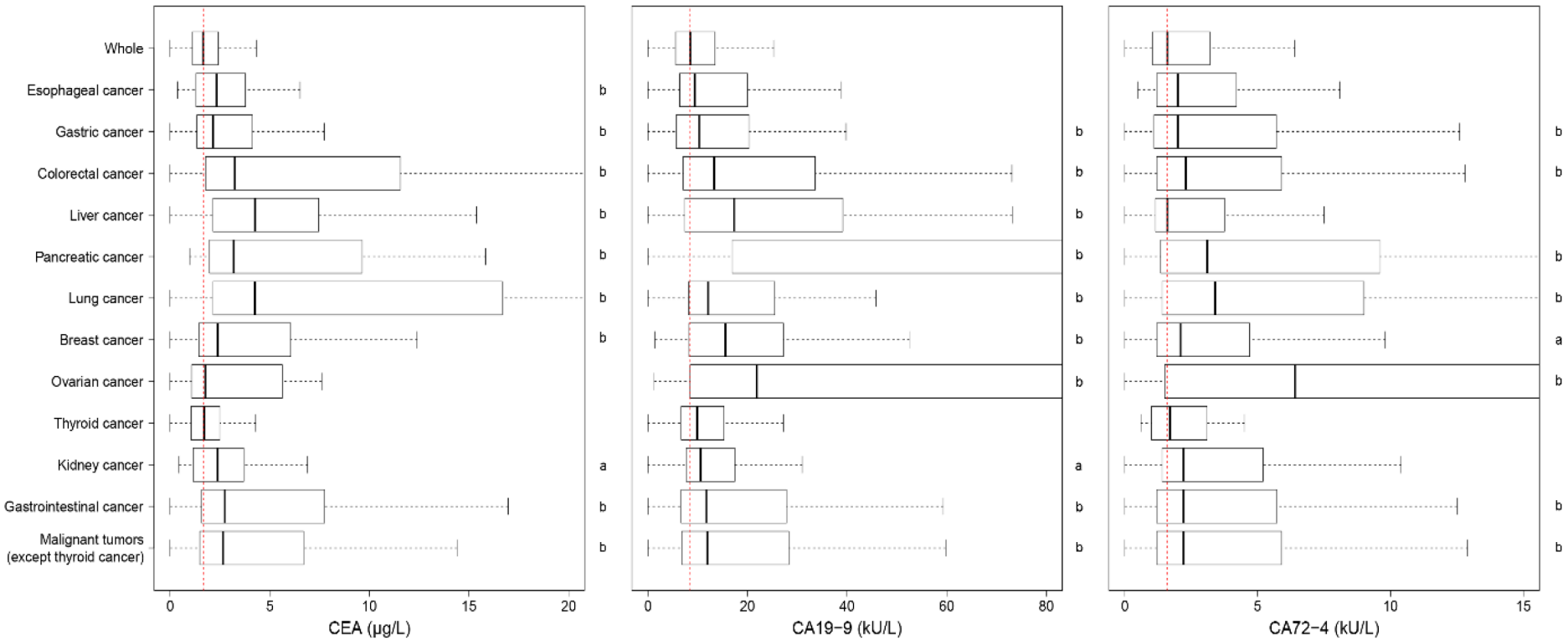
Table 10 The best single biomarker and the best combination of biomarkers for gastric cancer, colorectal cancer and gastrointestinal cancers

	Best combination		Best single biomarker		*P* value
	Biomarkers	AUC	Biomarker	AUC	
Gastric cancer	CEA + CA19-9 + CA72-4	0.653	CEA	0.625	0.067
Colorectal cancer	CEA + CA19-9	0.761	CEA	0.736	< 0.001
Gastrointestinal cancers	CEA + CA19-9	0.727	CEA	0.705	< 0.001

The bold font indicates that the *P* value was less than 0.05 in Delong's test. AUC: Area under the curve; CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; CA72-4: Carbohydrate antigen 72-4.

In terms of threshold selection, we found that the traditional threshold of CEA (5 μg/L) was exactly between the CEA level under the minimum total cost-effectiveness ratio (4.3 μg/L) and that under the minimum total cost (equal to cost-effectiveness ratio per capita, 8.7 μg/L). If we decrease the cut-off value, the four indicators grew rapidly. If we increase the cut-off value, then the total cost-effectiveness ratio rose sharply, while the other three indicators had fewer changes. One can use 5 μg/L for CEA as an economic cut-off value. For CA19-9, we found that a similarly high economic cut-off value was approximately 30 kU/L, not the traditional threshold of 37 kU/L. Compared with that at the threshold of 30 kU/L, the total cost-effectiveness ratio at the threshold of 37 kU/L was greatly increased because of the lower sensitivity of the marker. We evaluated the economic efficiencies as the qualified standard: all four indicators in Scheme 2 were lower than those in Scheme 1. CEA met the standards at the threshold of 1.8 μg/L to 10.4 μg/L. CA19-9 and CA72-4 failed at the whole threshold, caused by the high total cost-effectiveness ratio in Scheme 2.

Compared with CEA, the combination of the three biomarkers in pairs or altogether caused the cost and cost-effectiveness ratio to be higher (Table 11). From an economic perspective, the combination of



DOI: 10.3748/wjg.v29.i4.706

Figure 3 Boxplots of biomarker levels of malignant tumors. The red dotted line is the biomarker level for all subjects. The *P* value was calculated between the malignant tumor patients and the subjects without any malignant tumors by the Wilcoxon test. [a]*P* < 0.05, [b]*P* < 0.01. CEA: Carcinoembryonic antigen; CA 19-9: Carbohydrate antigen 19-9; CA 72-4: Carbohydrate antigen 72-4.

biomarkers is not superior to the single biomarker, CEA.

Economic analysis of tumor biomarkers in different subgroups

The subgroup analysis under the traditional threshold is displayed in Table 12, Figures 8-10.

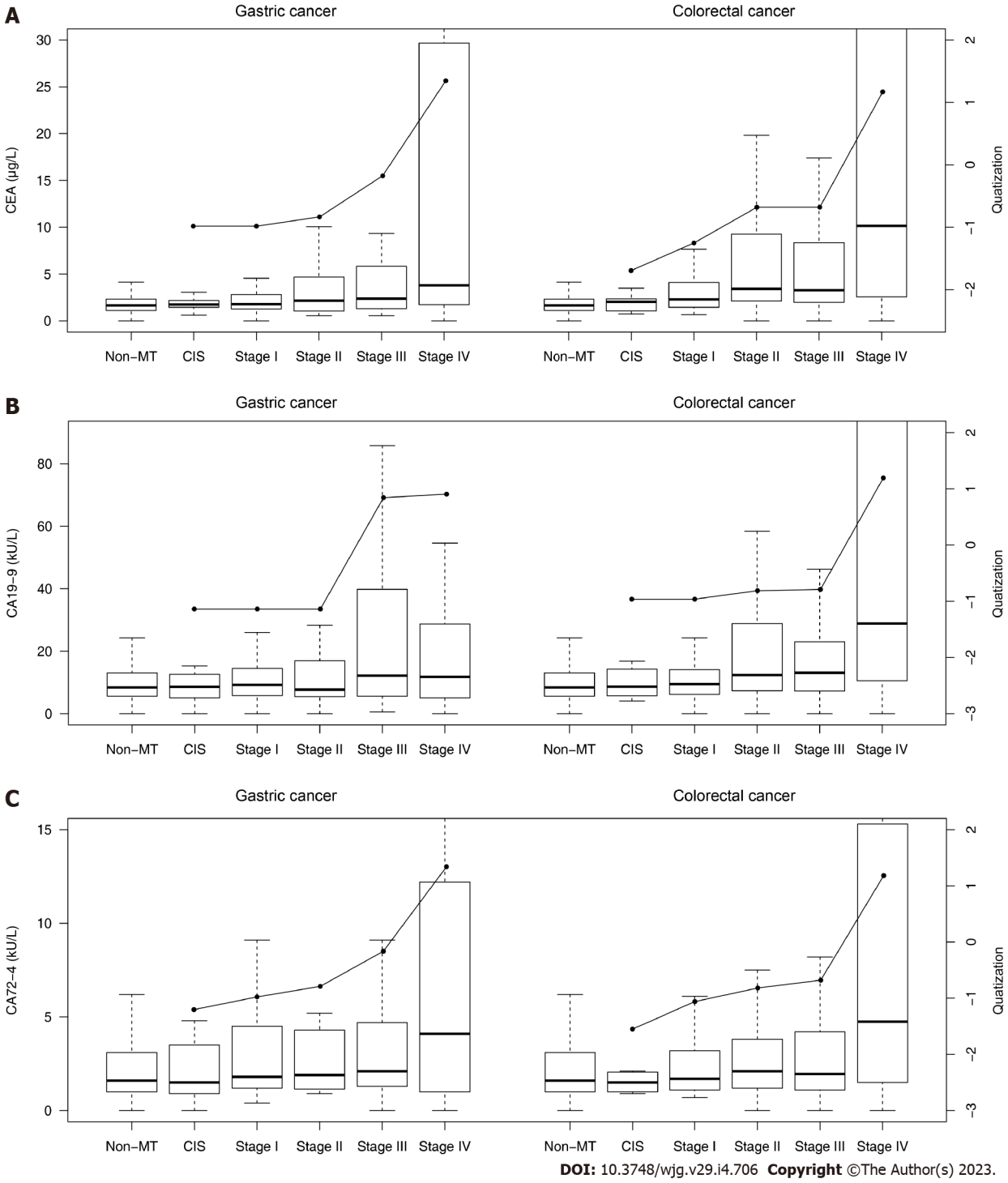
As we expected, for all ages, the four economic indicators of CEA in the health checkup subgroup were much higher than those in the active consultation subgroup. In the subgroup of health checkup subjects above 65 years old, all four indicators of CEA in Scheme 2 were lower than those in Scheme 1, while the total cost-effectiveness ratio in Scheme 2 was higher than that in Scheme 1 in the subgroup of health checkup subjects under 60 years. This highlights that conducting CEA testing in the health checkup for people over 65 years old is economically valuable, especially the lower cost per capita ($40.9 in Scheme 2 *vs* $146.6 in Scheme 1).

Table 11 Economic analysis of carcinoembryonic antigen, carbohydrate antigen 19-9, and carbohydrate antigen 72-4 in several situations for gastrointestinal cancers

	Cut-off value	Proportion of endoscopy	Missed diagnosis rate	Total cost ($)	Cost per capita ($)	Total C/E ($)	C/E per capita ($)	Remarks
Non-blood test	-	1.000	0.000	3574.3	146.9	3574.3	146.9	Gold standard
CEA (μg/L)	0.0	1.000	0.000	3691.9	151.7	3691.9	151.7	Lowest cut-off value
	2.5	0.230	0.451	1718.1	38.7	3130.1	70.6	Highest youden index
	4.3	0.065	0.642	990.0	14.6	2767.1	40.7	Lowest total cost-effectiveness ratio
	5.0	0.049	0.674	903.1	12.1	2770.9	37.1	Traditional diagnostic cut-off value
	8.7	0.020	0.759	783.9	7.8	3246.2	32.2	Lowest total cost & lowest cost-effectiveness ratio per capita
CA19-9 (kU/L)	0.0	1.000	0.000	3755.4	154.3	3755.4	154.3	Lowest cut-off value & lowest total cost-effectiveness ratio
	20.0	0.121	0.665	1836.7	25.3	5485.7	75.5	Highest youden index
	36.9	0.033	0.787	1398.5	12.2	6578.5	57.5	Lowest total cost & lowest cost-effectiveness ratio per capita
	37.0	0.032	0.789	1405.2	12.2	6656.1	57.7	Traditional diagnostic cut-off value
CA72-4 (kU/L)	0.0	1.000	0.000	3755.4	154.3	3755.4	154.3	Lowest cut-off value & lowest total cost-effectiveness ratio
	3.4	0.231	0.623	2670.7	41.4	7083.5	109.7	Highest youden index
	6.0	0.126	0.756	2584.5	25.9	10605.1	106.2	Traditional diagnostic cut-off value
	10.5	0.064	0.833	2451.6	16.8	14709.6	100.7	Lowest total cost & lowest cost-effectiveness ratio per capita
CEA	5.0	0.069	0.601	1365.1	22.4	3419.2	56.1	Traditional diagnostic cut-off value in parallel
CA19-9	37.0							
CEA	6.9	0.036	0.676	1309.0	17.4	4034.6	53.8	Lowest cut-off value & lowest total cost-effectiveness ratio in parallel
CA19-9	69.2							
CEA	3.9	0.098	0.554	1455.6	26.7	3264.3	59.8	Lowest total cost-effectiveness ratio in parallel
CA19-9	38.1							
CEA	5.0	0.012	0.862	2433.3	13.8	17661.0	100.0	Traditional diagnostic cut-off value in serial
CA19-9	37.0							
CEA	5.4	0.042	0.689	1437.7	18.4	4621.3	59.1	Lowest cut-off value & lowest total cost-effectiveness ratio in serial
CA19-9	0.0							
CEA	2.1	0.335	0.361	2339.4	61.4	3659.5	96.1	Lowest total cost-effectiveness ratio in serial
CA19-9	0.0							
CEA	5.0	0.044	0.666	1362.9	18.7	4079.6	56.0	Traditional diagnostic cut-off value in the logistic model
CA19-9	37.0							
CEA	4.9	0.052	0.641	1341.0	19.8	3732.7	55.1	Lowest cut-off value & lowest total cost-effectiveness ratio in the logistic model
CA19-9	23.2							
CEA	2.0	0.213	0.436	1874.8	43.5	3321.5	77.0	Lowest total cost-effect-

CA19-9	33.5	iveness ratio in the logistic model

The economic indicators were total cost, cost per capita and their cost-effectiveness ratios. The cut-off value with the lowest total cost equaled that of the lowest cost-effectiveness ratio per capita. In the parallel test, any positive result of carcinoembryonic antigen (CEA) or carbohydrate antigen 19-9 (CA 19-9) was considered positive, while both of the positive results of CEA and CA19-9 were considered positive in the serial test. The logistic model was CEA × 2.02 + CA19-9 × 0.06, which made the area under the curve highest. C/E: Cost-effectiveness ratio; CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; CA72-4: Carbohydrate antigen 72-4.



DOI: 10.3748/wjg.v29.i4.706

Figure 4 Boxplots of biomarker levels for each stage of gastric cancer and colorectal cancer. A: Carcinoembryonic antigen; B: Carbohydrate antigen 19-9; C: Carbohydrate antigen 72-4. CEA: Carcinoembryonic antigen; CA 19-9: Carbohydrate antigen 19-9; CA 72-4: Carbohydrate antigen 72-4; CIS: Carcinoma *in situ*.

Table 12 Subgroup analysis of economic indicators

			Scheme 2							Scheme 1	
			Cut-off value	Proportion of endoscopy	Missed diagnosis rate	Total cost ($)	Cost per capita ($)	Total C/E ($)	C/E per capita ($)	Total cost & C/E ($)	Cost & C/E per capita ($)
CEA	Whole	Whole	5.0	0.049	0.674	903.1	12.1	2770.9	37.1	3574.3	146.9
		≥ 80 yr	5.0	0.258	0.543	381.8	45.6	835.9	99.8	584.4	152.7
		≥ 75 yr	5.0	0.240	0.635	472.1	41.9	1294.7	115.0	623.2	151.8
		≥ 70 yr	5.0	0.214	0.627	463.5	37.7	1242.1	101.2	691.5	150.9
		≥ 65 yr	5.0	0.174	0.634	486.4	31.6	1329.1	86.3	844.6	149.9
		≥ 60 yr	5.0	0.137	0.636	523.6	25.8	1438.6	71.0	1099.1	149.0
		≥ 55 yr	5.0	0.110	0.639	574.1	21.6	1588.8	59.8	1424.3	148.3
		≥ 50 yr	5.0	0.085	0.643	662.6	17.7	1854.8	49.6	1972.8	147.6
		≥ 45 yr	5.0	0.065	0.658	758.5	14.6	2220.9	42.7	2614.6	147.2
		≥ 40 yr	5.0	0.055	0.668	837.4	13.1	2520.1	39.4	3121.4	147.0
		≥ 35 yr	5.0	0.051	0.671	882.1	12.4	2684.9	37.8	3427.4	146.9
		≥ 30 yr	5.0	0.049	0.674	902.2	12.2	2764.8	37.3	3552.0	146.9
	HC	Whole	5.0	0.021	0.883	6834.3	7.7	58218.5	65.4	15277.9	146.1
		≥ 80 yr	5.0	0.238	0.000	446.3	42.5	446.3	42.5	1565.3	149.1
		≥ 75 yr	5.0	0.129	0.500	941.8	24.4	1883.7	48.7	2843.9	147.1
		≥ 70 yr	5.0	0.101	0.538	693.8	20.0	1503.3	43.3	2356.2	146.9
		≥ 65 yr	5.0	0.070	0.630	1046.6	15.1	2832.1	40.9	3755.2	146.6
		≥ 60 yr	5.0	0.049	0.744	1677.6	12.0	6542.7	46.7	5254.5	146.4
		≥ 55 yr	5.0	0.040	0.794	2611.7	10.5	12685.3	51.1	7474.5	146.3
		≥ 50 yr	5.0	0.033	0.824	3519.3	9.5	19989.5	53.8	9558.2	146.2
		≥ 45 yr	5.0	0.026	0.848	4577.8	8.5	30179.8	55.7	12010.0	146.2
		≥ 40 yr	5.0	0.023	0.871	5726.3	8.0	44326.1	61.8	13537.7	146.2
		≥ 35 yr	5.0	0.021	0.879	6443.2	7.8	53455.1	64.6	14572.3	146.1
		≥ 30 yr	5.0	0.021	0.881	6737.6	7.7	56396.5	64.7	15225.1	146.1
	AC	Whole	5.0	0.126	0.631	515.4	24.2	1397.6	65.5	1170.9	148.8
		≥ 80 yr	5.0	0.260	0.557	378.1	45.8	853.5	103.4	559.6	153.0
		≥ 75 yr	5.0	0.260	0.640	449.7	45.2	1249.2	125.5	547.0	152.7
		≥ 70 yr	5.0	0.256	0.634	439.0	44.4	1200.5	121.3	551.5	152.4
		≥ 65 yr	5.0	0.240	0.634	433.8	42.0	1186.4	114.8	574.1	152.0
		≥ 60 yr	5.0	0.219	0.624	436.5	38.9	1161.3	103.4	639.4	151.5
		≥ 55 yr	5.0	0.197	0.621	445.2	35.4	1173.3	93.4	719.0	150.9
		≥ 50 yr	5.0	0.171	0.616	471.6	31.2	1229.4	81.5	868.1	149.9
		≥ 45 yr	5.0	0.146	0.626	493.5	27.4	1319.3	73.2	1006.5	149.3
		≥ 40 yr	5.0	0.134	0.628	508.3	25.5	1367.6	68.6	1103.8	149.0
		≥ 35 yr	5.0	0.129	0.629	513.2	24.6	1383.2	66.3	1151.7	148.9
		≥ 30 yr	5.0	0.126	0.631	516.1	24.2	1400.2	65.7	1168.9	148.8
CA19-9	Whole	Whole	37.0	0.032	0.789	1405.2	12.2	6656.1	57.7	3574.3	146.9
		≥ 80 yr	37.0	0.168	0.741	494.9	33.5	1908.7	129.3	584.4	152.7

		≥ 75 yr	37.0	0.164	0.735	505.6	32.7	1906.7	123.2	623.2	151.8
		≥ 70 yr	37.0	0.137	0.761	546.5	28.5	2288.5	119.3	691.5	150.9
		≥ 65 yr	37.0	0.115	0.762	589.9	25.0	2474.1	104.7	844.6	149.9
		≥ 60 yr	37.0	0.090	0.754	633.2	21.2	2568.7	85.8	1099.1	149.0
		≥ 55 yr	37.0	0.070	0.764	736.3	18.1	3114.0	76.7	1424.3	148.3
		≥ 50 yr	37.0	0.054	0.774	913.9	15.5	4035.0	68.4	1972.8	147.6
		≥ 45 yr	37.0	0.042	0.782	1108.4	13.6	5075.1	62.4	2614.6	147.2
		≥ 40 yr	37.0	0.036	0.785	1254.6	12.7	5833.6	59.1	3121.4	147.0
		≥ 35 yr	37.0	0.033	0.789	1359.0	12.3	6434.6	58.2	3427.4	146.9
		≥ 30 yr	37.0	0.032	0.789	1398.6	12.2	6634.7	57.8	3552.0	146.9
	HC	Whole	37.0	0.014	0.917	11789.9	9.3	142719.5	112.8	15277.9	146.1
		≥ 80 yr	37.0	0.143	0.500	622.7	29.7	1245.5	59.3	1565.3	149.1
		≥ 75 yr	37.0	0.078	0.833	2187.1	18.9	13122.9	113.1	2843.9	147.1
		≥ 70 yr	37.0	0.048	0.808	1207.9	14.5	6281.3	75.3	2356.2	146.9
		≥ 65 yr	37.0	0.043	0.783	1621.1	13.8	7457.1	63.3	3755.2	146.6
		≥ 60 yr	37.0	0.032	0.808	2252.2	12.1	11711.6	62.8	5254.5	146.4
		≥ 55 yr	37.0	0.026	0.853	3855.6	11.1	26218.2	75.5	7474.5	146.3
		≥ 50 yr	37.0	0.020	0.873	5259.2	10.2	41488.9	80.5	9558.2	146.2
		≥ 45 yr	37.0	0.016	0.899	7832.3	9.6	77452.6	95.3	12010.0	146.2
		≥ 40 yr	37.0	0.014	0.909	9540.9	9.4	104950.4	103.0	13537.7	146.2
		≥ 35 yr	37.0	0.014	0.915	10937.8	9.3	128950.9	109.7	14572.3	146.1
		≥ 30 yr	37.0	0.014	0.916	11530.0	9.3	137146.2	110.7	15225.1	146.1
	AC	Whole	37.0	0.082	0.763	663.4	20.0	2793.3	84.3	1170.9	148.8
		≥ 80 yr	37.0	0.170	0.747	488.5	33.8	1929.4	133.5	559.6	153.0
		≥ 75 yr	37.0	0.180	0.731	469.9	35.2	1749.5	131.1	547.0	152.7
		≥ 70 yr	37.0	0.171	0.757	502.4	33.7	2069.9	138.9	551.5	152.4
		≥ 65 yr	37.0	0.159	0.760	503.3	32.0	2093.5	133.2	574.1	152.0
		≥ 60 yr	37.0	0.144	0.748	496.7	29.7	1967.4	117.7	639.4	151.5
		≥ 55 yr	37.0	0.126	0.753	519.6	26.9	2105.0	109.0	719.0	150.9
		≥ 50 yr	37.0	0.109	0.759	581.1	24.2	2411.0	100.4	868.1	149.9
		≥ 45 yr	37.0	0.095	0.762	620.3	21.9	2601.4	92.0	1006.5	149.3
		≥ 40 yr	37.0	0.087	0.761	644.3	20.8	2694.8	87.0	1103.8	149.0
		≥ 35 yr	37.0	0.083	0.763	659.0	20.2	2780.6	85.2	1151.7	148.9
		≥ 30 yr	37.0	0.082	0.763	663.9	20.0	2805.1	84.5	1168.9	148.8
CA72-4	Whole	Whole	6.0	0.126	0.756	2584.5	25.9	10605.1	106.2	3574.3	146.9
		≥ 80 yr	6.0	0.194	0.790	676.1	37.1	3221.6	176.7	584.4	152.7
		≥ 75 yr	6.0	0.190	0.762	627.4	36.3	2641.0	152.8	623.2	151.8
		≥ 70 yr	6.0	0.180	0.755	651.5	34.8	2661.4	142.2	691.5	150.9
		≥ 65 yr	6.0	0.173	0.749	749.3	33.4	2980.7	133.0	844.6	149.9
		≥ 60 yr	6.0	0.166	0.745	933.2	32.3	3653.5	126.5	1099.1	149.0
		≥ 55 yr	6.0	0.158	0.746	1167.6	30.9	4599.8	121.6	1424.3	148.3
		≥ 50 yr	6.0	0.147	0.749	1552.7	29.1	6194.2	116.2	1972.8	147.6
		≥ 45 yr	6.0	0.139	0.753	2003.3	27.9	8106.4	112.8	2614.6	147.2

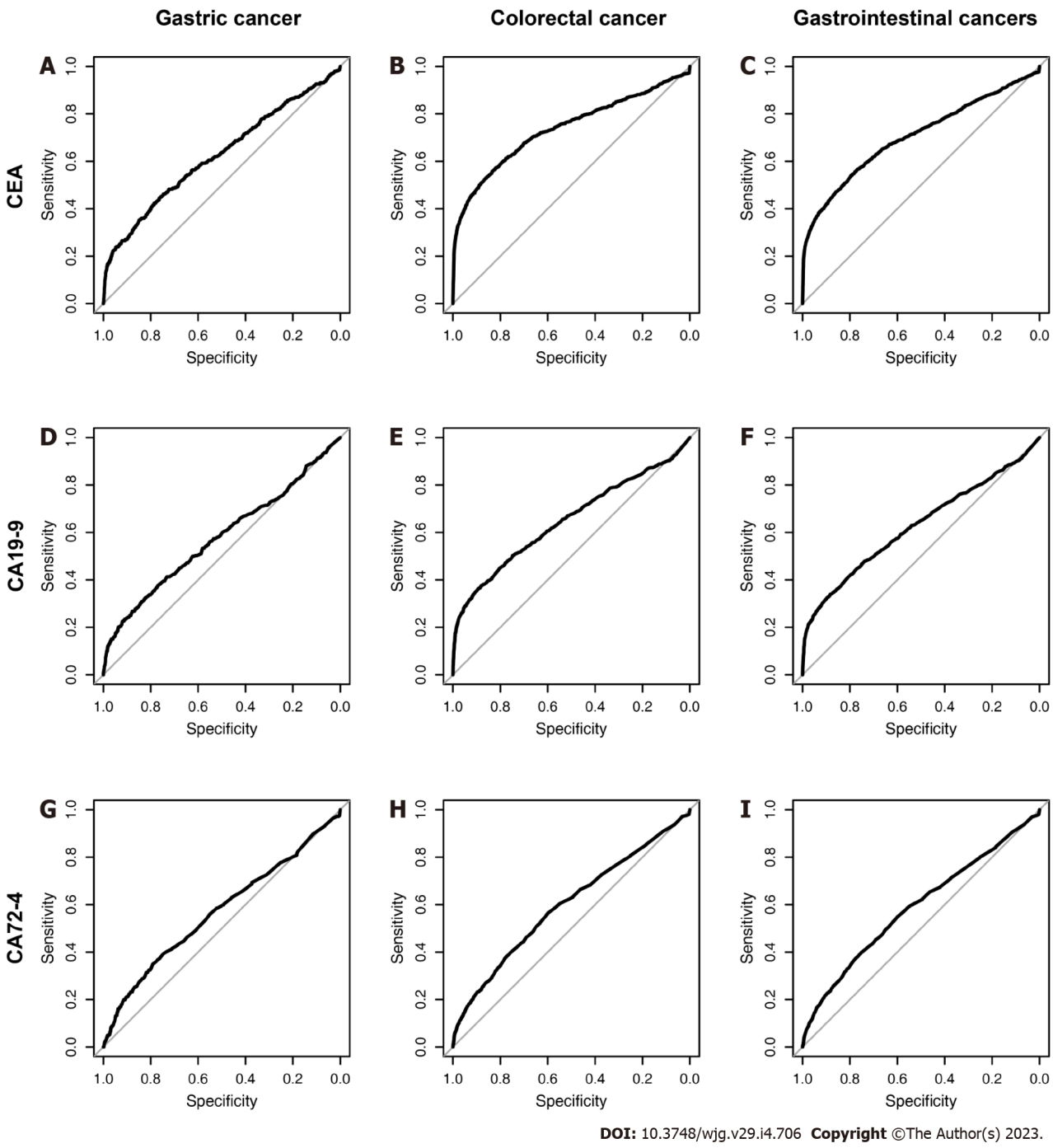
	≥ 40 yr	6.0	0.132	0.752	2293.2	26.7	9259.2	108.0	3121.4	147.0
	≥ 35 yr	6.0	0.128	0.755	2488.4	26.2	10145.7	106.7	3427.4	146.9
	≥ 30 yr	6.0	0.127	0.755	2565.2	25.9	10489.2	106.1	3552.0	146.9
HC	Whole	6.0	0.108	0.870	18401.4	23.0	141077.7	176.0	15277.9	146.1
	≥ 80 yr	6.0	0.333	0.500	1206.6	57.5	2413.3	114.9	1565.3	149.1
	≥ 75 yr	6.0	0.190	0.667	2042.4	35.2	6127.2	105.6	2843.9	147.1
	≥ 70 yr	6.0	0.144	0.808	2375.7	28.5	12353.8	148.1	2356.2	146.9
	≥ 65 yr	6.0	0.126	0.848	4345.5	25.8	28556.3	169.7	3755.2	146.6
	≥ 60 yr	6.0	0.118	0.821	4898.1	24.5	27289.4	136.5	5254.5	146.4
	≥ 55 yr	6.0	0.119	0.843	8033.4	24.7	51212.7	157.2	7474.5	146.3
	≥ 50 yr	6.0	0.118	0.866	11985.7	24.5	89577.1	183.4	9558.2	146.2
	≥ 45 yr	6.0	0.116	0.854	13653.0	24.3	93470.7	166.2	12010.0	146.2
	≥ 40 yr	6.0	0.111	0.861	15690.0	23.5	113076.5	169.4	13537.7	146.2
	≥ 35 yr	6.0	0.109	0.866	17224.4	23.1	128608.7	172.7	14572.3	146.1
	≥ 30 yr	6.0	0.108	0.867	18051.9	23.0	135991.3	173.3	15225.1	146.1
AC	Whole	6.0	0.177	0.733	997.5	33.8	3736.5	126.8	1170.9	148.8
	≥ 80 yr	6.0	0.183	0.797	643.0	35.6	3174.8	175.8	559.6	153.0
	≥ 75 yr	6.0	0.190	0.766	558.4	36.5	2383.4	155.8	547.0	152.7
	≥ 70 yr	6.0	0.194	0.751	539.5	37.2	2165.0	149.1	551.5	152.4
	≥ 65 yr	6.0	0.202	0.739	554.2	38.2	2126.5	146.7	574.1	152.0
	≥ 60 yr	6.0	0.212	0.736	634.8	39.7	2405.9	150.4	639.4	151.5
	≥ 55 yr	6.0	0.206	0.735	694.1	38.6	2617.8	145.6	719.0	150.9
	≥ 50 yr	6.0	0.194	0.732	793.2	36.7	2963.2	137.0	868.1	149.9
	≥ 45 yr	6.0	0.186	0.736	901.9	35.4	3410.7	133.8	1006.5	149.3
	≥ 40 yr	6.0	0.182	0.731	953.6	34.6	3547.9	128.7	1103.8	149.0
	≥ 35 yr	6.0	0.179	0.732	984.8	34.1	3674.4	127.3	1151.7	148.9
	≥ 30 yr	6.0	0.177	0.733	995.6	33.9	3723.6	126.8	1168.9	148.8

The economic indicators were total cost, cost per capita and their cost-effectiveness ratios. The units of carcinoembryonic antigen, carbohydrate antigen 19-9, and carbohydrate antigen 72-4 are μg/L, kU/L, and kU/L, respectively. C/E: Cost-effectiveness ratio; CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; CA72-4: Carbohydrate antigen 72-4; HC: Health checkup; AC: Active consultation.

In the active consultation subgroup, the total cost-effectiveness ratio in Scheme 2 was higher than that in Scheme 1 for all ages. CA19-9 and CA72-4 had higher total cost-effectiveness ratios in almost all subgroups, different from CEA (Figures 9 and 10). This also indicates that blood tests for the active consultation group are not enough and that the necessary gastrointestinal endoscopy procedure is more important.

DISCUSSION

This study included more than 32000 subjects who received CEA, CA19-9, CA72-4, gastroscopy and colonoscopy assessments. In our study, CEA and CA19-9 again have been proved to be ideal serum biomarkers for screening GICs. The specificity of CEA and CA19-9 was approximately 95.0%-97.5% at the traditional cut-off value, which was highly consistent with previous studies[5,6]. While for the diagnostic value of CA72-4, there is a discrepancy between the results of previous literatures and our clinical practice. In our study, the specificity of CA72-4 was less than 90%, indicating that the cut-off value could be higher, which made the sensitivity even lower. If the cut-off value of CA72-4 was 10, the sensitivity and specificity of GC were 0.163 and 0.933, respectively, and the sensitivity and specificity of CRC were 0.177 and 0.935, respectively.

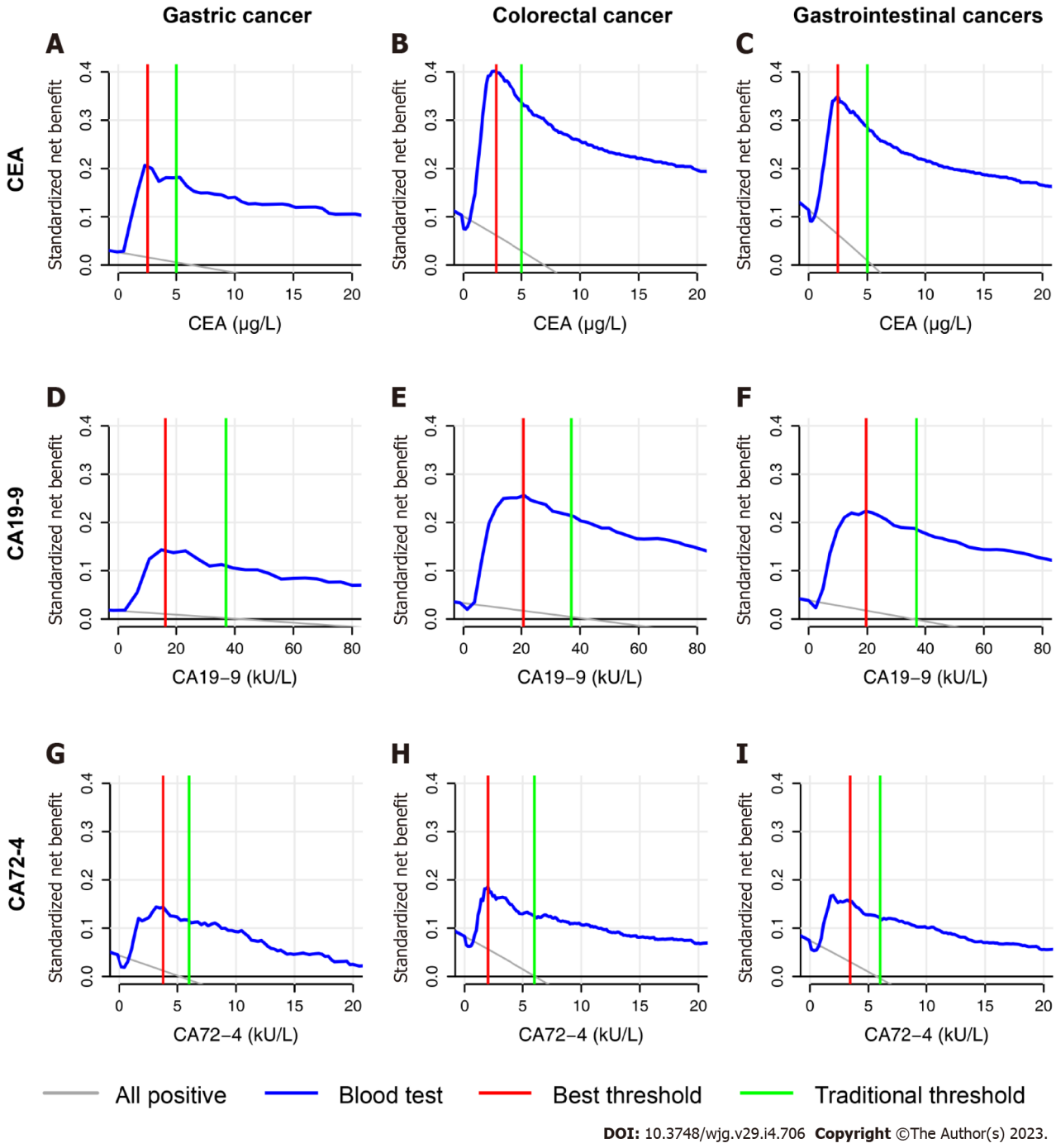


DOI: 10.3748/wjg.v29.i4.706

Figure 5 Receiver operating characteristic curves of carcinoembryonic antigen, carbohydrate antigen 19-9, and carbohydrate antigen 72-4 for gastric cancer, colorectal cancer and gastrointestinal cancers. A-C: Carcinoembryonic antigen; D-F: Carbohydrate antigen 19-9; G-I: Carbohydrate antigen 72-4. CEA: Carcinoembryonic antigen; CA 19-9: Carbohydrate antigen 19-9; CA 72-4: Carbohydrate antigen 72-4.

Besides the sensitivity and specificity, another important indicator is the PPV. Even for the best performing CEA, the PPV for GC was as low as 5.6% and that for CRC was only 21.2%. At the traditional cut-off value, the PPV of CA72-4 for GC was 2.3%, which meant that 97.7% of CA72-4-positive patients were false positive. The PPV also explained why there was no evidence of malignant disease in a large number of CA72-4-positive patients after a full set of auxiliary examinations. Of course, in view of the fact that the PPV is greatly affected by the prevalence, the real-world PPV would be lower. Therefore, our data on the predictive value is mainly used for comparison among the three biomarkers.

Several novel indicators are proposed to evaluate the economic value of blood markers for GICs. To calculate the economic value of a blood biomarker, it is inadequate to focus on the biomarker itself. A blood test is used as a screening test, and its significance also lies in the following gold standard test. By combining blood tests and endoscopy, the total cost and cost per capita of correctly diagnosing one case of GIC are excellent indicators, which are related to the cost, prevalence rate and sensitivity of blood



DOI: 10.3748/wjg.v29.i4.706

Figure 6 Decision curves of tumor biomarkers for gastrointestinal cancers. A-C: Carcinoembryonic antigen; D-F: Carbohydrate antigen 19-9; G-I: Carbohydrate antigen 72-4. CEA: Carcinoembryonic antigen; CA 19-9: Carbohydrate antigen 19-9; CA 72-4: Carbohydrate antigen 72-4.

tests. However, these two indicators are not sufficient. If the prevalence of a disease increases, the cost per capita would also increase owing to more endoscopy examinations. It seemed that the cost increased, but the effect had actually improved even more. Therefore, it was necessary to calculate the cost-effectiveness ratio. What is the 'effect'? As a screening test, the sensitivity is its effect. The cost-effectiveness ratio is cost divided by sensitivity, which means the total cost for correctly diagnosing all subjects, including missed patients. We found that the total cost and the cost-effectiveness ratio per capita are positively correlated and change synchronously. Through our economic research, we have discovered the impacts of the order of gastrointestinal endoscopy and diagnostic thresholds on economic benefits. It is also clear that the economic value of combined blood biomarkers is not as good as that of the single CEA. Subgroup analysis shows that CEA had qualified diagnostic value for health checkup subjects above 65 years old.

In this study, only the subjects who received CEA, CA19-9, CA72-4, gastroscopy and colonoscopy were included. These inclusion criteria avoided or reduced several biases, such as workup bias, spectrum bias and measurement bias. For example, all of the included cases were examined by the gold

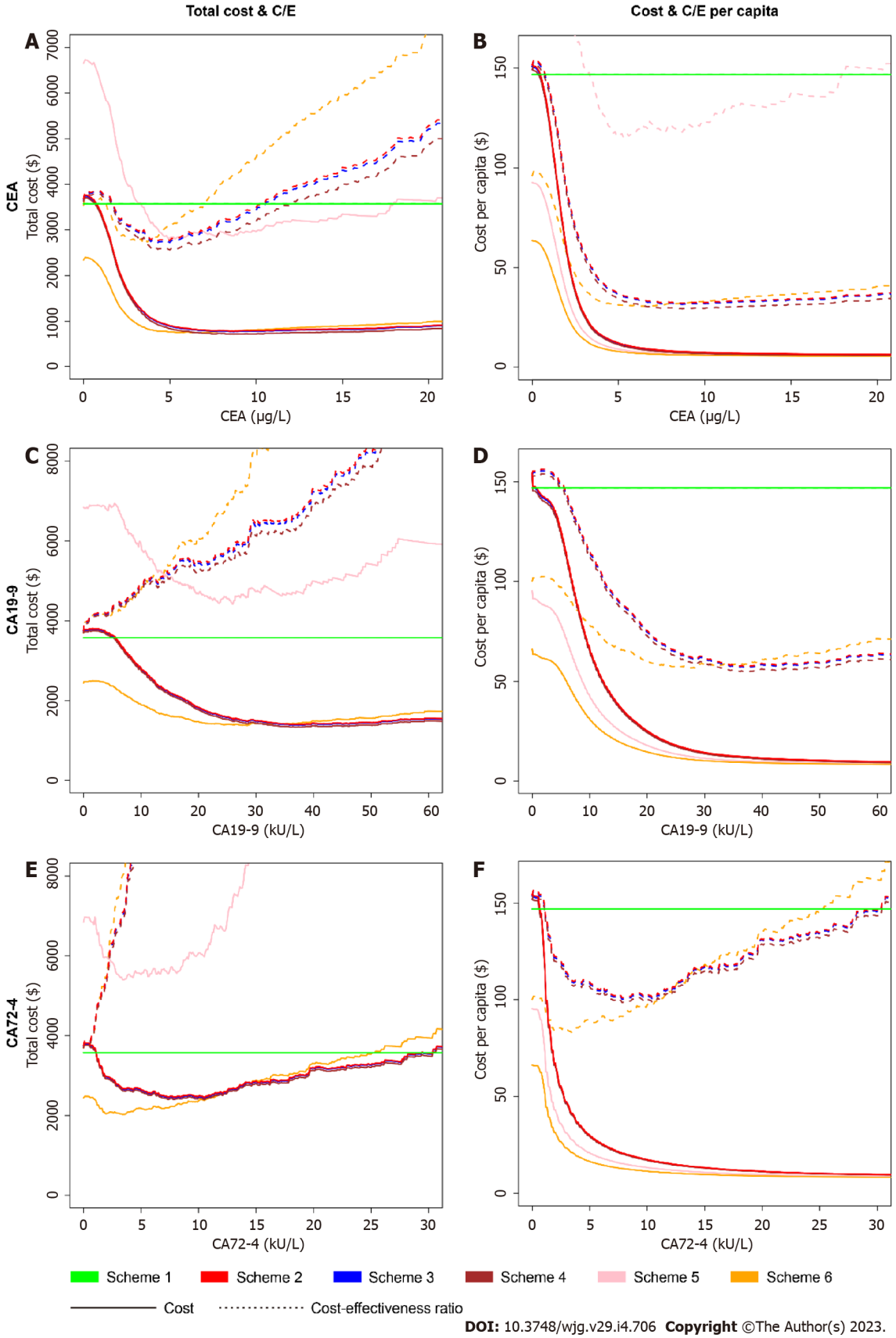


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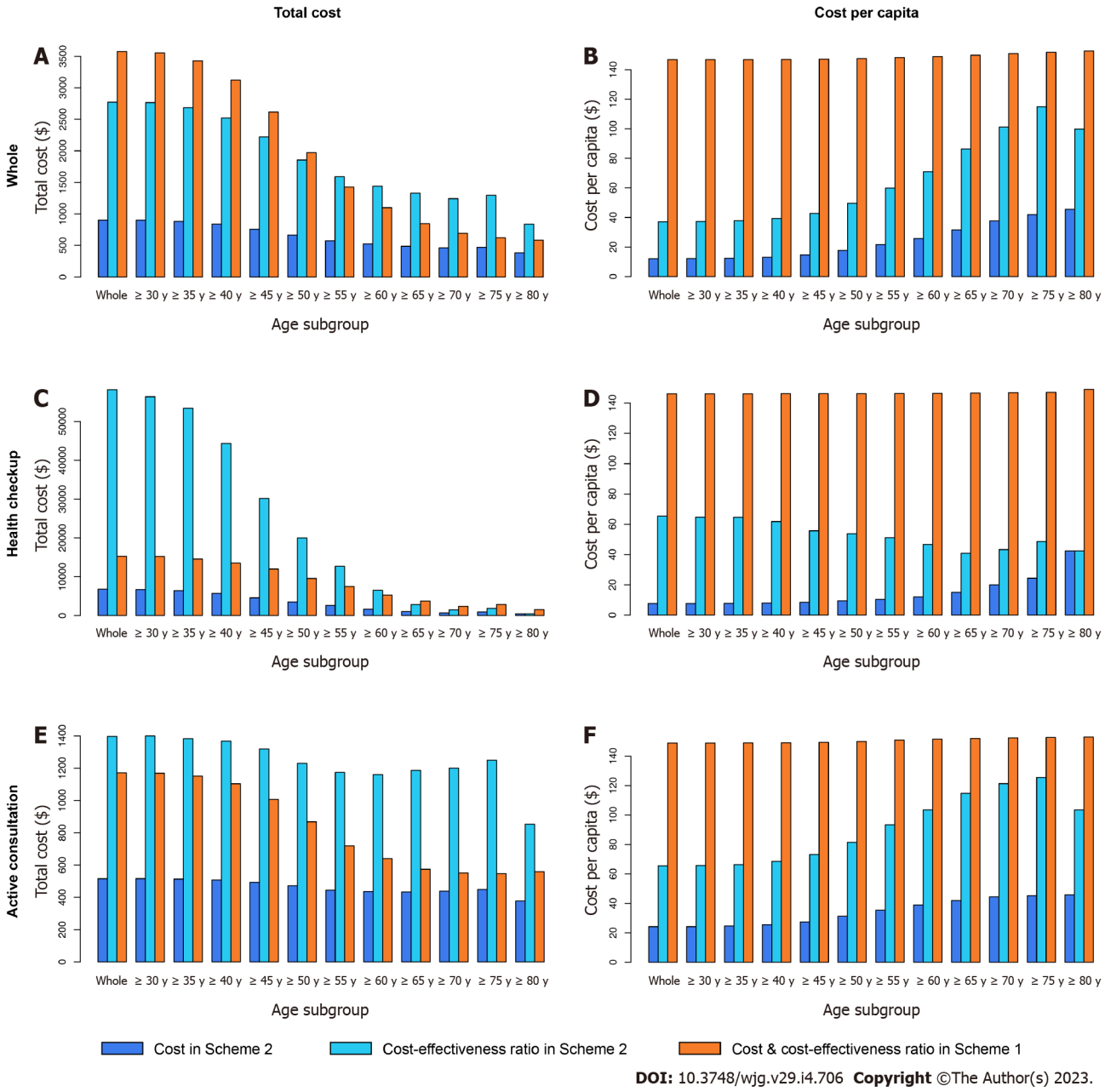
Figure 7 Economic analysis of tumor biomarkers in six schemes for gastrointestinal cancers. A and B: Carcinoembryonic antigen; C and D: Carbohydrate antigen 19-9; E and F: Carbohydrate antigen 72-4. CEA: Carcinoembryonic antigen; CA 19-9: Carbohydrate antigen 19-9; CA 72-4: Carbohydrate antigen 72-4.

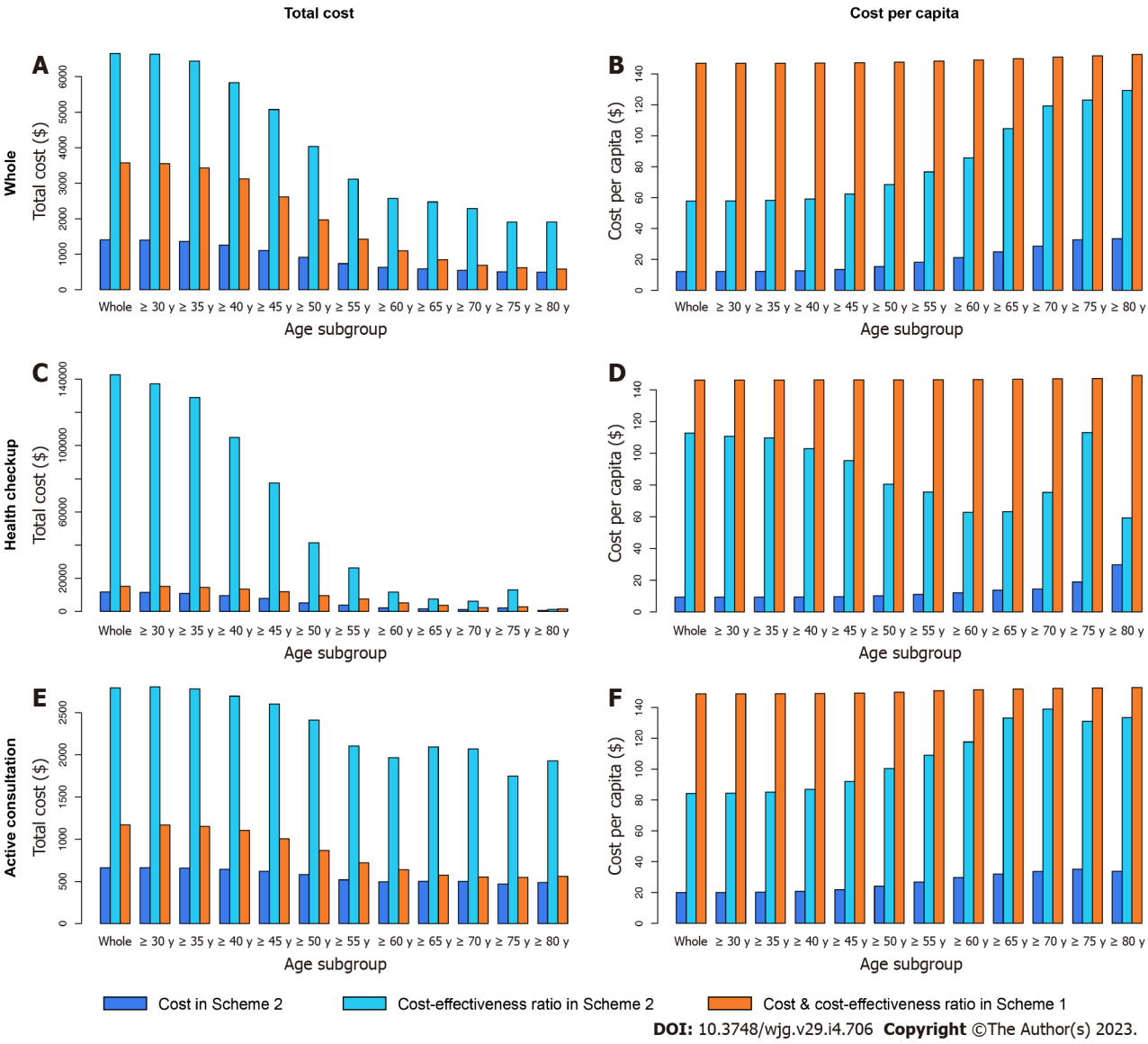


DOI: 10.3748/wjg.v29.i4.706

Figure 8 Bar plots of subgroup analysis of economic indicators for carcinoembryonic antigen. A and B: Whole; C and D: Health checkup; E and F: Active consultation.

standard test, so there was no situation in which the subject with negative blood test results was not examined with the gold standard test. But on the other hand, the inclusion criteria led to an inevitable selection bias because the subjects undergoing gastrointestinal endoscopy are those with a high risk of digestive diseases, and the incidences of GC and CRC in this study were higher than that in the real world[15]. Many people undergo only blood tests but not gastrointestinal endoscopy when receiving a health checkup. As a result, some early GIC patients with normal CEA, CA19-9, CA72-4 Levels were not included. If these patients were included, the number of false negative subjects might have increased, and the sensitivity would have further decreased.

The advantages of this study are its continuous inclusion of subjects, use of the cohort study inclusion method (not case-control study), large sample size, inclusion of multiple tumors and use of multiple indicators. Especially for CA72-4 test, our sample size exceeded the sum of all previous reported studies. The comparison among multiple indicators highlighted the shortcomings of the diagnostic and economic value of CA72-4. In particular, the results of the classic markers CEA and CA19-9 were consistent with previous studies. We also proposed a new evaluation method for the economic efficiencies of tumor biomarkers for GIC and provided a reference for medical insurance policies.

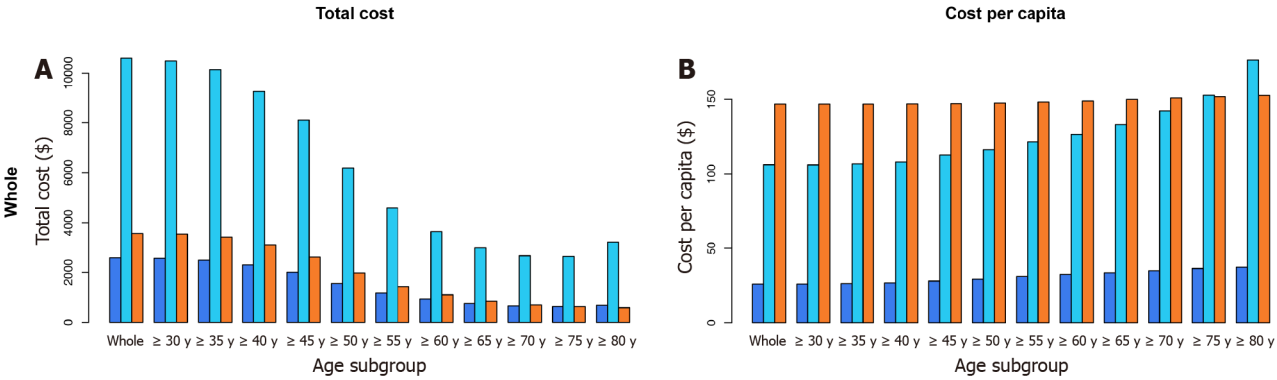


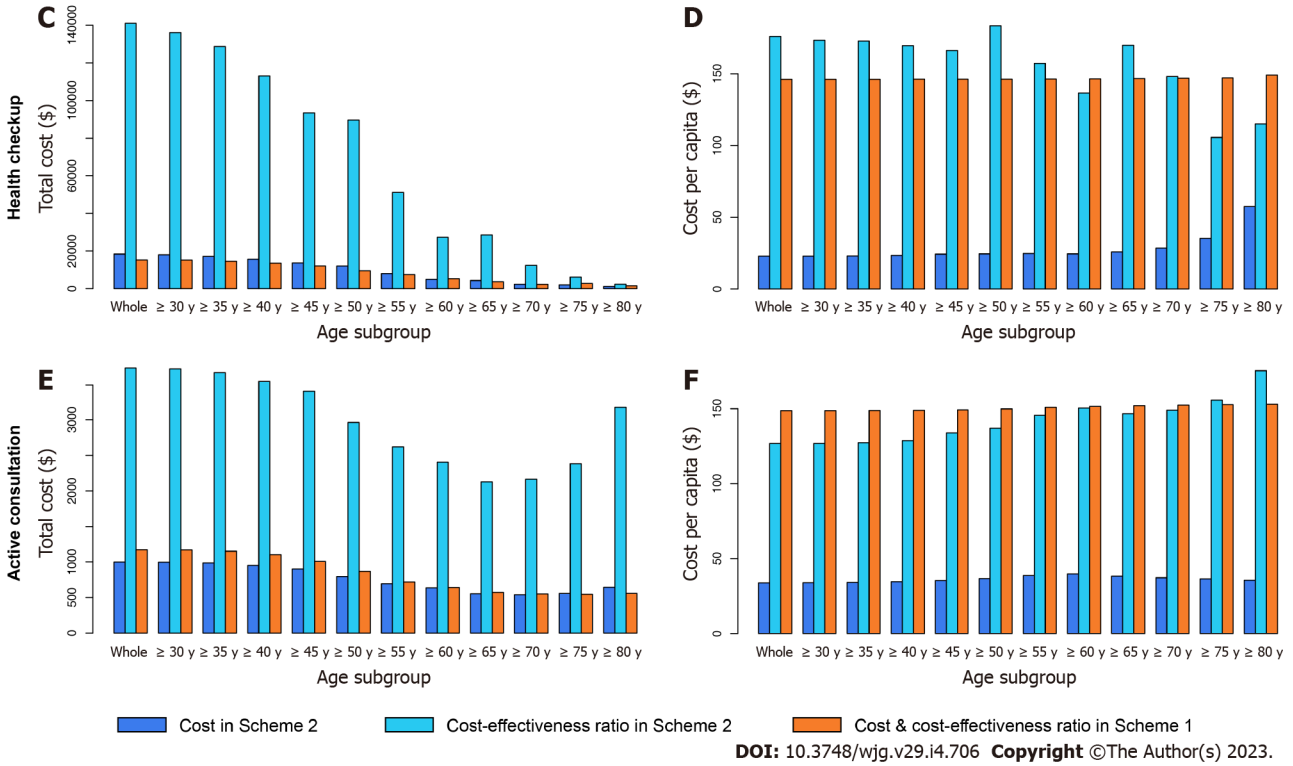
DOI: 10.3748/wjg.v29.i4.706

Figure 9 Bar plots of subgroup analysis of economic indicators for carbohydrate antigen 19-9. A and B: Whole; C and D: Health checkup; E and F: Active consultation.

CONCLUSION

CEA had qualified diagnostic value for CRC and superior economic value for GICs, especially for health checkup subjects above 65 years old. CA72-4 was not suitable as a diagnostic biomarker.





DOI: 10.3748/wjg.v29.i4.706

Figure 10 Bar plots of subgroup analysis of economic indicators for carbohydrate antigen 72-4. A and B: Whole; C and D: Health checkup; E and F: Active consultation.

ARTICLE HIGHLIGHTS

Research background

Studies showed that blood carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9) could be used to diagnose gastric cancer (GC) and colorectal cancer (CRC). Blood CA72-4 could be a potential biomarker to diagnose GC and CRC. A positive result in blood test would lead the subject to undergo further examinations.

Research motivation

Large-scale clinical application showed an extremely high false positive rate of CA72-4 for diagnosis, which leads to the waste of medical resources and heave social medical burden. The massive data and real-world diagnostic cohorts make it possible to further explore the diagnostic and economic value of biomarkers.

Research objectives

Through a real-world diagnostic cohort, we aimed to reassess the diagnostic and economic value of CEA, CA19-9, and CA72-4 for gastrointestinal malignant tumors in a large sample.

Research methods

Data from patients the medical examination center, outpatient department or inpatient department of Zhongshan Hospital of Fudan University from October 2006 to May 2018 were retrospectively evaluated. Four economic indicators were used to evaluate the economic value of tumor biomarkers. The diagnostic value of the three biomarkers was further evaluated.

Research results

The clinical benefits of CEA were higher than those of CA19-9, while the clinical benefits of CA72-4 were the lowest. The combination of biomarkers in the CRC and gastrointestinal malignant tumors significantly increased the AUC by less than 0.3, while that in GC did not. Compared to the economic indicators of the single biomarker CEA, the combination of biomarkers is not superior. At the threshold of 1.8 μg/L to 10.4 μg/L, all four indicators of CEA were lower than those in the scheme that conducted gastrointestinal endoscopy only. Subgroup analysis implied that the health checkup of CEA for people above 65 years old was economically valuable.

Research conclusions

CEA had qualified diagnostic value for CRC and superior economic value for gastrointestinal cancers, especially for health checkup subjects above 65 years old while CA72-4 was not suitable as a diagnostic biomarker.

Research perspectives

In real world, many people undergo only blood tests but not gastrointestinal endoscopy when receiving a health checkup. Those undergone gastrointestinal endoscopy were at a higher risk of digestive diseases, which leads to an inevitable selection bias. Future researches may emphasize on the involvement of patients with normal CEA, CA19-9, CA72-4 Levels to decrease the number of false negative subjects.

ACKNOWLEDGEMENTS

The authors would like to thank the members of Professor Xi-Zhong Shen's laboratory for helpful discussions and critical reading of the manuscript.

FOOTNOTES

Author contributions: Liu HN, Yao C, and Wang XF contributed equally to this work; Liu HN, Wu H, and Liu TT conceived and designed the experiments; Liu HN, Yao C, and Wang XF drafted the manuscript; Liu HN, Yao C, Wang XF, and Pan D extracted the data; Liu HN, Zhang NP, and Chen YJ performed the statistical analyses; Zhao GP and Shen XZ revised the article; all authors finished reading and approving the final manuscript of this study.

Institutional review board statement: The study was reviewed and approved by the Zhongshan Hospital of Fudan University Institutional Review Board (Approval No. B2018-234).

Informed consent statement: The informed consent was waived from the patients.

Conflict-of-interest statement: All the authors have no conflict of interest related to the manuscript.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at liu.taotao@zs-hospital.sh.cn. Participants gave informed consent for data sharing.

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S-Editor: Chen YL
L-Editor: A
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