A pooled analysis of the diagnostic efficacy of plasmic methylated septin-9 as a novel biomarker for colorectal cancer

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Abstract. The methylation status of septin-9 gene in plasma has been developed as a promising biomarker to aid in the diagnosis of colorectal cancer (CRC). In this study, we aimed to evaluate the overall diagnostic ability of septin-9 methylation for detection of CRC. Studies on the diagnostic performance of plasma septin-9 in CRC were searched from the online databases up to January 31st, 2017. Risk of bias among the studies was estimated according to the Quality Assessment of Studies of Diagnostic Accuracy included in the Systematic Reviews (QUADAS) II checklist. The aggregation of the effect sizes was enabled by utilizing a bivariate analysis model. A meta-regression test and influence analysis were conducted to determine the underlying sources of heterogeneity. According to the predefined criteria, 1,462 patients with CRC from 14 eligible trials were included. The quantitative meta-analyses showed that methylated septin-9 in plasma sustained a pooled sensitivity of 0.67 (95% CI, 0.61-0.73) and specificity of 0.89 (95% CI, 0.86-0.92) in discriminating CRC patients from cancer-free individuals, along with an area under the curve of 0.87. Moreover, the stratified analyses grouped by ethnicity demonstrated that methylayted septin-9 testing achieved a better sensitivity of 0.72 (95% CI, 0.68-0.76) in the European-based population group and a higher specificity of 0.90 (95% CI, 0.88-0.92) in the Asian-based population group. Plasmic methylated septin-9 suggests a promising diagnostic efficacy in confirming CRC. However, more studies are required to confirm our findings.

Introduction

Colorectal cancer (CRC) remains one of the leading cancers worldwide. According to the newly issued cancer statistics in China, between 2000 and 2011, CRC ranked as the third and fifth cause of mortality among females and males, respectively (1). In clinic, the management of CRC at an early stage continues to be the main approach to reduce mortality and morbidity (2). Nevertheless, early and accurate diagnosis have posed a challenge for the diagnosis of CRC due to a lack of high sensitivity and specific tumor markers or detection techniques in clinic (3).

Epigenetic modifications such as gene or DNA methylation in tumors have placed increased attention on the early identification of CRC. Among the methylated genes in CRC, septin-9 has been highlighted as an ideal candidate biomarker (4-19). Septin-9 was initially identified in myeloid neoplasia (20). It acts as a suppressor gene in numerous cancer types (21,22). In previous years, an increasing number of studies have focused on the investigation of plasma methylated septin-9 for the detection of CRC (4-17). Consequently, several types of assay kits regarding methylated septin-9 are being developed and have become commercial products. Nevertheless, results from single studies are often inconsistent due to limited sample size and single-center design. For instance, some studies reported that septin-9 testing presented a limited sensitivity from 51 to 56% (14,15). By constrast, some research presented an estimated sensitivity of septin-9 methylation up to 90% (6).

In the present study, we conducted a comprehensive meta-analysis and assessed the overall diagnostic efficacy of plasma methylated septin-9 for CRC detection.

Materials and methods

Search strategy. Two reviewers independently searched the published articles through the online PubMed/Medline, BioMed Central and CNKI databases up to January 31st, 2017. The search terms were utilized in a single or parallel pattern as ('septin-9' or 'septin 9') and ('colon cancer' or 'colorectal neoplasm' or 'CRC' or 'colorectal carcinoma' or 'carcinoma of colon') and/or ('sensitivity' or 'specificity' or 'diagnosis' or 'accuracy' or 'ROC' or 'AUC'. We also manually searched the references in the studies for retrieval.

Eligibility criteria. Inclusion criteria for the meta-analysis were: i) Studies estimated the diagnostic feature of plasma septin-9 for CRC; ii) studies with sufficient information to

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Table I. Main features of the included studies for plasma septin-9 methylation in the identification of CRC.

Author	Year	Area	Patient vs. controls	Patient/ control size	Sample type	Test method	Reference gene	Cut-off value	(Refs.)
Potter *et al*	2014	Germany	CRC vs. Non-CRC	44/1500	Plasma	RT-qPCR	β-actin	CP<45.0	(4)
Lee *et al*	2013	Korea	CRC vs. Normal	101/96	Plasma	RT-qPCR	β-actin	1/3 algorithms	(5)
Tóth *et al*	2012	Hungary	CRC vs. Normal	93/94	Plasma	RT-qPCR	β-actin	CP<40.5	(6)
Warren *et al*	2011	America	CRC vs. Non-CRC	50/94	Plasma	RT-qPCR	β-actin	CP<39.0	(7)
Ahlquist *et al*	2012	America	CRC vs. Non-CRC	52/48	Plasma	RT-qPCR	β-actin	Unclear	(8)
Grützmann *et al*	2008	America	CRC vs. Non-CRC	252/183	Plasma	RT-qPCR	CFF1 and HB14	2/3 algorithms	(9)
Chen *et al*	2016	Taiwan	CRC vs. Normal	Sep-51	Plasma	RT-qPCR	β-actin	Unclear	(10)
He *et al*	2010	China	CRC vs. Normal	182/170	Plasma	RT-qPCR	β-actin	Unclear	(11)
Jin *et al*	2015	China	CRC vs. Non-CRC	135/341	Plasma	RT-qPCR	Unclear	Unclear	(12)
Johnson *et al*	2014	America	CRC vs. Non-CRC	101/200	Plasma	RT-qPCR	Unclear	Unclear	(13)
Church *et al*	2013	America	CRC vs. Non-CRC.	53/1457	Plasma	RT-qPCR	β-actin	CP<50.0	(14)
deVos *et al*	2009	America	CRC vs Non-CRC	Training: 97/172 Test: 90/155	Plasma	RT-qPCR	β-actin	1/3 and 2/3 algorithms	(15)
Tänzer *et al*	2010	Germany	CRC vs. Non-CRC	33/34	Plasma	RT-qPCR	Unclear	1/3 and 2/3 algorithms	(16)
Ørntoft *et al*	2015	Denmark	CRC vs. Non-CRC	150/150	Plasma	RT-qPCR	β-actin	1/3 and 2/3 algorithms	(17)

CRC, colorectal cancer; CP, crossing point.

generate the statistical elements as true positive, true negative, false positive and false negative; and iii) the control sources were from cancer-free individuals.

Studies were excluded based on the following criteria: i) studies with unclear definition of the control sources or the paired controls were other types of tumors; ii) extracted data were insufficient to establish the 2x2 table; and iii) basic studies, review articles, letters and conference articles.

Data extraction. Essential data from enrolled articles were extracted twice by two authors and the information included: The name of the author, publication data, study population, sample numbers, control types, measure method, cut-off value, sensitivity, and specificity. The two-stage study comprised both training and validation cohorts, and the data from each group were considered to be independent and were meta-analyzed as individual studies. Any disagreements on data extraction were solved by group discussion.

Study bias assessment. Study bias of the included articles was judged according to the Quality Assessment of Studies of Diagnostic Accuracy included in the Systematic Reviews (QUADAS) II checklist (23), wherein, the concerns for risk of bias and applicability were rated as 'low', 'high' or 'unclear', with an evaluation score of '1', '0' and '0', respectively.

Statistical analyses. The quantitative meta-analyses were carried out based on Stata 12.0 (StataCorp LP, College Station, TX, USA) and Meta-disc 1.4 (XI Cochrane Colloquium, Barcelona, Spain) programs using a bivariate quantitative model. Heterogeneity among the studies was estimated utilizing Spearman's correlation coefficient, I-squared (I^2) and Chi-squared (χ^2) Q tests. Either $P<0.05$ or $I^2>50\%$ were deemed as statistically different (24). If significant heterogeneity existed among studies, a random-effect model was employed for the aggregation of the effect sizes; otherwise, a fixed-effect model was used (25). Potential sources of heterogeneity were traced by influence analysis and meta-regression test. Bias of the publications was determined using Deek's funnel plot asymmetry test. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Article filtration and quality assessment. Fig. 1 shows the procedure of article filtration based on the PRISMA statement: In total, 291 citations were obtained from the online databases according to the specified criteria, of which 276 records were excluded after a careful review of the title and abstracts. The following 15 eligible studies then received full text evaluation and 1 of them was eliminated due to lack of relevance (26). Finally, 14 cohorts comprising 23 single studies were enrolled for the meta-analysis (4-17).

The study quality of the included cohorts was assessed by the QUADAS II tool (23). Fig. 2 plots the proportions of studies with low, high, or unclear concerns regarding risk of bias and applicability and the included studies showed low risk of bias.

Study features. In the current study, 1,462 CRC patients and 4,703 CRC-free subjects were enrolled for the final meta-analyses. The CRC patients enrolled had not previously undergone treatment and the final diagnoses were confirmed histologically via the surgical specimen. The control sources comprised healthy participants, hyperplastic polyps and individuals with normal colonoscopy examinations. The patient size varied from 30 to 252 and the control size varied from 9 to 1,500. Blood samples were collected and tested in plasma and the methylated status of septin-9 was examined via the qPCR. The reference genes involved, *β-actin*, *CFF1* and *HB14* were employed for determining the validity of the results. Study ethnicity comprised Asian, American and European. The main characteristics of included studies are summarized in Table I.

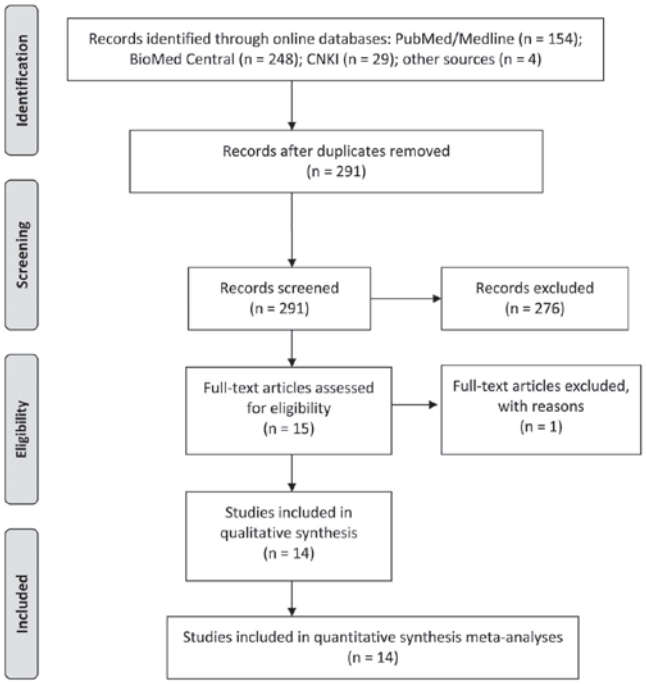

Figure 1. Flow diagram of literature selection process.

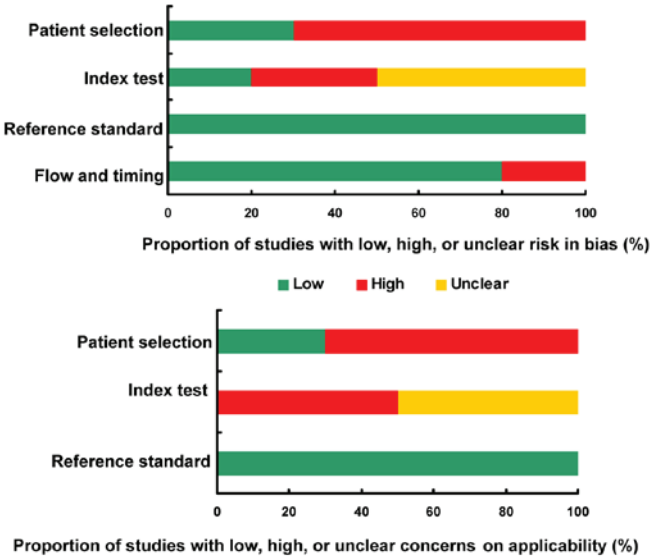

Figure 2. Proportions of studies regarding and applicability assessed by QUADAS II checklist.

Table II. Exploration of study heterogeneity using Meta-disc 1.4 software.

Tests	Spearman's correlation coefficient	Cochran's Q test	I^2 test (%)	Heterogeneity sources	
				Threshold effect	Non-threshold effect
Overall	0.065[a] P=0.745	111.58[b] P<0.01	77.6	No	Yes
Outliers elimination	0.235[a] P=0.291	92.18[b] P<0.01	77.2	No	Yes
Ethnicity					
Asian	-0.200[a] P=0.800	19.70[b] P=0.0002	84.8	No	Yes
American	0.574[a] P=0.800	41.40[b] P=0.0003	63.8	No	Yes
European	-0.886[a] P=0.019	43.15[b] P<0.01	88.9	Yes	Yes

[a]Value of Spearman's correlation coefficient; [b]Q-value.

Table III. The pooled analyses of diagnostic efficacy of methylated septin-9 in confirming colorectal cancer.

Analysis	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	Pooled PLR (95% CI)	Pooled NLR (95% CI)	Pooled DOR (95% CI)	AUC
Overall	0.67 (0.61-0.73)	0.89 (0.86-0.92)	6.26 (4.76-8.22)	0.37 (0.31-0.44)	16.93 (11.56-24.77)	0.87
Outliers excluded	0.70 (0.64-0.76)	0.90 (0.86-0.92)	6.68 (5.08-8.77)	0.33 (0.27-0.40)	20.1 (13.92-29.04)	0.88
Ethnicity						
Asian	0.64 (0.59-0.68)	0.90 (0.88-0.92)	6.89 (3.42-13.89)	0.42 (0.22-0.80)	17.23 (5.68-52.27)	0.94
American	0.64 (0.62-0.67)	0.89 (0.88-0.90)	5.99 (4.72-7.61)	0.38 (0.33-0.45)	17.18 (12.78-23.10)	0.85
European	0.72 (0.68-0.76)	0.80 (0.78-0.82)	3.75 (2.05-6.85)	0.33 (0.18-0.61)	14.1 (4.17-47.72)	0.85

CI, confidence interval; PLR, positive likelihood ratio; NLR, negative likelihood ratio; DOR, diagnostic odds ratio; AUC, area under the curve.

Heterogeneity. Heterogeneity underlying eligible studies was mirrored by the examination of threshold and non-threshold effects among studies (25,27). As shown in Table II, Spearman's correlation coefficient of the overall effect size revealed a P>0.05, suggesting that no significant heterogeneity generated from the threshold effect. Moreover, I^2 and χ^2-based Q tests were conducted to evaluate heterogeneity caused by the non-threshold effect. As the data indicated, either the overall pooled analysis (Q=111.58, P<0.01, I^2=77.6%) or the stratified analyses (Table II) presented significant heterogeneity from the threshold effect. As a result, we selected a random-effect model for the aggregation of the effect sizes.

Pooled diagnostic performance. For efficacy when differentiating CRC patients from non-CRC ones, methylated septin-9 in plasma retained a combined sensitivity of 0.67 (95% CI, 0.61-0.73) and specificity of 0.89 (95% CI, 0.86-0.92) (Fig. 3A and B and Table III). Moreover, the pooled positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR) and AUC were 6.26 (95% CI, 4.76-8.22), 0.37 (95% CI, 0.31-0.44), 16.93 (95% CI, 11.56-24.77) and 0.87, respectively (Fig. 3C and Table III).

Subgroup analyses. In the stratified studies analyzed according to ethnicity, the data demonstrated that European-based septin-9 methylation test had the optimal sensitivity of 0.72 (95% CI, 0.68-0.76), whereas the Asian-based analysis achieved the highest specificity of 0.90 (95% CI, 0.88-0.92) (Table III). In addition, testing of septin-9 in Americans conferred a sensitivity of 0.64 (95% CI, 0.62-0.67) at a

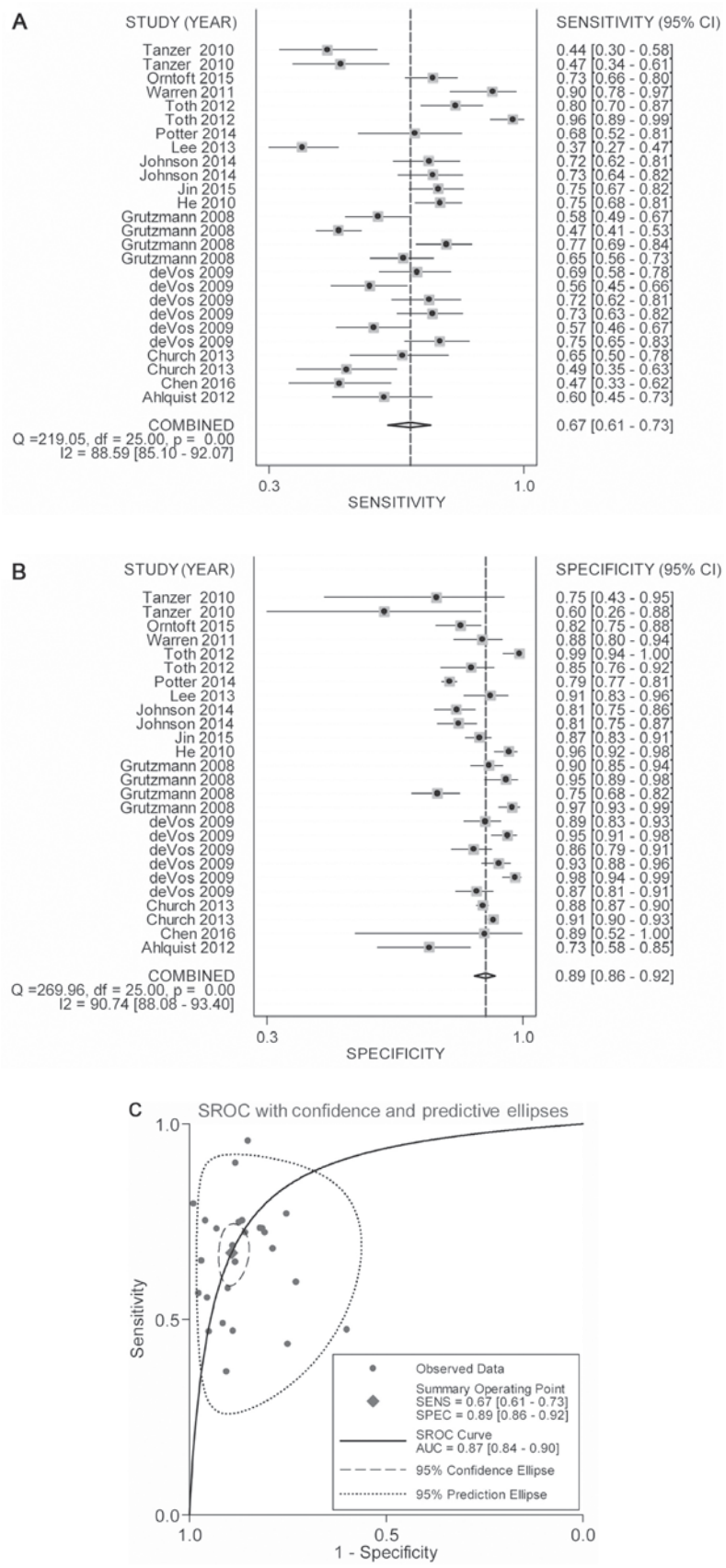

Figure 3. Forest plots of pooled parameters for plasma septin-9 methylation in diagnosing CRC. (A) Sensitivity, (B) specificity, (C) SROC curve. SENS, sensitivity; SPEC, specificity.

specificity of 0.89 (95% CI, 0.88-0.90), corresponding to an AUC of 0.85, PLR of 5.99 (95% CI, 4.72-7.61), NLR of 0.38 (95% CI, 0.33-0.45) and DOR of 17.18 (95% CI, 12.78-23.10) (Table III).

Table IV. Exploration of the potential sources of heterogeneity by the meta-regression test.

Study characteristic	P-value	RDOR (95% CI)
Study ethnicity (Asian vs. American vs. European)	0.0972	1.70 (0.90-3.22)
CRC cases (<100 vs. ≥100)	0.6843	0.82 (0.29-2.29)
Control size (control <100 vs. control ≥100)	0.2159	1.85 (0.68-5.02)
Reference gene (β-actin vs. other)	0.887	1.09 (0.31-3.79)
Study quality (QUADAS scores)	0.7141	0.88 (0.43-1.81)
Test algorithms (1/3 vs. 2/3 algorithm)	0.1603	0.72 (0.45-1.15)

CRC, colorectal cancer; RDOR, relative diagnostic odds ratio; CI, confidence interval; QUADAS, quality assessment for studies of diagnostic accuracy.

Influence analysis and meta-regression. Influence analysis and meta-regression test were applied to deeply analyze the characteristics of included studies to better explain the sources of heterogeneity. As indicated by Fig. 4, four individual studies were evaluated as outliers. We further adjusted the analyses by removing the outlier studies. Accordingly, the combined effects size of sensitivity elevated from 0.67 to 0.70, NLR was reduced from 0.37 to 0.33 and I^2 increased from 77.6 to 77.2%. On the other hand, the univariate meta-regression test was applied to further trace the underlying sources of study heterogeneity. We conducted the test relying on six predefined covariates: Study ethnicity (Asian vs. American vs. European), CRC cases (<100 vs. ≥100), control size (control <100 vs. control ≥100), reference gene (β-actin vs. other), test algorithms (1/3 vs 2/3 algorithm) and article quality (QUADAS scores) (28). However, all these factors showed a low likelihood of causes of heterogeneities (Table IV).

Publication bias. Risk of bias among publications was examined by the Deeks' funnel plot asymmetry test among the included studies. In Fig. 5, the slope coefficient of the regression line exhibited a P-value of 0.193, suggesting that no clear bias existed among the eligible studies due to publication.

Discussion

Methylated septin-9 has recently been developed as a novel, non-invasive biomarker for CRC diagnosis (2,3). The technique has developed rapidly for the testing of plasmic septin-9 methylation and several kinds of assay kits have been developed and become commercial products (22). The current meta-analysis assessed the diagnostic utility of plasma methylated septin-9 as a serological marker for the identification of CRC.

Our analysis revealed that the overall testing of methylated septin-9 in plasma retained a relatively low sensitivity of 0.67, but maintained a high specificity of 0.89. In the SROC curve analysis, the combined AUC was estimated to be 0.87, revealing a relatively high efficacy for the septin-9 methylation testing in the diagnosis of CRC. The DOR is also recommended as an important indicator in mirroring the overall diagnostic performance (24). In the present study, the DOR of plasmic septin-9 methylation test was shown to be 16.93, suggesting a powerful discriminatory performance in confirming CRC. Moreover, a pooled PLR of 6.26 means that testing of methylated septin-9 in plasma reached a ratio of 6.26 between the true and false-positive rate. For the false-negative rate reflected by NLR (25), the value was estimated to be 0.37, which is not low enough to eliminate CRC. In general, our data have shown that analysis of methylated septin-9 in plasma achieved an overall high efficacy and is acceptable as a routine biomarker for CRC detection.

Recent evidence has substantiated an independent association between ethnicity and DNA methylation status (29). We therefore further conducted a stratified analysis according to ethnicity. Our findings revealed that testing of septin-9 methylation in Asians and Europeans achieved a better efficacy than in Americans. Nevertheless, our analysis stratified by ethnicity yielded a small study size and exhibited high heterogeneity. Thus, more investigations are required to confirm our findings.

On the other hand, we observed a large degree of heterogeneity in our meta-analyses. Heterogeneity can be interpreted by both threshold and non-threshold effects (25,27). The threshold effect can be caused by different cut-off value settings as well as objective methods. In the present study, the P-values from Spearman's correlation coefficient were >0.05, suggesting that there was no clear heterogeneity from the threshold effect. Nevertheless, significant heterogeneity from the non-threshold effect seemed to be present in all the meta-analyses as well as in the subgroup analyses. The causes of heterogeneity from the non-threshold effect can be interpreted by the different disease conditions and other concomitant diseases among the participants. In addition, different test conditions involved in the detection technique, operators as well as standard tests also constitute major causes of non-threshold effect (25). In the present study, we hypothesized that the outlier studies, ethnicity, case or control size, reference gene, cut-off value setting and study quality may contribute to the sources of heterogeneity. As a result, we first conducted influence analysis and identified four outlier studies. After removing the outliers, the pooled sensitivity was elevated from 0.67 to 0.70, NLR was reduced from 0.37 to 0.33, but I^2 was elevated from 77.6 to 77.2%. Accordingly, we further conducted a meta-regression test and found that variations such as ethnicity, case or control size, reference gene, test algorithms and article quality were not likely to be sources of heterogeneity among eligible studies.

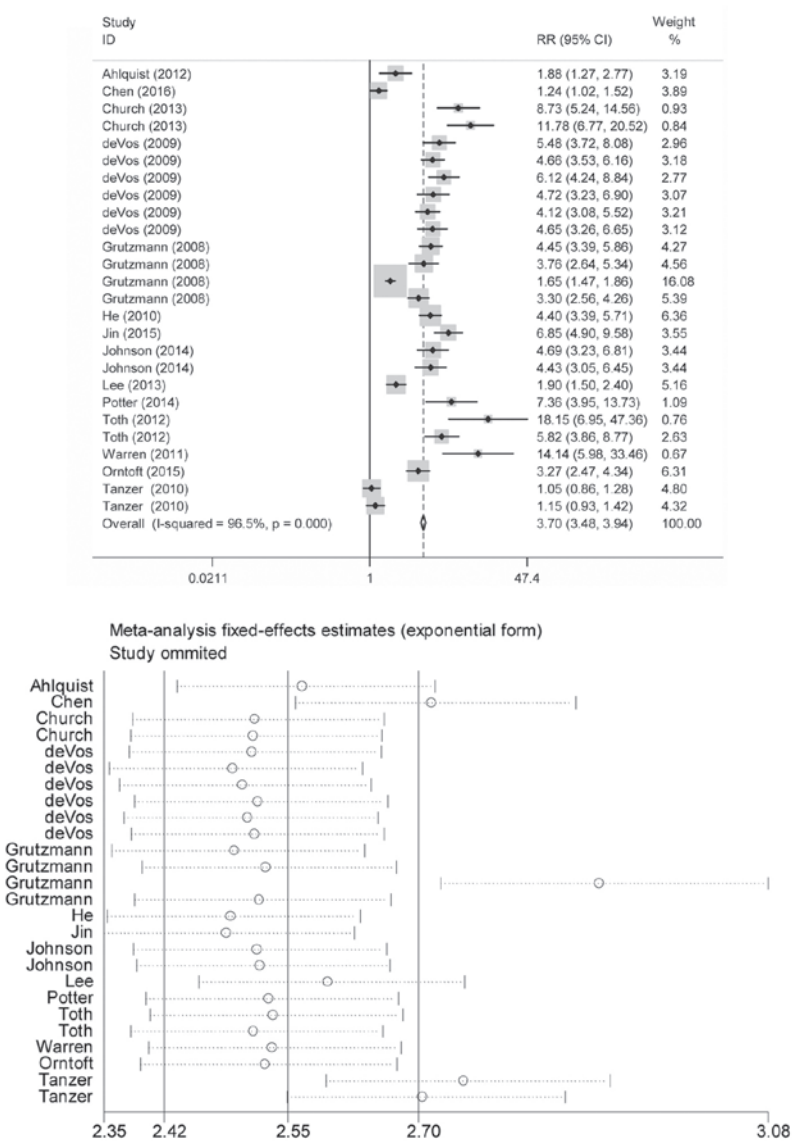

Figure 4. Influence analysis of the outliers among the overall pooled studies.

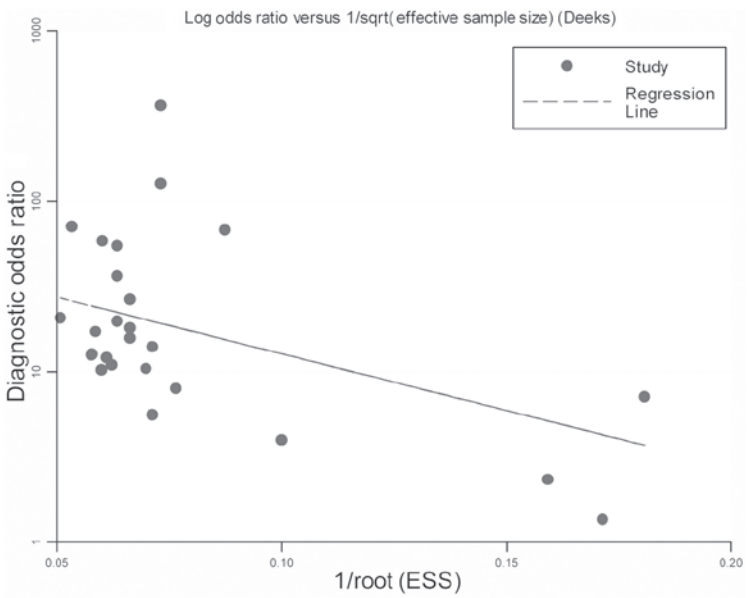

Figure 5. Funnel chart of the publication bias assessed by Deek's funnel plot asymmetry test (P=0.193).

Our analysis has several limitations. Firstly, a large number of heterogeneities were observed in our analyses, which compromised the pooled accuracy of the effect sizes. Secondly, the sample numbers in the subgroup studies were small and the findings require verification. Finally, the control types were complicated and thus the meta-analyzed data may not completely mirror the real diagnostic efficacy of plasma septin-9 methylation for CRC detection.

Despite these limitations, plasma methylated septin-9 testing showed a relatively high accuracy and may be optimal for CRC diagnosis. Further investigations are required to confirm the preliminary evidence from the present study.

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