Research Article

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Serum CA72-4 as a biomarker in the diagnosis of colorectal cancer: A meta-analysis

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Abstract: The purpose of this meta-analysis was to investigate the serum CA72-4 as a biomarker in the diagnosis of colorectal cancer by pooling the open published data. Methods. An electronic search of databases Pubmed, Medline, Web of Science, Cochrane Embase CBM, and CNKI were performed by two reviewers (Han Yanqing, Dong Cheng) independently to identify the studies relevant to serum CA72-4 as a biomarker in the diagnosis of colorectal cancer. The patient number of true positive(tp), false positive(fp), false negative(fn) and true negative(tn) were extracted from each included study. The diagnostic performance of serum CA72-4 as a biomarker in the diagnosis of colorectal cancer was assessed by pooled sensitivity, specificity and hierarchical summary receiver operating characteristic curve (HSROC). All the data was pooled by MetaDiSc 1.4 and Stata/SE 11.0 statistical software. Results A total of 22 studies with 2474 colorectal patients and 1576 controls were included in the present study and meta-analysis. The combined diagnostic sensitivity and specificity were 0.50 (95%CI:0.48-0.52) and 0.86 (95%CI:0.84-0.88) for serum CA72-4 as a biomarker in the diagnosis of colorectal cancer. The pooled positive and negative likelihood ratio were 3.41(95%CI:2.57-4.53) and 0.62(0.55-0.71). The pooled area under the ROC curve (AUC) was 0.73. Deeks'funnel plot and Egger's line regression test (p=0.49) showed no significant publication bias in the present meta-analysis. Conclusion Due toits low diagnostic sensitivity, the diagnostic performance of serum CA72-4 as a biomarker for colorectal cancer screening is limited.

Keywords: Colorectal cancer; CA72-4; Biomarker; Diagnosis; Meta-analysis

1 Introduction

Colorectal cancer(CRC) is one of the most diagnosed malignant carcinoma in the digestive system [1]. In the United States, it was the 4th most diagnosed cancer with an estimate of more than 140,000 new cases and 50,000 deaths in year 2012 [2]. However, the mortality from colorectal cancer has decreased by about 35% in recent decades attributing the success to effective colorectal screening methods and treatment modalities. The occurrence and development of colorectal cancer is accompanied by a series of molecular biological changes. The ideal tumor marker for screening colorectal cancer should have high sensitivity and specificity with easy management.

CA72-4 is a glycoprotein found on the surface of many malignant carcinoma cells [3], including colorectal cancer, ovarian cancer [4], gastric cancer [5] and pancreatic cancer. Several published studies have evaluated the diagnostic performance of serum CA72-4 as biomarker for colorectal cancer diagnosis. In our present study, we included the previously published relevant studies about CA72-4 as a biomarker for colorectal diagnosis and pooled the data in order to further evaluate its clinical value.

2 Materials and methods

2.1 Publication identification

In order to identify all the relevant studies, the electronic databases of Pubmed, Medline, Web of Science, Cochrane Embase, CBMand CNKI were systematically searched by two reviewers (Han Yanqing, Dong Cheng) independently. The publication searching terms were as follows: "colorectal cancer", "colorectal carcinoma", "colon cancer",

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"rectal cancer", "CA72-4", "CA724", "Tumor-associated glycoprotein 72 (TAG-72)". The references of included studies were also screened to identify potential suitable publications.

2.2 Study inclusion and exclusion criteria

Inclusion criteria: (1) The patients were diagnosed with colorectal cancer with pathology conformation; (2)Serum level of CA72-4 was extracted from the original publications; (3)Enough data such as tpfpfn and tnwas extracted from the included studies to calculate the diagnostic sensitivity and specificity; (4) The language was limited to English and Chinese; Exclusion criteria: (1) Studies without enough data or cases, and use of abstract publications; (2) Colorectal cancer patients were not confirmed by pathology examination; (3) Duplicated publications or data; (4) Papers published in other languages other than English or Chinese.

2.3 Quality assessment of the included studies

The general methodological qualities of the 22 included publications were assessed by two reviewers (Dong Cheng and Xu Ling) independently through an eleven items questionnaire provided by Cochrane Reviews Handbook.

2.4 Statistical method

The statistical heterogeneity among the 22 included publications was evaluated by I^2 test. If I^2>50%, the data was pooled by Dersimonian-Laird method (random effect

Table 1: The main character of the included 22 publications

Author	Year	tp	fp	fn	tn	Sensitivity	Specificity
Fiorella	1993	86	2	114	98	0.43 (0.36-0.50)	0.98 (0.93-1.00)
Sun Wei	2000	21	2	37	27	0.36 (0.24-0.50)	0.93 (0.77-0.99)
He Hui	2004	20	2	36	28	0.36 (0.23-0.50)	0.93 (0.78-0.99)
Yue Lin	2006	30	3	57	57	0.34 (0.25-0.45)	0.95 (0.86-0.99)
Zhu Zili	2006	45	15	22	63	0.67 (0.55-0.78)	0.81 (0.70-0.89)
Liu Shengli	2007	34	2	57	33	0.37 (0.27-0.48)	0.94 (0.81-0.99
QiuBing	2008	14	2	24	28	0.37 (0.22-0.54)	0.93 (0.78-0.99)
Dai Peng	2008	55	14	85	19	0.39 (0.31-0.48)	0.58 (0.39-0.75)
Pan Aiping	2009	56	13	29	65	0.66 (0.55-0.78)	0.83 (0.73-0.91)
Jiang Xiaoting	2010	62	20	99	80	0.39 (0.31-0.46)	0.80 (0.71-0.87)
Huang Fujiao	2011	14	3	27	43	0.34 (0.20-0.51)	0.93 (0.82-0.99)
Wan Caifeng	2011	68	10	34	40	0.67 (0.57-0.76)	0.80 (0.66-0.90)
Yao Aiping	2011	73	10	117	40	0.38 (0.31-0.46)	0.80 (0.66-0.90)
Hu Xiaoai	2011	14	3	27	43	0.34 (0.20-0.51)	0.93 (0.82-0.99)
Chen Jun	2012	292	7	62	46	0.82 (0.78-0.86)	0.87 (0.75-0.95)
Wang Xiuyin	2012	64	34	48	182	0.57 (0.47-0.66)	0.84 (0.79-0.89)
Song Peidong	2012	10	1	40	29	0.20 (0.10-0.34)	0.97 (0.83-1.00)
TianHua	2013	35	27	25	93	0.58 (0.45-0.71)	0.78 (0.69-0.85)
Zhu Xiaofei	2013	141	18	104	128	0.58 (0.51-0.64)	0.88 (0.81-0.93)
GuoQinhua	2013	15	1	61	97	0.20 (0.11-0.30)	0.99 (0.94-1.00)
LvZhongchuan	2013	63	21	97	79	0.39 (0.32-0.47)	0.79 (0.70-0.87)
Cheng Jinling	2017	15	9	45	39	0.25 (0.15-0.38)	0.81 (0.67-0.91)

model). Otherwise, the data was calculated by fixed-effect methods. The diagnostic performance of serum CA72-4 as a biomarker in the diagnosis of colorectal cancer was evaluated by sensitivity and specificity. [sensitivity=true positive/(true positive+ false negative), specificity=true negative/(true negative+ false positive)]. All the data was analyzed by MetaDiSc 1.4 and Stata/SE 11.0 statistical software.

3 Results

3.1 Main character of the included studies

A total of 22 studies [6-27] with 2474 colorectal patients and 1576 controls were includedwith meta-analysis. Initially, 872 studies were identified through the electronic databases search. After reviewing the title, abstract and full text, 22 publications were finally included according to the study inclusion and exclusion criteria (Figure 1). The main character of the included 22 original studies is demonstrated by Table 1.

3.2 Methodological qualities of the included studies

The methodological quality of the included 22 publications was evaluated by an 11 items questionnaire (Figure 2) and indicates the general quality was poor.

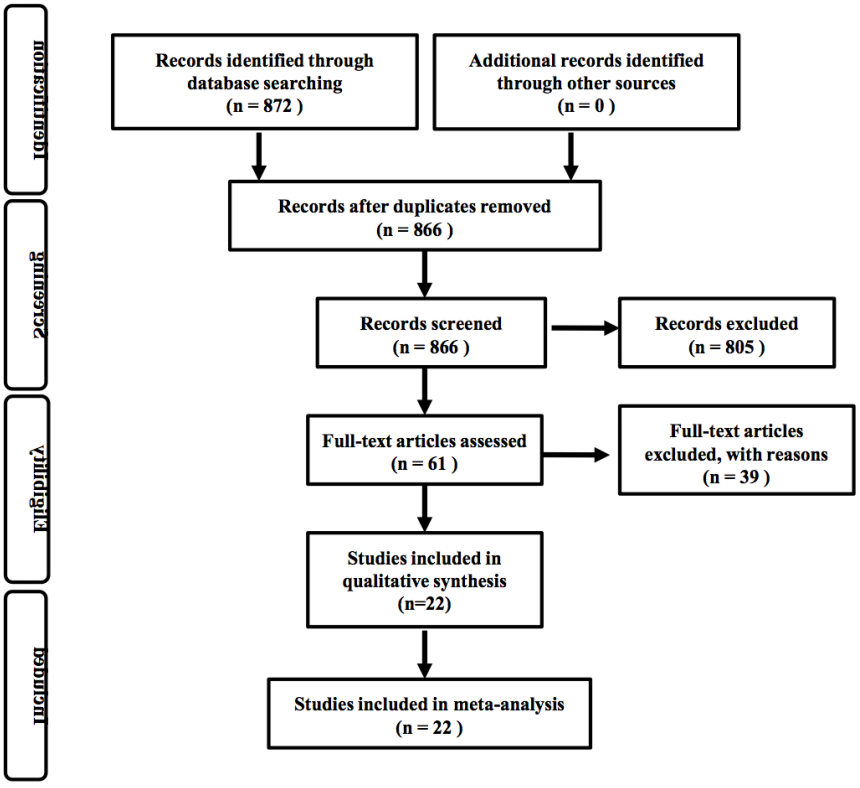
3.3 Combined sensitivity for serum CA72-4 in diagnosis of colorectal cancer

Due to statistical heterogeneity across the 22 studies (I^2=93.7%), the data was pooled by Dersimonian-Laird method. The combined diagnostic sensitivity was 0.50 (95%CI:0.48-0.52) for serum CA72-4 as a biomarker in the diagnosis of colorectal cancer, Figure 3.

3.4 Combined specificity for serum CA72-4 in diagnosis of colorectal cancer

The diagnostic specificity was pooled by random effect model because of statistical heterogeneity (I^2=78.2%). The pooled specificity was 0.86 (95%CI:0.84-0.88) for serum CA72-4 as a biomarker in the diagnosis of colorectal cancer, Figure 4.

Figure 1: The publication searching flow chart



3.5 Combined positive likelihoodratio (Positive LR)

The data was pooled through random effect model because of significant statistical heterogeneity among the 22 publications (I^2=73.1%). The combined Positive LR was 3.41 (95%CI:2.57-4.53), Figure 5.

3.6 Combined negative likelihoodratio (negative LR)

The negative LR was pooled by random effect model for significant statistical heterogeneity across the publications (I^2=89.5%). The combined negative LR was 0.62 (0.55-0.71), Figure 6.

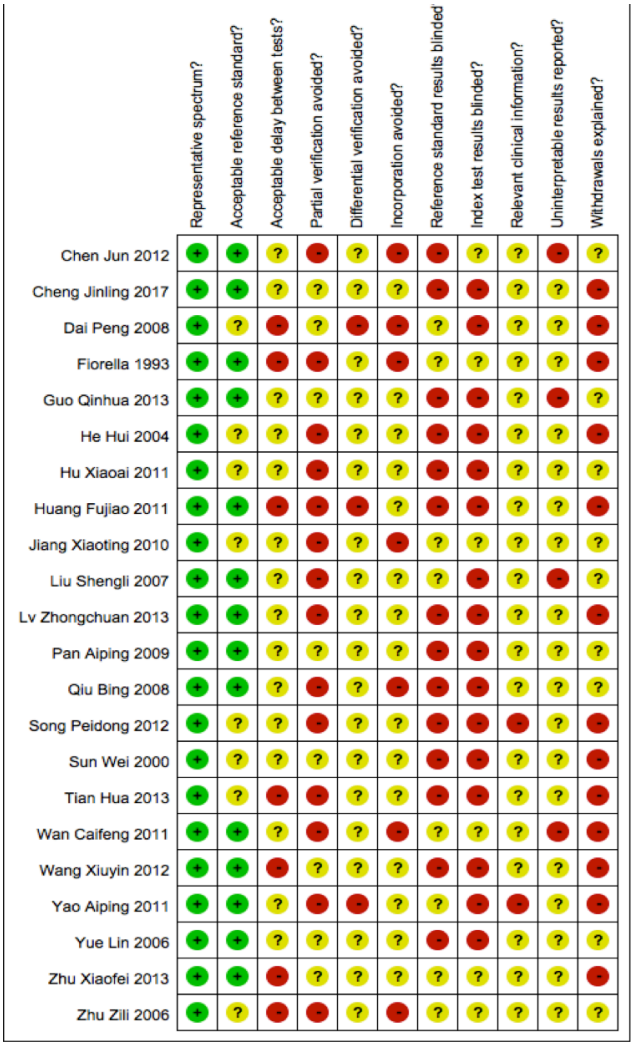


Figure 2: The methodological quality summary for each included study. (The authors'judgments for each risk of bias item. + is "low risk"; - is "high risk"; ?is"moderate risk").

3.7 Combined diagnosed odds ratio(DOR)

The diagnostic odds ratio (DOR) for serum CA72-4 as a biomarker in the diagnosis of colorectal cancer was pooled by random effects model. The pooled DOR was 6.18 with the 95%CI of 4.17-9.17, Figure 7.

3.8 The diagnostic HSROC of serum CA72-4 in the diagnosis of colorectal cancer

The pooled HSROC curve was calculated by sensitivity against (1-specificity). The pooled area under the ROC curve (AUC) was 0.73 for serum CA72-4 in the diagnosis of colorectal cancer, Figure 8.

3.9 Publication bias analysis

There was no publication bias of serum CA72-4 in the diagnosis of colorectal cancer assessed by Deeks'funnel plot (Figure 9) and Egger's line regression test(p=0.49).

4 Discussion

Colorectal cancer remains one of the most diagnosed malignant carcinomas that represents a global health problem [28]. It has previously been indicated that delayed diagnosis is the main reason for a poor prognosis. Over the past few decades, investigations have focused on the serum tumor markers for screening or early diagnosis of colorectal cancer. The most clinically used serum biomarkers for colorectal cancer screening or diagnosis in high risk population were CEA, CA199, CA125 CA72-4 and et al [29, 30].

Carbohydrate antigen 724(CA72-4), a specific glycoprotein antigen of the tumor associated glycoprotein (TAG-72), is initially used as serum biomarker for pancreatic cancer diagnosis. And recently, it was found that the serum CA72-4 level was elevated in patients with gastric cancer, ovarian cancer and colorectal cancer. Several studies [16-18] have evaluated its diagnostic performance as serum biomarkers for colorectal cancer. He *et al* [8] evaluated the serum levels of CA72-4 in diagnoses of colorectal cancer. They found that the serum concentration of CA72-4 was significantly higher in colorectal cancer patients compared to healthy controls. The serum level of CA72-4 was also positively correlated with the Duke's stage. Peidong S evaluated the diagnostic performance of serum CA72-4 as

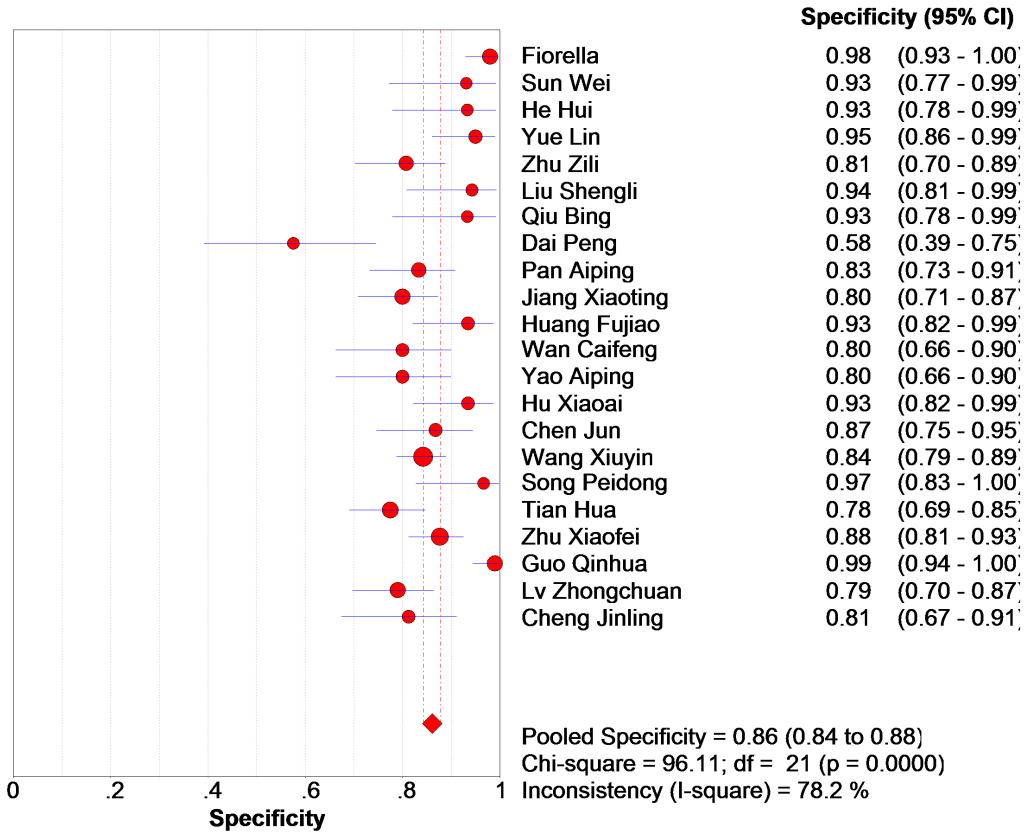


Figure 3: The diagnostic sensitivity of serum CA72-4 in the diagnosis of colorectal cancer

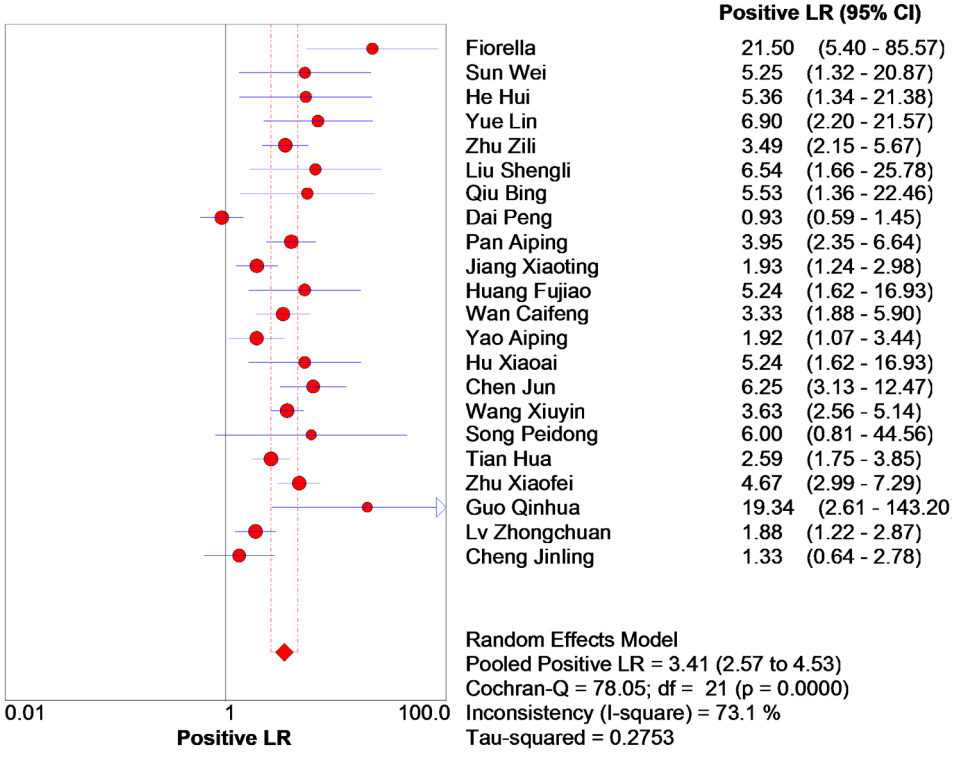


Figure 4: The diagnostic specificity of serum CA72-4 in the diagnosis of colorectal cancer

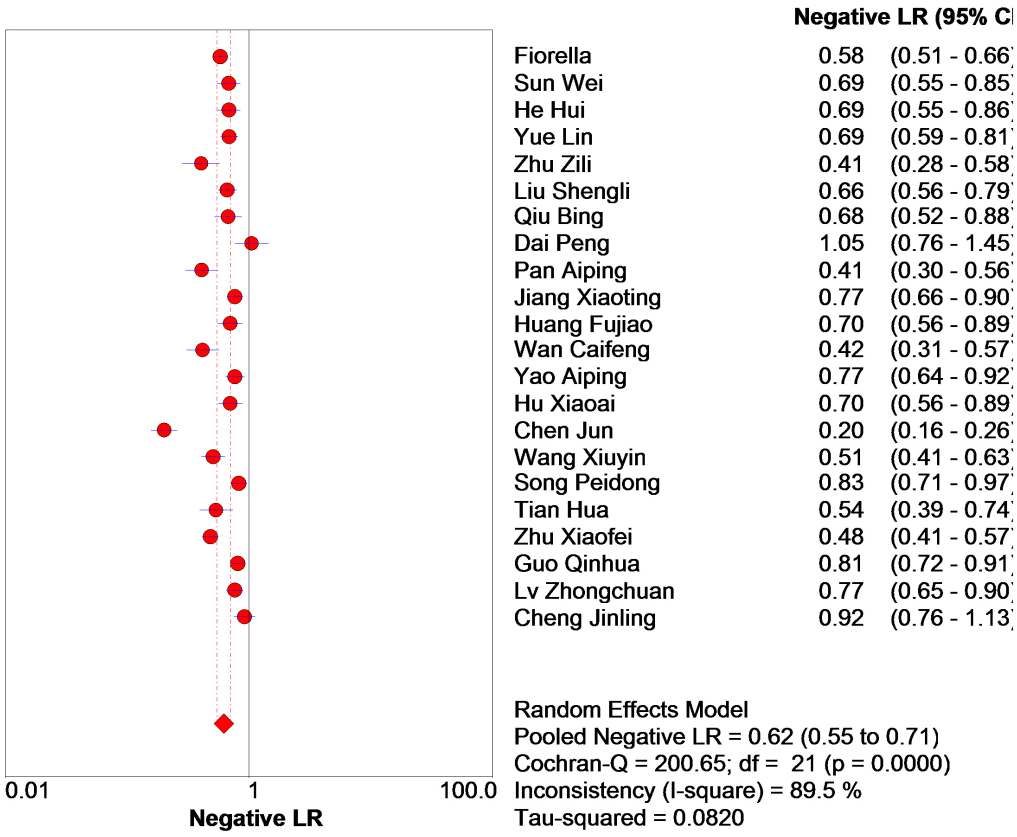


Figure 5: Combined positive likelihoodratio(Positive LR) for serum CA72-4 in the diagnosis of colorectal cancer

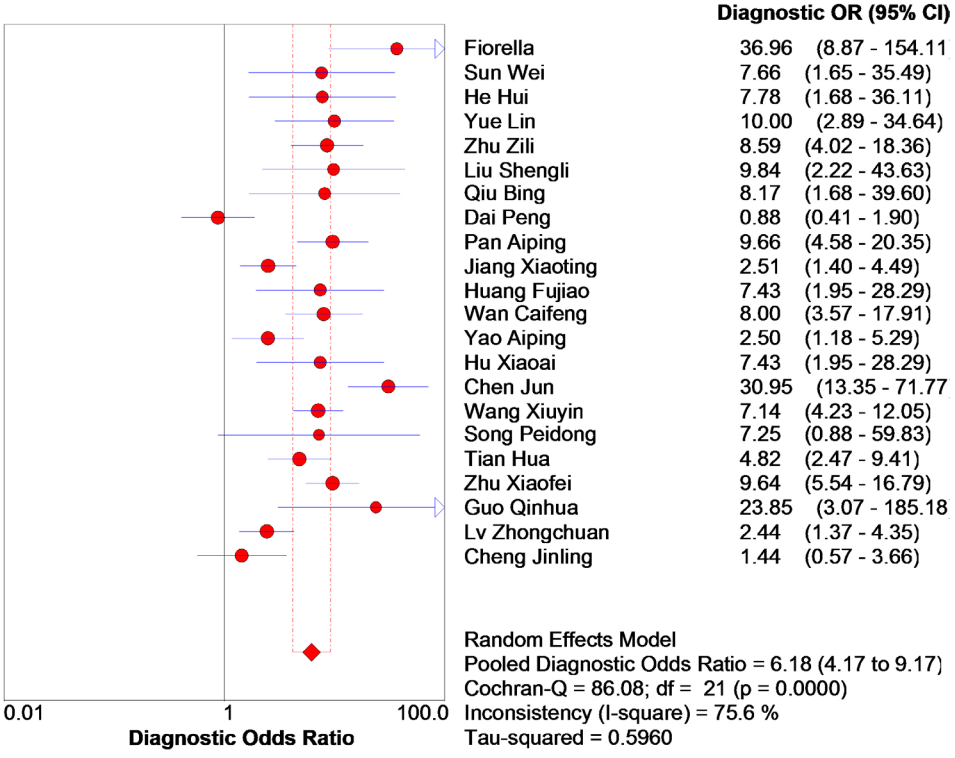


Figure 6: Combined negative likelihoodratio(negative LR) for serum CA72-4 in the diagnosis of colorectal cancer

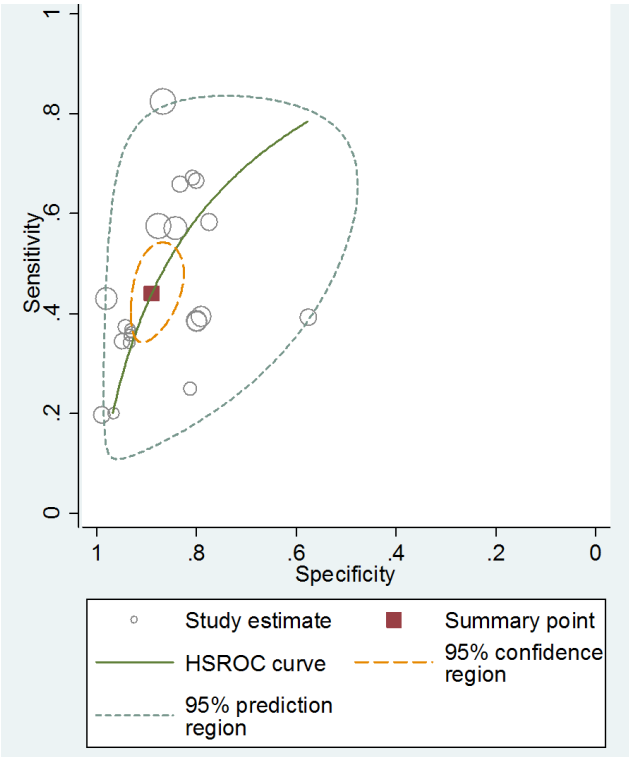


Figure 7: Combined DOR for serum CA72-4 in the diagnosis of colorectal cancer

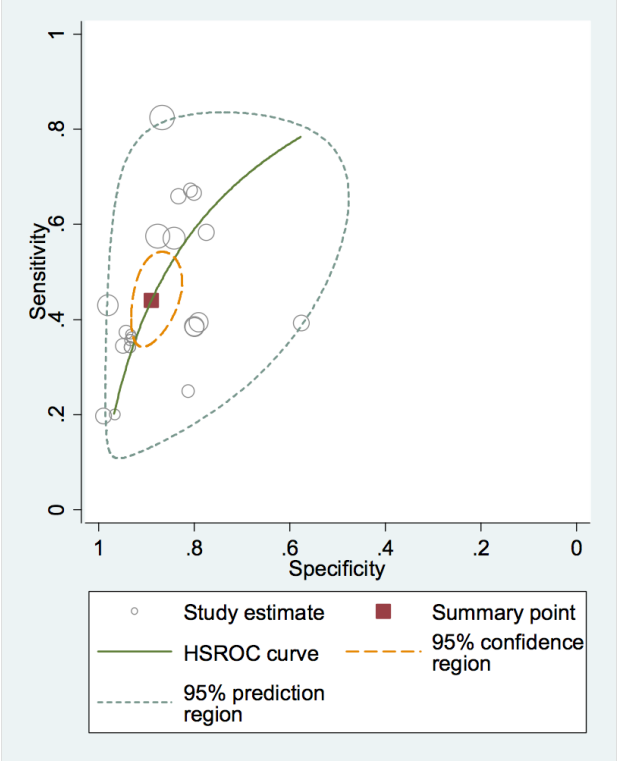


Figure 8: The pooled HSROC for serum CA72-4 in the diagnosis of colorectal cancer

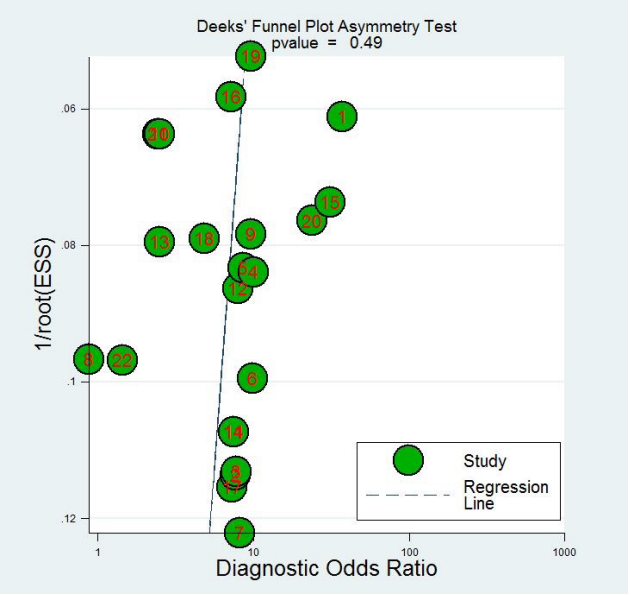


Figure 9: Deeks'funnel plot for evaluation of the publication bias

a biomarker for colorectal cancer diagnosis [22]. However, they found the diagnostic sensitivity of serum CA72-4 asunsuitable for colorectal cancer screening or diagnosis.

In our meta-analysis, we included 22 publications relevant to serum CA72-4 as a biomarker for colorectal cancer diagnosis and pooled the diagnostic sensitivity, specificity and hierarchical summary receiver operating characteristic curve (HSROC). The combined results demonstrated the diagnostic sensitivity and specificity as 0.50 (95%CI:0.48-0.52) and 0.86 (95%CI:0.84-0.88) respectively for serum CA72-4 as a biomarker in the diagnosis of colorectal cancer. The pooled area under the ROC curve (AUC) was 0.73. The diagnostic performance was especially poor for sensitivity which shows serum CA72-4 is unsuitable as a biomarker for colorectal cancer screening. The low sensitivity for diagnosis of colorectal cancer always leads to high false negative which usually causes a high rate of missed diagnosis.

Several limitations were found in our present meta-analysis: (1) The general methodological quality of the included 22 studies was poor; (2) Significant heterogeneity was found across the 22 publications; (3) Only English and Chinese publications were searched and included in this meta-analysis.

Conflicts of interest: The authors have no conflicts of interest to declare.

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