Systematic Review and Meta-Analysis

Medicine

OPEN

Diagnostic value of serum human epididymis protein 4, carbohydrate antigen 125 and their combination in endometrial cancer

A meta-analysis

Qi Wu, MD[a], Su-ning Bai, MD[a], Li-yun Song, MD[a], Wen-fei Wu, MD[a], Li-na Han, MD[a,*]

Abstract

Background: To systematically analyze the value of human epididymis protein 4 (HE4) and carbohydrate antigen 125 (CA125) in the diagnosis of endometrial cancer, so as to provide evidence-based medical evidence for the selection of serum tumor markers in the early screening of endometrial cancer.

Methods: We comprehensively searched relevant literature in the Cochrane Library, EMBASE, PubMed, Web of Science, CNKI, VIP, WanFang, and CBM from the date of establishment to November 31, 2021. Quality assessment of diagnostic accuracy studies 2 was applied to evaluate the quality of the included literature. We used Stata 16.0 to calculate the pooled sensitivity (SEN), specificity (SPE), positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic odds ratio (DOR) and plot summary receiver operating characteristic curve, as well as to assess diagnostic accuracy using the area under the curve (AUC).

Results: A total of 25 studies, including 1980 patients and 2345 controls, were included in this meta-analysis. The pooled SEN, SPE, PLR, NLR, DOR, and AUC of HE4 were 0.58 (95% CI 0.52–0.63), 0.95 (95% CI 0.92–0.97), 11.57 (95% CI 6.88–19.48), 0.45 (95% CI 0.39–0.51), 25.92 (95% CI 14.84–45.26), and 0.80 (95% CI 0.76–0.83), respectively. The pooled SEN, SPE, PLR, NLR, DOR, and AUC of CA125 were 0.41 (95% CI 0.34–0.49), 0.91 (95% CI 0.85–0.95), 4.55 (95% CI 2.73–7.58), 0.65 (95% CI 0.57–0.74), 7.03 (95% CI 3.92–12.62), and 0.68 (95% CI 0.64–0.72), respectively. The pooled SEN, SPE, PLR, NLR, DOR, and AUC of HE4 + CA125 were 0.67 (95% CI 0.60–0.73), 0.92 (95% CI 0.87–0.95), 8.59 (95% CI 5.32–13.86), 0.36 (95% CI 0.30–0.44), 23.80 (95% CI 13.86–40.86), and 0.85 (95% CI 0.82–0.88), respectively.

Conclusion: This Meta-analysis found that HE4 alone or in combination with CA125 showed better diagnostic efficacy than CA125, regardless of clinical stage and pathological type. HE4 + CA125 had slightly higher diagnostic efficiency than HE4, but did not show significant advantages. While the studies were heterogeneous, the credibility of the findings needs to be further confirmed by more homogeneous, prospective, and large sample size studies.

Abbreviations: AUC = the area under the curve, CA125 = carbohydrate antigen 125, CI = confidence interval, DOR = diagnostic odds ratio, EC = endometrial cancer, ET = endometrial thickness, HE4 = human epididymis protein 4, NLR = negative likelihood ratio, PLR = positive likelihood ratio, QUADAS-2 = the quality assessment of diagnostic accuracy studies 2, SEN = sensitivity, SPE = specificity, SROC = summary receiver operating characteristic curve.

Keywords: carbohydrate antigen 125, diagnostic accuracy, endometrial cancer, meta-analysis, serum human epididymis protein 4

1. Introduction

Endometrial cancer (EC) is an epithelial malignant tumor originating from the endometrium, which is one of the 3 most common malignant reproductive system tumors in women, accounting for about 20% to 30% of the female reproductive system malignancies.[1] In recent years, the incidence of EC has been on the rise worldwide with the increase of high-risk factors such as obesity, hypertension, diabetes, and female endocrine diseases, etc. More than 90% of patients with EC have an age of onset above 50 years, and the median age of diagnosis is 63 years, while 4% of patients with EC have an age of onset below 40 years, with an increasing trend towards younger age of onset.[2] Unlike patients with ovarian cancer, most patients with EC can show symptoms such as menstrual disorders or

The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

The data used in this study were extracted from the published literature, therefore, ethical approval was waived.

[a] Department of Obstetrics and Gynecology, Hebei General Hospital, Shijiazhuang, Hebei, China.

**Correspondence: Li-na Han, Department of Obstetrics and Gynecology, Hebei General Hospital, 348, Heping West Road, Shijiazhuang, Hebei 050051, China (e-mail: HanlinaHB@163.com).*

How to cite this article: Wu Q, Bai S-n, Song L-y, Wu W-f, Han L-n. Diagnostic value of serum human epididymis protein 4, carbohydrate antigen 125 and their combination in endometrial cancer: A meta-analysis. Medicine 2023;102:33(e34737).

Received: 29 May 2023 / Received in final form: 19 July 2023 / Accepted: 24 July 2023

http://dx.doi.org/10.1097/MD.0000000000034737

Key points

- Our study compared the diagnostic accuracy of HE4, CA125, and HE4 + CA125 in EC.
- HE4 + CA125 had slightly higher diagnostic accuracy than HE4 in EC.
- CMIA, CLIA, and ECLIA may have better sensitivity than ELISA and RIA.

postmenopausal uterine bleeding, making it possible for about 80% of patients to be diagnosed at an early stage, with a good prognosis compared to other gynecologic malignancies and a 5-year survival rate >95%.[3] However, 20% of patients are still asymptomatic and have local spread or distant metastases at the time of detection, losing the optimal period of treatment, with a significantly lower 5-year survival rate of 68% and 17%, respectively.[2] Therefore, improving the early diagnosis rate of EC is the key to improve the prognosis and overall survival of patients. Early screening modalities commonly used in clinical practice include pelvic ultrasound, computed tomography, magnetic resonance imaging, endometrial aspiration biopsy, diagnostic curettage, hysteroscopic diagnostic curettage, and tumor markers. For women with initial bleeding symptoms, transvaginal ultrasound is recommended and endometrial thickness (ET) will provide an important referral basis. However, CLARKE et al found that ET did not provide meaningful risk stratification: women with ET >4 mm and ≤4 mm had an almost equal risk of EC/endometrial intraepithelial neoplasia.[4]

Serum tumor markers are the most widely used tumor detection tools in clinical practice. Compared with pathological biopsies or tissue biomarkers of surgical specimens, they have the advantages of convenient detection, less invasive, and easily accepted by patients. However, there are no serum tumor markers routinely used for early diagnosis, prognosis or recurrence monitoring of EC yet. Carbohydrate antigen 125 (CA125) is the most studied tumor marker in diagnosis and treatment of EC, but it may also be elevated in physiological or pathological conditions other than cancer, such as menstruation, pregnancy, endometriosis, and pelvic inflammatory diseases, etc.[5] The specificity (SPE) of screening for EC is poor and the sensitivity (SEN) is not ideal.[6] Human epididymis protein 4 (HE4) is one of the most promising tumor markers and has been approved for the diagnosis and recurrence monitoring of ovarian cancer. Notably, except for epithelial ovarian cancer, HE4 is significantly expressed in EC, while it is lowly expressed in endometriosis and other benign gynecological diseases.[7] Currently, the diagnostic value of serum HE4, CA125, and their combination is still controversial. Degez et al pooled 52 articles on HE4 and EC and found that the SEN of HE4 for the diagnosis of EC varied from 44.2% to 91% and its SPE from 65.5 to 100%, versus 24.1% to 71.5% and from 65.6% to 100% for CA125.[8] Therefore, the purpose of this meta-analysis was to evaluate the value of HE4, CA125, and their combination in the early screening of EC.

2. Materials and methods

2.1. Literature search

The following terms were used: "Uterine neoplasms," "Uterine cancer," "EC," Endometrial neoplasms," "Human epididymis protein 4," "HE4," "CA125," "Cancer antigen 125." "CA125," "Cancer antigen 125" and "CA125." The Cochrane Library, EMBASE, PubMed, Web of Science, CNKI, VIP, WanFang, and CBM were searched until November 31, 2021. EndNote X9 was applied to manage the preliminary search of relevant literature.

2.2. Inclusion and exclusion criteria

2.2.1. Inclusion criteria The case group was patients with primary EC with a clear histopathological diagnosis; the control group was a healthy population or with a benign uterine disease that was easily confused with endometrium and testified to be free of any malignancy; a complete 2-by-two table on the diagnostic value of serum HE4, CA125 and their combination in EC could be extracted or calculated in the study data; blood samples were collected prior to initiation of antineoplastic therapy.

2.2.2. Exclusion criteria Duplicate literature, reviews, cases, conference proceedings, incomplete study subgroups, or unavailable full text; combination of other malignancies; erroneous data or inability to extract complete 2-by-two table data from the literature; <30 patients with EC in the study group; literature with the quality assessment of diagnostic accuracy studies 2 (QUADAS-2) quality scores <8.

All literatures were independently screened by 2 investigators, and any disagreement would be discussed or consulted with a third investigator.

2.3. Quality assessment

QUADAS-2[9] was applied to evaluate the quality of the included literatures in 4 aspects: patient selection, index test, reference standard, and flow and timing. The QUADAS-2 quality score ≥8 was considered as high-quality literature. Two investigators independently assessed the methodological quality of the included literatures and extracted data using Review Manager 5.3. Any disagreement would be discussed or consulted with a third investigator.

2.4. Data extraction

The extracted data consisted of: the first author name, year of publication, country, type of study design, diagnostic gold standard, mean age of the case group, and type of control group; test methods and threshold levels of serum HE4 and CA125; and 2-by-two table information extracted directly from the original literature or by calculation, including true positive, false positive, true negative, and false negative. Data extraction of the included literatures was independently performed by 2 investigators, and any disagreement would be discussed or consulted with a third investigator.

2.5. Statistical analysis

Statistical analysis of the data was performed using the Midas command of Stata 16.0. The Midas command uses a bivariate mixed effects model, which is essentially a random effects model. The Q test and I^2 test were used to analyze the heterogeneity among studies. If there was no significant heterogeneity ($I^2 < 50\%$, $P > .1$), we used a fixed effect model, otherwise a random effect model was used to calculate the pooled SEN, SPE, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and their 95% confidence interval (CI) for serum HE4, CA125 and HE4 + CA125, plot summary receiver operating characteristic curve (SROC) and summarize the area under the curve (AUC) to assess diagnostic accuracy. If there was significant heterogeneity, the magnitude of heterogeneity due to threshold effects was quantified, and Meta-regression analysis and subgroup analysis were performed to find the source of heterogeneity. Deek funnel plot was used to evaluate publication bias. Metaninf command was used to perform SEN analysis of the included studies. Meta-regression analysis was performed by two of HE4, CA125, and HE4 + CA125 to compare the differences in diagnostic

accuracy. All statistical tests were 2-sided and $P < .05$ was considered statistically significant.

3. Results

3.1. Characteristics of the included studies and quality assessment

A total of 25 of 1159 studies were included,[10–34] and the literature screening process is shown in Figure 1. A total of 1980 cases were included in the case group, and the age of several case groups was around 50 years old, of which the minimum mean age was 32.5 years and the maximum was 66 years. The control group consisted of 2345 individuals, of which 7 studies[11,14,21,23,24,31,33] had only healthy population as controls, 7 studies[10,15,17,19,22,32,34] had only benign uterine disease as control, and 11 studies[12,13,16,18,21,25–30] had benign uterine disease combined with healthy population as control. The basic characteristics of the included studies are shown in Table 1. Quality evaluation of the literature showed a high, unclear and low risk of bias of 13%, 18%, and 69%, respectively. High, unclear, and low applicability issues were 8%, 7%, and 85%, respectively. Selection bias was present in all included 25 studies. The literature quality evaluation is shown in Figure 2.

3.2. Analysis of the diagnostic value of serum HE4

The total heterogeneity of the 25 included studies was significant ($I^2 = 99\%$, $P < .001$), and the exploration of the heterogeneity of each effect variable revealed high heterogeneity in pooled SEN ($I^2 = 85.38\%$, $P < .001$), SPE ($I^2 = 93.80\%$, $P < .001$), PLR ($I^2 = 86.50\%$, $P < .001$), NLR ($I^2 = 82.30\%$, $P < .001$), and DOR ($I^2 = 100\%$, $P < .001$). However, the threshold effect was not significant (correlation = –0.27, $P = .07$) and accounted for only 7% of the overall heterogeneity. Meta-regression and subgroup analysis (Table 2) were performed on population, study type, test method, age of case group, type of control group and cutoff value, which found that type of control group ($I^2 = 78\%$, $P = .01$), test method ($I^2 = 93\%$, $P < .001$), age of case group ($I^2 = 92\%$, $P < .001$) and cutoff value ($I^2 = 96\%$, $P < .001$) significantly affected the diagnostic accuracy. We used bivariate mixed-effects model to pool effect variables, and the pooled SEN, SPE, PLR, NLR, DOR and AUC were 0.58 (95% CI 0.52–0.63), 0.95 (95% CI 0.92–0.97), 11.57 (95% CI 6.88–19.48), 0.45 (95% CI 0.39–0.51), 25.92 (95% CI 14.84–45.26), and 0.80 (95% CI 0.76–0.83), respectively. The forest plot for SEN and SPE and the SROC curve are shown in Figures 3 and 4A, respectively.

3.3. Analysis of the diagnostic value of serum CA125

There was significant heterogeneity in the 25 included studies ($I^2 = 99\%$, $P < .001$), with significant heterogeneity in pooled SEN ($I^2 = 91.82\%$, $P < .001$), SPE ($I^2 = 94.11\%$, $P < .001$), PLR ($I^2 = 87.23\%$, $P < .001$), NLR ($I^2 = 86.82\%$, $P < .001$), and DOR ($I^2 = 100\%$, $P < .001$). However, the threshold effect was not significant (correlation = –0.25, $P = .07$), accounting for 7% of the total heterogeneity. Therefore, Meta-regression and subgroup analysis (Table 3) of different populations, study designs, test methods, age of case group and types of control group included in the study revealed that different test methods ($I^2 = 90\%$, $P < .001$) and age of case group ($I^2 = 94\%$, $P < .001$) significantly affected diagnostic accuracy. Bivariate mixed-effects models were applied to count the pooled SEN, SPE, PLR, NLR, DOR and AUC were 0.41 (95% CI 0.34–0.49), 0.91 (95% CI 0.85–0.95), 4.55 (95% CI 2.73–7.58), 0.65 (95% CI 0.57–0.74), 7.03 (95% CI 3.92–12.62), and 0.68 (95% CI 0.64–0.72). The forest plot for SEN and SPE and the SROC curve are shown in Figures 4B and 5, respectively.

3.4. Analysis of the diagnostic value of HE4 + CA125

The overall heterogeneity of the 25 included studies was significant ($I^2 = 99\%$, $P < .001$) and there was significant heterogeneity in pooled SEN ($I^2 = 86.68\%$, $P < .001$), SPE ($I^2 = 92.61\%$, $P < .001$), PLR ($I^2 = 87.81\%$, $P < .001$), NLR ($I^2 = 84.32\%$, $P < .001$), and DOR ($I^2 = 100\%$, $P < .001$), while the threshold effect was not significant

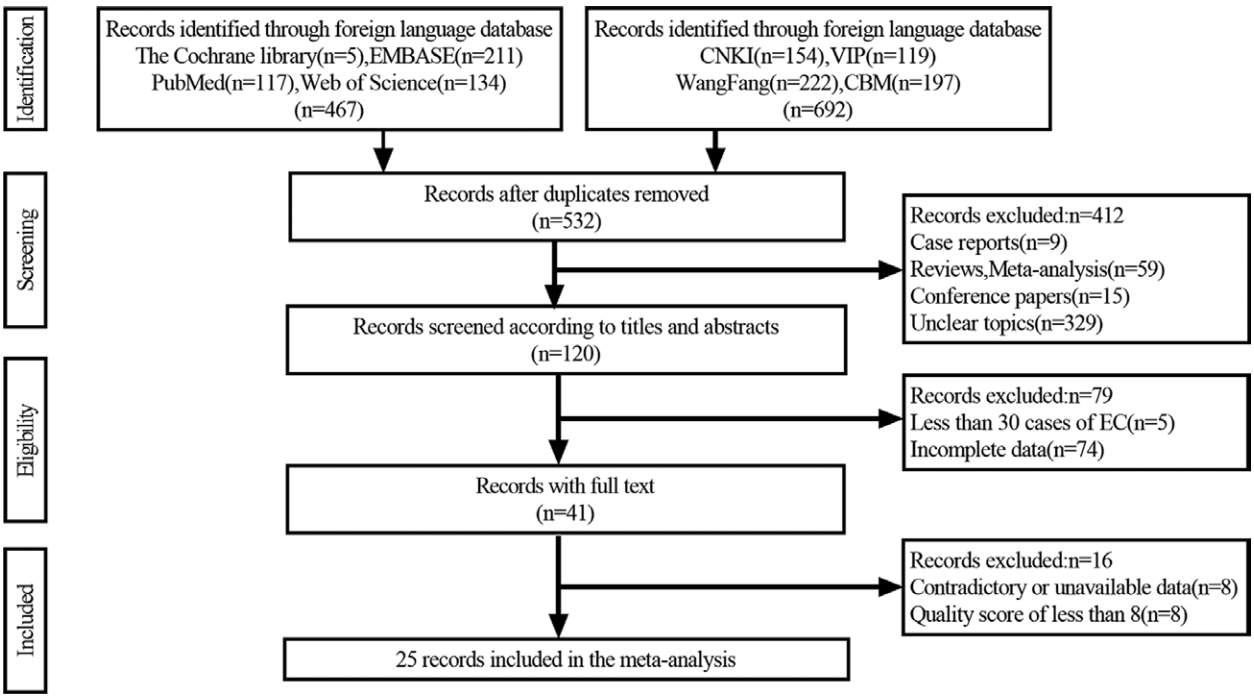

Figure 1. Flow chart of literature search.

Table 1

The basic characteristics of the enrolled studies.

				HE4			CA125			HE4 + CA125	
Studies	Country	Design	Cases/ Controls	Test methods	Cutoff (pmol/L)	TP/FP/FN/TN	Test methods	Cutoff (U/mL)	TP/FP/FN/TN	TP/FP/FN/TN	Quality score
Angioli 2012	Italy	Prospective	101/103	ELISA	70	60/0/41/103	RIA	35	20/39/81/64	61/0/50/103	14
					150	36/0/65/103				35/0/66/103	
Bignotti 2011	Italy	Prospective	138/76	ELISA	NR	92/4/46/72	CMIA	NR	41/4/97/72	94/4/44/72	9
Dewan 2017	India	Prospective	60/60	CMIA	69.7	52/0/8/60	CMIA	34.5	26/0/34/60	52/0/8/60	8
Dong 2017	China	Retrospective	150/200	ELISA	86	86/8/64/192	ECLIA	35	78/12/72/188	110/18/40/182	13
Jafari 2016	Iran	Prospective	40/60	ECLIA	70	23/4/17/56	CLIA	35	16/3/24/57	25/4/15/56	13
LIU 2018	China	Prospective	40/50	ELISA	51.83	22/5/18/35	ELISA	35	12/2/28/48	25/5/15/45	10
Moore 2008	America	Prospective	171/156	NR	NR	78/8/93/148	NR	NR	42/8/129/148	86/8/85/148	9
Omer 2013	Turkey	Prospective	64/34	ECLIA	59.7	48/12/16/22	ECLIA	14.2	34/23/30/11	50/9/14/25	8
Zanotti 2012	Italy	Retrospective	193/125	CMIA	51	152/19/41/106	CMIA	12.7	138/43/55/82		11
					63.5	127/6/66/119		24.8	68/6/125/119	124/6/69/119	
Chen 2016	China	Retrospective	56/125	ELISA	150	23/2/33/123	ECLIA	35	19/13/37/112	30/7/26/118	13
Cui 2018	China	Retrospective	60/120	ECLIA	65.42	39/3/21/117	CMIA	25.52	47/2/13/118	59/6/1/114	12
Ding 2016	China	Prospective	31/87	ECLIA	65.25	21/30/10/57	ECLIA	33.58	13/21/18/66	25/23/6/64	12
Dong 2017	China	Retrospective	75/70	ELISA	72.6/104*	41/1/34/69	ECLIA	35	21/6/54/64	44/7/31/63	10
Gao 2016	China	Retrospective	80/120	ELISA	150	33/9/47/111	ECLIA	35	22/16/58/104	48/26/32/94	12
Lin 2014	China	Prospective	85/100	ECLIA	69.45	43/0/42/100	ECLIA	35	24/0/61/100	50/0/35/100	10
Liu 2020	China	Retrospective	60/70	ECLIA	140	36/8/24/62	ECLIA	35	31/15/29/55	44/12/16/58	10
Qu 2018	China	Retrospective	84/142	ECLIA	140	51/2/33/140	ECLIA	35	43/13/41/129	64/13/20/129	12
Sun 2014	China	Retrospective	30/60	ELISA	150	11/4/19/56	RIA	35	9/2/21/58	19/5/11/55	11
Tang 2019	China	Retrospective	47/87	ELISA	150	27/39/20/48	ECLIA	35	35/37/12/50	39/45/8/42	10
Tao 2016	China	Retrospective	56/163	ELISA	150	25/5/31/158	RIA	35	20/2/36/161	30/4/26/159	12
Wu 2011	China	Retrospective	30/60	ELISA	150	13/3/17/57	RIA	35	11/1/19/59	16/3/14/57	12
Yang 2015	China	Retrospective	68/100	ECLIA	150	52/18/16/82	ECLIA	35	46/29/22/71	52/20/16/80	10
Zhang 2012	China	Prospective	124/97	ELISA	83.14	51/6/78/91	ECLIA	35	28/10/96/87	57/16/67/81	11
Zhang 2016	China	Prospective	57/53	ELISA	150	40/1/17/52	ECLIA	35	41/10/16/43	48/11/10/42	8
Zhao 2012	China	Retrospective	80/27	ELISA	NR	32/4/48/23	ECLIA	NR	10/7/70/20	34/10/46/17	10

CA125 = carbohydrate antigen 125, CLIA = chemiluminescent immunoassay, CMIA = chemiluminescent microparticle immunoassay, ECLIA = electrochemiluminescent immunoassay, ELISA = enzyme-linked immunosorbent assay, FN = false negative, FP = false positive, HE4 = human epididymis protein 4, NR = not reported, RIA = radioimmunoassays, TN = true negative, TP = true positive.
*HE4 had premenopausal and postmenopausal thresholds.

(correlation = -0.30, $P = .09$), accounting for 9% of the total heterogeneity. Meta-regression and subgroup analysis (Table 4) revealed statistically significant differences in the pooled effect variables for different populations ($I^2 = 77\%$, $P = .01$) and age of case group ($I^2 = 93\%$, $P < .001$). Using a bivariate mixed-effects model for each effect variable, the pooled SEN, SPE, PLR, NLR, DOR, and AUC were 0.67 (95% CI 0.60–0.73), 0.92 (95% CI 0.87–0.95), 8.59 (95% CI 5.32–13.86), 0.36 (95% CI 0.30–0.44), 23.80 (95% CI 13.86–40.86), and 0.85 (95% CI 0.82–0.88), respectively. The forest plot for SEN and SPE and the SROC curve are shown in Figures 4C and 6, respectively.

3.5. Comprehensive comparison of diagnostic accuracy of serum HE4, CA125, and HE4 + CA125

We performed 2-by-two meta-regression analysis of HE4, CA125, and HE4 + CA125. The difference in diagnostic accuracy between HE4 and CA125 was statistically significant ($I^2 = 87\%$, $P < .001$). The difference in diagnostic accuracy between HE4 and HE4 + CA125 was not statistically significant ($I^2 = 56\%$, $P = .10$). The difference in diagnostic accuracy between CA125 and HE4 + CA125 was statistically significant ($I^2 = 91\%$, $P < .001$).

3.6. Sensitivity analysis and publication bias

SEN analysis showed that the stability of this study was satisfactory and the results were reliable (Fig. 4D–F). Deek funnel plots showed no publication bias ($P = .25$, $P = .79$, and $P = .40$) in the included studies (Fig. 4G–I).

4. Discussion

There are many studies on the diagnostic value of HE4 alone or in combination with CA125 in EC, and many systematic reviews and Meta-analyses have been reported, but only the Meta-analysis reported by Chen et al comprehensively compared the diagnostic value of HE4, CA125 and their combination in EC. The results of a meta-analysis that included 8 studies showed that the AUC of serum HE4, CA125, and HE4 + CA125 for the diagnosis of EC were 0.77, 0.37, and 0.83, respectively. HE4 alone or in combination with CA125 was more accurate in diagnosing EC, and HE4 + CA125 had better accuracy than HE4.[35] However, there are only 5 studies on the value of serum HE4 combined with CA125 for the diagnosis of EC, so the reliability of the conclusion needs to be further confirmed by more research data.

Our study showed that the SEN of HE4 + CA125 was 0.67, which was the highest, and the SEN of CA125 was 0.41, which was the lowest, indicating that the combined detection of HE4 and CA125 could improve the detection rate of EC. However, the SEN of all 3 tests did not show outstanding efficacy, which may lead to a part of the clinical underdiagnosis rate. The SPE of all 3 tests was above 0.90, thus all 3 tests could significantly reduce the misdiagnosis rate of EC. The likelihood ratio is a more stable composite index than the SEN and SPE and not affected by the prevalence, including PLR and NLR. When PLR > 10 and NLR < 0.1, the diagnostic test was considered to present good diagnostic performance.[36] The PLR of HE4 was the highest at 11.57, and the NLR of HE4 + CA125 was the lowest at 0.36, indicating that when HE4 levels were above cutoff value, it showed a significant advantage in predicting the probability of EC, but conversely, the probability of EC still remained 45%. CA125 had no significant

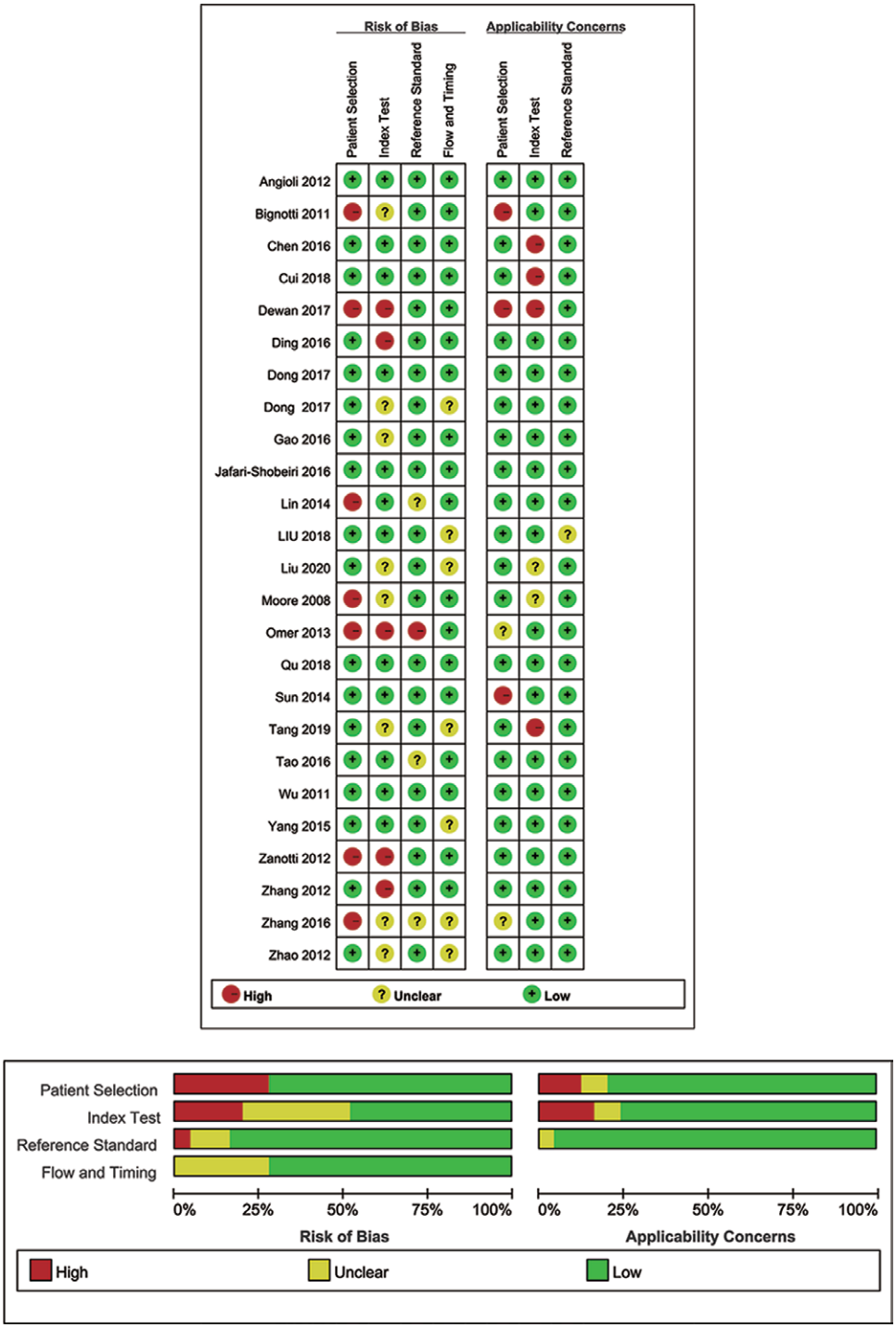

Figure 2. Quality assessment results of included studies based on the quality assessment of diagnostic accuracy studies 2 (QUADAS-2) tool criteria.

advantage in predicting the probability of EC, and the effect of HE4 + CA125 was moderate. DOR is an evaluation index combining SEN, SPE, and likelihood ratio, and the higher the DOR value, the higher accuracy of diagnosing EC. HE4 had the highest DOR of 25.92, slightly higher than HE4 + CA125 (DOR = 23.80), and CA125 had the lowest DOR of 7.03. Compared with CA125, HE4 alone or in combination with CA125 showed a higher diagnostic accuracy. AUC is currently considered to be a good indicator for evaluating diagnostic efficacy in diagnostic tests, with AUC values closer to 1 indicating higher diagnostic efficacy and closer to 0.5 indicating poorer diagnostic efficacy. One study had shown that the bias of AUC due to heterogeneity is <6% even in the case of significant heterogeneity.[37] The results of this meta-analysis showed that the AUC of serum HE4, CA125 and their combination for the diagnosis of EC were 0.80 (95% CI 0.76–0.83), 0.68 (95% CI 0.64–0.72), and 0.85 (95% CI 0.82–0.88), respectively, and the AUC of HE4 + CA125 was higher than that of HE4 and CA125 by 5% and 17%, respectively. Combining the results of 2-by-two Meta-regression analysis of the 3 tests revealed that HE4 alone or in combination with CA125 had a good comprehensive effect in diagnosing EC, with HE4 + CA125 having a slightly higher diagnostic accuracy than HE4, but the difference was not statistically significant. Similarly, Behrouzi et al found that the combination of HE4 with CA125 or other biomarkers showed only marginal improvements in utility.[38]

Table 2

Meta-regression and subgroup analysis of diagnostic accuracy of HE4 in EC.

Subgroup	Studies	SEN	SPE	PLR	NLR	DOR	AUC	I^2 (%)	*P*
Population								0	.40
Asia	21	0.57 (0.51–0.63)	0.94 (0.90–0.97)	9.83 (5.48–17.64)	0.46 (0.40–0.53)	21.46 (11.23–40.99)	0.78 (0.74–0.81)		
Non-Asia	4	0.59 (0.47–0.71)	0.97 (0.91–0.99)	18.50 (6.81–49.99)	0.42 (0.32–0.55)	43.84 (17.49–109.91)	0.86 (0.83–0.89)		
Design								0	.53
Prospective	11	0.60 (0.50–0.68)	0.97 (0.90–0.99)	19.80 (5.70–68.50)	0.42 (0.34–0.52)	47.53 (13.12–172.16)	0.80 (0.76–0.83)		
Retrospective	14	0.56 (0.49–0.63)	0.94 (0.90–0.97)	9.19 (5.40–15.65)	0.47 (0.40–0.55)	19.68 (11.01–35.15)	0.80 (0.76–0.83)		
Age								92	.00
≥50 yr	19	0.56 (0.49–0.62)	0.95 (0.91–0.97)	11.36 (5.92–21.80)	0.46 (0.40–0.54)	24.50 (12.18–49.27)	0.78 (0.74–0.81)		
<s50 yr	4	0.61 (0.47–0.73)	0.94 (0.85–0.98)	10.89 (4.41–26.86)	0.42 (0.31–0.56)	26.13 (11.53–59.23)	0.83 (0.80–0.86)		
Control type*								78	.01
Healthy	7	0.68 (0.58–0.76)	0.96 (0.88–0.99)	16.66 (5.44–51.66)	0.33 (0.25–0.44)	50.12 (15.46–162.50)	0.86 (0.83–0.89)		
Benign disease	7	0.51 (0.43–0.59)	0.96 (0.86–0.99)	12.52 (3.59–43.73)	0.51 (0.44–0.60)	24.50 (6.74–89.07)	0.68 (0.63–0.72)		
Benign disease + Healthy	11	0.54 (0.46–0.61)	0.94 (0.89–0.97)	9.09 (4.70–17.56)	0.49 (0.42–0.57)	18.44 (9.11–37.32)	0.74 (0.70–0.78)		
Test methods								93	.00
CIA	10	0.69 (0.62–0.74)	0.94 (0.85–0.98)	11.10 (4.60–26.76)	0.33 (0.28–0.40)	33.23 (13.51–81.77)	0.81 (0.77–0.84)		
Non-CIA	14	0.50 (0.44–0.56)	0.96 (0.92–0.98)	11.99 (5.98–24.06)	0.52 (0.46–0.59)	22.92 (10.81–48.60)	0.71 (0.67–0.75)		
cutoff value									
≤70 pmol/L	9	0.67 (0.60–0.74)	0.96 (0.85–0.99)	11.32 (5.92–21.67)	0.50 (0.44–0.58)	45.47 (12.72–162.50)	0.80 (0.76–0.83)	96	.00
>70 pmol/L	13	0.52 (0.45–0.59)	0.95 (0.91–0.98)	15.52 (4.48–53.75)	0.50 (0.44–0.58)	22.42 (11.43–44.00)	0.75 (0.71–0.79)		

AUC = area under the curve, CIA = chemiluminescent assays, DOR = diagnostic odds ratio, EC = endometrial cancer, HE4 = human epididymis protein 4, NLR = negative likelihood ratio, PLR = positive likelihood ratio, SEN = sensitivity, SPE = specificity.

**P* value of Meta-regression between healthy and those containing benign diseases.

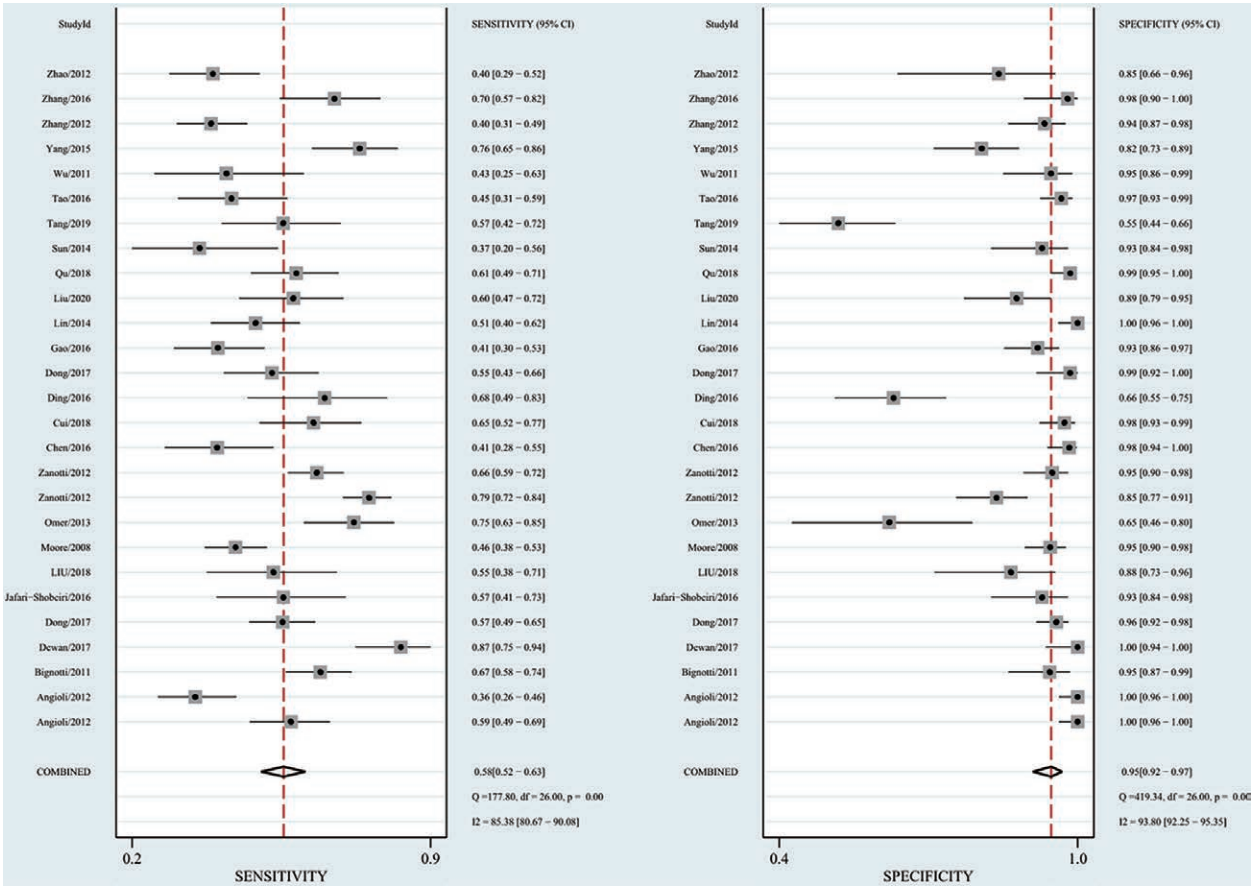

Figure 3. Forest plot of sensitivity and specificity of HE4. Left panel: sensitivity, right panel: specificity.

The results of all 3 tests in this Meta-analysis were highly heterogeneous, but none of the heterogeneity caused by threshold effects was significant. The meta-regression and subgroup analysis showed that the sources of heterogeneity could be the following: Type of control group. By comparing AUC values in subgroup analysis of people who are healthy, with benign disease and healthy combined with benign disease, we found that all 3 tests were more accurate in identifying normal population and EC than in identifying benign and malignant disease. This result suggests that the inclusion of only healthy populations may overestimate accuracy of diagnostic tests. However, during clinical practice, the identification of benign and malignant

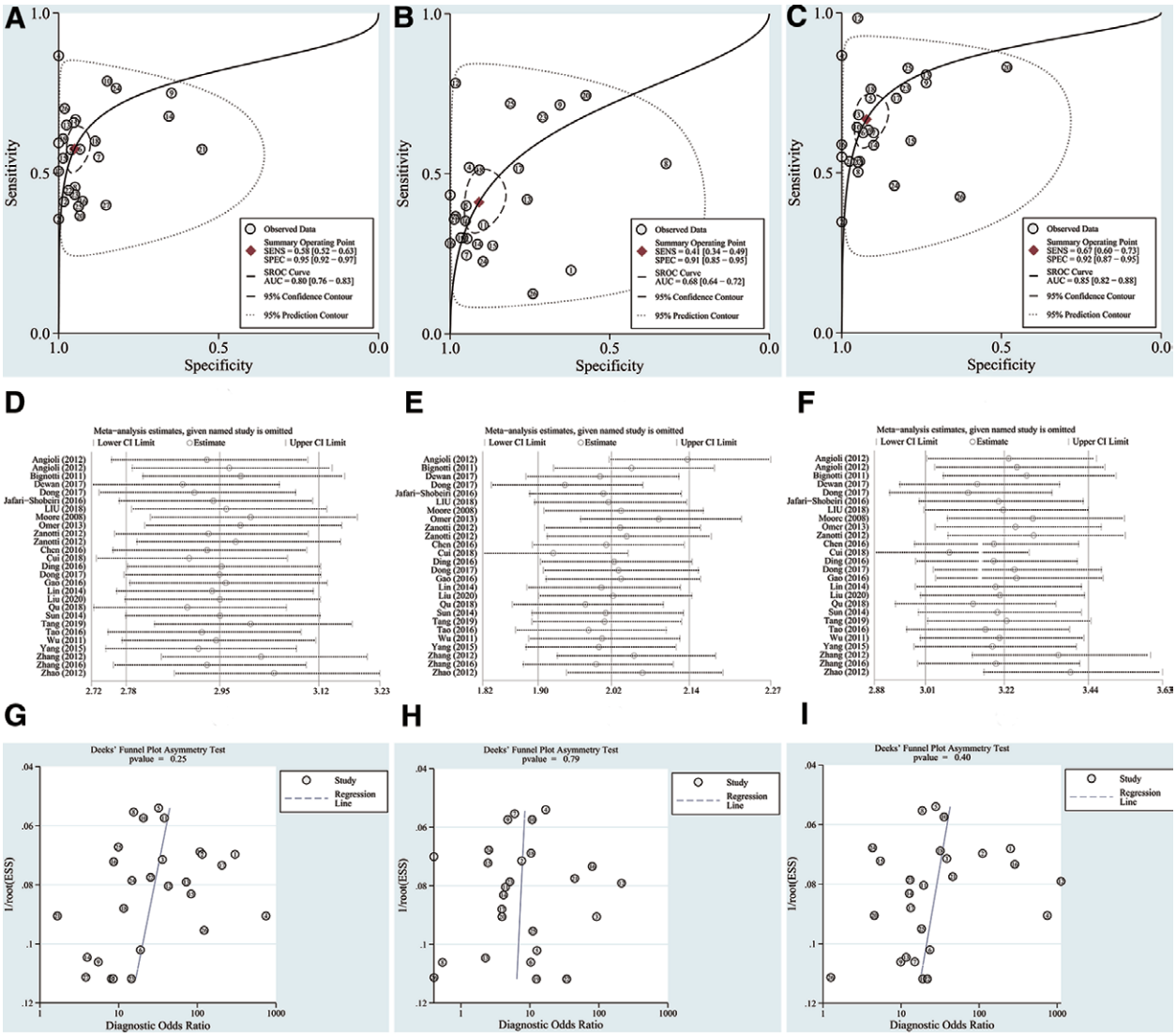

Figure 4. Summary receiver operating characteristic curve (SROC) of HE4 (A), CA125 (B), and HE4 + CA125 (C). Sensitivity analysis of HE4 (D), CA125 (E), and HE4 + CA125 (F). Deke funnel plots of HE4 (G), CA125 (H), and HE4 + CA125 (I). CA125 = carbohydrate antigen 125, HE4 = human epididymis protein 4.

Table 3

Meta-regression and subgroup analysis of diagnostic accuracy of CA125 in EC.

Subgroup	Studies	SEN	SPE	PLR	NLR	DOR	AUC	I^2 (%)	*P*
Population								0	.54
Asia	21	0.43 (0.35–0.51)	0.92 (0.85–0.96)	5.16 (2.83–9.41)	0.63 (0.54–0.72)	8.25 (4.18–16.29)	0.69 (0.65–0.73)		
Non-Asia	4	0.35 (0.21–0.53)	0.88 (0.71–0.95)	2.90 (1.19–7.05)	0.74 (0.58–0.94)	3.93 (1.36–11.36)	0.64 (0.60–0.68)		
Design								0	.44
Prospective	11	0.35 (0.27–0.45)	0.92 (0.79–0.97)	4.39 (1.64–11.77)	0.70 (0.61–0.81)	6.25 (2.12–18.44)	0.56 (0.51–0.60)		
Retrospective	14	0.45 (0.35–0.56)	0.90 (0.84–0.95)	4.75 (2.71–8.32)	0.61 (0.50–0.73)	7.85 (4.00–15.40)	0.75 (0.71–0.79)		
Age								94	.00
≥50 yr	19	0.38 (0.31–0.46)	0.91 (0.83–0.95)	4.11 (2.24–7.56)	0.68 (0.61–0.77)	6.01 (3.04–11.90)	0.62 (0.58–0.66)		
<50 yr	4	0.53 (0.32–0.74)	0.93 (0.78–0.98)	7.19 (2.07–24.96)	0.50 (0.31–0.82)	14.29 (2.97–68.74)	0.83 (0.79–0.86)		
Control type*								0	.77
Healthy	7	0.44 (0.31–0.57)	0.93 (0.76–0.98)	6.17 (1.90–20.00)	0.60 (0.50–0.73)	10.23 (3.11–33.56)	0.66 (0.62–0.70)		
Benign disease	7	0.29 (0.20–0.40)	0.83 (0.73–0.90)	1.70 (0.88–3.30)	0.86 (0.71–1.03)	1.99 (0.85–4.63)	0.57 (0.53–0.61)		
Benign disease + Healthy	11	0.47 (0.36–0.59)	0.93 (0.86–0.97)	6.92 (3.51–13.62)	0.57 (0.46–0.70)	12.21 (5.78–25.83)	0.77 (0.73–0.80)		
Test methods								90	.00
CIA	19	0.45 (0.36–0.54)	0.89 (0.81–0.94)	4.07 (2.40–6.91)	0.62 (0.53–0.73)	6.60 (3.53–12.34)	0.71 (0.66–0.74)		
Non-CIA	5	0.30 (0.23–0.38)	0.96 (0.84–0.99)	7.12 (1.51–33.53)	0.73 (0.63–0.86)	9.73 (1.79–52.74)	0.44 (0.40–0.49)		

AUC = area under the curve, CA125 = carbohydrate antigen 125, CIA = chemiluminescent assays, DOR = diagnostic odds ratio, EC = endometrial cancer, NLR = negative likelihood ratio, PLR = positive likelihood ratio, SEN = sensitivity, SPE = specificity.

**P* value of Meta-regression between healthy and those containing benign diseases.

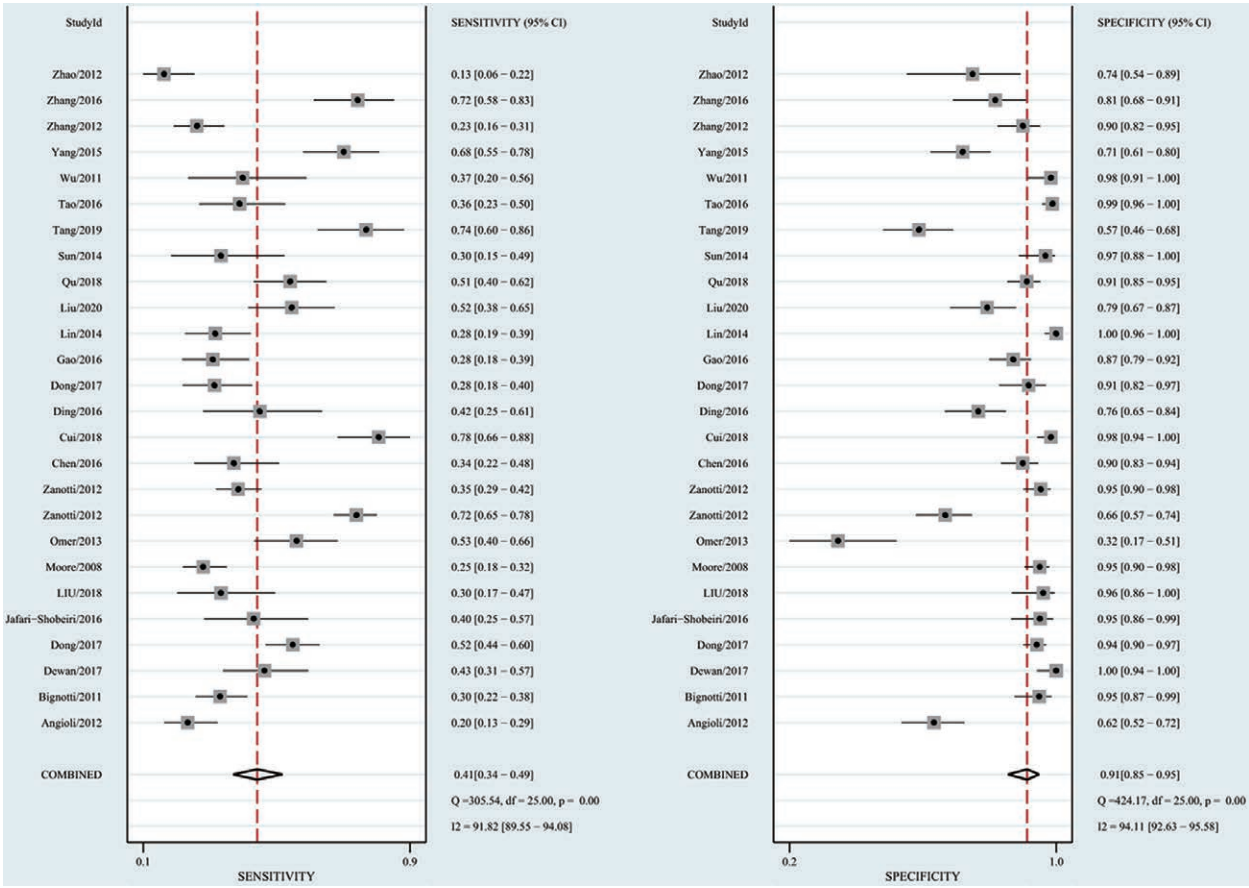

Figure 5. Forest plot of sensitivity and specificity of CA125. Left panel: sensitivity, right panel: specificity. CA125 = carbohydrate antigen 125.

Table 4

Meta-regression and subgroup analysis of diagnostic accuracy of HE4 + CA125 in EC.

Subgroup	Studies	SEN	SPE	PLR	NLR	DOR	AUC	I^2 (%)	*P*
Population								77	.01
Asia	21	0.70 (0.62–0.76)	0.89 (0.84–0.93)	6.61 (4.18–10.47)	0.34 (0.27–0.43)	19.48 (10.77–35.24)	0.86 (0.83–0.89)		
Non-Asia	4	0.55 (0.44–0.65)	0.98 (0.92–0.99)	26.59 (7.25–97.50)	0.46 (0.37–0.58)	57.35 (16.47–199.68)	0.83 (0.79–0.86)		
Design								17	.30
Prospective	11	0.65 (0.55–0.73)	0.96 (0.88–0.99)	15.63 (5.19–47.04)	0.37 (0.29–0.47)	42.47 (13.91–129.70)	0.84 (0.80–0.87)		
Retrospective	14	0.68 (0.59–0.77)	0.89 (0.83–0.93)	6.24 (3.81–10.22)	0.35 (0.27–0.47)	17.60 (9.07–34.19)	0.86 (0.83–0.89)		
Age								93	.00
≥50 yr	19	0.63 (0.57–0.70)	0.93 (0.87–0.96)	8.99 (4.73–17.11)	0.39 (0.33–0.47)	22.82 (11.48–45.35)	0.80 (0.77–0.84)		
<50 yr	4	0.80 (0.49–0.94)	0.91 (0.84–0.95)	9.00 (4.23–18.99)	0.22 (0.07–0.70)	40.28 (7.23–224.29)	0.93 (0.91–0.95)		
Control type*								22	.28
Healthy	7	0.70 (0.60–0.79)	0.95 (0.86–0.99)	15.09 (4.84–47.02)	0.31 (0.23–0.42)	48.62 (14.75–160.24)	0.87 (0.84–0.89)		
Benign disease	7	0.56 (0.46–0.66)	0.93 (0.77–0.98)	7.89 (2.37–26.33)	0.47 (0.38–0.59)	16.74 (4.70–59.55)	0.73 (0.69–0.76)		
Benign disease + Healthy	11	0.71 (0.60–0.80)	0.90 (0.83–0.94)	7.08 (4.14–12.09)	0.32 (0.23–0.45)	21.94 (11.09–43.41)	0.88 (0.85–0.91)		

AUC = area under the curve, CA125 = carbohydrate antigen 125, DOR = diagnostic odds ratio, EC = endometrial cancer, HE4 = human epididymis protein 4, NLR = negative likelihood ratio, PLR = positive likelihood ratio, SEN = sensitivity, SPE = specificity.

**P* value of Meta-regression between healthy and those containing benign diseases.

uterine diseases is difficult, so the clinical value of HE4 in identifying benign and malignant uterine diseases needs to be further explored. Test Method. In this study, the test methods of serum HE4 and CA125 included enzyme-linked immunosorbent assay, radioimmunoassay, chemiluminescent microparticle immunoassay, chemiluminescent immunoassay, and electrochemiluminescent immunoassay, with slight differences in the technique and type of antibodies used in the different methods, and possible differences in the results. Subgroup analysis of the test methods revealed that the AUC values of serum HE4 and CA125 by chemiluminescent assays (including chemiluminescent microparticle immunoassay, chemiluminescent immunoassay, and electrochemiluminescent immunoassay) were greater than those of non-chemiluminescent assays (including enzyme-linked immunosorbent assay and radioimmunoassay), indicating that chemiluminescent assays have higher SEN. Therefore, a more sensitive chemiluminescent assays may be applied clinically to improve the accuracy of serum HE4 for the diagnosis of EC. Population. Subgroup analysis of the study population revealed that the AUC value of serum HE4 was higher in non-Asian populations (mainly European and American populations) (AUC = 0.86) than in Asian populations (mainly Chinese populations) (AUC = 0.78),

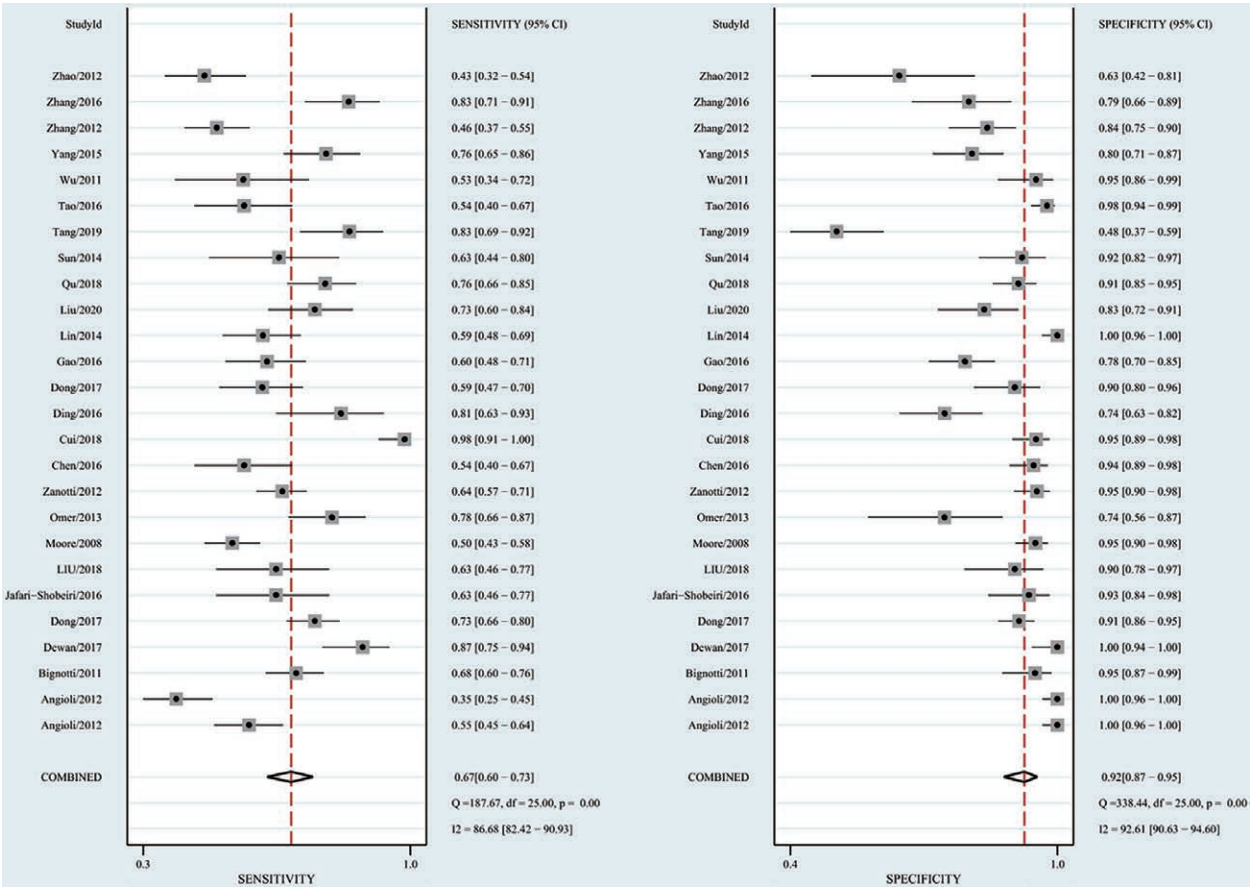

Figure 6. Forest plot of sensitivity and specificity of HE4 + CA125. Left panel: sensitivity, right panel: specificity. CA125 = carbohydrate antigen 125.

suggesting that the diagnostic accuracy of HE4 is better in non-Asian populations than in Asian populations, a conclusion similar to that of Li et al.[39] Another study showed that the overall reference value of HE4 in the Chinese apparently healthy population was 105.10 pmol/L, which is slightly lower than the HE4 level (140 pmol/L) in Western apparently healthy women,[40] while the range of HE4 reference values in most of the included studies refer to the European and American populations, which may be one of the sources of heterogeneity. Age of case group. It has been shown that serum HE4 levels increase with age, and postmenopausal women have higher serum HE4 levels than premenopausal women.[41] The risk of developing EC increases with age, and more than 90% of patients develop the disease at the age of 50 years or older. Therefore, a subgroup analysis was performed to compare the AUC values of the included studies using the mean age of 50 years as the cutoff for EC patients, and it was found that the diagnostic accuracy of all 3 tests was higher in patients with a mean age of <50 years than in patients with a mean age of more than 50 years. The diagnostic value of HE4 alone or in combination with CA125 was also found to be better than that of CA125 in the group with a mean age of 50 years or older, but in the group with a mean age of <50 years, HE4 alone was comparable to CA125, with an AUC of 0.83 for both. These differences may be due to the fact that most of the included studies used a uniform reference range established by the reagent manufacturers when setting the threshold for HE4, without taking into account the effect of age on HE4. Therefore, in clinical application, it may be necessary to develop appropriate serum HE4 threshold levels for patients of different ages to improve its diagnostic accuracy for EC. Other factors. Serum HE4 levels are significantly associated with impaired renal function and are the most common cause of elevated HE4 levels in patients with benign uterine disease.[42] In addition, serum HE4 levels were 29% higher in smokers than in nonsmokers, and women with a body mass index of 30 kg/m^2 had lower serum HE4 levels than those with a body mass index of 25 kg/m^2.[42] However, information describing the above factors was not available in most of the included studies and therefore the source of heterogeneity could not be explored further.

Limitations of this study: The heterogeneity of the included studies was significant, and Meta-regression analysis was performed to find many sources of heterogeneity, so the reliability of the results needs to be further confirmed by more homogeneous studies. The majority of the included studies were retrospective and single-center studies, which may have led to selection bias. Only a few studies analyzed the diagnostic value of HE4 or CA125 in different clinical stages and pathological types, so they were not analyzed for comparison. There were no uniform norms for HE4 cutoff values in the included studies, as individualized thresholds were developed by combining stages, subtypes and physiological factors. Most of the included populations were Asian, and the conclusions lacked more data support from non-Asian populations.

In recent years, in addition to biomarkers, molecular diagnosis has also been widely used in the exploration of minimally invasive early screening of EC. At present, the most studied are the PapSEEK detection using endometrial exfoliated cells for the common mutant genes and aneuploidies of EC, and the methylation detection using endometrial exfoliated cells for the common DNA methylation characteristics of EC.[43,44] The SEN of PapSEEK detection combined with Tao Brush uterine cavity brush to obtain endometrial cells was 93% (114/123), and the SPE was 100% (0/125). PapSEEK detection using intrauterine lavage fluid specimens combined with next-generation sequencing technology may achieve higher detection efficiency. It is conceivable that the detection of molecular diagnosis combined with CA125 and HE4 may further improve the accuracy of the diagnosis of EC. This view will be the focus of the research on the diagnosis of EC.

In conclusion, serum HE4 is the most promising biomarker for the diagnosis of EC. Without considering clinical stage and pathological type, HE4 alone or combined with CA125 showed better diagnostic efficacy, and HE4 + CA125 had slightly higher diagnostic efficacy than HE4, but did not show significant advantages. In clinical application, to further improve the diagnostic accuracy of serum HE4 for EC, individualized threshold levels should be developed by taking the influence of test methods, population, and age on serum HE4 levels into account, or by combining the above factors to develop relevant algorithms. However, there was a large heterogeneity in this Meta-analysis, so the credibility of the conclusions requires further confirmation by more homogeneous, prospective, and large sample size studies. In addition, with the rise of molecular diagnosis, the combination of multiple detection methods may provide new ideas for the diagnosis of EC.

Author contributions

Data curation: Qi Wu, Su-ning Bai, Li-yun Song, Wen-fei Wu.
Investigation: Su-ning Bai.
Methodology: Qi Wu, Su-ning Bai, Li-yun Song.
Software: Qi Wu, Wen-fei Wu, Lina Han.
Writing – original draft: Qi Wu, Li-yun Song, Wen-fei Wu.
Writing – review & editing: Qi Wu, Lina Han.

References

[1] Siegel R, Ward E, Brawley O, et al. Cancer statistics, 2011. CA Cancer J Clin. 2011;61:212–36.
[2] Colombo N, Creutzberg C, Amant F, et al. ESMO-ESGO-ESTRO consensus conference on endometrial cancer: diagnosis, treatment and follow-up. Ann Oncol. 2016;27:16–41.
[3] Lu KH, Broaddus RR. Endometrial cancer. Reply. N Engl J Med. 2021;384:586.
[4] ACOG committee opinion No. 734 summary: the role of transvaginal ultrasonography in evaluating the endometrium of women with postmenopausal bleeding. Obstet Gynecol. 2018;131:945–6.
[5] Buamah P. Benign conditions associated with raised serum CA-125 concentration. J Surg Oncol. 2000;75:264–5.
[6] Abdalla N, Pazura M, Słomka A, et al. The role of HE4 and CA125 in differentiation between malignant and non-malignant endometrial pathologies. Ginekol Pol. 2016;87:781–6.
[7] Li J, Dowdy S, Tipton T, et al. HE4 as a biomarker for ovarian and endometrial cancer management. Expert Rev Mol Diagn. 2009;9:555–66.
[8] Degez M, Caillon H, Chauviré-Drouard A, et al. Endometrial cancer: a systematic review of HE4, REM and REM-B. Clin Chim Acta. 2021;515:27–36.
[9] 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;155:529–36.
[10] Angioli R, Plotti F, Capriglione S, et al. The role of novel biomarker HE4 in endometrial cancer: a case control prospective study. Tumor Biol. 2013;34:571–6.
[11] Bignotti E, Ragnoli M, Zanotti L, et al. Diagnostic and prognostic impact of serum HE4 detection in endometrial carcinoma patients. Brit J Cancer. 2011;104:1418–25.
[12] Chen Y, Wu X, Chen M. Clinical value of combined detection of HE4, CA125 in application of endometrial carcinoma. Hainan Med J. 2016;27:1054–6.
[13] Cui P, Zhang Y, Han B, et al. Clinical significance of serum CA125 and HE4 tests in endometrial cancer. Mod Digest Intervention. 2019;0:905.
[14] Dewan R, Dewan A, Hare S, et al. Diagnostic performance of serum human epididymis protein 4 in endometrial carcinoma: a pilot study. J Clin Diagnostic Res. 2017;11:C1–5.
[15] Ding W, Li Y, Zhu Y. Clinical value of human epididymal protein 4 in the diagnosis of endometrial carcinoma in atypical endometrial hyperplasia patients. J Int Obstet Gynecol. 2016;43:165–8.
[16] Dong C, Liu P, Li C. Value of HE4 combined with cancer antigen 125 in the diagnosis of endometrial cancer. Pak J Med Sci. 2017;33:1013–7.
[17] Dong D, Gu J, Zhao S. Changes and significance of serum HE4 and CA125 levels in patients with endometrial carcinoma. Shandong Med J. 2017;57:73–5.
[18] Gao D. Clinical value of combined detection of serum human epididymal secretory protein E4 and cancer antigen 125 in diagnosis of endometrial carcinoma. J Med Forum. 2016;37:49–52.
[19] Jafari-Shobeiri M, Jangi M, Tabrizi AD, et al. Diagnostic value of novel biomarker human epididymis protein 4 (HE4) in detecting endometrial cancer. Int J Women's Health Reprod Sci. 2016;4:29–33.
[20] Lin Y, Chen Y, Hu M, et al. Diagnostic and prognostic value of serum HE4 detection for endometrial carcinoma patients compared with CA 125. Curr Immunol. 2014;34:47–51.
[21] Liu JL, Gao XL, Hou CZ, et al. Diagnostic significance of changes in serum human epididymis epithelial secretory protein 4 and carbohydrate antigen 125 in endometrial carcinoma patients. Acta Med Mediterr. 2018;34:785–9.
[22] Liu T. Value of combined detection of three serum tumor markers in diagnosis of endometrial cancer. Int Med Health Guidance News. 2020;26:1093–6.
[23] Moore RG, Brown AK, Miller MC, et al. Utility of a novel serum tumor biomarker HE4 in patients with endometrioid adenocarcinoma of the uterus. Gynecol Oncol. 2008;110:196–201.
[24] Omer B, Genc S, Takmaz O, et al. The diagnostic role of human epididymis protein 4 and serum amyloid-A in early-stage endometrial cancer patients. Tumour Biol. 2013;34:2645–50.
[25] Qu J, Liu G, Wang X. The values of the combined detection of CA125, CA153 and HE4 in diagnosis of endometrial carcinoma. Oncol Progress. 2018;16:1903–6.
[26] Sun S, Xiao X, Zhang D. Clinical value of combined detection of CA125 and HE4 in diagnosis of endometrial carcinoma. Heilongjiang Med Pharm. 2014;37:2–3.
[27] Tang X, Yi T, Liu D. Clinical value of serum human epididymis protein E4 combined with cancer antigen 125 in the diagnosis of endometrial cancer. Contemp Med. 2019;25:1–3.
[28] Tao W. Clinical value of human epididymis protein 4 and CA125 joint detection in diagnosis of endometrial cancer. J Medi Forum. 2016;37:25–7.
[29] Wu F, Zhou H, Cui M. Clinical value of combined detection of CA125 and HE4 in diagnosis of endometrial cancer. Matern Child Health Care China. 2011;26:1559–61.
[30] Yang Q. Diagnostic value of HE4 and tumor markers in endometrial cancer. J Clin Med Pract. 2015;19:220–2.
[31] Zanotti L, Bignotti E, Calza S, et al. Human epididymis protein 4 as a serum marker for diagnosis of endometrial carcinoma and prediction of clinical outcome. Clin Chem Lab Med. 2012;50:2189–98.
[32] Zhang A, Zhang P. Clinical value of combined detection of serum human epididymal secretory protein E4 and CA125 in the diagnosis of endometrial carcinoma. Chin J Obstet Gynecol. 2012;47:125–8.
[33] Zhang C. Clinical significance on detection of HE4 combined with CA125 in patients' serum with gynecologic oncology. Genomics Appl Biol. 2016;35:1604–7.
[34] Zhao L, Chen X, Chen L, et al. Differential diagnostic value of combined detection of serum HE4 and CA125 in patients with endometrial carcinoma from benign uterus tumor. China Oncol. 2012;22:820–4.
[35] Chen Y, Ren YL, Li N, et al. Serum human epididymis protein 4 vs. carbohydrate antigen 125 and their combination for endometrial cancer diagnosis: a meta-Analysis. Eur Rev Med Pharmacol. 2016;20:1974–85.
[36] Pepe MS, Feng Z, Janes H, et al. Pivotal evaluation of the accuracy of a biomarker used for classification or prediction: standards for study design. J Natl Cancer Inst. 2008;100:1432–8.
[37] Walter SD. Properties of the summary receiver operating characteristic (SROC) curve for diagnostic test data. Stat Med. 2002;21:1237–56.
[38] Behrouzi R, Barr CE, Crosbie EJ. HE4 as a biomarker for endometrial cancer. Cancers. 2021;13:4764.
[39] Li J, Wang X, Qu W, et al. Comparison of serum human epididymis protein 4 and CA125 on endometrial cancer detection: a meta-analysis. Clin Chim Acta. 2019;488:215–20.
[40] Tian Y, Wang C, Cheng L, et al. Determination of reference intervals of serum levels of human epididymis protein 4 (HE4) in Chinese women. J Ovarian Res. 2015;8:72.
[41] Cheng HY, Zeng L, Ye X, et al. Age and menopausal status are important factors influencing the serum human epididymis secretory protein 4 level: a prospective cross-sectional study in healthy Chinese people. Chin Med J (Engl). 2020;133:1285–91.
[42] Bolstad N, Øijordsbakken M, Nustad K, et al. Human epididymis protein 4 reference limits and natural variation in a Nordic reference population. Tumour Biol. 2012;33:141–8.
[43] Den Helder RV, Wever BM, van Trommel JA, et al. DNA methylation markers for endometrial cancer detection in minimally invasive samples: a systematic review. Epigenomics. 2020;12:1661–72.
[44] Wang Y, Li L, Douville C, et al. Evaluation of liquid from the Papanicolaou test and other liquid biopsies for the detection of endometrial and ovarian cancers. Sci Transl Med. 2018;10:eaap8793.