European Review for Medical and Pharmacological Sciences 2016; 20: 1974-1985

Serum human epididymis protein 4 *vs.* carbohydrate antigen 125 and their combination for endometrial cancer diagnosis: a meta-analysis

Y. CHEN[1], Y.-L. REN[2], N. LI[3], X.-F. YI[1], H.-Y. WANG[2]

[1]Department of Obstetrics and Gynecology, Obstetrics and Gynecology Hospital of Fudan University, Huangpu District, Shanghai, China
[2]Department of Gynecologic Oncology, Fudan University Shanghai Cancer Center, Xuhui District, Shanghai, China
[3]Department of Ultrasound, Fudan University Shanghai Cancer Center, Xuhui District, Shanghai, China

Abstract. – OBJECTIVE: Cancer antigen 125 (CA125) and Human epididymis protein 4 (HE4) appear to be promising predictors for endometrial cancer (EC). However, conflicting results exist in the diagnostic performance comparison among CA125 and HE4.

MATERIALS AND METHODS: A systematic review was conducted using PubMed, EMBASE and other databases till December 2015. All studies included were closely assessed with the QUADAS. Diagnostic value of HE4, CA125 and HE4+CA125 was systematically evaluated, and comparison among the predictive performances of HE4, CA125 were conducted. Sensitivity, specificity, DOR (diagnostic odds ratio), and area under the SROC curve were summarized with a random model. Meta-regression was used to explore the heterogeneity.

RESULTS: 8 studies including 1832 cases (1129 in the study group and 703 in the control group) were included in our meta-analysis. Mean estimates of HE4 and their 95% CIs were: sensitivity 0.53 (95% CI: 0.50-0.56), specificity 0.91 (95% CI: 0.89-0.93), DOR 17.01 (95% CI: 7.88-36.72). The area under the SROC curve of HE4 in the diagnosis of EC was 0.77. However, CA125 had lower sensitivity, specificity, DOR, and the area under the SROC in diagnosis of EC with sensitivity 0.26 (95% CI: 0.24-0.29), specificity 0.81 (95% CI: 0.78-0.84), DOR 2.61 (95% CI: 0.92-7.41), and the area under the SROC 0.37. In patients with EC diagnosed by HE4+CA125, the overall sensitivity was 0.58 (95% CI: 0.54-0.62) and a specificity of 0.92 (95% CI: 0.89-0.94) in predicting EC. DOR and the area under the SROC curve of HE4+CA125 for diagnosis of EC were 21.86 (95% CI: 11.08-43.15) and 0.83 respectively, which showed a higher level of diagnostic accuracy than HE4 alone.

CONCLUSIONS: HE4 is helpful for distinguishing EC from healthy and benign disease. CA125 is not better than HE4 either for EC diagnosis. HE4+CA125 is promising a predictor of EC to replace He4, but its utilization requires further exploration.

Key Words:
Epididymis protein 4, Carbohydrate antigen 125, Endometrial cancer, Meta-analysis.

Introduction

Endometrial cancer (EC) is the most common gynecological malignancy in the China and Western world[1]. Generally, patients with EC have a favorable prognosis because most patients are diagnosed early because of postmenopausal bleeding[2]. However, EC's high incidence, as well as the poor prognosis in patients with advanced stage, demonstrates the need to identify accuracy diagnostic biomarkers for EC[3]. One or more markers that could identify the high-risk persons who would benefit from lymphadenectomy and more extensive surgery performed by specialized gynecologic oncologists[4].

CA125 is indicated for use as an aid in the detection of residual ovarian carcinoma in patients who have undergone first-line therapy. In addition, serum CA125 levels elevated in various benign gynecological diseases (including EC)[5,6] and non-gynecologic malignancies[7]. Elevated serum CA125 levels were originally described in patients with recurrent and advanced EC by Niloff

Corresponding Author: Xiao-Fang Yi, MD; e-mail: xyi@fudan.edu.cn
Hua-Ying Wang, MD; e-mail: wanghuaying270@163.com

et al in 1984[8]. Afterwards, several researchers described elevations in CA125 levels in primary and recurrent EC patients[9]. However, recent studies have focused on the limitations in CA125 due to the fact that serum concentrations are elevated in only 10-20% women with early stage EC[10,11]. CA125 alone cannot be considered for the diagnosis of endometrial cancer.

Human epididymis protein 4 (HE4) is found in blood and overexpressed in patients with ovarian and uterine cancer[12]. Preliminary figures have shown elevated serum levels of HE4 in EC patients, identifying interest in HE4 as an EC biomarker[13]. With the difference to CA125, HE4 does not overexpress in endometriosis and other benign gynecological diseases[14]. But, more importantly, there was evidence that the diagnostic efficacy of HE4 alone for the diagnosis of endometrial cancer was superior to CA125. However, conflicts arise on the sensitivity of HE4[15], and the diagnostic accuracy of HE4 alone is still controversial[16].

As we all known, combinations of biomarkers improve the sensitivity or specificity in diagnosis for several malignancies. However, only a few studies[17] have combined levels of HE4 and CA125 between patients with EC and healthy controls. To our knowledge, no meta-analysis has combined values for these two markers in the diagnostic accuracy assessment in EC patients.

The aim of this study was to evaluate whether HE4 and CA125, alone or combined, was suitable for the diagnosis of endometrial cancer. Therefore, we performed this meta-analysis of the available evidence on screening accuracy of HE4 and CA125. We suggest that HE4 alone for the diagnosis of endometrial cancer than CA125, and their combination is able to further enhance the diagnostic efficiency.

Materials and Methods

Literature search Strategy

In a comprehensive electronic searching of PubMed, EMBASE, Web of Science and the Cochrane Database, two investigators independently carried many articles up to date December 31, 2015. Keywords used in the search process is as follows: ("endometrial cancer" OR "endometrial neoplasm" OR "endometrium carcinoma" OR "endometri*") AND ("HE4"OR"human epididymis protein 4" OR "human epididymis secretory protein 4"AND ("carbohydrate antigen 125" or "CA125"or"CA-125"). In addition, we pay the relevant articles to determine related information is not to be missed and we manually search for a reference list of articles selected to determine the more relevant publications.

Criteria for Inclusion and Exclusion of Published Studies

Inclusion criteria was as follows: (1) Only articles published in English were included; (2) The primary aim of the study was at least the report of HE4, CA125 and the combination in sensitivity and specificity versus the 'gold standard' method for EC diagnosis, which is histological evaluation of biopsy material. (3) Have the availability of information on for both EC patients and Control groups. (4) Diagnostic parameters were estimated according to a decisional threshold level and not to a fixed specificity or sensitivity. Papers were excluded in the following instances: (1) Duplicative results from the same authors' group were being reported.(2) Serum HE4 or CA125 levels were measured to monitor EC progression or the effect of therapy.(3) Only case reports.

Data Extraction

Data extracted by two independent investigators from the article encountered was in accordance with the inclusion and exclusion criteria. The following data extracted from the study included as follows: "Study Design, Endometrial Cancer and control group, Test Indicators and cutoff values and Test methods". Any differences on data extraction were solved by a third independent investigator. The process of study selection was shown in Figure 1.

Quality Assessment

The quality of the selected studies was assessed according to the QUADAS criteria. A score of 1 was given when a specific item was fulfilled, 0 if this item was unclear, and −1 for the item not achieved. Any article with a QUADAS score < 8 was excluded based on inadequate methodological quality.

Statistical Analysis

Statistical analysis was used by the MetaDisc 1.4 (Cochrane Colloquium; Barcelona, Spain). Cochran Q test and I^2 Heterogeneity was used to estimate the value of including research. Heterogeneity analysis was taken using Spearman's correlation analysis, checking threshold effects,

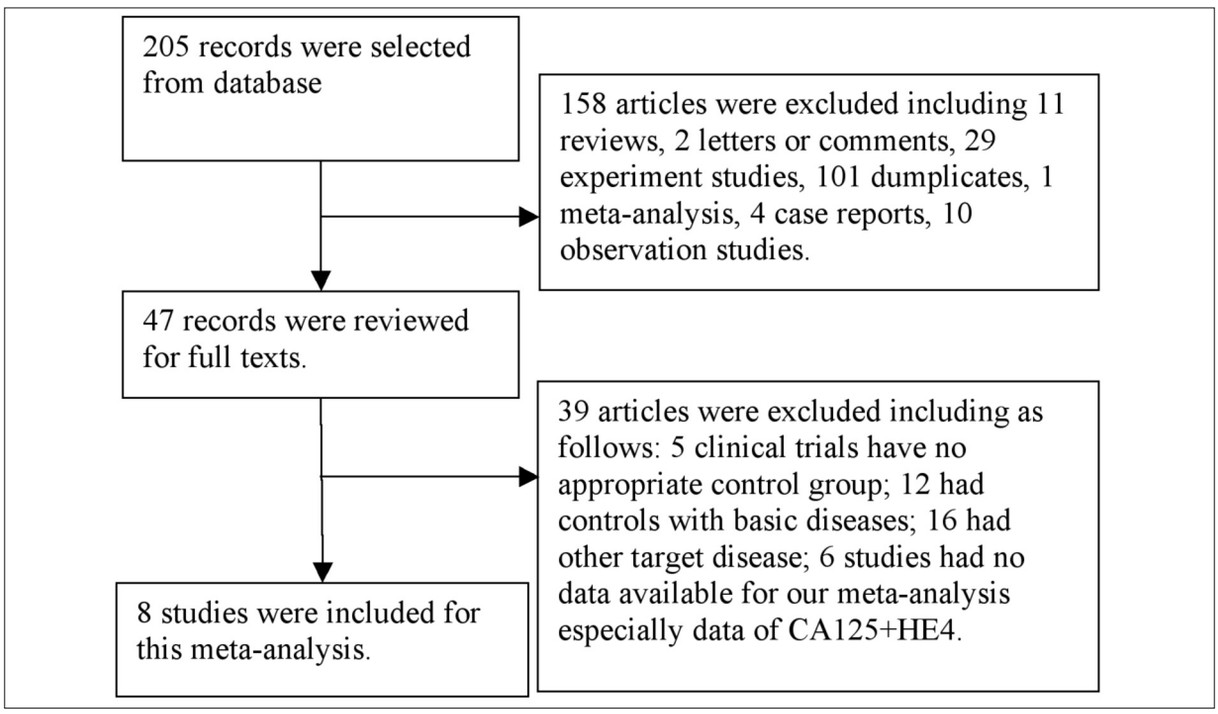

Figure 1. Flow diagram of study selection for our meta-analysis.

which described the proportion of total variation observed between each study. We extracted the original data from each study and evaluated the overall sensitivity, specificity, and diagnostic odds ratio (DOR). A summary receiver operation characteristic (SROC) curve was generated by MetaDisc 1.4 to assess the diagnostic accuracy, and to calculate the area under the curve (AUC). Publication bias was evaluated by Begg's test.

Results

Study Selection Process

A total of 205 potentially relevant articles were determined by searching PubMed and EMBASE and other databases. After reviewing their titles and abstracts, 158 articles were excluded, including repeated studies, case reports, expert commentary and observational studies. After reviewing the full text, some studies or meta-analysis not related to our study design were excluded, but also some studies lack of sufficient data to estimate the sensitivity and specificity of HE4 and CA125 in the diagnosis of EC, and not meeting the study group and the control group inclusion criteria. In searching for all the references in the study included, we found no articles met our inclusion criteria. Finally, eight studies were included in our meta-analysis (Figure 1). Characteristics contained the study as shown in Table I, including 1832 cases (1129 in the study group and 703 in the control group)[18-25]. Five studies[18-22] with 883 cases compared the diagnosis of performance in HE4, CA125 alone and HE4+CA125 for EC. And 3 studies[23-25] compared the clinical and prognostic performance between HE4 and CA125 in EC. The quality of including literatures was satisfactory according to the assessment score of QUADAS.

Performance Comparison Between HE4 and CA125

Forest plots of sensitivity, specificity and diagnostic odds ratio (DOR) of HE4 for diagnosis of EC were shown in Figure 2-4. Mean estimates and their 95%CIs were: sensitivity 0.53 (95% CI: 0.50-0.56), specificity 0.91 (95% CI: 0.89-0.93), DOR 17.01 (95% CI: 7.88-36.72). High level of heterogeneity lay in sensitivity ($I^2 = 90.0\%$), specificity ($I^2 = 91.2\%$) and DOR (I2 = 75.3%). Threshold effect existed (Spearman correlation coefficient = 0.667, $p = 0.071$). Thus, the random model was used to pool estimates. SROC plots showed the summary estimates of sensitivity and specificity (shown in Figure 5) and the area under the

Table I. Summary of the 8 trials included in our meta-analysis.

Authors	Year	Study design	Endometrial cancer group	Control group	Types of the control	Test indicators and cutoff values	Test methods	Reference
Moore RG, et al	2008	Prospective	171	156	Healthy	HE4+CA125 the cutoff values is not reported	Not reported	[18]
Bignotti E, et al	2011	Prospective	138	76	Healthy	HE4+CA125 the cutoff values is not reported	ELISA and CMIA	[19]
Zanotti L, et al	2012	Retrospective	193	125	Healthy	HE4: 63.5 pmol/L CA125: 24.8 U/mL	CMIA	[20]
Angioli R, et al	2013	Prospective	101	103	Benign disease	HE4: 70 pmol/L; CA125: 35 U/mL	ELISA and RIA	[21]
Omer B,et al	2013	Prospective	64	94	Benign disease + Healthy	HE4: 59.7 pmol/L CA125: 14.2 U/mL	ECLIA	[22]
Antonsen SL, et al	2013	Prospective	335	17	Benign disease	HE4: 70 pmol/L; CA125: 35 U/mL	CMIA	[23]
Presl J,et al	2014	Prospective	34	32	Healthy	HE4: 90 pmol/L; CA125: 35 U/mL	CMIA	[24]
Liu X, et al	2015	Prospective	93	100	Healthy	HE4: 150 pmol/L; CA125: 35 U/mL	ELISA and CMIA	[25]

CMIA, chemiluminescent microparticle immunoassay; ECLIA, electrochemiluminescent immunoassay; ELISA, enzyme-linked immunosorbent assay.

SROC curve of HE4 in the diagnosis of EC was 0.77. However, CA125 had lower sensitivity, specificity and DOR in diagnosis of EC with sensitivity 0.26 (95% CI: 0.24-0.29), specificity 0.81 (95% CI: 0.78-0.84) and DOR 2.61(95% CI: 0.92-7.41). There were also high level of heterogeneity in sensitivity (I^2 = 82.4%), specificity (I^2 = 96.6%) and DOR (I2 = 90.8%) (Figures 6 to 8) with threshold effect existed (Spearman correlation coefficient = -0.095, p = 0.823). SROC plots showed the summary estimates of the area under the SROC curve of CA125 in the diagnosis of EC was 0.37 (Figure 9) that was much lower than HE4 in the diagnosis of EC.

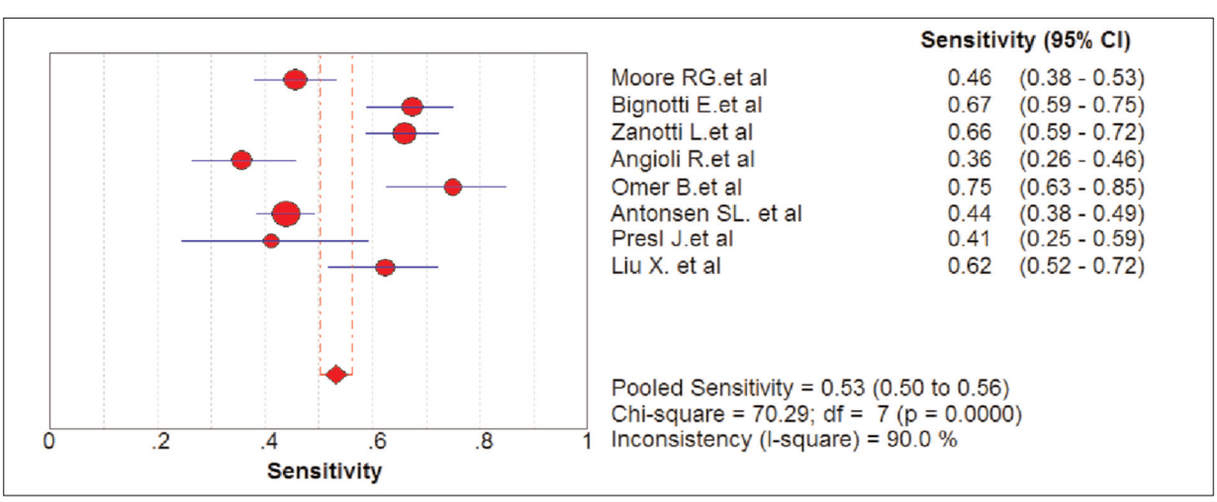

Figure 2. Forest plot of estimate of sensitivity using HE4 in diagnosis of EC.

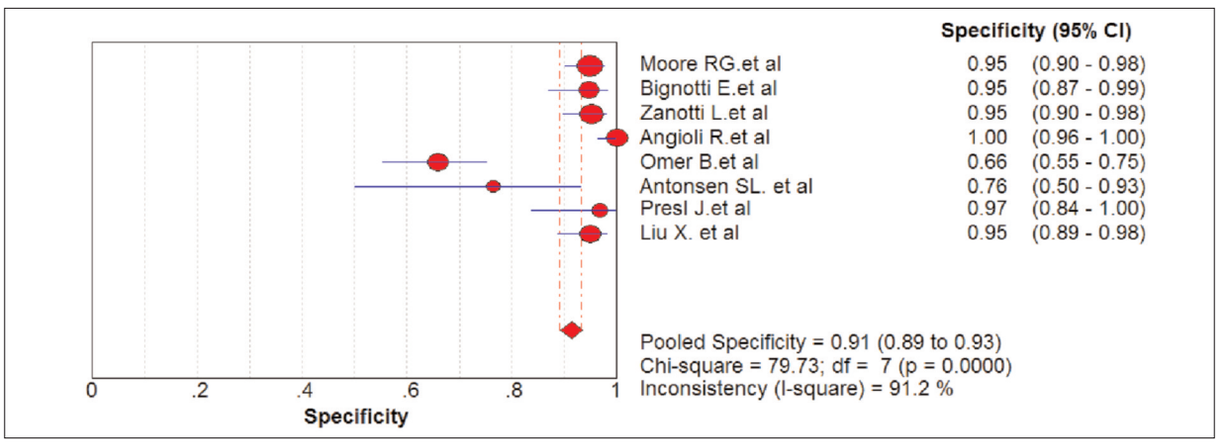

Figure 3. Forest plot of estimate of specificity using HE4 in diagnosis of EC.

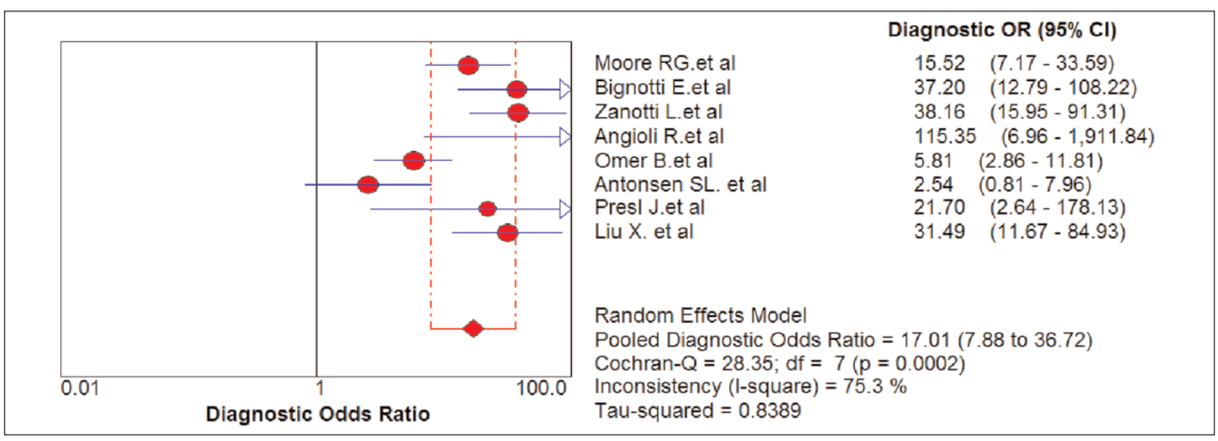

Figure 4. Forest plot of estimate of DOR using HE4 in diagnosis of EC.

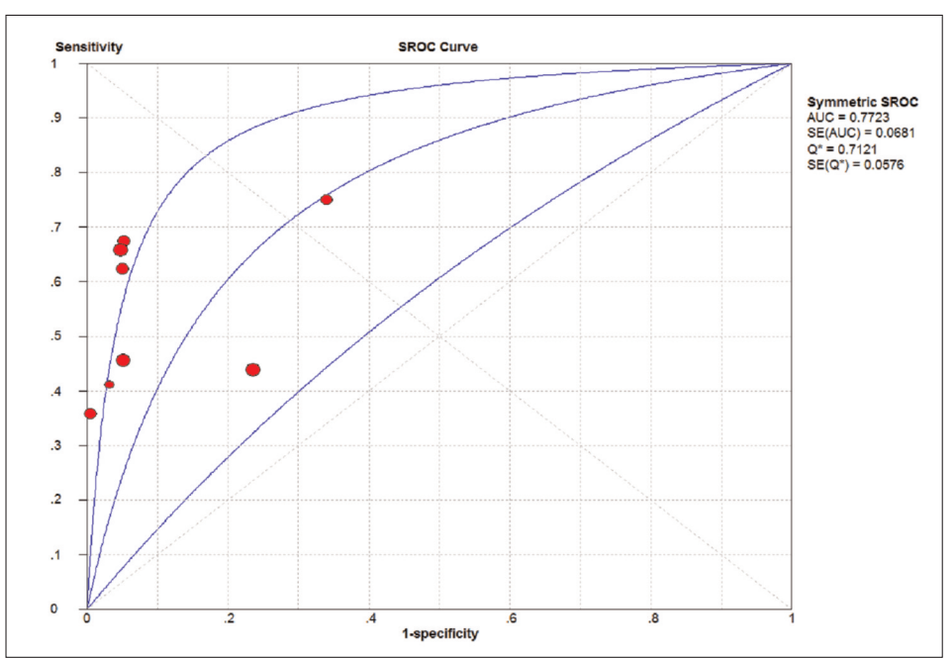

Figure 5. Estimate of SROC using HE4 in diagnosis of EC.

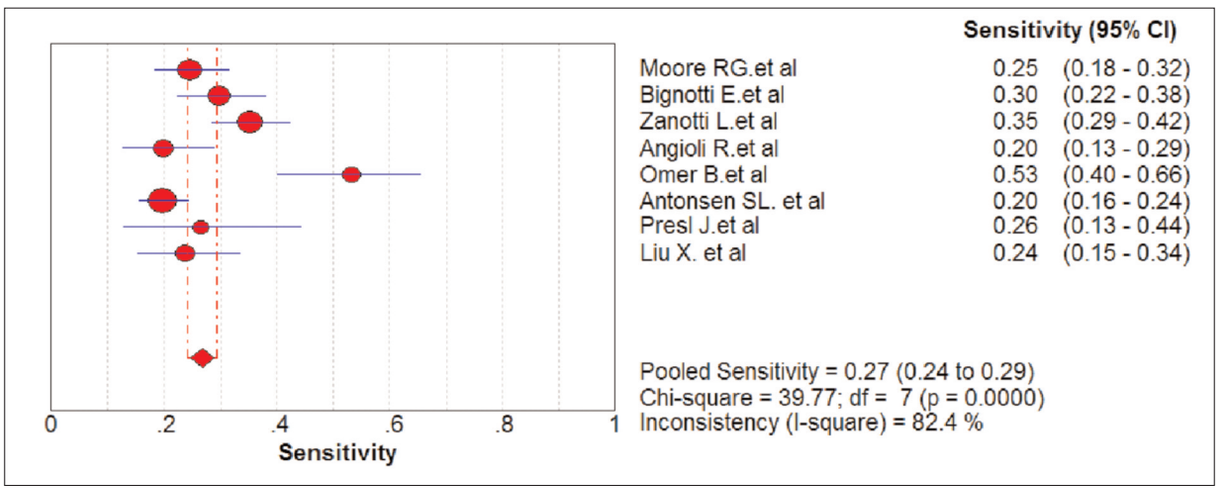

Figure 6. Forest plot of estimate of sensitivity using CA125 in diagnosis of EC.

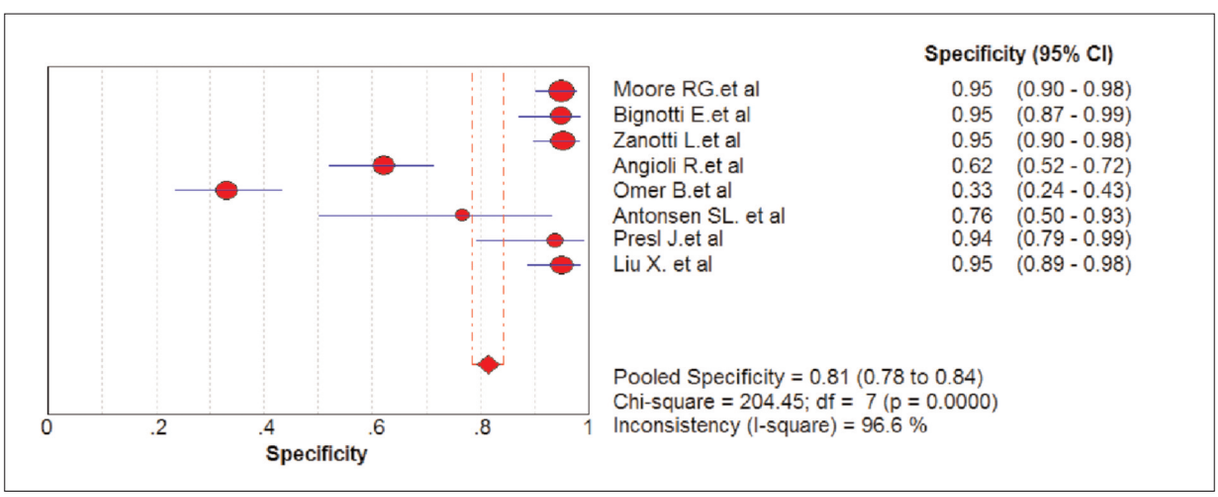

Figure 7. Forest plot of estimate of specificity using CA125 in diagnosis of EC.

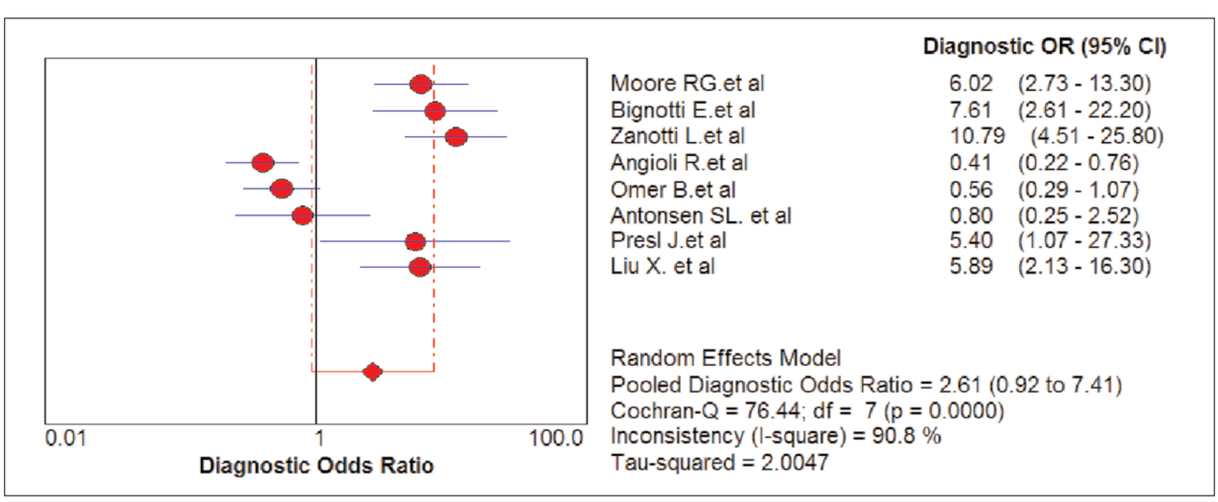

Figure 8. Forest plot of estimate of DOR using CA125 in diagnosis of EC.

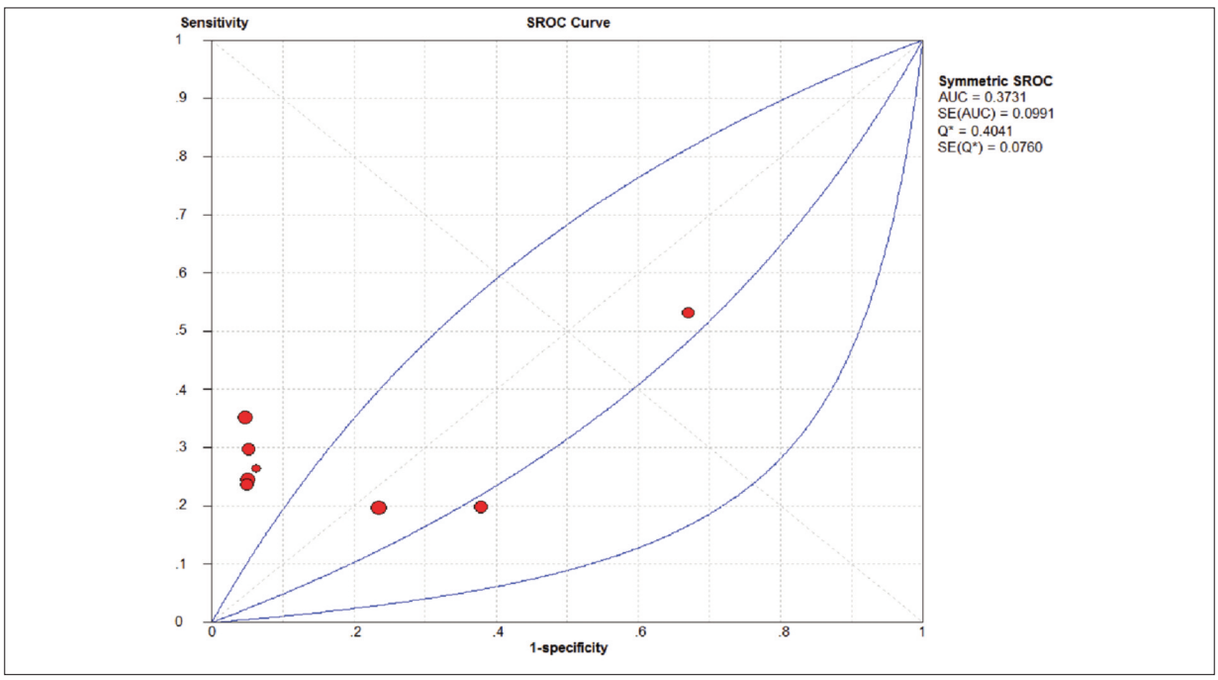

Figure 9. Estimate of SROC using HE4 in diagnosis of EC.

Performance of HE4 Plus CA125 in Diagnosis of EC

In patients with EC diagnosed by HE4+CA125, the overall sensitivity was 0.58 (95% CI: 0.54-0.62) and a specificity of 0.92 (95% CI: 0.89-0.94) in predicting EC. As a result of I^2 = 91.7% in sensitivity and I^2 = 92.5% in specificity, the random model was used to estimate. In this meta-analysis, DOR and the area under the SROC curve of HE4+CA125 for diagnosis of EC were 21.86 (95% CI: 11.08-43.15) and 0.83 respectively, which showed a higher level of diagnostic accuracy than HE4 alone. Sensitivity, specificity, DOR, and the area under the SROC curve in the individual study were shown in Figures 10 to 13.

Meta-Regression

Due to the heterogeneity caused by non-threshold effect from the analysis above, in vari-

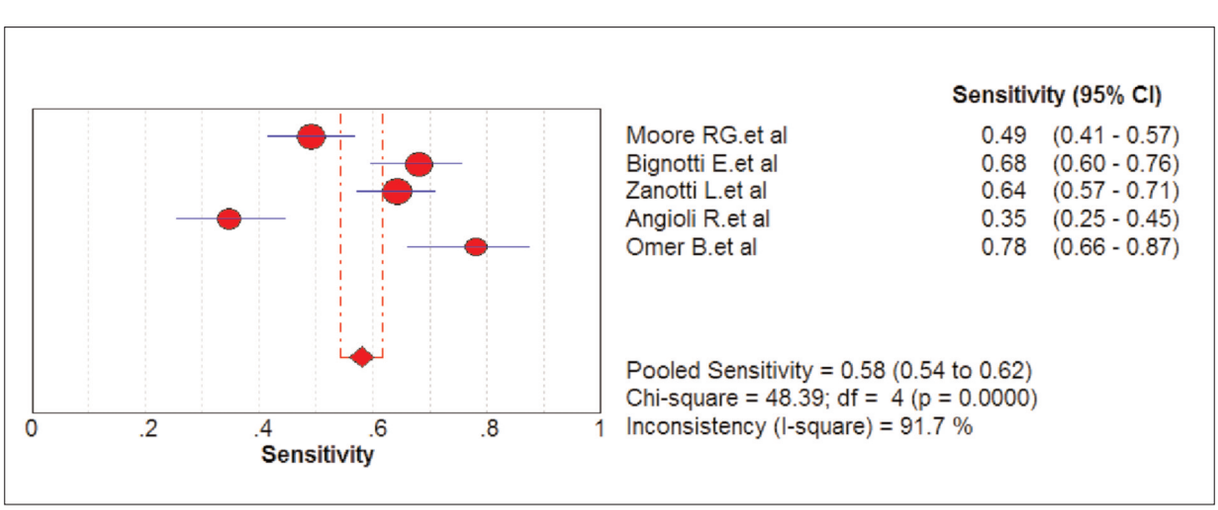

Figure 10. Forest plot of estimate of sensitivity using HE4+CA125 in diagnosis of EC.

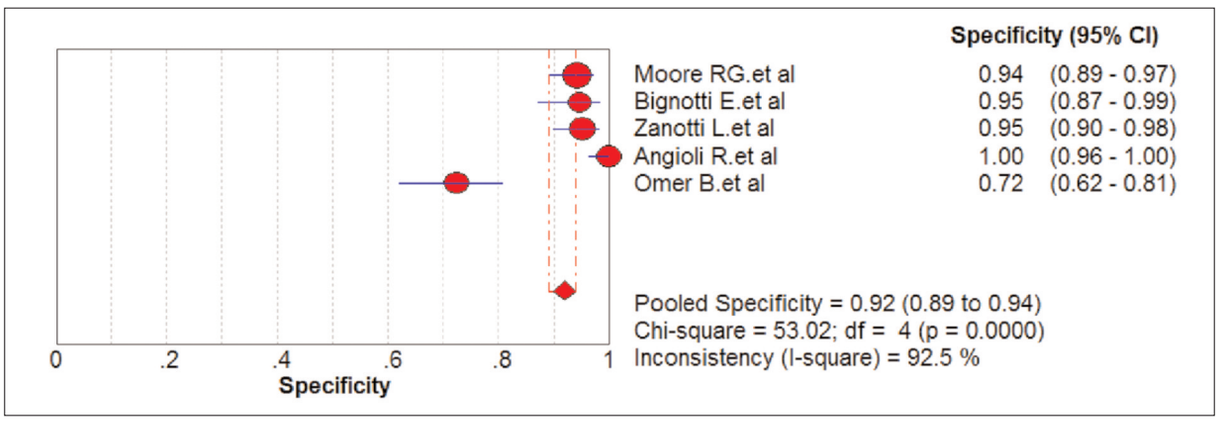

Figure 11. Forest plot of estimate of specificity using HE4+CA125 in diagnosis of EC.

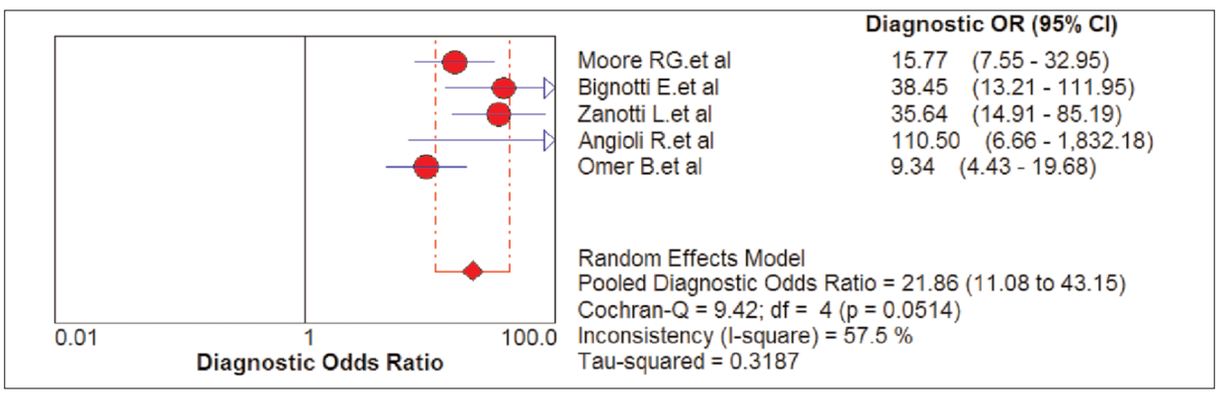

Figure 12. Forest plot of estimate of DOR using HE4+CA125 in diagnosis of EC.

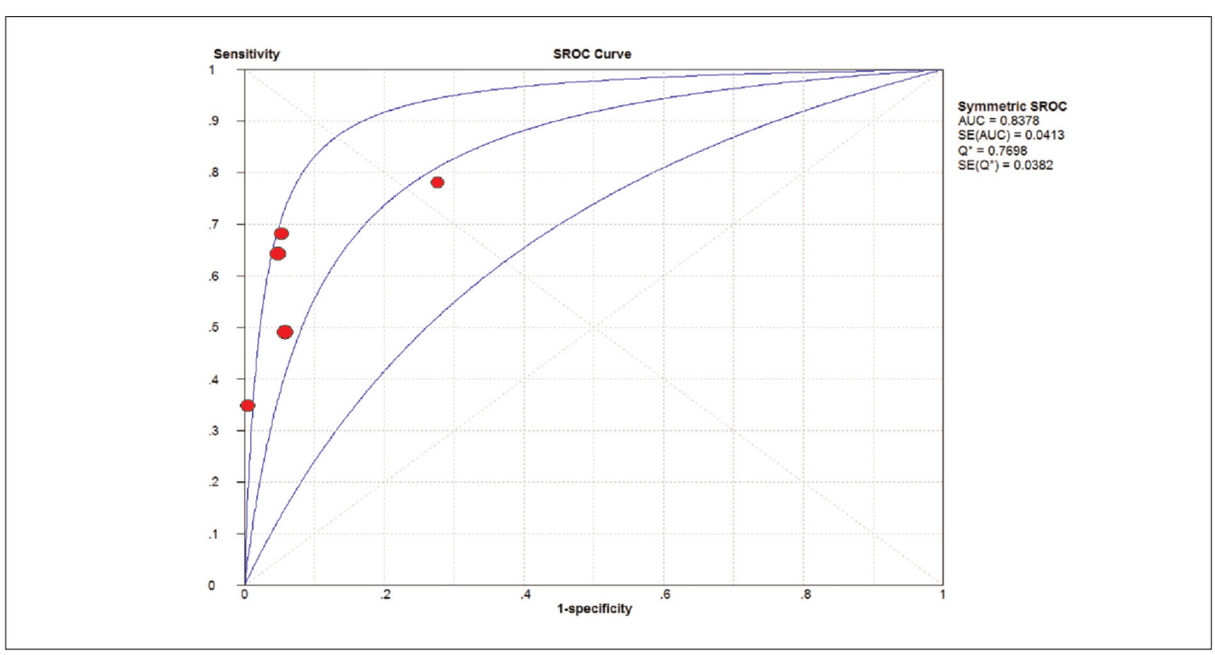

Figure 13. Estimate of SROC using CA125+HE4 in diagnosis of EC.

Table II. Meta-regression of the potential risk factors affecting the diagnostic accuracy of EC.

Covariates	Coefficient (SE)	RDOR	95% CI	*p*-value
Study design	1.048	2.85	(0.01, 1614.88)	0.55
Test methods*	0.390	1.48	(0.00, 2393.22)	0.84
QUADAS**	-0.422	0.66	(0.00, 132.06)	0.76
Typeofcontro ***	-0.245	0.78	(0.01, 60.54)	0.78

*Test methods was divided into CMIA and others. **QUADAS was divided into ≥ 10 and < 10 score. ***Types of control was divided into Healthy, Benign disease and Healthy + Benign disease.

ous studies, QUADAS scores, type of control, test methods, etc. might affect the diagnostic value. Therefore, meta-regression analysis was used to explore sources of this heterogeneity. However, there were no such covariates significantly affecting the accuracy of diagnosis (all $p > 0.05$) (shown in Table II) in this study.

Publication Bias

Begg's test was used to evaluate publication bias among these studies. The slope coefficient of the regression line had a *p*-value of 0.65, which indicated that our meta data did not have a likelihood of publication bias (Figure 14).

Discussion

Endometrial carcinoma is the most common gynecologic malignancy in the developed countries. Endometrial carcinoma has generally a good prognosis, mainly because the majority of patients presented with postmenopausal bleeding. The treatment of endometrial carcinoma is surgical staging, including a hysterectomy, bilateral salpingo-oophorectomy, peritoneal fluid sampling, and a pelvic and periaortic lymphadenectomy[26]. However, the need for a routine lymphadenectomy recently has been debated in the case of the low-risk or stage IA disease. Therefore, an accurate serum marker for screening and early diagnosis would certainly be useful for those patients that may experience an increased risk of developing EC, such as those with severe obesity and diabetes, PTEN gene defects and so on[27].

Cancer antigen 125 (CA125) commonly used in ovarian cancer has been investigated for endometrial carcinoma[28]. A cut-off value that defines normal and pathologic serum levels for

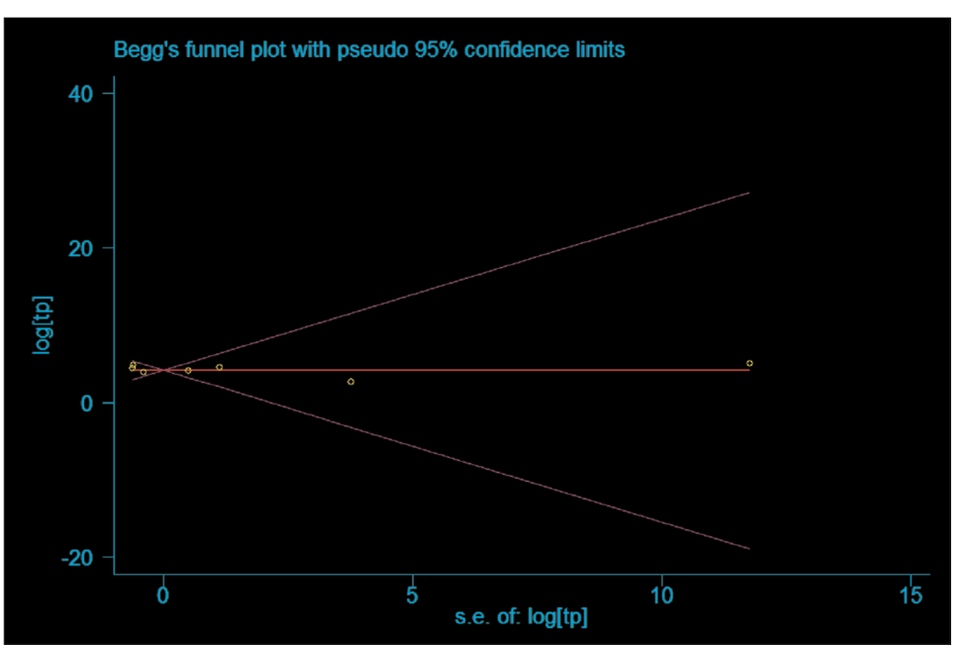

Figure 14. Assessment of the potential publication bias in the diagnosis of EC.

ovarian cancer was 35 U/mL, but in endometrial carcinoma, it had not yet been defined. An elevated CA125 level may be associated with EC, but with a variety of diagnostic cutoff value, serum CA125 measurements in EC patients and control have a variety of test results

Human epididymis protein 4 (HE4) was isolated originally from the human epididymis but is also expressed in other tissues of the body. Since its introduction, the biomarker capability of HE4 has been studied in various malignancies, including gastric, breast, ovarian and lung cancer[29]. In researches of endometrial carcinoma, serum HE4 level has been shown to correlate with the depth of myometrial invasion and the stage of the disease[30]. Currently, the analysis of the concentration of HE4 in serum is used in parallel with CA125 to detect EC in different stages, especially in premenopausal women, but the result is not clear. Moore et al[18] observed significantly higher serum HE4 levels in EC patients compared with healthy women. Considering all EC stages, the sensitivity of serum HE4 was higher than that of serum CA125 in detecting cancer patients. A few other smaller studies have investigated HE4's efficacy as a serum marker for EC. A recent study[20] found that median HE4 levels were significantly elevated in patients with endometrioid tumors and MI > 50% compared with those with < 50%. Angioli et al[21] demonstrated that HE4 was an accurate and sensitive serum marker for the detection of EC patients when compared with patients with benign uterine conditions, exhibiting a better diagnostic performance compared with CA125. Bignotti et al[19] demonstrated improved sensitivity for the detection of EC by combining HE4 and CA125. However, Omer et al[22] believed that HE4 in the diagnosis of EC and could not get a better diagnostic performance, with 75% sensitivity and only 65.5% specificity. Thus, in our meta-analysis, we obtain the data from bove literates when serum HE4 is tested for the detection of EC. Finally, our study showed an acceptable HE4 sensitivity and good specificity in diagnosis for EC, regardless of the EC stage. The area under the SROC curve of HE4 in diagnosis of EC was 0.77, which suggested much higher than CA125 (0.37)

There are not many studies assessing the combined value of HE4 and CA125 when evaluating the diagnostic accuracy of EC[19,20]. Two diagnostic methods in combination may be able to improve the diagnostic sensitivity, but it needs supporting data. Recently, Mutz-Dehbalaie et al[31] found both HE4 and CA125 to be an independent prognostic marker for survival with higher hazard ratio than HE4 alone. But in diagnostic accuracy of EC, it still remains unclear. We found only 5 studies provided these important data. The AUC was higher for the combination compared with the HE4 alone, regardless of disease stages.

Heterogeneity is an important potential problem in our study. However, the result of the Spearman correlation showed that heterogeneity could not be explained by threshold effect. Meta-regression showed that study design, test methods and cut-off values did not exert a statistically significant effect on diagnostic accuracy. In addition to heterogeneity, there are other limitations in our meta-analysis. Firstly, we included control group not totally enrolling healthy women, which may influence the final outcome. Secondly, not all literature provided HE4 + CA125 in diagnostic efficacy of EC. Only 5 manuscripts provided this data. Our preliminary findings based on these data and the conclusion still need more data to support. Third, there were some factors that may affect the outcome had not been mentioned in the original study, including the nationality of the patients, stage of the tumor, different therapy and pathology and other factors.

Conclusions

Our work illustrates that serum HE4 is a better biomarker for diagnosis of EC than CA125. More importantly, serum HE4 + CA 125 suggests to be superior to HE4 alone in the diagnosis of EC. Serum HE4 has a positive role and a better prospect in detecting EC, and its combination with CA125 is also of great importance.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Bourgin C, Saidani M, Poupon C, Cauchois A, Foucher F, Leveque J, Lavoue V. Endometrial cancer in elderly women: Which disease, which surgical management? A systematic review of the literature. Eur J Surg Oncol 2016; 42: 166-175.

2) Falcone F, Balbi G, Di Martino L, Grauso F, Salzillo ME, Messalli EM. Surgical management of early endometrial cancer: an update and proposal of a therapeutic algorithm. Med Sci Monit 2014; 20: 1298-1313.

3) Lheureux S, Wilson M, Mackay HJ. Recent and current Phase II clinical trials in endometrial cancer: review of the state of art. Expert Opin Investig Drugs 2014; 23: 773-792.
4) Lheureux S, Oza AM. Endometrial cancer-targeted therapies myth or reality? Review of current targeted treatments. Eur J Cancer 2016; 59: 99-108.
5) Calis P, Yuce K, Basaran D, Salman C. Assessment of cervicovaginal cancer antigen 125 Levels: a preliminary study for endometrial cancer screening. Gynecol Obstet Invest. 2016 Feb 13. [Epub ahead of print]
6) Mckinnon B, Mueller MD, Nirgianakis K, Bersinger NA. Comparison of ovarian cancer markers in endometriosis favours HE4 over CA125. Mol Med Rep 2015; 12: 5179-5184.
7) Huo YR, Huang Y, Liauw W, Zhao J, Morris DL. Prognostic value of carcinoembryonic antigen (CEA), AFP, CA19-9 and CA125 for patients with colorectal cancer with peritoneal carcinomatosis treated by cytoreductive surgery and intraperitoneal chemotherapy. Anticancer Res 2016; 36: 1041-1049.
8) Niloff JM, Knapp RC, Schaetzl E, Reynolds C, Bast RC Jr. CA125 antigen levels in obstetric and gynecologic patients. Obstet Gynecol 1984; 64: 703-707.
9) Goksedef BP, Gorgen H, Baran SY, Api M, Cetin A. Preoperative serum CA 125 level as a predictor for metastasis and survival in endometrioid endometrial cancer. J Obstet Gynaecol Can 2011; 33: 844-850.
10) Sadowski EA, Robbins JB, Guite K, Patel-Lippmann K, Munoz del Rio A, Kushner DM, Al-Niaimi A. Preoperative pelvic MRI and serum cancer antigen-125: selecting women with grade 1 endometrial cancer for lymphadenectomy. AJR Am J Roentgenol 2015; 205: W556-564.
11) Kang S, Todo Y, Watari H. Risk assessment of lymph node metastasis before surgery in endometrial cancer: do we need a clinical trial for low-risk patients? J Obstet Gynaecol Res 2014; 40: 322-326.
12) Jiang J, Bo D, Chang X, Cheng H, Ye X, Cui H. Discrepant clinicopathologic characteristics and HE4 performance in type I and type II epithelial ovarian cancer. Int J Clin Exp Med. 2015 Nov 15; 8: 21303-21310.
13) Capriglione S, Plotti F, Miranda A, Ricciardi R, Scaletta G, Aloisi A, Guzzo F, Montera R, Angioli R. Utility of tumor marker HE4 as prognostic factor in endometrial cancer: a single-center controlled study. Tumour Biol 2015; 36: 4151-4156.
14) Brennan DJ, Hackethal A, Mann KP, Mutz-Dehbalaie I, Fiegl H, Marth C, Obermair A. Serum HE4 detects recurrent endometrial cancer in patients undergoing routine clinical surveillance. BMC Cancer 2015; 15: 33.
15) Minar L, Klabenesova I, Jandakova E, Zlamal F, Bienertova-Vasku J. Prognostic value of human epididymis protein 4 in endometrial cancer and its utility for surgical staging. J Obstet Gynaecol Res 2015; 41: 1644-1652.
16) Bie Y, Zhang Z. Diagnostic value of serum HE4 in endometrial cancer: a meta-analysis. World J Surg Oncol 2014; 12: 169.
17) Brennan DJ, Hackethal A, Metcalf AM, Coward J, Ferguson K, Oehler MK, Quinn MA, Janda M, Leung Y, Freemantle M; ANECS Group, Webb PM, Spurdle AB, Obermair A. Serum HE4 as a prognostic marker in endometrial cancer--a population based study. Gynecol Oncol 2014; 132: 159-165.
18) Moore RG, Brown AK, Miller MC, Badgwell D, Lu Z, Allard WJ, Granai CO, Bast RC Jr, Lu K. Utility of a novel serum tumor biomarker HE4 in patients with endometrioid adenocarcinoma of the uterus. Gynecol Oncol 2008; 110: 196-201.
19) Bignotti E, Ragnoli M, Zanotti L, Calza S, Falchetti M, Lonardi S, Bergamelli S, Bandiera E, Tassi RA, Romani C, Todeschini P, Odicino FE, Facchetti F, Pecorelli S, Ravaggi A. Diagnostic and prognostic impact of serum HE4 detection in endometrial carcinoma patients. Br J Cancer 2011; 104: 1418-1425.
20) Zanotti L, Bignotti E, Calza S, Bandiera E, Ruggeri G, Galli C, Tognon G, Ragnoli M, Romani C, Tassi RA, Caimi L, Odicino FE, Sartori E, Pecorelli S, Ravaggi A. Human epididymis protein 4 as a serum marker for diagnosis of endometrial carcinoma and prediction of clinical outcome. Clin Chem Lab Med 2012; 50: 2189-2198.
21) Angioli R, Plotti F, Capriglione S, Montera R, Damiani P, Ricciardi R, Aloisi A, Luvero D, Cafà EV, Dugo N, Angelucci M, Benedetti-Panici P. The role of novel biomarker HE4 in endometrial cancer: a case control prospective study. Tumour Biol 2013; 34: 571-576.
22) Omer B, Genc S, Takmaz O, Dirican A, Kusku-Kiraz Z, Berkman S, Gurdol F. The diagnostic role of human epididymis protein 4 and serum amyloid-A in early-stage endometrial cancer patients. Tumour Biol 2013; 34: 2645-2650.
23) Antonsen SL, Høgdall E, Christensen IJ, Lydolph M, Tabor A, Loft Jakobsen A, Fagö-Olsen CL, Andersen ES, Jochumsen K, Høgdall C. HE4 and CA125 levels in the preoperative assessment of endometrial cancer patients: a prospective multicenter study (ENDOMET). Acta Obstet Gynecol Scand 2013; 92: 1313-1322.
24) Presl J, Novotny Z, Topolcan O, Vlasak P, Kucera R, Fuchsova R, Vrzalova J, Betincova L, Svobodova S. CA125 and HE4 levels in a Czech female population diagnosed with endometrial cancer in preoperative management. Anticancer Res 2014; 34: 327-331.
25) Liu X, Zhao F, Hu L, Sun Y. Value of detection of serum human epididymis secretory protein 4 and carbohydrate antigen 125 in diagnosis of early endometrial cancer of different pathological subtypes. Onco Targets Ther 2015; 8: 1239-1243.

26) Arem H, Irwin ML. Obesity and endometrial cancer survival: a systematic review. Int J Obes 2013; 37: 634-639.

27) Secord AA, Hasselblad V, Von Gruenigen VE, Gehrig PA, Modesitt SC, Bae-Jump V, Havrilesky LJ. Body mass index and mortality in endometrial cancer: a systematic review and meta-analysis. Gynecol Oncol 2016; 140: 184-190.

28) Ruan YQ, Liang WG, Huang SH. Analysis of laparoscopy on endometriosis patients with high expression of CA125. Eur Rev Med Pharmacol Sci 2015; 19: 1334-1337.

29) Tang QF, Zhou ZW, Ji HB, Pan WH, Sun MZ. Value of serum marker HE4 in pulmonary carcinoma diagnosis. Int J Clin Exp Med 2015; 8: 19014-19021.

30) Brennan DJ, Hackethal A, Metcalf AM, Coward J, Ferguson K, Oehler MK, Quinn MA, Janda M, Leung Y, Freemantle M; ANECS Group, Webb PM, Spurdle AB, Obermair A. Serum HE4 as a prognostic marker in endometrial cancer--a population based study. Gynecol Oncol 2014; 132: 159-165.

31) Mutz-Dehbalaie I, Egle D, Fessler S, Hubalek M, Fiegl H, Marth C, Widschwendter A. HE4 is an independent prognostic marker in endometrial cancer patients. Gynecol Oncol 2012; 126: 186-191.