Clinica Chimica Acta 488 (2019) 215–220

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Comparison of serum human epididymis protein 4 and CA125 on endometrial cancer detection: A meta-analysis

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ARTICLE INFO

Keywords:
Human epididymis protein 4
HE4
Endometrial cancer
Diagnostic accuracy
CA125

ABSTRACT

Background: Endometrial cancer (EC) is common type of gynecologic malignancy affecting a large number of females around the world. While most early stage cases are well managed with a relatively benign prognosis, the late stage cases have poor survival. Among the many biomarkers identified, serum human epididymis protein 4 (HE4) and CA125 are most promising surrogates for EC detection.
Methods: We performed a meta-analysis to estimate the diagnostic accuracy of HE4 and CA125 and compared their performance. A literature research was performed in Medline, Cochrane Literature Library and CNKI. After filtering, twelve studies evaluating the diagnostic value of serum HE4, alone or in comparison with CA125, were included. The total sample size was 1106 patients and 1480 controls. Pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic odds ratio (DOR) were calculated and summary receiver operating characteristic (SROC) curves were plotted to assess the diagnostic accuracy.
Results: The pooled estimates for HE4 were sensitivity: 0.71 (95%CI 0.56–0.82), specificity: 0.87 (95%CI 0.80–0.92), and area under ROC curve: 0.88 (0.85–0.91), compared to 0.35 (95% CI 0.25–0.46), 0.83 (95% CI 0.71–0.91), and 0.58 (95% CI 0.54–0.63), respectively, of CA125. Subgroup analysis demonstrated a better performance of HE4 in Caucasian population, compared to Chinese population.
Conclusion: This analysis suggested that when stage and histological type are not specifically considered, serum HE4 is generally a better tool than CA125 in EC diagnosis by its significantly higher sensitivity than CA125.

1. Introduction

Endometrial cancer (EC) is one of the common gynecological malignancies, with approximately 49,560 cases diagnosed annually in US along [1,2]. Unlike the cases of ovarian cancers, EC patients usually present signs such as irregular menstruation or postmenopausal bleeding that can often help the early diagnosis. Approximately 70% endometrial cancers can be diagnosed at their early stage, resulting in a better prognosis than other gynecologic malignancies, and a 5-year overall and cancer-specific survival rates of 80–85% and 90–95%, respectively [2]. However, the remaining 30% EC cases miss the time window for effective treatment at the diagnosis, and have a relatively low 5-year survival rate. These asymptomatic patients will especially benefit from the utility of a reliable tumor marker for screening or diagnosis at early stages. In addition, an efficient biomarker is required for prognosis, chemotherapy evaluation, and/or post-surgical surveillance of recurrence for virtually all EC cases.

In the past decades, several serum tumor markers of EC have been evaluated and compared for their efficiency in clinical settings. For instance, CA125, an epithelial ovarian carcinoma antigen [3] has been found to be elevated in 24.6% EC patients [4]. Unfortunately, this biomarker has limited utility in clinical practice of detection, monitoring and prognosis of EC, as it appears to be elevated in a variety of pathological as well as physiological conditions. A spectrum of benign diseases such as inflammation, endometriosis, benign ovarian cysts and pregnancy, and malignancies arise from ovary, breast and lung can all

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https://doi.org/10.1016/j.cca.2018.11.011
Received 18 September 2018; Received in revised form 29 October 2018; Accepted 6 November 2018
Available online 07 November 2018
0009-8981/

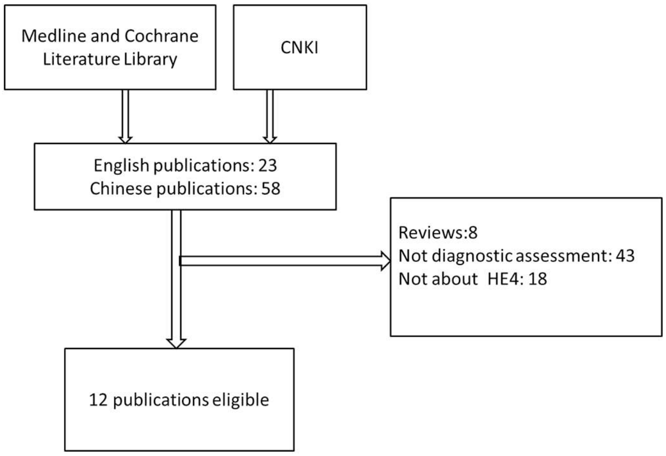

Fig. 1. Flow chart of literature search.

causes a significant increase in serum levels of CA125 [5]. Because of its low sensitivity and specificity for EC detection, especially the low specificity for early stage EC detection, CA125 is not recommended for routine usage [6–8].

Recently, human epididymis protein 4 (HE4) is considered a promising tumor marker of EC. HE4 gene *WDFC2*, first identified by Kirchhoff et al. [9] in 1991, is expressed in reproductive tract and upper airways, as well as in some cancer tissues [10,11]. Serum HE4 has been introduced as tumor marker for the diagnosis of ovarian cancer [12]. In 2008, Moore et al. [4] first evaluated the diagnosis impact of serum HE4 on endometrial cancer, demonstrating a higher sensitivity in discriminating EC patients from postmenopausal healthy controls compared to CA125, regardless of stage. A similar superiority of HE4 over CA125 was observed in several later studies [12,13]. Despite these progress, depending on the choice of study subjects and limited by small sample sizes in many studies, the efficiency of HE4 for the diagnosis of EC remains to be clarified. This study focuses on the meta-analysis of published data to assess the diagnostic accuracy of serum HE4 for EC detection in comparison with CA125.

2. Materials and methods

2.1. Literature search

A literature search was performed in Medline, Cochrane Literature Library and CNKI. There was no language restriction. The following search strategy was used: [“endometrial cancer” OR “endometrial carcinoma” OR “endometrial tumor” OR “uterine cancer”] AND [“HE4” OR “human epididymis protein 4”].

2.2. Inclusion/exclusion criteria and quality assessment

Only studies that fulfilled the following criteria were included for analyses: 1) evaluating the sensitivity and specificity of serum HE4 in EC detection; 2) histopathology as the reference test; 3) sufficient data to calculate TP (true-positive), FP (false-positive), FN (false-negative), TN (true-negative). Exclusion criteria were as follows: review, letter, and duplicated publication, to make sure only primary publications of original studies were included.

The quality of individual studies was assessed using the Quality Assessment for Studies of Diagnostic Accuracy (QUADAS) tool.

2.3. Data extraction

The following items of eligible studies were extracted by two reviewers independently: authors, publication year, country, type of design, number of cases and controls, threshold values, TP, FP, FN, FN, FIGO stage of cases, and type of controls. Agreement was reached after full discussion when discrepancy occurred.

2.4. Data analysis

This meta-analysis was performed using the MIDAS command [14] of Stata 11.0 software. The heterogeneity between studies was analyzed by Q test I^2 test. If no significant heterogeneity existed ($p > .1$, $I^2 < 50\%$), a fixed-effect model was used. Otherwise, a random-effect model was applied to calculate the pooled values of sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic odds ratio (DOR). Subgroup analysis was performed according to ethnicity and study design. Publication bias was assessed using Deeks' funnel plot asymmetry test.

Summary receiver operating characteristic (SROC) curves were constructed to measure the global performance of the test, as well as to assess the presence of threshold bias as a source of heterogeneity between studies.

3. Results

3.1. Data distribution

After a comprehensive literature selection and review, totally twelve studies were found to be eligible for meta-analysis, of which five recruited Caucasian patients [4,13,15–17] and seven recruited Chinese patients [18–24]. The process of literature search was shown in Fig. 1. The performance in EC detection was compared between HE4 and CA125 in ten studies, except two [23,24] assessing the diagnosis value of HE4 only. Seven studies [17–19,21–24] reported one cut-off value of HE4, three [13,15,20] set up two thresholds. Therefore, each threshold was taken into account in data analysis as an individual research. As for the selection of controls, five chose healthy women [4,13,16,17,20], four recruited those with benign uterine diseases [15,19,20,22], and the rest used a mixture of healthy and benign disease-affected women. Considering the study type, five were prospectively designed and seven were retrospectively designed. All these studies were in moderate to high quality (≥6 scores). The summary on information of each study was listed in Table 1.

3.2. Threshold effect assessment

To assess the presence of diagnostic threshold effect as a cause of heterogeneity, we constructed SROC curves. For studies assessing the diagnosis performance of HE4, the area under receiver operating characteristic (AUROC) was 0.88 (95% CI 0.85–0.91) as shown in Fig. 2. The SROC plot revealed significant evidence that threshold effect was the main cause of heterogeneity. For CA125, the AUROC was 0.58 (95% CI 0.54–0.63) and the plot suggested no obvious evidence of threshold effect (Fig. 3).

3.3. Overall efficiency of HE4 and CA125

Among studies assessing the diagnosis performance of HE4, high level heterogeneity existed in sensitivity ($I^2 = 92.08\%$) and specificity ($I^2 = 90.13\%$). Therefore, a random effect model was used. Forest plots were shown in Fig. 4. The pooled sensitivity was 0.71 (95% CI 0.56–0.82) and the pooled specificity was 0.87 (95% CI 0.80–0.92). Similarly, high between-study heterogeneity was observed in sensitivity ($I^2 = 94.22\%$) and specificity ($I^2 = 94.03\%$) of the CA125 assays. The pooled estimates were 0.35 (95% CI 0.25–0.46) for sensitivity and 0.83 (95% CI 0.71–0.91) for specificity, respectively. Moreover, we obtained other parameters, including positive LR, negative LR and DOR, to assess the performance of HE4 in EC diagnosis, and compared these parameters to those of CA125. The results were shown in Table 2.

Table 1
Summary of eligible studies evaluating or comparing the diagnostic values of serum HE4 and CA125.

Author	Year	Country	Design	Cases	Controls	HE4		CA125		FIGO stage	Control details
						Cut-off (pmol/L)	TP/FP/FN/TN	Cut-off (U/ml)	TP/FP/FN/TN		
Moore	2008	US	Prospective/retrospective	171	156	NR	78/8/93/148	NR	42/8/129/148	122 (I), 17 (II), 26 (III), 6 (IV)	Postmenopausal healthy controls
Bignotti	2011	Italy	Prospective	138	76	NR	92/4/46/72	NR	41/4/97/72	106 (I-II), 32 (III-IV)	Postmenopausal healthy controls
Cong PS	2011	China	Prospective	42	30	77.1	27/3/15/27	23.8	19/6/23/24	42 (I-II)	healthy controls
				42	30	79.8	27/3/15/27	40	10/5/32/25	42 (I-II)	benign uterine diseases
Liang YY	2011	China	Retrospective	23	77	114.8	17/13/6/64	–		19 (I-II), 4 (III-IV)	47 benign uterine tumors,30 healthy controls
Zhang XY	2011	China	Retrospective	31	43	150	11/1/20/42	–		23 (I),4 (II),4 (III)	19 endometrial hyperplasia,24 healthy controls
Wu F	2011	China	Retrospective	30	60	150	13/3/17/57	35	20/1/10/59	16 (I),10 (II),4 (III)	30 dysfunctional uterine bleeding,30 healthy women
Zhao LQ	2012	China	Retrospective	80	27	NR	32/4/48/23	NR	10/7/70/20	53 (I), 10 (II),8 (III), 9 (IV)	uterine leiomyoma
Zanotti	2012	Italy	Retrospective	193	125	51	152/41/19/106	12.7	138/43/55/82	106 (I), 34 (II), 31 (III), 9 (IV), 13 unknown	healthy volunteers
						63.5	127/6/66/119	24.8	68/6/127/119		
Angioli	2012	Italy	Prospective	101	103	70	60/41/0/103	35	20/39/81/64	50 (I),12 (II), 36 (III), 3 (IV)	benign uterine diseases
						150	36/65/0/103				
Omer	2013	Turkey	Prospective	64	34	59.7	48/16/10/19	14.2	34/22/30/11	40 (Ia), 20 (Ib), 4 (II-III)	healthy controls
Yu WQ	2013	China	Retrospective	30	32	150	14/5/16/27	35	10/8/20/24	NR	uterine leiomyoma
Zhang SG	2013	China	Retrospective	203	687	51.9	133/129/70/558	35	48/191/155/496	175 (I),7 (II),22 (III), 8 (IV)	453 uterine leiomyoma,126 adenomyosis,26 endometrial hyperplasia,10 endometrial polyps,72 healthy women

TP: true positive; FP: false positive; FN: false negative; TN: true negative.
NR: not reported.

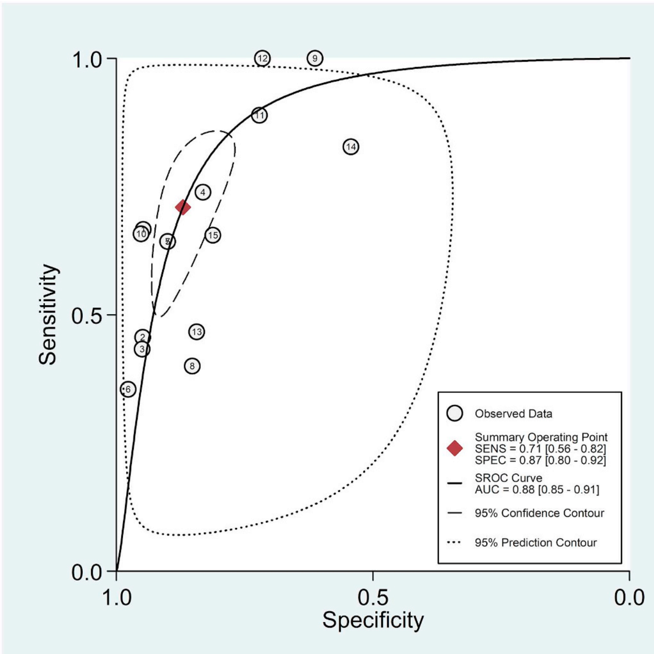

Fig. 2. SROC plot displaying diagnostic accuracy results of serum HE4. Summary sensitivity and specificity are marked by a red diamond. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

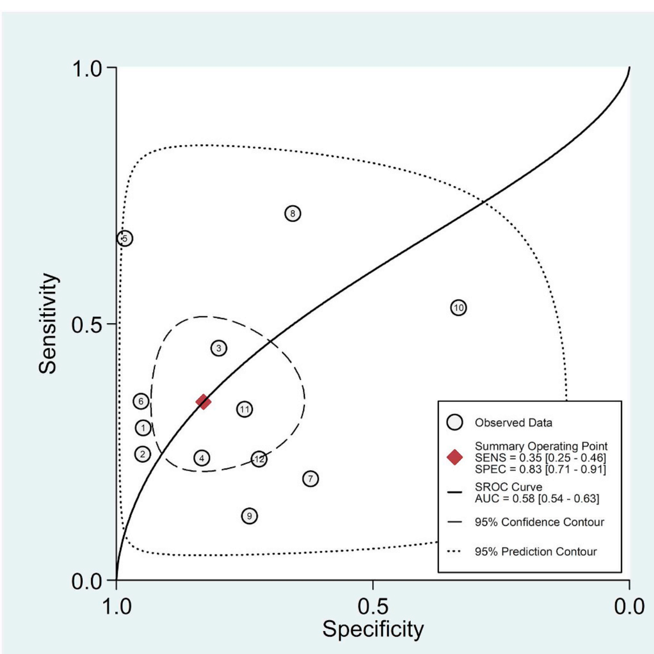

Fig. 3. SROC plot displaying the diagnostic accuracy of serum CA125. Summary sensitivity and specificity is marked by a red diamond. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.4. Subgroup analysis of HE4 tests

The studies were divided into different subgroups according to ethnicity and type of study design. Five studies enrolled patients and controls from the Caucasian populations. The pooled estimates of this subgroup were 0.86 (95% CI 0.64–0.96) for sensitivity, 0.84 (95% CI 0.68–0.92) for specificity and 31.9 (95% CI 12.8–79.5) for DOR, respectively. For the Chinese subgroup consisted of seven studies, these parameters were estimated to be 0.53 (95% CI 0.44–0.62), 0.89 (95% CI 0.83–0.93) and 8.82 (95% CI 5.98–13.1). Similar analyses were performed in subgroups of different study design, of which five were prospectively designed and seven were retrospectively designed. However, huge heterogeneity still remained in each subgroup. The results were shown in Table 3.

3.5. Publication bias

To determine whether publication bias existed, we applied the Deeks' funnel plot test. As shown in Fig. 5, the plot was basically symmetrical (p = .82), indicating there was no obvious publication bias in meat-analysis relating to the diagnostic performance of HE4.

4. Discussion

Most EC patients can be diagnosed at early stage due to certain manifestations. Thus, appropriate surgery or chemotherapy can be applied timely. However, those without typical symptoms have higher risk to develop into advanced malignancies, which often means poor prognosis and lower survival rate. HE4, a novel biomarker of ovarian cancer, has been introduced to the diagnosis of EC. Several studies have assessed the diagnostic value of HE4 in EC detection, alone or in comparison with CA125, an important but not EC-specific tumor marker.

The results of our meta-analysis demonstrated that serum HE4 level performs better in the diagnosis of EC, compared to CA125. The pooled sensitivity of HE4 was 0.71 (95% CI 0.56–0.82), much higher than that of CA125 (0.35, 95% CI 0.25–0.46), indicating that more patients would be diagnosed accurately. The pooled specificity of HE4 was marginally better than that of CA125, without a significant difference. Overall, with its much higher AUROC of 0.88 than CA125 of 0.58, serum HE4 test can be used as a good tool for the diagnosis of EC in clinical practice. On the contrast, CA125 may be not a good choice. Thus, we should attach importance to the increased level of serum HE4 in early stage EC detection, including those asymptomatic cases.

Subgroup analyses have revealed an interesting point. The pooled sensitivity was significantly higher in Caucasian subgroup (0.86, 95% CI 0.64–0.96) than in Chinese subgroup (0.53, 95% CI 0.44–0.62). It appears that serum HE4 test has a better performance in Caucasian population than in Chinese population. This gap may be caused by genetic differences between these two populations.

There are some limitations in our meta-analysis. First, due to the relatively large heterogeneity, the results should be interpreted cautiously. The SROC curves we plotted suggested that threshold effect bias was the major cause of heterogeneity. Second, we did not evaluate the role of HE4 on the diagnosis of EC in different stages, especially stage I. Similarly, endometrial cancers are classified into type 1 and type 2, with different etiologies and genetic backgrounds. Although most studies have enrolled patients in all stages and types, few have specifically addressed the performance in a stage- and type-specific manner, making more detailed analysis difficult. From this pint of view, more samples need to be collected to reach a definitive conclusion. Thirdly, 58.3% of studies included in the present study were retrospective studies, the participants were all EC cases. Thus, although our results showed that HE4 is an important marker of EC, a large population-based analysis is necessary to evaluate the impact of HE4 on early diagnosis of asymptomatic EC. Fourthly, the control subjects used in published are different among the studies, ranging from healthy women, endometrial hyperplasia, to uterine leiomyoma. This may

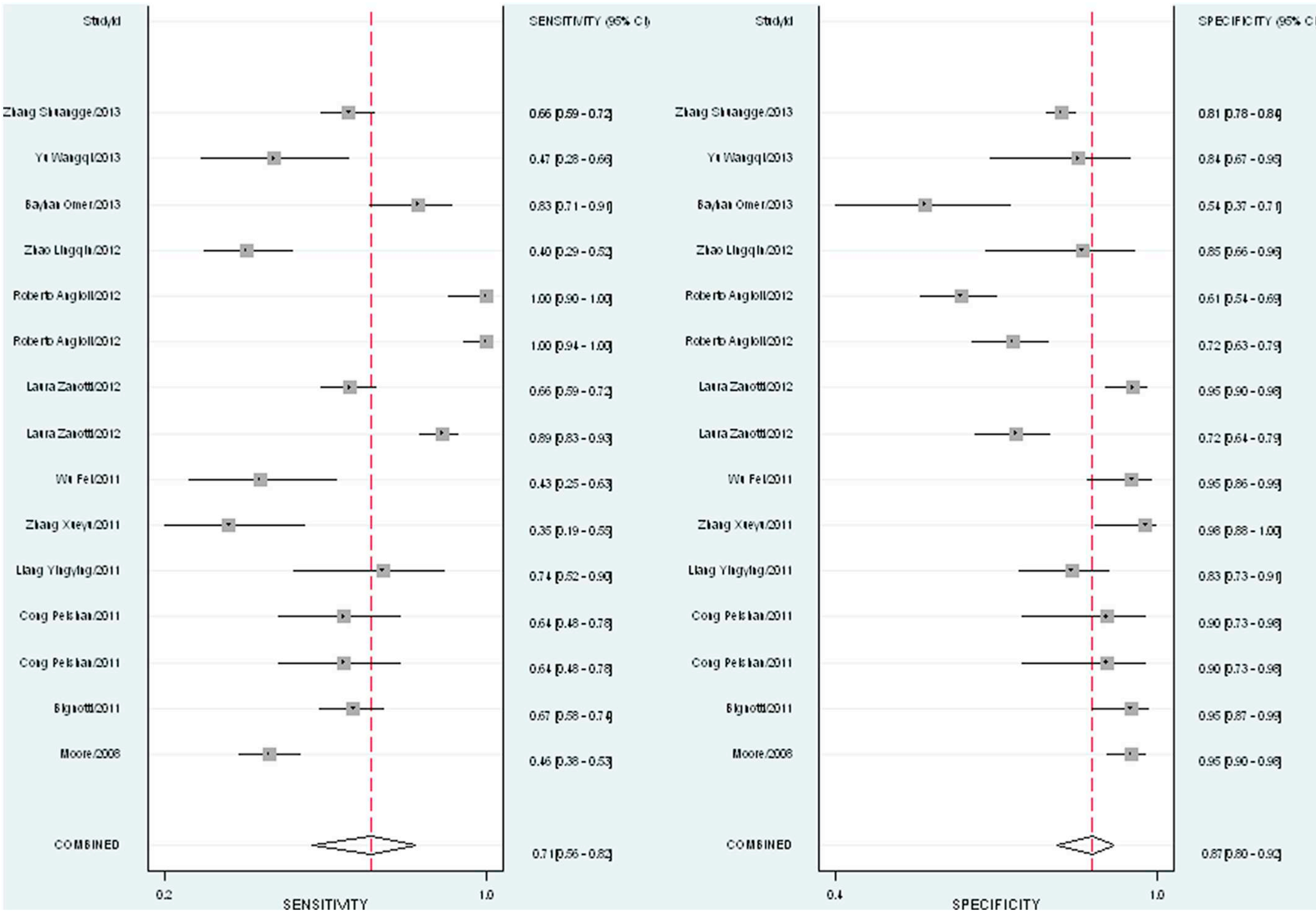

Fig. 4. Forest plot of sensitivity and specificity of HE4. The sensitivity and specificity are represented by circles in squares. Diamonds represent the pooled estimates (95% CI).

Table 2
Pooled analysis of diagnostic accuracy of HE4 and CA125 in endometrial cancer detection.

	Pooled sensitivity	Pooled specificity	Pooled PLR	Pooled NLR	Pooled DOR
HE4	0.71(0.56–0.82)	0.87(0.80–0.92)	5.47(3.93–7.62)	0.33(0.22–0.51)	16.4(10.3–26.1)
CA125	0.35(0.25–0.46)	0.83(0.71–0.91)	2.05(1.06–3.96)	0.79(0.64–0.96)	2.61(1.12–6.06)

PLR: positive likelihood ratio; NLR: negative likelihood ratio; DOR: diagnostic odds ratio.

Table 3
Subgroup analysis of diagnostic accuracy of HE4 in endometrial cancer detection.

	No. of studies	Pooled sensitivity	Pooled specificity	Pooled DOR	AUROC	I^2 (%)	*P*
Ethnicity	12						
Caucasian	5	0.86(0.64–0.96)	0.83(0.68–0.92)	31.9(12.8–79.5)	0.91(0.88–0.93)	99%	0.000
Chinese	7	0.53(0.44–0.62)	0.89(0.83–0.93)	8.82(5.98–13.1)		91%	0.000
Study design	12						
Prospective	5	0.84(0.58–0.96)	0.85(0.71–0.92)	29.3(10.4–82.8)		99%	0.000
Retrospective	7	0.60(0.45–0.73)	0.89(0.82–0.94)	12.0(7.13–20.0)		98%	0.000

DOR: diagnostic odds ratio; AUROC: area under receiver operating characteristic.

introduce bias for the observation of biomarkers' performance in this analysis as well as the original studies.

In summary, our meta-analysis demonstrated that, compared to CA125, serum HE4 has a higher sensitivity and overall accuracy in the diagnosis of all EC cases, when stage and histological types are not specifically considered. Furthermore, for some unidentified reasons,

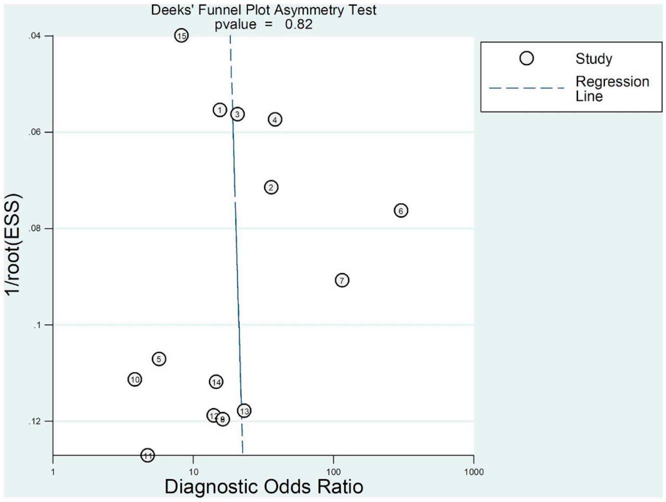

Fig. 5. Deeks' funnel plot of HE4.

HE4 tends to perform better in Caucasian population than in Chinese population. It remains to be investigated if the combination of the two markers could significantly improve the outcome in medical practice.

Declaration of interest

None.

Acknowledgements

This project is supported by the Zhejiang Provincial Natural Science Foundation (LY18H040012), and (LY18H160052).

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