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The value of serum HE4 and CA125 levels for monitoring the recurrence and risk stratification of endometrial endometrioid carcinoma

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ABSTRACT

To evaluate the role of serum human epididymis secretory protein 4 (HE4) and carbohydrate antigen 125 (CA125) levels for predicting and monitoring the recurrence of endometrial endometrioid carcinoma (EEC) and assessing preoperative risk stratification in EEC patients. A total of 434 EEC patients were selected for this retrospective study between May 2011 and August 2018. Serum HE4 and CA125 levels were analyzed before the initial treatment, at the first postoperative follow-up, and at recurrence or the last follow-up. Patients were risk stratified according to the European Society for Medical Oncology (ESMO), European Society for Radiotherapy & Oncology (ESTRO) and European Society of Gynaecological Oncology (ESGO) guideline. We compared the ability of these biomarkers for prediction and monitoring by performing receiver operating characteristic curve analysis and identified optimal cut-off values by determining the Youden index. Kaplan-Meier analyses were also performed to determine prognostic value. Preoperative serum HE4 was identified as a significant predictor for the recurrence of EEC ($p = 0.014$). Preoperative serum HE4 and CA125 levels were related to depth of myometrial invasion, lymph node status and FIGO stage. Serum HE4 and CA125 levels were both statistically significant markers for monitoring the recurrence of EEC ($P = 0.000$ for each biomarker). When combined, the two markers showed higher levels of sensitivity and specificity. The two biomarkers were also significant biomarkers for evaluating the risk stratification of patients undergoing lymphadenectomy ($P = 0.000$ for each biomarker). For premenopausal stage I patients, preoperative serum HE4 and CA125 levels were significant predictors of the need for ovarian preservation ($P = 0.000$ and $P = 0.002$, respectively). For premenopausal patients with stage I intramucosal differentiation, preoperative serum levels of HE4 were significant predictors for fertility preservation ($P = 0.024$). Preoperative serum HE4 level can be used to predict the recurrence of EEC. Postoperative serum HE4 and CA125 levels can be used to monitor the recurrence of EEC and are more sensitive when combined. Preoperative serum levels of CA125 and HE4 levels are of significant value for risk stratification in EEC patients.

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1. Introduction

Endometrial carcinoma (EC) is one of the most common malignant cancers of the female reproductive system with approximately 320,000 new diagnoses globally each year [1]. The global incidence of EC is rising and tends to be diagnosed at a younger age. There are 34,000 deaths per year due to EC in Europe and North America and the five-year overall survival rate for recurrent EC is 15%–17%. Statistical analysis has shown that approximately 4.2% of low-grade EC patients are younger than 40 years-of-age [1,2]. There are several histological categories of EC, including endometrioid carcinoma and non-endometrioid carcinoma (such as serous carcinoma, clear cell carcinoma and carcinosarcoma). Of these categories, endometrial endometrioid carcinoma (EEC) accounts for 80%–90% of cases and has a better prognosis with a 5-year survival rate of 85% [1,2]. However, due to the lack of simple and effective monitoring indicators for EC, it remains difficult to provide early preventative methods for the recurrence of patients and to optimize survival, thus resulting in a poor prognosis. According to National Comprehensive Cancer Network (NCCN) guidelines, the primary treatment of EC diagnosed by preoperative endometrial biopsy is total hysterectomy and bilateral salpingo-oophorectomy and surgical staging and with/without full pelvic lymphadenectomy. The subsequent treatment plan is determined by postoperative pathological results. However, fertility could be preserved in patients with low-risk and an early stage of disease [3]. Given that the population of patients with EEC is increasing, there is an urgent need to develop economical and effective indicators that can be adopted by all levels of medical structures for long-term postoperative management and follow-up in gynecology clinics.

At present, there is no non-invasive and validated biomarker that is recognized internationally and can be used to monitor the recurrence of EC. Currently, imaging examinations, such as magnetic resonance imaging (MRI), are commonly used in the diagnosis and follow-up of EC, and have been shown to play an outstanding role in determining the location of recurrent EC lesions [4]. However, the widespread application of this technology is limited by high costs and technological requirements. The 2020 NCCN guidelines and WHO guidelines have proposed TCGA molecular typing to predict the prognosis of EC, including: POLE mut, MMRd, NSMP and p53abn [5]. Most EEC patients belong to POLE mut. However, its clinical application is still in its infancy, and serological markers are still needed for postoperative follow-up and monitoring of recurrence in patients. Serum human epididymis secretory protein 4 (HE4) and

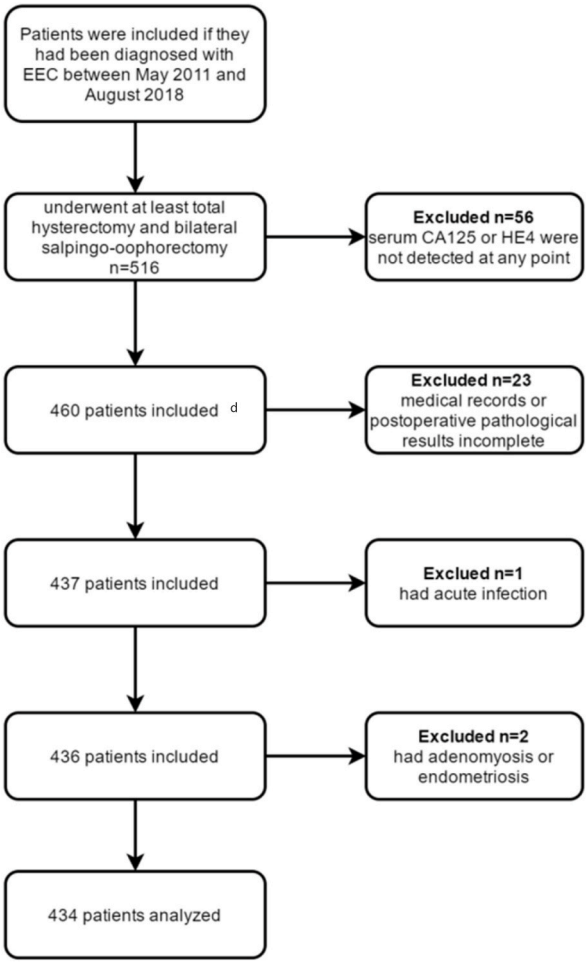

Fig. 1. Flow chart.

carbohydrate antigen 125 (CA125) are simple and convenient for detection in the clinic and are widely recognized as reliable diagnostic and follow-up biomarkers for epithelial ovarian cancer (EOC) [6]. We expected that a more comprehensive, economical and simple way could be adopted to assess the prognosis of EEC, and therefore sought to determine whether serum CA125 and HE4 levels could be used as routine indicators to monitor the recurrence of patients after surgery.

There is no widely recognized and commonly available clinical parameter to monitor the recurrence of EEC in the clinic. As the most common subtype of EC, EEC involves a large number of patients and is associated with a good prognosis [2,7]. However, the prognosis of patients after recurrence is extremely poor and mortality rates are high [7,8]. Therefore, it would be beneficial to explore potential and convenient serological markers to allow the identification of patients with recurrent EEC. HE4 is a secretory protein encoded by the whey-acidic four-disulfide core domain protein 2 (WFDC2) gene, which is expressed in the human epididymis, respiratory tract, prostate and kidney [9]. In 2009, HE4 was approved by the Food and Drug Administration (FDA) in US as a new serological marker for monitoring the recurrence of EOC [10]. CA125 is also an epithelial cell surface antigen that is commonly used in the evaluation and follow-up of EOC [11]. Over recent years, many studies have validated the role of CA125 as a biological marker for the prognosis of EC [12]. Nevertheless, only a few studies have proposed the use of HE4 and CA125 for EC, especially with regards to monitoring the recurrence this disease [13].

Although surgery is a reasonably effective treatment option, it can also lead to the permanent loss of fertility and can reduce the quality of life in premenopausal patients. It is still controversial as to whether lymphadenectomy is necessary for patients with early stage disease. The European Society for Medical Oncology (ESMO), European SocieTy for Radiotherapy & Oncology (ESTRO) and European Society of Gynaecological Oncology (ESGO) guideline suggested that low-risk EC is less likely to involve lymph node metastasis and lymph node resection is not recommended [14,15].

Therefore, the purpose of this study was to investigate the role of HE4 and CA125 for predicting and monitoring the recurrence of EEC.

2. Materials and methods

2.1. Patients

In this retrospective study, we recruited 434 EEC patients (age range: 24–81 years; media age: 52.47 years) who received surgical treatment in the First Affiliated Hospital of Chongqing Medical University between May 2011 and August 2018. All patients diagnosed with EEC by postoperative pathological records were included in this study according to FIGO 2009 staging. All patients underwent at least total hysterectomy and bilateral salpingo-oophorectomy. Our exclusion criteria were as follows: 1. No serum CA125 or HE4 were collected before the first treatment after diagnosis or at the first postoperative follow-up or at the last visit or at relapse; 2. The patients were complicated with infection of other organs; 3. Patients with other diseases affecting CA125 levels (such as endometriosis and adenomyosis); 4. Patients with incomplete medical records or medical examination results. Fig. 1 shows the flow chart for inclusion and exclusion criteria. Histological classification was performed according to WHO standards, and disease staging was determined according to FIGO guidelines adopted in 2009. The period of follow-up was from primary diagnosis to September 2020 or death. Interval time for the first three years was approximately 3–6 months, and twice or once a year for up to 5 years. The study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University and informed consent was obtained from all patients (ethical approval number: 2020-425). The study was performed in accordance with the tenets of the Declaration of Helsinki. According to the ESMO-ESGO-ESTRO classification, we divided EEC patients into low-risk (G1/2, myometrial invasion $<50\%$), medium-risk (G1/2, myometrial invasion $>50\%$ or G3, myometrial invasion $<50\%$) and high-risk (G3, myometrial invasion $>50\%$); this classification allowed us to decide whether to perform lymphadenectomy.

2.2. Quantitative determination of the serum levels of HE4 and CA125

The serum levels of HE4 and CA125 were obtained from the electronic medical records system of the First Affiliated Hospital of Chongqing Medical University. A 3 mL serum sample was collected from each patient on an empty stomach before surgery or during follow-up. Serum levels of HE4 and CA125 were measured by a chemiluminescence approach (Abbott Laboratories, US) using a fully automated Architect instrument. Patients were sampled every 3–6 months for the first 3 years after treatment and followed up every 6–12 months thereafter. The normal reference values were as follows: premenopausal HE4 $\leq$ 70 pmol/L, postmenopausal HE4 $\leq$ 140 pmol/L; CA125 $<$ 35U/mL.

2.3. Statistical analysis

All calculations were performed with SPSS 25.0 statistical software. A P value < 0.05 was considered statistically significant. Serum levels of HE4 and CA125 were compared across groups with Wilcoxon's Mann-Whitney test. Receiver operator curves (ROCs) were used to compare the ability of HE4 and CA125 to predict and monitor patients with recurrent disease. We also calculated area under the curve (AUC) values and optimal cut-off values. The optimal cut-off values for serum HE4 and CA125 levels were determined with the maximum Youden index (YI = Sensitivity + Specificity − 1). Disease-free survival (DFS) referred to the time interval between the date of surgery and the date of disease recurrence. Overall survival (OS) was calculated from the date of diagnosis to the date of death or last follow-up. Kaplan-Meier analysis was used to generate survival curves.

3. Results

3.1. Population characteristic

This retrospective study included a total of 434 patients with EEC and a median follow-up of 53.26 months (range: 6–111 months). Of these, 37 patients relapsed and 22 patients died, with a recurrence rate of 8.53% and a mortality rate of 5.07%. Table 1 shows key patient characteristics. The median age of all patients was 51 y (24-81 y). A total of 70 patients with G3 (16.02%). Table 2 shows the median levels of preoperative CA125 and HE4 in patients who were classified as low, medium or high risk according to the ESMO-ESGO-ESTRO guideline. We found that the preoperative serum HE4 level in the high-risk group was significantly higher than that in the low and medium risk groups.

3.2. Role of serum CA125 and HE4 in predicting and monitoring relapse

Analysis showed that serum HE4 and CA125 levels decreased after initial treatment but increased again during relapse. According to ROC curve analysis, we evaluated the role of these two serological markers as recurrent indicators of EEC. We found that preoperative HE4 level was a significant predictor for the recurrence of EEC ($P = 0.014$), and the cut-off value for preoperative HE4 was 66.5 pmol/L, with a sensitivity of 63.3% and a specificity of 63.4%; the AUC was 0.638. However, preoperative CA125 level was not a significant predictor of recurrence ($P > 0.05$). At the time of recurrence, both CA125 and HE4 levels were significant factors for monitoring the recurrence of EEC ($P = 0.000$ for both biomarkers). The cut-off value for CA125 was 26.4U/mL, with a sensitivity of 63.6% and a specificity of 96.4%; the AUC was 0.826. The cut-off value for HE4 was 45.5 pmol/L, with a sensitivity of 78.6% and a specificity of 78.3%; the AUC was 0.822. When the two biomarkers were combined, the sensitivity was 0.857, and the specificity was 0.856. It indicated that the combination of the two was more effective in monitoring recurrence ($P = 0.000$) (Table 3 and Fig. 2(a–f)). According to Kaplan-Meier analysis, we found that higher preoperative CA125 levels were associated with a worse DFS while patients with higher preoperative HE4 levels were associated with a worse DFS and OS (Fig. 3(a–b) and Fig. 4(c–d)). Therefore, these two serological markers were significantly associated with the prognosis of EEC patients.

3.3. Preoperative serum CA125 and HE4 in predicting risk factors

In addition, we stratified the risk of all EEC patients and predicted risk factors based on the levels of serum HE4 and CA125. Table 4 shows the relationships between serum preoperative CA125 and HE4 and pathological factors. Our results showed that preoperative serum levels of HE4 and CA125 were significantly related to the depth of myometrial invasion, lymph node status and FIGO stage. Analysis showed that preoperative serum HE4 was a significant factor for identifying the need for ovarian preservation ($P = 0.000$) for premenopausal stage I patients and the preservation of uterine ($P = 0.024$) for premenopausal stage I patients with intra-mucous well-differentiated disease. However, preoperative serum CA125 was only a significant marker for ovarian preservation in stage I patients ($P = 0.002$). We classified all patients as low risk, medium risk, and high risk based on tumor grade and myometrium invasion. For low-risk patients with early-stage disease without lymph node metastasis, lymph node dissection could not be performed when the HE4 level was lower than 69.5 pmol/L and the CA125 level was lower than 26.15U/ml.

Table 1
Patients' characteristics.

clinical characteristics	n = 434
Age (years; range)	51 (24–81)
FIGO stage	
I	334 (76.96%)
II	56 (12.90%)
III	44 (10.14%)
IV	0 (0%)
Histology	
Endometrioid adenocarcinoma G1	120 (27.46%)
Endometrioid adenocarcinoma G2	244 (56.52%)
Endometrioid adenocarcinoma G3	70 (16.02%)
Myometrial Invasion	
<1/2	315 (72.58%)
≥1/2	119 (27.42%)
Lymph node metastases	
Yes	17 (3.92%)
No	417 (96.08%)
Lymphadenectomy	
Yes	368 (84.79%)
No	66 (15.21%)
Recurrence	
Yes	37 (8.52%)
No	397 (91.47%)

Table 2
The levels of preoperative CA125 and HE4 of patients which were classified as lowmedium or high risk according to the ESMO-ESGO-ESTRO guideline.

Subgroup	N	Median preoperative CA125(IQR)[U/mL]	Median preoperative HE4(IQR)[pmol/L]
Low-risk according to ESMO-ESGO-ESTRO guideline	281	19.90 (12.65–31.80)	53.00 (41.00–73.00)
Medium-risk according to ESMO-ESGO-ESTRO guideline	117	26.60 (14.70–54.25)	70.50 (47.75–107.50)
High-risk according to ESMO-ESGO-ESTRO guideline	36	25.70 (14.35–59.98)	78.00 (53.00–101.00)

Table 3
Prediction performance of EEC recurrence assessment by serum CA125, HE4 at three points.

	Cut-off value	sensitivity (%)	Specificity (%)	AUC (95%CI)	P value
Pre-CA125 (U/mL)	30.4	0.516	0.682	0.559 (0.446,0.672)	0.277
Pre-HE4 (pmol/L)	66.5	0.633	0.634	0.638 (0.538,0.732)	0.014
Post-CA125 (U/mL)	68.35	0.455	0.84	0.661 (0.490,0.831)	0.081
Post-HE4 (pmol/L)	47.5	0.727	0.516	0.551 (0.419,0.684)	0.578
Following-up CA125 (U/mL)	26.4	0.636	0.964	0.826 (0.709,0.943)	0.000
Following-up HE4 (pmol/L)	45.5	0.786	0.783	0.822 (0.678,0.966)	0.000
Both pre-CA125 and pre-HE4		0.586	0.734	0.594 (0.474,0.714)	0.094
Both Following-up CA125 and HE4		0.857	0.856	0.919 (0.840,0.999)	0.000

Pre means preoperative. Post means postoperative. CI means confidence interval.

3.3.1. Discussion

Our analyses showed that preoperative HE4 levels could predict recurrence in patients with EEC. Patients with high preoperative levels of HE4 were more likely to experience recurrence. During postoperative follow-up, serum HE4 and CA125 levels could both be used to monitor the recurrence of EEC. When the two biomarkers were combined, sensitivity and specificity both increased. Higher preoperative levels of HE4 and CA125 were related to a late stage of disease, poor differentiation, deep myometrial invasion and lymph node metastasis. We stratified the risk of patients by preoperative levels of HE4 and CA125 to evaluate the necessity for lymph node resection in early low-risk patients and the possibility of preserving ovarian and reproductive function in premenopausal early stage patients.

Serum levels of HE4 and CA125 are both reliable serum biomarkers for monitoring the recurrence of EOC and have been used in the clinic for many years [6,16]; furthermore, levels of these biomarkers are readily available at all levels of healthcare. Some published clinical findings have demonstrated that high serum levels of HE4 and high expression levels of HE4 in EC tumor tissues are associated with a poor prognosis, late stages, deep myometrial invasion and lymph node metastasis in EC. Previous studies reported that the overexpression of HE4 could promote the proliferation, invasion and metastasis of EC cells [17–19]; however, the precise mechanism responsible for the up-regulation of HE4 and the tumor promoting effect remains unknown. Some recent studies have focused on the function of HE4 and have shown that high expression levels of HE4 in a tumor immune microenvironment may increase the expression of PD-L1 in tumor cells and suppress the anti-tumor immunity of NK cells, CTL cells and M2 macrophages, thus promoting the immune escape of tumor cells and inducing the progression of disease [18,20]. HE4 has been found to be associated with tumor growth through the EGFR-MAPK signaling pathway and steroid biosynthesis pathway [21,22]. Therefore, we hypothesize that HE4 also has a similar role in EEC although it requires further researches. We found that serum levels of HE4 increased during tumor recurrence, as reported previously by Behrouzi et al. [23]. Other research showed that renal function and age could both influence the levels of HE4 [24]. However, we need to consider that the levels of CA125 can be influenced by many benign diseases, including adenomyosis, ongoing inflammation and the presence of other malignancies [25].

The molecular typing of TCGA and metabolomics have attracted much attention in recent years, and their roles in predicting the prognosis of EC have been widely discussed, but their value may be affected by histological subtypes [26]. Molecular typing requires whole genome sequencing of tumor tissue, which is costly and time-consuming, and could not be widely carried out in clinic. Due to the limited clinical application time, more studies are needed to summarize. Therefore, more comprehensive and simple methods are important to predict the prognosis of EC. Most patients with EC have significantly reduced tumor load after surgery, resulting the changes in metabolomics. According to the changes of metabolic biomarkers in the pathway, the prognosis could be preliminarily judged. A variety of metabolic biomarkers related to prognosis have been detected, including phosphatidic acid, arachidonic acid, palmitamide, linoleic acid, phosphatidylserine, etc. [27]. As a malignant tumor closely related to metabolism, EC could be studied by metabolomics of blood, urine and other samples, which has a good development prospect in predicting recurrence and judging prognosis. However, most of the current research is still in the primary exploration stage, with few relevant clinical studies. The study of metabolites is relatively extensive, and there is no recognized specific metabolites. Despite the widely recognized value of molecular typing and metabolomics in EC prognosis, these are not routinely available approaches to follow up and monitor recurrence during the actual follow-up of patients. Therefore, further studies are needed to comprehensively evaluate the role of molecular typing, metabolomics, and serum CA125 and HE4 in the prognosis and risk stratification of patients with EEC.

Previous research found that the poor prognosis of EEC is related to high-risk factors such as deep myometrial invasion, an advanced stage and lymph node metastasis [28]. Lymphadenectomy for patients with early EC remains controversial [15]. In recent years, many findings suggest that lymphadenectomy should not be recommended for early-staging and low-risk patients based on

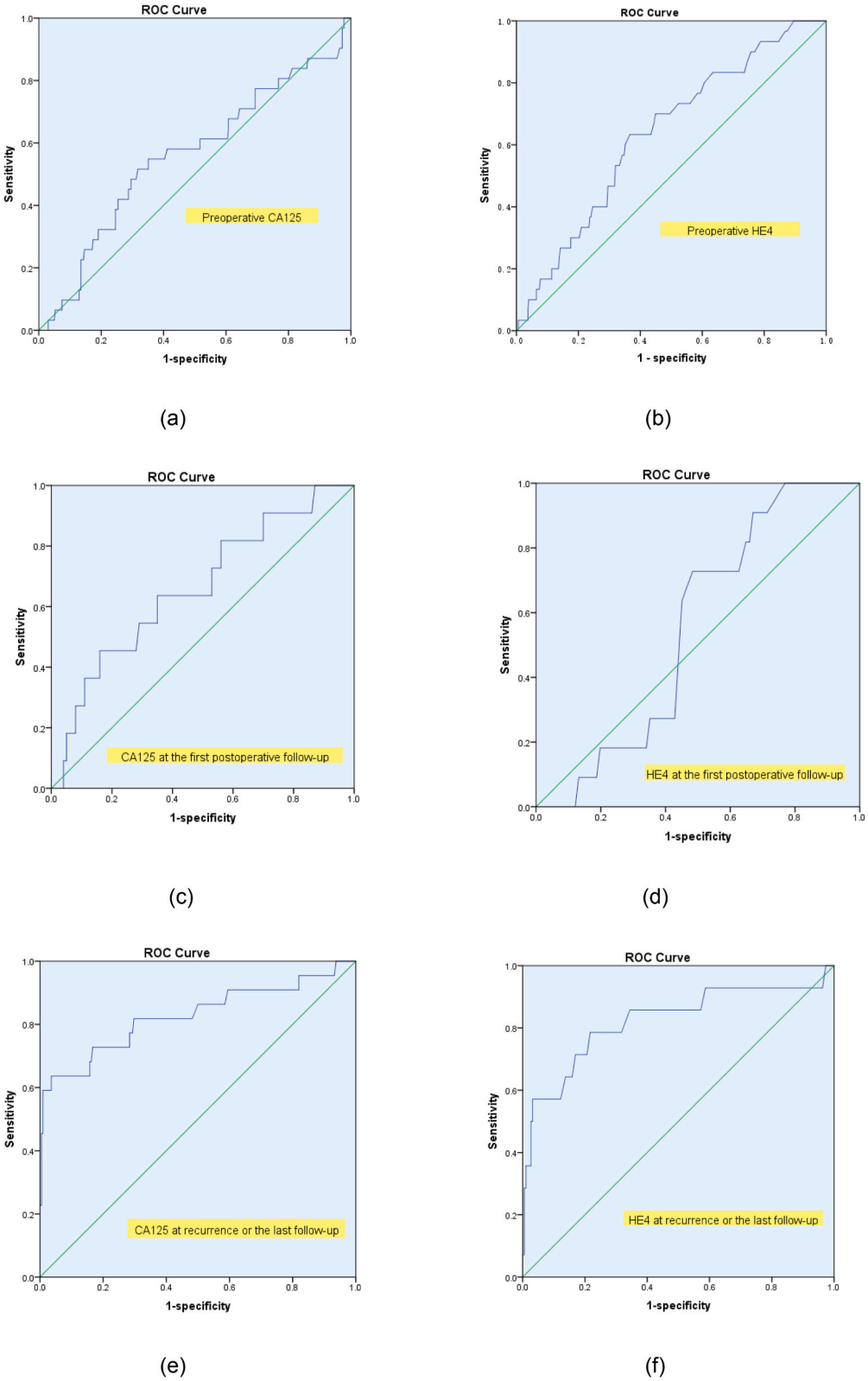

Fig. 2. The ROC curve of preoperative serum CA125 and HE4 (a, b). The ROC curve of postoperative serum CA125 and HE4 (c, d). The ROC curve of serum CA125 and HE4 at recurrence or the last follow-up (e, f).

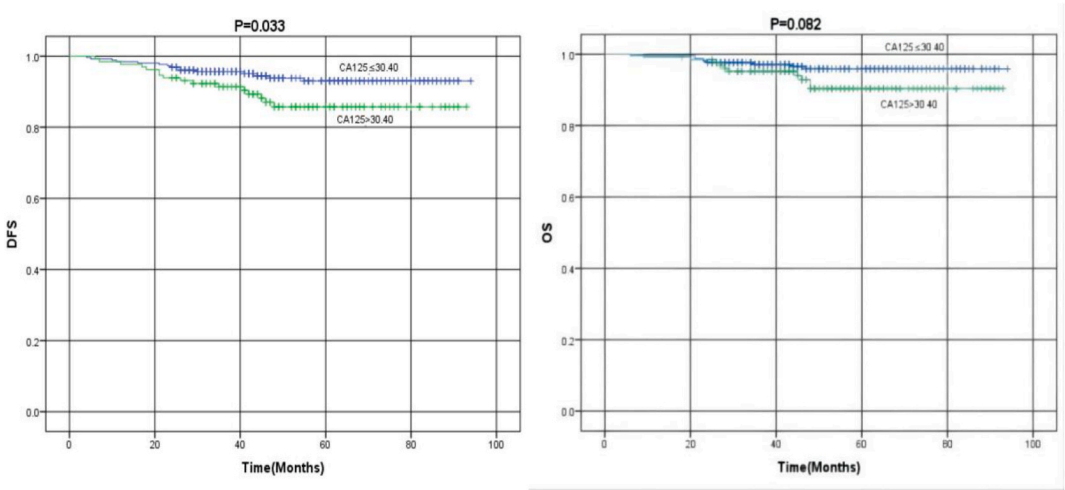

Fig. 3. Kaplan–Meier curves for the disease-free survival (a) and overall survival (b), according to preoperative CA125. Cut-off values were 30.40 pmol/L.

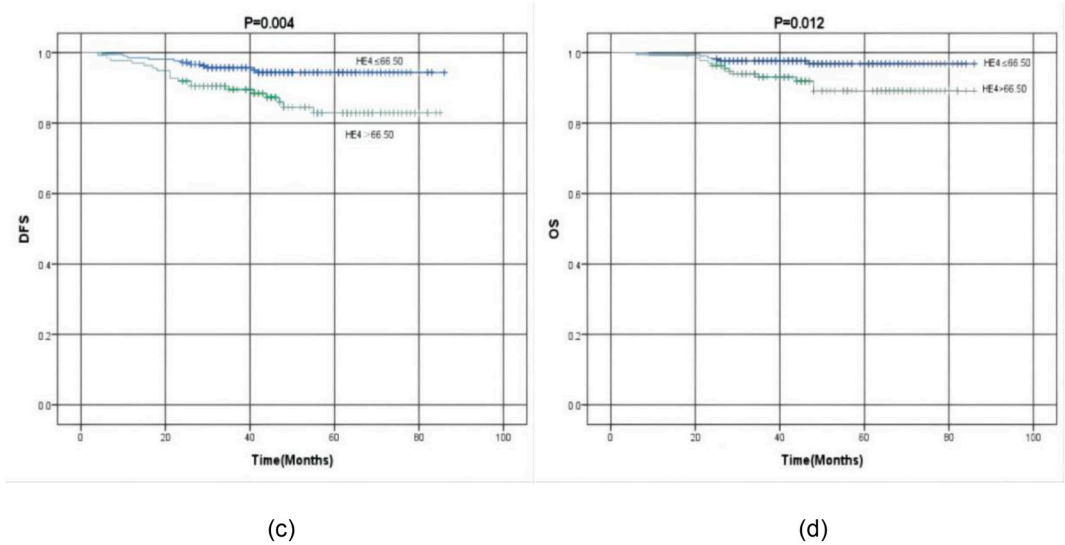

Fig. 4. Kaplan–Meier curves for the disease-free survival (c) and overall survival (d), according to preoperative HE4. Cut-off values were 66.50 pmol/L.

grade and myometrial invasion. In such cases, lymphadenectomy does not improve prognosis and can be associated with a variety of complications, such as lymphedema, lymphocysts, pelvic nerve injury and deep vein thrombosis [15,29]. In this study, we found that preoperative levels of CA125 and HE4 could act as biomarkers for lymphadenectomy, as described previously by O'Toole et al. [30]. By combining these two biomarkers with preoperative endometrial biopsy and MRI, we observed that when CA125 was <26.15 U/mL and HE4 was <69.5 pmol/L, low-risk patients with stage IA and medium-high differentiated EEC were less likely to exhibit lymph node metastasis; thus, lymphadenectomy could not be performed.

It is of great importance to preserve fertility in young women with a strong desire to conceive. Studies have found that ovarian preservation does not affect survival in patients with early EC. In contrast, surgical menopause caused by hysterectomy or ovariectomy is known to increase the risk of cardiovascular disease, osteoporosis and other perimenopausal syndromes in young women and may even increase the rate of recurrence and death [31]. In the present study, we found that preoperative levels of CA125 and HE4 can play a role for evaluating the need for ovarian preservation in premenopausal stage I patients. For stage I intra-mucous patients with good differentiation and of childbearing age, uterine preservation might be an option when HE4 levels are <55.5 pmol/L, after excluding myometrial invasion. However, the endometrium must be evaluated regularly and standard surgery is recommended after childbirth

Table 4
Pathological factors associated with serum levels of preoperative HE4 and CA125 and corresponding predictive cut-off values.

Subgroup		Cut-off value	Sensitivity (%)	Specificity (%)	AUC (95%CI)	P
Myometrial invasion	Pre-CA125 (U/mL)	52	0.324	0.887	0.585 (0.520,0.651)	0.008
	Pre-HE4 (pmol/L)	73.5	0.54	0.753	0.675 (0.610,0.739)	0.000
Grading	Pre-CA125 (U/mL)	24.65	0.54	0.579	0.549 (0.474,0.624)	0.218
	Pre-HE4 (pmol/L)	66.5	0.538	0.637	0.565 (0.485,0.645)	0.133
FIGO stage	Pre-CA125 (U/mL)	38.3	0.707	0.807	0.819 (0.747,0.890)	0.000
	Pre-HE4 (pmol/L)	81.5	0.676	0.789	0.770 (0.686,0.855)	0.000
Lymph node involvement	Pre-CA125 (U/mL)	28.25	0.867	0.643	0.784 (0.668,0.900)	0.000
	Pre-HE4 (pmol/L)	57.5	0.786	0.525	0.691 (0.546,0.836)	0.015
Lymphadenectomy according to ESMO	Pre-CA125 (U/mL)	26.15	0.517	0.695	0.609 (0.552,0.666)	0.000
	Pre-HE4 (pmol/L)	69.5	0.543	0.793	0.704 (0.650,0.758)	0.000
Death related to EEC	Pre-CA125 (U/mL)	30.4	0.5	0.675	0.538 (0.397,0.679)	0.578
	Pre-HE4 (pmol/L)	1281.5	0.006	1	0.627 (0.500,0.754)	0.07
Ovarian preservation	Pre-CA125 (U/mL)	28.65	0.581	0.73	0.656 (0.557,0.755)	0.002
	Pre-HE4 (pmol/L)	69.5	0.615	0.79	0.733 (0.641,0.825)	0.024
Uterine preservation	Pre-CA125 (U/mL)	25.3	0.448	0.8	0.596 (0.500,0.692)	0.079
	Pre-HE4 (pmol/L)	41.5	0.76	0.448	0.635 (0.526,0.744)	0.024

Pre-means Preoperative.

[3]. Furthermore, it is meaningful for clinical doctors to practice personalized treatment and carry out follow-up closely in high-risk patients. In this retrospective study, preoperative serum levels of HE4 and CA125 were shown to predict high risk factors of EEC, including deep muscle infiltration, late stage disease and lymph node metastasis. These results indicated that preoperative levels of CA125 and HE4 could be used for risk stratification in patients with EEC. Thus far, it has not been reported whether HE4 and CA125 levels can play a role in risk stratification; prospective multicenter studies are now needed to confirm it.

In our study, the cut-off value for serum preoperative HE4 in the prediction of EEC recurrence was 66.5 pmol/L with a sensitivity of 63.3% and a specificity of 63.4%. There have been few reports on the cut-off values for preoperative HE4 and CA125 levels for the prediction of EC recurrence; furthermore, previous studies included patients with all pathological types of EC [32]. During the recurrence of EEC, we found that the cut-off value for HE4 was 45.5 pmol/L with a sensitivity of 78.6% and a specificity of 78.3%; for CA125, the cut-off value was 26.4U/mL with a sensitivity of 63.6% and a specificity of 96.4%. When the two biomarkers were combined, there was a higher sensitivity of 85.7% and a higher specificity of 85.6%. In a previous study, Brennan et al. selected 70 pmol/L as the cut-off value for HE4 when evaluating the recurrence of EC, with a sensitivity of 81% and a specificity of 64%. However, these authors chose 35U/mL as the cut-off value for CA125, although this was not statistically significant for evaluating the recurrence of EC [33]. In other studies, median HE4 or median CA125 levels were selected as the cut-off values for monitoring the recurrence of EC [34,35]. In the present study, we selected cut-off values directly by ROC curve analysis.

There are some limitations to our study that need to be considered. Firstly, this was a retrospective study; as such, there was a risk of underlying bias. Secondly, the sample size was insufficient, and our study lack stage IV patients. While not all patients were able to collect CA125 and HE4 serum samples at all three time points, resulting in a certain missing rate. Thirdly, a total of 66 patients in this study were not performed lymphadenectomy. The influence of the omitting of lymphadenectomy on prognosis may be ignored in this study. In future, larger prospective studies should be performed to confirm the use of serum CA125 and HE4 levels as biomarkers for EEC.

4. Conclusions

In summary, our analysis found that CA125 and HE4 levels can be used to predict the recurrence of EC prior to surgery in patients with EEC and monitor early recurrence post-surgery. When these biomarkers were combined, there was an improvement in specificity and sensitivity. In particular, preoperative levels of CA125 and HE4 could be used as preliminary screening criteria for preserving reproductive function and lymph node resection in stage I patients. In the future, we hope to combine TCGA molecular typing, metabolomics, imaging with serum CA125 and HE4 to conduct more prospective studies, so as to better predict and monitor the recurrence of EEC to improve the survival of patients.

Author contributions

Sainan Gong: Performed the experiments; Wrote the paper.
Quan Quan; Shuang Yang: Analyzed and interpreted the data.
Yu Meng: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.
Jingxian Wu; Jiaming Hu: Contributed reagents, materials, analysis tools or data.
Xiaoling Mu: Conceived and designed the experiments.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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