MEDICAL SCIENCE MONITOR

META-ANALYSIS

e-ISSN 1643-3750
© Med Sci Monit, 2016; 22: 3409-3418
DOI: 10.12659/MSM.900590

Received: 2016.07.14
Accepted: 2016.08.16
Published: 2016.09.25

Diagnostic Value of Methylated Septin9 for Colorectal Cancer Screening: A Meta-Analysis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BCDEF 1 Shirong Yan*
BCF 2 Zijing Liu*
BE 1 Shuang Yu
ABCDEFG 1 Yixi Bao

1 Department of Clinical Laboratory Medicine, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, P.R. China
2 Department of Clinical Medicine, Xinjiang Medical University, Urumqi, Xinjiang, P.R. China

* These authors contributed equally to this work

Corresponding Author: Yixi Bao, e-mail: yixibao@163.com

Source of support: The study was supported by National Natural Science Foundation of China (No. 81274144 and 81473388)

Background: Septin9 is a member of GTP-binding protein family, and is used as a predictive diagnostic index. However, it has not been widely adopted due to inconsistent results reported in the literature. The present study was performed to determine the diagnostic accuracy of methylated Septin9 (mSEPT9) for colorectal cancer (CRC) and to evaluate its utility in CRC screening.

Material/Methods: After reviewing relevant studies, accuracy measures (pooled sensitivity and specificity, positive/negative likelihood ratio [PLR/NLR], and diagnostic odds ratio [DOR]) were calculated for mSEPT9 in the diagnosis of CRC. Overall test performance was summarized using summary receiver operating characteristic curve analysis. Potential between-study heterogeneity was explored by use of a meta-regression model. We divided included studies into Epi proColon test and non-Epi proColon test subgroups. We compared the effects of mSEPT9 and fecal occult blood test (FOBT) for CRC screening.

Results: A total of 9870 subjects in 14 studies were recruited. Pooled sensitivity and specificity, PLR, NLR, DOR, and corresponding 95% confidence intervals (CI) of mSEPT9 for CRC diagnosis were 0.66 (95% CI: 0.64–0.69), 0.91 (95% CI: 0.90–0.91), 5.59 (95% CI: 4.03–7.74), 0.37 (95% CI: 0.29–0.48), and 16.79 (95% CI: 10.54–26.76), respectively. The area under the summary ROC curve (AUC) was 0.8563. The AUCs in the Epi proColon test and non-Epi proColon test for CRC diagnosis were 0.8709 and 0.7968, respectively. In head-to-head comparison, AUC of mSEPT9 and FOBT for CRC diagnosis were 0.7857 and 0.6571, respectively.

Conclusions: The present study demonstrates that mSEPT9 can be a good diagnostic biomarker complementary to FOBT as a screening tool for CRC.

MeSH Keywords: Colorectal Neoplasms • Septins • Sunscreening Agents

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/900590

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Background

Colorectal cancer (CRC) is the third most common cancer among men and women. It is estimated that approximately 1.2 million new cases of CRC are diagnosed, and about 608 000 deaths caused by CRC are reported annually [1]. In spite of advances in the treatment of CRC, an advanced stage of CRC at the time of diagnosis is still associated with a very unfavorable prognosis [1–5]. Screening tests improve patient prognosis and predict long-term survival by detecting tumors at early stages, leading to decreased CRC-related mortalities [6].

Currently, the most common screening modality for CRC is the fecal occult blood test (FOBT), which detects hemoglobin in stool enzymatically or immunologically [7]. However, FOBT has inadequate sensitivity and specificity, which limit its application in the detection of early-stage cancer [8,9]. Although colonoscopy or sigmoidoscopy have higher sensitivity, they are considered time-consuming, invasive, and cumbersome [10–12]. Therefore, non-invasive screening biomarkers are critical for the early detection of CRC.

Recently, researchers have become interested in methylated Septin9 (mSEPT9), a new tumor marker that encodes Septin-9, which is a member of the conserved Septin family of GTP-binding proteins that function in key processes, including vesicle trafficking, apoptosis, cytoskeletal remodeling, and cell division [13]. MSEPT9 is released from tumor cells into the bloodstream, and can be detected in blood plasma [14]. Much related research has been carried out on mSEPT9 in CRC screening. Some studies [14–27] have demonstrated that the ratio of mSEPT9 can be used for the early diagnosis of CRC. For CRC at early stages (I and II), 86.8% cases were identified by mSEPT9 [15]. In some Western countries, mSEPT9 assay has been used for early-stage CRC screening, but the value of mSEPT9 assay has not been widely accepted in other countries, especially in Asia [26], because conclusions are inconsistent or even conflicting. The Epi proColon test is a new blood-based CRC screening test designed to identify the mSEPT9 (Septin9) gene in cell-free DNA isolated from plasma [28]. It is a qualitative real-time assay in which each sample is tested in triplicate during PCR analysis. A sample is considered to be positive for Septin9 if at least 1 of the 3 Septin9 PCRs are positive and a sample is considered to be negative for Septin9 if all 3 Septin9 PCR replicates are negative [16]. In the present study we attempted to evaluate the value of mSEPT9 assay for the diagnosis of CRC using the results of published studies. We also compared the effect of mSEPT9 with that of FOBT for CRC screening. Then, we compared the Epi proColon test with the non-Epi proColon test for mSEPT9 detection by performing a meta-analysis.

Material and Methods

Literature search

Studies published in English were carefully searched in biological databases (PubMed, Embase, EBSCO, Web of Science, Science Direct, and Cochrane Library) up to September 2015. The search terms were as follows: (Colorectal cancer, Colorectal carcinoma, or CRC) AND (SEPT9 gene methylation, Methylated SEPT9 DNA, methylated Septin9 or mSEPT9).

Inclusion and exclusion criteria

Studies eligible for inclusion met the following criteria: i) articles investigated the association between mSEPT9 DNA expression levels and CRC diagnosis using a clear test method; ii) articles measured the expression of mSEPT9 in plasma or serum; iii) articles were published as full-text paper in English; and iv) sensitivity and specificity of mSEPT9 were obtained from the text. Studies for exclusion met the following criteria: i) abstracts, letters, and reviews; ii) non-English-language papers; iii) articles reported mSEPT9 RNA or protein only; iv) laboratory studies; v) articles contained insufficient data for calculating sensitivity and specificity; vi) samples came from tissues or other body fluids; and vii) unknown detection methods.

Study selection

Two investigators reviewed the articles independently, including titles and abstracts, and then full texts were read to select potentially eligible studies. Selections were based on the inclusion and exclusion criteria and any disagreement was resolved by consensus.

Data extraction

Two independent reviewers extracted useful data from the selected studies. The following data were extracted: location, year of publication, authors, number of patients in experimental group and control group, test method, cut-off values, and raw data (the numbers of true positive, false positive, false negative, and true negative subjects).

Assessment of methodological quality

The same 2 reviewers assessed the quality of each study independently using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool, which consists of 4 key domains: patient selection, index test, reference standard, and flow and timing, supported by signaling questions to aid judgment on risk of bias, rating risk of bias, and concerns about applicability. According to the QUADAS-2 tool, the quality of each study was rated as “high”, “unclear”, or “low” [29].

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

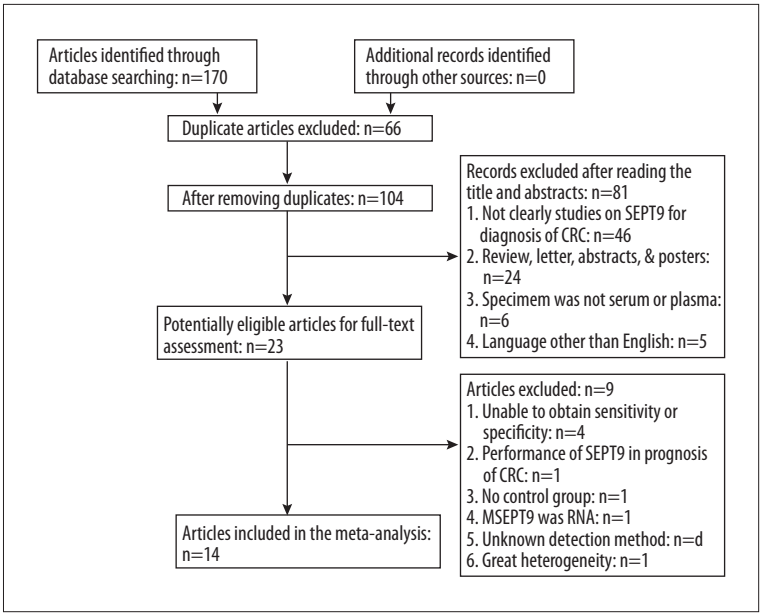

Figure 1. Flow diagram of the selection process for identifying and selecting eligible studies.

Subgroups

Two subgroups were evaluated in our meta-analysis using the Epi proColon test and non-Epi proColon test. According to the literature [30], the Epi proColon test was defined as the test method that uses the Epi proColon kit, while the non-Epi proColon test was defined as the test method that uses kits other than the Epi proColon kit.

Data analysis

The pooled diagnostic parameters, including sensitivity, specificity, PLR, NLR, and DOR, and corresponding 95% confidence interval (CI) were calculated using the DerSimonian-Laird method and are presented as forest plots. SROC curve was plotted to analyze test accuracy [31–34] and to calculate the area under curve (AUC). The pooled AUC was used for grading the overall accuracy as a potential summary of the SROC curve [35]. We examined the threshold effect by observing the ROC curve pattern. Spearman correlation coefficient was also calculated to determine the threshold effect [36]. Heterogeneity induced by non-threshold effect was assessed by means of the Cochran Q method and the test of inconsistency (I^2). Heterogeneity was defined as $p<0.10$ or $I^2 >50\%$ [37]. Meta-regression analysis can be used to explore the sources of heterogeneity. We used 5 variables (location, sample size, number of controls, number of CRCs, and test method) in this meta-analysis. The meta-analysis was performed using Meta DiSc statistical software v1.4 (*http://www.hrc.es/investigacion/metadisc_en.htm*), and statistical significance was defined as $P<0.05$.

Results

Characteristics of the eligible studies

Our search yielded 170 citations, including 66 duplicate records. After removing the duplicates, 23 out of 104 articles were considered as potentially eligible for full-text assessment based on their titles and abstracts. According to the inclusion and exclusion criteria, 9 articles [28,38–45] were excluded, and the remaining 14 articles [14–27] were included in our meta-analysis (1 cohort study [24] and 13 case-control studies [3,25,26]) (Figure 1). There were 9870 cases in total and the numbers of CRC patients, non-CRC patients (adenoma, polyp, and benign diseases), and healthy subjects were 1205, 3735, and 4930, respectively. All patients with CRC were diagnosed based on pathological confirmation (Tables 1, 2).

Quality assessment of the included studies

To perform quality assessment of these 14 eligible studies, a graph of risk of bias and applicability concerns was made for the included studies. The major bias of the studies was focused on "patient selection" and "index test". Specifically, in the domain of patient selection, 13 studies [14–23,25–27] did not avoid case-control design and 3 studies [14,25,27] did not state whether consecutive or random samples of patients were enrolled. In the domain of index test, 6 studies [14,16,17,25–27] did not use blind method and 3 studies [21,22,24] were unclear. The threshold was not pre-specified in 3 studies [14,17,24] and was unknown in 5 studies [16,21,22,25,26]. The follow-up and timing domain in 2 studies [19, 25] were labeled as high because some participants were excluded from the analysis (Figure 2).

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Table 1. Main characteristics of the fourteen studies in the diagnostic meta-analysis.

Studies	Locations	Test methods	Cut-off	CRC	NCRC	Healthy
Tóth K. 2014	Germany	Epi proColon test	0.01% PMR	34	26	24
Lee H.S. 2013	Korea	RT-PCR	Unk	101	–	96
Warren J.D. 2011	USA	Epi proColon test	6.25 pg/ml	50	94	–
Jin P. 2015	China	RT-PCR	2/3 rule	135	250	91
Church T.R. 2014	USA	Epi proColon test	1/3 rule	53	3025	3796
Grützmann R. 2008	USA	Epi proColon test	2/3rule	126	–	183
Johnson D.A. 2014	Germany	qRT-PCR	Unk	101	106	94
Tänzer M. 2010	USA	Epi proColon test	2/3 rule	33	137	34
Tóth K. 2012	Germany	qRT-PCR	2/3 rule	92	–	92
deVos T. 2009	Germany	Epi proColon test	2/3 rule	90	–	155
Tham C. 2014	Germany	RT-PCR	Unk	30	97	–
Herbst A. 2011	Germany	Epi proColon test	Unk	45	–	16
He Q. 2010	Germany	RT-PCR	Unk	182	–	170
Lofton-Day C. 2008	Singapore	RT-PCR	Unk	133	–	179

qRT-PCR – quantitative reverse transcription polymerase chain reaction; RT-PCR – reverse transcription polymerase chain reaction; 1/3 rule or 2/3 rule – the SEPT9 result was considered to be positive if at least one or two of the three replicates were positive; PMR – percent of methylated reference; CRC – colorectal cancer; NCRC – non-colorectal cancer, including adenoma, polyp, and benign diseases.

Table 2. Sensitivity and specificity of mSEPT9 and FOBT.

Studies	Index test	Sensitivity	Specificity	TP	FP	FN	TN
Tóth K. 2014	mSEPT9	88.2%	80%	30	10	4	40
Lee H.S. 2013	mSEPT9	36.6%	90.6%	37	9	64	87
Warren J.D. 2011	mSEPT9	90%	88%	45	11	5	83
Jin P. 2015	mSEPT9	74.8%	87.4%	101	43	34	298
	FOBT	58%	82.4%	40	19	29	89
Church T.R. 2014	mSEPT9	48.2%	91.5%	26	580	27	6241
Grützmann R. 2008	mSEPT9	58%	90%	73	18	53	165
Johnson D.A. 2014	mSEPT9	73.3%	81.5%	74	37	27	163
	FOBT	73.3%	97.4%	74	6	27	194
Tänzer M. 2010	mSEPT9	73%	69%	24	53	9	118
Tóth K. 2012	mSEPT9	79.3%	98.9%	73	1	19	91
	FOBT	68.2%	70.6%	15	5	7	12
deVos T. 2009	mSEPT9	57%	98%	55	4	42	168
Tham C. 2014	mSEPT9	56.7%	80%	17	19	13	78
Herbst A. 2011	mSEPT9	46.6%	81.3%	21	3	24	13
He Q. 2010	mSEPT9	75%	96.47%	136	6	46	164
Lofton-Day C. 2008	mSEPT9	69%	86%	92	25	41	154

FOBT – fecal occult blood test; mSEPT9 – methylated Septin9; TP – true positive; FP – false positive; FN – false negative; TN – true negative.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

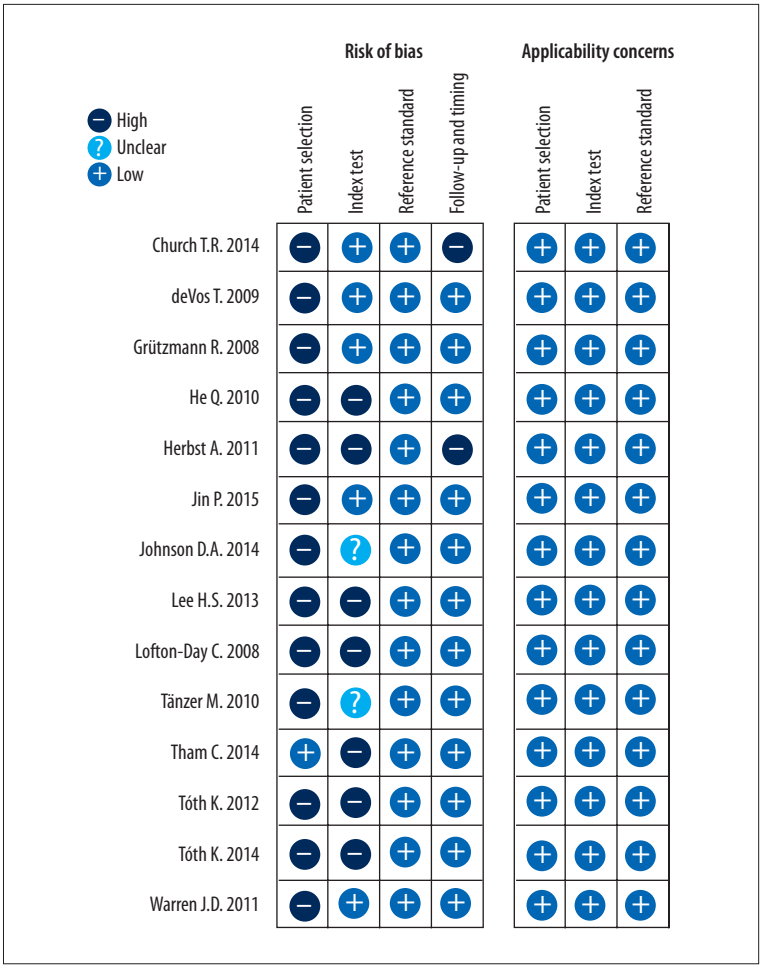

Figure 2. Summary of risk of bias and applicability concerns. Authors' judgments about each domain for each included article were reviewed.

Exploring the heterogeneity

Spearman correlation coefficient was 0.033 and P value was 0.911, indicating that there was no heterogeneity from threshold effects. Heterogeneity induced by factors other than threshold effects was observed in the meta-analysis. To find the source of the heterogeneity, meta-regression analysis was performed. Due to the small number of studies, there was no statistically significant difference.

Diagnostic accuracy of mSEPT9

Table 2 presents the recalculated sensitivity and specificity of each included study with mSEPT9 or FOBT for CRC. The pooled sensitivity (Figure 3A) and specificity (Figure 3B) of mSEPT9 for the diagnosis of CRC were 0.66 (95% CI: 0.64–0.69) and 0.91 (95% CI: 0.90–0.91), respectively. The PLR, NLR, and DOR with their corresponding 95% CIs for mSEPT9 levels in the 14 studies were 5.59 (95% CI: 4.03–7.74), 0.37 (95% CI: 0.29–0.48), and 16.79 (95% CI: 10.54–26.76), respectively (Figure 4A–4C), and the AUC was 0.8563. The summary values of diagnosis accuracy of mSEPT9 for CRC are shown in the SROC graph (Figure 5).

The pooled sensitivity (Figure 6A) and specificity (Figure 6B) of 7 studies (Epi proColon test) in subgroup analysis were 0.63 (95% CI: 0.58–0.67) and 0.91 (95% CI: 0.90–0.92), respectively. In addition, the summary DOR was 15.99 (8.13–31.42) and the AUC was 0.8709. The pooled sensitivity (Figure 7A) and specificity (Figure 7B) of 7 studies (non-Epi proColon test) in subgroup analysis were 0.68 (95% CI: 0.65–0.72) and 0.88 (95% CI: 0.86–0.90), respectively. The summary DOR was 17.92 (95% CI: 8.89–36.5), and the AUC was 0.7968.

Comparison of mSEPT9 and FOBT for the diagnosis of CRC

Three studies were included in the comparative analysis of mSEPT9 and FOBT [16,18,21]. A direct comparison of these 2 markers of interest was performed by applying both tests to the same participants in these studies. Three pairings of diagnostic accuracy estimates at the study level showed that the AUC for mSEPT9 (0.7857) was higher than that for FOBT (0.6571) in these 3 studies. mSEPT9 [(26.82 (9.33–77.14)] also had a significantly higher DOR value than FOBT [14.65 (2.30–93.44)] in these 3 studies (Table 3).

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

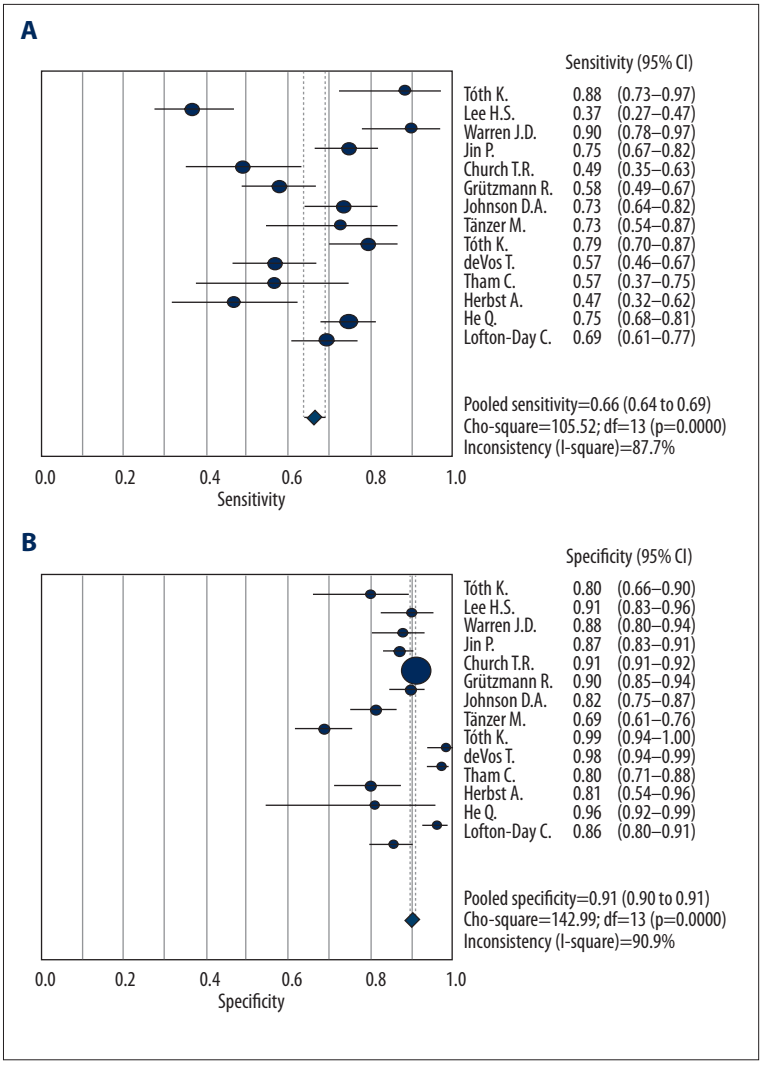

Figure 3. Forest plots of (**A**) sensitivity and (**B**) specificity for methylated Septin9 assays in the diagnosis of colorectal cancer (CRC) of the 14 included studies.

Discussion

It is clear that CRC patients benefit from early diagnosis of CRC. Biomarkers for CRC have been widely studied, but few have satisfactory performance for clinical use [46,47]. At present, genetic testing has attracted much attention, and usually has higher sensitivity and specificity than the older methods. Circulating methylated Septin9 has attracted more attention as an easily administered blood-based test for the early detection of CRC and has led to dozens of studies [14]. Therefore, the aim of the present meta-analysis was to integrate these published results for the first time and systematically evaluate the diagnostic performance of mSEPT9.

Currently, it is generally agreed that the main non-invasive diagnostic biomarker for CRC screening is FOBT, which includes guaiac FOBT (gFOBT) and immunological FOBT (iFOBT) [47,48]. Neither gFOBT nor iFOBT is specific for CRC because any bleeding into the colon can cause a positive test result [49]. However, mSEPT9 is released from tumor cells into the bloodstream [14] and has better specificity than FOBT. The pooled sensitivity and specificity of gFOBT were 0.60 (95% CI 0.50–0.70) and 0.91 (95% CI 0.90–0.93), respectively [50]. In the present study, the pooled sensitivity of mSEPT9 was 0.66, which is higher than that of gFOBT, and the pooled specificity of mSEPT9 was 0.91, which is equal to that of gFOBT. When test results for mSEPT9 and FOBT were combined, CRC detection was 88.7% at a specificity of 78.8% [21]. At lower specificity, the sensitivity of individual tests will also increase. Therefore, we think that the combination of mSEPT9 with FOBT might improve diagnostic accuracy, but further studies are still needed. DOR is a single indicator of test accuracy [32] that combines the data from sensitivity and specificity into a single number. The value of DOR ranges from 0 to infinity, with higher values indicating better discriminatory test performance. The AUC is regarded as the overall test performance, and optimal value is infinitely close to 1 [51]. In our study, the DOR value of 16.79 (95% CI: 10.54–26.76) and AUC of 0.8563 prompt an exact diagnostic accuracy

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

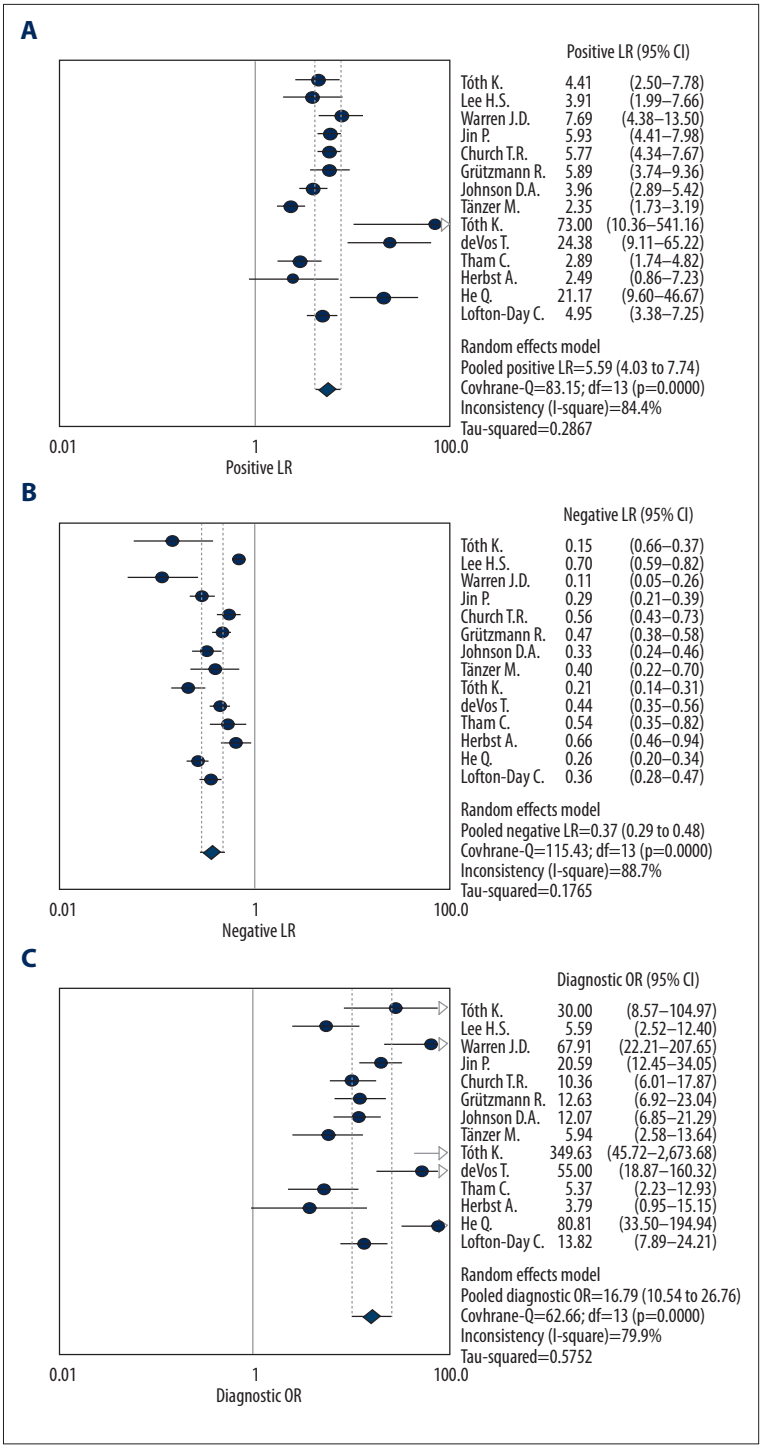

Figure 4. Forest plots of (**A**) positive likelihood (PLR), (**B**) negative likelihood (NLR), and (**C**) pooled diagnostic odds ratio (DOR) for methylated Septin9 assays in the diagnosis of colorectal cancer (CRC) of the 14 included studies.

for diagnosing CRC. The pooled PLR was 5.59, suggesting that patients with cancer have about 5-fold higher chance of being mSEPT9-positive compared with patients without cancer. The pooled NLR was 0.37, suggesting that the probability for the patient to have cancer is 37% if mSEPT9 is negative. The American Gastroenterological Association states that the goal of CRC screening is to reduce mortality through reducing the incidence of advanced conditions [52]. Therefore, the ability of a screening tool to detect precursor lesions such as advanced adenomas should also be considered in the evaluation. Some studies have reported the diagnostic accuracy of mSEPT9 for adenomas [18,19,24,27]; the sensitivity for adenomas varies among studies, mostly from 11.2% to 30.8%. Currently, there might be more value for mSEPT9 to be combined with FOBT

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

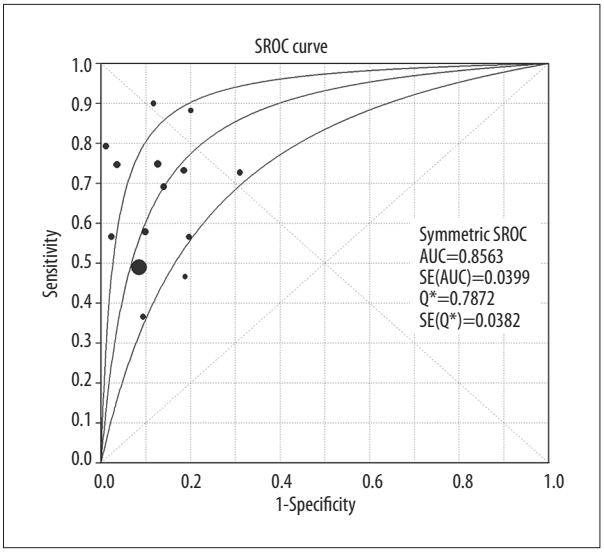

Figure 5. Summary receiver operating characteristic (SROC) curve for methylated Septin9 assays in the diagnosis of colorectal cancer (CRC) of the 14 included studies.

with or without other biomarkers such as ALX4 [22], TAC1 [24], NEUROG1, vimentin [25], or EYA4 [40] for CRC screening. In addition, the value of mSEPT9 for the prediction and prognosis of CRC has been confirmed in a number of settings [53]. In our head-to-head comparison of mSEPT9 and FOBT for the diagnosis of CRC, the AUC showed that mSEPT9 (0.7857) has higher diagnostic efficiency compared to FOBT (0.6571). As shown above, mSEPT9 has the power to discriminate CRC patients from controls.

In the present study we performed comparison between the Epi proColon test and non-Epi proColon test for detecting mSEPT9 in the 2 subgroups. The AUC of the Epi proColon test (0.8709) is significantly higher than that of the non-Epi proColon test (0.7968), suggesting that the Epi proColon test is better for the diagnosis of CRC by mSEPT9. It has been suggested that earlier versions of the Epi proColon test (Epi proColon 2.0) may have improved the performance of SEPT9 in CRC diagnosis [18]. Since the number of studies that have used Epi proColon 2.0 test was too small, we did not perform subgroup analysis.

There are some potential limitations in this study. Firstly, it was impossible for us to determine the sources of heterogeneity due to the small number of studies, and the presence of clinical heterogeneity in the study may have affected the generalizability of the results. Secondly, this meta-analysis mostly included case-control studies, which may be prone to spectrum bias because controls are selected on the basis of not having the target condition [54]. In addition, there are only 3 well-designed head-to-head comparisons in the studies. The results of our head-to-head comparisons and the results of the comparison of our study of mSEPT9 are in line with the study of FOBTs by Rosman et al. [52].

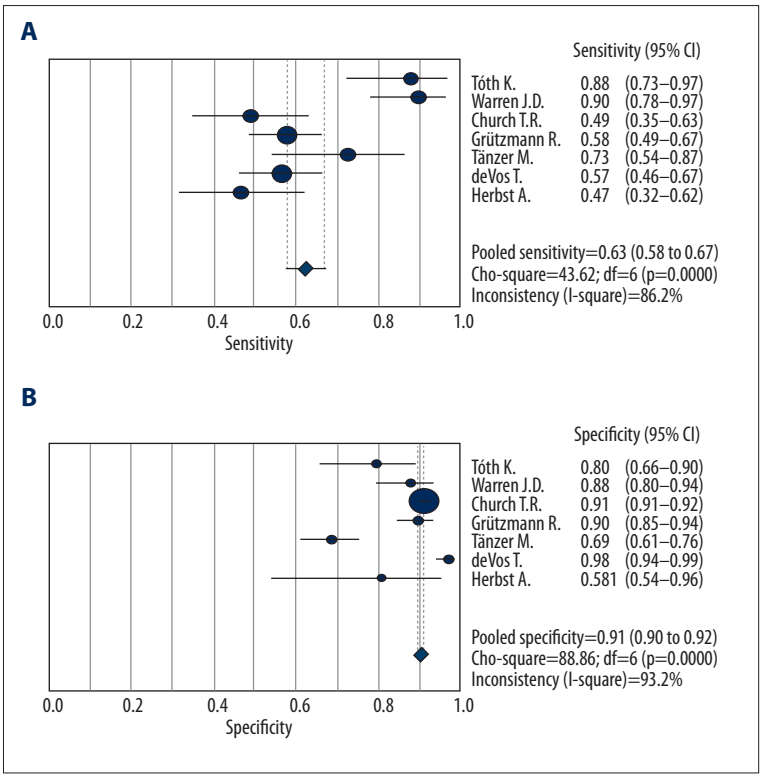

Figure 6. Forest plots of (**A**) sensitivity and (**B**) specificity for the Epi proColon test subgroup with the diagnostic indicator of the 7 included studies.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

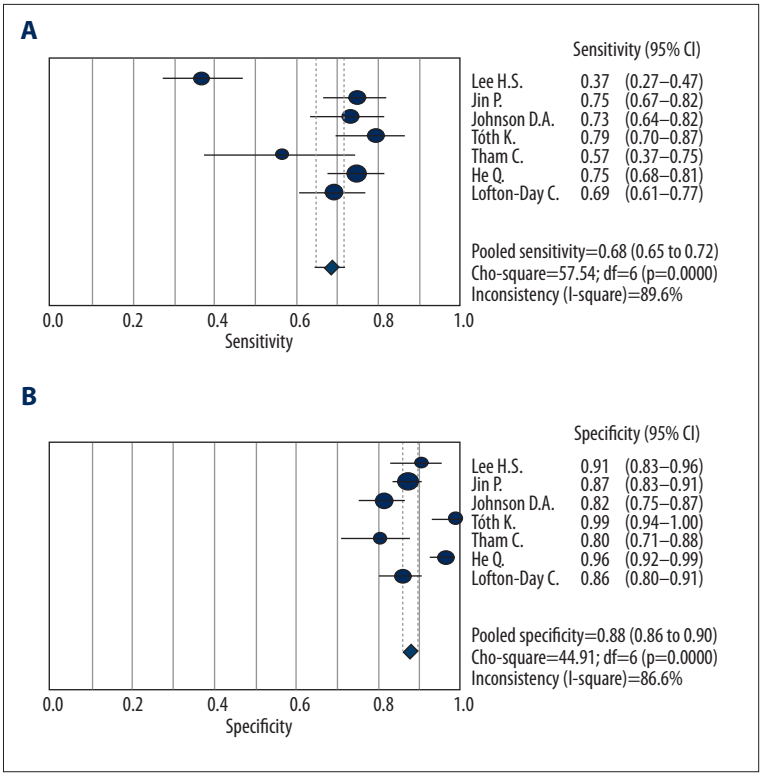

Figure 7. Forest plots of (**A**) sensitivity and (**B**) specificity for the non-Epi proColon test subgroup with the diagnostic indicator of the 7 included studies.

Table 3. Summary of diagnostic accuracy of mSEPT9 and FOBT in three studies.

	Sensitivity (95% CI)	Specificity (95% CI)	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)	AUC
mSEPT9	0.76	0.87	6.54	0.28	26.82	0.7857
	(0.71–0.80)	(0.84–0.90)	(3.13–13.67)	(0.22–0.35)	(9.33–77.14)	
FOBT	0.67	0.91	5.63	0.39	14.65	0.6571
	(0.60–0.74)	(0.87–0.94)	(1.40-22.70)	(0.25-0.63)	(2.30–93.44)	

mSEPT9 – methylated Septin9; FOBT – fecal occult blood test; PLR – positive likelihood ratio; NLR – negative likelihood ratio; DOR – diagnostic odds ratio; AUC – area under the SROC curve; CI – confidence interval.

Conclusions

mSEPT9 has better diagnostic biomarker complementary to FOBT as a screening tool for CRC, because mSEPT9 has superior sensitivity compared to FOBT. However, further high-quality studies are needed to confirm our results. The combination of mSEPT9 with FOBT or other biomarkers may provide a new tool for use in clinical practice.

Disclosures

All authors declare no financial competing interests.

References:

1. Vatandoost N, Ghanbari J, Mojaver M et al: Early detection of colorectal cancer: From conventional methods to novel biomarkers. J Cancer Res Clin Oncol, 2016; 142(2): 341–51
2. Shrubsole MJ, Cai Q, Wen W et al: Urinary prostaglandin E2 metabolite and risk for colorectal adenoma. Cancer Prev Res, 2012; 5(2): 336–42
3. Siegel R, Ward E, Brawley O, Jemal A: Cancer statistics, 2011: The impact of eliminating socioeconomic and racial disparities on premature cancer deaths. Cancer j Clin, 2011; 61(4): 212–36
4. Hewitson P, Glasziou P, Watson E et al: Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (hemoccult): An update. Am j Gastroenterol, 2008; 103(6): 1541–49

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

5. Baxter NN, Goldwasser MA, Paszat LF: Association of colonoscopy and death from colorectal cancer. Ann Intern Med, 2009; 150(1): 1–8
6. Tan E, Gouvas N, Nicholls RJ et al: Diagnostic precision of carcinoembryonic antigen in the detection of recurrence of colorectal cancer. Surg Oncol, 2009; 18(1): 15–24
7. Huang CS, LS, Farraye FA: Colorectal cancer screening in average risk individuals. Cancer Causes Control, 2005; 16(2): 171–88
8. Locker GY, Hamilton S, Harris J: ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. J Clin Oncol, 2006; 24(33): 5313–27
9. Collins JF, Lieberman DA, Durbin TE: Accuracy of screening for fecal occult blood on a single stool sample obtained by digital rectal examination: A comparison with recommended sampling practice. Ann Intern Med, 2005; 142(2): 81–85
10. Ramos M, Llagostera M, Esteva M et al: Knowledge and attitudes of primary healthcare patients regarding population-based screening for colorectal cancer. BMC Cancer, 2011; 11(1): 408
11. Pengjun Z, Xinyu W, Feng G et al: Multiplexed cytokine profiling of serum for detection of colorectal cancer. Future Oncol, 2013; 9(7): 1017–27
12. Bünger S, Haug U, Kelly M et al: A novel multiplex-protein array for serum diagnostics of colon cancer: A case-control study. BMC Cancer, 2012; 12: 393
13. Hall PA, Russell SE: The pathobiology of the septin gene family. J Pathol, 2004; 204(4): 489–505
14. Lofton-Day C, Model F, Devos T et al: DNA methylation biomarkers for blood-based colorectal cancer screening. Clin Chem, 2008; 54(2): 414–23
15. Warren JD, Xiong W, Bunker AM et al: Septin 9 methylated DNA is a sensitive and specific blood test for colorectal cancer. BMC Med, 2011; 9: 133
16. Tóth K, Sipos F, Kalmár A et al: Detection of methylated SEPT9 in plasma is a reliable screening method for both left- and right-sided colon cancers. PLoS One, 2012; 7(9): e46000
17. Lee HS, Hwang SM, Kim TS et al: Circulating methylated Septin 9 nucleic acid in the plasma of patients with gastrointestinal cancer in the stomach and colon. Transl Oncol, 2013; 6(3): 290–94
18. Jin P, Kang Q, Wang X et al: Performance of a second-generation methylated SEPT9 test in detecting colorectal neoplasm. J Gastroenterol Hepatol, 2015; 30(5): 830–33
19. Church TR, Wandell M, Lofton-Day C et al: Prospective evaluation of methylated SEPT9 in plasma for detection of asymptomatic colorectal cancer. Gut, 2014; 63(2): 317–25
20. Grutzmann R, Molnar B, Pilarsky C et al: Sensitive detection of colorectal cancer in peripheral blood by septin 9 DNA methylation assay. PloS One, 2008; 3(11): e3759
21. Johnson DA, Barclay RL, Mergener K: Plasma Septin9 versus fecal immunochemical testing for colorectal cancer screening: A prospective multicenter study. PLoS One, 2014; 9(6): e98238
22. Tanzer M, Balluff B, Distler J et al: Performance of epigenetic markers SEPT9 and ALX4 in plasma for detection of colorectal precancerous lesions. PloS One, 2010; 5(2): e9061
23. deVos T, Tetzner R, Model F et al: Circulating methylated SEPT9 DNA in Plasma is a biomarker for colorectal cancer. Clin Chem, 2009; 55(7): 1337–46
24. Tham C, Chew M, Soong R et al: Postoperative serum methylation levels of TAC1 and SEPT9 are independent predictors of recurrence and survival of patients with colorectal cancer. Cancer, 2014; 120(20): 3131–41
25. Herbst A, Rahmig K, Stieber P et al: Methylation of NEUROG1 in serum is a sensitive marker for the detection of early colorectal cancer. Am J Gastroenterol, 2011; 106(6): 1110–18
26. He Q, Chen HY, Bai EQ et al: Development of a multiplex MethyLight assay for the detection of multigene methylation in human colorectal cancer. Cancer Genet Cytogenet, 2010; 202(1): 1–10
27. Toth K, Wasserkort R, Sipos F et al: Detection of methylated septin 9 in tissue and plasma of colorectal patients with neoplasia and the relationship to the amount of circulating cell-free DNA. PloS One, 2014; 9(12): e115415
28. Potter NT, Hurban P, White MN et al: Validation of a real-time PCR-based qualitative assay for the detection of methylated SEPT9 DNA in human plasma. Clin Chem, 2014; 60(9): 1183–91
29. Whiting PF, Rutjes AW, Westwood ME et al: QUADAS-2: A revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med, 2011; 155(8): 529–36
30. Johnson DA, Barclay RL, Mergener K: Plasma Septin9 versus fecal immunochemical testing for colorectal cancer screening: A prospective multicenter study. PLoS One, 2014; 9(6): e98238
31. Reitsma JB, Glas AS, Rutjes AW et al: Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. J Clin Epidemiol, 2005; 58(10): 982–90
32. Glas AS, Lijmer JG, Prins MH et al: The diagnostic odds ratio: A single indicator of test performance. J Clin Epidemiol, 2003; 56(11): 1129–35
33. Jaeschke R, Guyatt GH, Sackett DL: Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? The Evidence-Based Medicine Working Group. JAMA, 1994; 271(9): 703–7
34. Moses LE, Shapiro D, Littenberg B: Combining independent studies of a diagnostic test into a summary ROC curve: Data-analytic approaches and some additional considerations. Stat Med, 1993; 12(14): 1293–316
35. Walter SD: Properties of the summary receiver operating characteristic (SROC) curve for diagnostic test data. Stat Med, 2002; 21(9): 1237–56
36. Moses LE1 SD, Littenberg B: Combining independent studies of a diagnostic test into a summary ROC curve: Data-analytic approaches and some additional considerations. Stat Med, 1993; 12(14): 1293–316
37. Huedo-Medina TB, Sanchez-Meca J, Marin-Martinez F, Botella J: Assessing heterogeneity in meta-analysis: Q statistic or I2 index? Psychol Methods, 2006; 11(2): 193–206
38. Mitchell SM, Ross JP, Drew HR et al: A panel of genes methylated with high frequency in colorectal cancer. BMC Cancer, 2014; 14: 54
39. Ladabaum U, Alvarez-Osorio L, Rosch T, Brueggenjuergen B: Cost-effectiveness of colorectal cancer screening in Germany: Current endoscopic and fecal testing strategies versus plasma methylated Septin 9 DNA. Endosc Int Open, 2014; 2(2): E96–104
40. Liu Y, Tham CK, Ong SY et al: Serum methylation levels of TAC1. SEPT9 and EYA4 as diagnostic markers for early colorectal cancers: A pilot study. Biomarkers, 2013; 18(5): 399–405
41. Tierling S, Schuster M, Tetzner R, Walter J: A combined HM-PCR/SNuPE method for high sensitive detection of rare DNA methylation. Epigenetics Chromatin, 2010; 3(1): 12
42. Yi JM, Dhir M, Van Neste L et al: Genomic and epigenomic integration identifies a prognostic signature in colon cancer. Clin Cancer Res, 2011; 17(6): 1535–45
43. Danese E, Minicozzi AM, Benati M et al: Comparison of genetic and epigenetic alterations of primary tumors and matched plasma samples in patients with colorectal cancer. PloS One, 2015; 10(5): e0126417
44. Toth K, Galamb O, Spisak S et al: The influence of methylated septin 9 gene on RNA and protein level in colorectal cancer. Pathol Oncol Res, 2011; 17(3): 503–9
45. Ahlquist DA, Taylor WR, Mahoney DW et al: The stool DNA test is more accurate than the plasma septin 9 test in detecting colorectal neoplasia. Clin Gastroenterol Hepatol, 2012; 10(3): 272–77.e271
46. Qaseem A, Denberg TD, Hopkins RH Jr.: Screening for colorectal cancer: A guidance statement from the American College of Physicians. Ann Intern Med, 2012; 156(5): 378–86
47. Center MM, Jemal A, Smith RA, Ward E: Worldwide variations in colorectal cancer. Cancer J Clin, 2009; 59(6): 366–78
48. Lee BI, Hong SP, Kim SE et al: Korean guidelines for colorectal cancer screening and polyp detection. Clin Endoscop, 2012; 45(1): 25–43
49. Duffy MJ, van Rossum LG, van Turenhout ST et al: Use of faecal markers in screening for colorectal neoplasia: A European group on tumor markers position paper. Int J Cancer, 2011; 128(1): 3–11
50. Rosman AS, Korsten MA: Effect of verification bias on the sensitivity of fecal occult blood testing: A meta-analysis. J Gen Intern Med, 2010; 25(11): 1211–21
51. Jones CM, Athanasiou T: Summary receiver operating characteristic curve analysis techniques in the evaluation of diagnostic tests. Ann Thorac Surg, 2005; 79(1): 16–20
52. Levin B, Lieberman DA, McFarland B et al: Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: A joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. Gastroenterology, 2008; 134(5): 1570–95
53. Danese E, Minicozzi AM, Benati M et al: Comparison of genetic and epigenetic alterations of primary tumors and matched plasma samples in patients with colorectal cancer. PloS One, 2015; 10(5): e0126417
54. Rutjes AW, Reitsma JB, Vandenbroucke JP et al: Case-control and two-gate designs in diagnostic accuracy studies. Clin Chem, 2005; 51(8): 1335–41

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]