Abstract

Objective: To investigate the combined predictive value of the preoperative serum cancer antigen 125 (CA125) level and age at diagnosis among patients with early-stage endometrial cancer (EC) after initial treatment.

Methods: We retrospectively analyzed data from patients with early-stage EC from 1999 to 2015 in multiple institutions in China. All 447 patients received postoperative adjuvant radiotherapy for FIGO 2009 stage I and II EC with complete data on preoperative serum CA125 levels. All patients were divided into four groups according to the ESMO-ESGO-ESTRO risk classification. The predictive probability of 5-year overall survival (OS) and the sensitivity and specificity of CA125 and age were calculated.
Results: The median follow-up time was 59 months (3–201 months). The 5-year OS and disease-free survival rates were 94.4% and 89.1%. Multivariate analysis showed that the preoperative CA125 level and age at diagnosis were independent prognostic factors for 5-year OS. The area under the curve for CA125 combined with age at diagnosis for 5-year OS was .692, and the corresponding sensitivity and specificity were 68.2% and 68.2% (p < .002), which were significantly better than the corresponding values for CA125 or age alone. After all 447 patients were divided into four groups according to CA125 combined with age, the 5-year OS of the elderly and higher CA125 group was only 73.7%.

Conclusions: Although preoperative CA125 had limited sensitivity in predicting the prognosis for early-stage EC after initial treatment, it remains a useful serum marker for risk assessment of early-stage EC. Combining CA125 with age may increase its predictive sensitivity.

KEYWORDS
age at diagnosis, early-stage endometrial cancer, preoperative serum CA125

1 | INTRODUCTION

Endometrial cancer (EC) is the most common gynecological malignant tumor, and its incidence is increasing. Although most patients are diagnosed early and cured by hysterectomy, 15%–20% of patients experience recurrence without locally advanced or metastatic disease. Therefore, identifying adverse factors related to recurrence and metastasis from clinicopathological information for patients with early-stage EC and providing appropriate treatment is especially beneficial for improving overall survival (OS). Serum biomarkers are of great value for the early detection of primary and recurrent diseases, monitoring responses to adjuvant therapy, preoperative selection of high-risk patients, and more personalized treatment. Cancer antigen 125 (CA125) levels have been shown to be associated with a number of clinicopathological factors in EC. However, most of the current studies on CA125 in EC are focused on the prediction of advanced EC, and the literature on the predictive role of CA125 in early-stage EC is limited. This study aimed to analyze the predictive value of preoperative serum CA125 combined with clinicopathological factors in patients with early-stage EC after initial treatment.

2 | METHODS AND MATERIALS

2.1 | Ethics approval and informed consent

This retrospective study was approved by the Ethics Review Committee of Peking Union Medical College Hospital, Chinese Academy of Medical Sciences (protocol number: S-K139). The clinical trial ID of the study is ChiCTR-PRC-17010712.

Evaluation of all data met the requirements of the Helsinki Declaration.

2.2 | Materials and evaluation

A total of 1268 patients with early-stage EC treated at 13 grade A tertiary hospitals in China between January 1999 and December 2015 were included. Preoperative serum CA125 levels were recorded for 447 of the 1268 patients (Figure 1). All patients underwent primary hysterectomy ± bilateral salpingo-oophorectomy, had confirmed FIGO2009 stage I or stage II EC, and had a World Health Organization performance score between 0 and 2. All patients received postoperative adjuvant radiotherapy. The median follow-up time was 59 months (3–201 months). Risk classification was carried out according to ESMO-ESGO-ESTRO risk classification. Treatment-related late toxicity was evaluated according to the Radiation Therapy Oncology Group criteria. The electrochemiluminescence method of Roche Cobas was used to detect CA125. The normal range of CA125 was ≤35 U/ml.

2.3 | Radiotherapy modalities

All patients received postoperative pelvic external beam radiotherapy (EBRT) ± vaginal brachytherapy (VBT) or VBT alone. The target volume of EBRT included the upper vagina, parauterine, presacral, obturator, internal and external iliac and common iliac lymphatic drainage areas. Conventional four-field "box" radiotherapy, three-dimensional conformal radiotherapy, and intensity-modulated radiotherapy were used in external beam irradiation. The target for VBT after hysterectomy
was no more than the upper two-thirds of the vagina with single-channel or multichannel applicators, and two- and three-dimensional HDR brachytherapy plans were used for brachytherapy.

2.4 Follow-up

All patients had complete clinical, pathological, and follow-up information. The prognostic factors analyzed included age at diagnosis, preoperative serum CA125 levels, surgical type, pathological type, grade, myometrial invasion (MI), lymphatic vascular space invasion (LVSI), lower uterine segmental invasion (LUSI), cervical stromal invasion (CSI), FIGO 2009 stage, ESMO-ESGO-ESTRO risk classification, time interval between surgery and radiotherapy, radiotherapy mode, and use of chemotherapy.

The primary endpoint was the effect of CA125 and age on 5-year OS. The secondary endpoint was 5-year disease-free survival (DFS). The primary endpoint was defined as the time from the operation to death from any cause or the last follow-up. The secondary endpoint was defined as the time from the operation to disease recurrence or metastasis or the last follow-up. After the initial treatment, new lesions in the pelvic area were defined as local regional recurrence (including vaginal recurrence), and new lesions beyond the pelvic area were defined as distant metastasis.

2.5 Statistical analysis methods

The Kaplan–Meier method was used to calculate OS and DFS. Cox proportional hazard regression was used for multivariate analysis. Binary logistic regression was used to calculate the predictive probability of 5-year OS for each patient, and the receiver operating characteristic curve was used to calculate the sensitivity and specificity of the variables, as well as the combined predictive value of CA125 and age. All analyses were performed using IBM SPSS Statistics for Windows version 19.0, and p < .05 was considered statistically significant.

3 RESULTS

3.1 Clinical characteristics

The median follow-up time was 59 months (3–201 months). The clinical characteristics and initial treatment of the patients are shown in Table 1. The cut-off value of the time interval between surgery and radiotherapy for OS and DFS was 49.5 days. The median number of lymph nodes removed was 18(range 1–65). The dose range to EBRT was 40–50.4 Gy in 25–28 fractions. When VBT was used as a boost to EBRT and postoperative VBT alone, the dose to the vaginal mucosa was respectively 8–25 Gy in 2–5 fractions and 25–40 Gy in 5–8 fractions. Ninety-five patients (21.3%) underwent adjuvantly chemotherapy.

3.2 Preoperative serum CA125 level and age at diagnosis

Serum CA125 levels were negatively correlated with age (p = .001). The best cut-off value of age at diagnosis was 61 years (AUC = .654, sensitivity = 54.5%, specificity = 76.5%).

According to its cut-off value, age was divided into two groups: ≤61 years and >61 years. For patients aged ≤61 years, the CA125 cut-off value was 37.7 U/ml (AUC = .535, sensitivity = .4, specificity = .751). For patients aged >61 years, the CA125 cut-off value was 39.35 U/ml (AUC = .609, sensitivity = .417, specificity = .840). Patients aged >61 years with CA125 > 39.35 U/ml and patients aged ≤61 years with CA125 > 37.7 U/ml were classified as the CA125-positive group. In contrast, patients aged >61 years with CA125 < 39.35 U/ml and patients aged ≤61 years with CA125 < 37.7 U/ml were classified as the CA125-negative group.

3.3 Survival analysis

The 5-year OS and DFS rates were 94.4% and 89.1%, respectively. Among all 447 patients, 22 patients died, among whom 14 died of EC, seven died of cardiovascular comorbidities, and one died of secondary primary cancer. Recurrence or metastasis occurred in 32 patients after initial treatment. In the first disease progression, eight patients had local regional recurrence, five patients had both distant metastasis and local regional recurrence, and 19 patients had distant metastasis. The
### TABLE 1  Clinical characteristics and initial treatment of all 447 patients and univariate analysis for overall survival (OS) and disease-free survival (DFS)

| Variable | Number | p for OS | p for DFS |
|----------|--------|----------|-----------|
| **Age**  |        |          |           |
| ≤61 years| 335 (74.9%) | .001 | .002 |
| >61 years| 112 (25.1%)  |      |          |
| **Preoperative serum CA125** | |          |           |
| Positive | 341 (76.3%)  | .033 | .154 |
| Negative | 106 (23.7%)   |      |          |
| **Surgical type** | |          |           |
| Completely surgically staged | 313 (70.0%) | .036 | .095 |
| Incompletely surgically staged | 134 (30.0%) |      |          |
| **Pathology** | |          |           |
| Endometrioid carcinoma | 416 (93.1%) | .673 | .614 |
| Nonendometrioid carcinoma | 31 (6.9%) |      |          |
| **Grade**<sup>a</sup> | |          |           |
| Grade1 | 161 (36.0%) | .314 | .321 |
| Grade 2| 187 (41.8%) |      |          |
| Grade 3| 99 (22.2%)  |      |          |
| **MI** | |          |           |
| ≥1/2 | 216 (48.3%) | .306 | .374 |
| <1/2 | 231 (51.7%) |      |          |
| **LVSI** | |          |           |
| Positive | 68 (15.2%) | .300 | .008 |
| Negative | 379 (84.8%) |      |          |
| **LUSI** | |          |           |
| Yes | 171 (38.3%) | .681 | .454 |
| No | 276 (61.7%) |      |          |
| **CSI** | |          |           |
| Yes | 39 (8.7%) | .537 | .109 |
| No | 408 (91.3%) |      |          |
| **FIGO2009stage** | |          |           |
| Ia | 213 (47.7%) | .495 | .252 |
| Ib | 194 (43.4%) |      |          |
| II | 40 (8.9%) |      |          |
| **ESMO-ESGO-ESTRO** | |          |           |
| Low risk | 136 (30.4%) | .887 | .129 |
| Intermediate risk | 140 (31.3%) |      |          |
| High-intermediate risk | 75 (16.8%) |      |          |
| High risk | 96 (21.5%) |      |          |
| **Time interval between S and R** | |          |           |
| ≤49 days | 314 (70.2%) | .019 | .023 |
| >49 days | 133 (29.8%) |      |          |
| **Radiotherapy mode** | |          |           |
| EBRT alone | 20 (4.5%) | .150 | .517 |
| VBT alone | 295 (66.0%) |      |          |
| EBRT + VBT | 132 (29.5%) |      |          |
| **Chemotherapy** | |          |           |
| Yes | 95 (21.3%) | .601 | .583 |
| No | 352 (78.7%) |      |          |

Abbreviations: CSI, cervical stromal invasion; EBRT, external beam radiotherapy; LUSI, lower uterine segment invasion; LVSI, lymphatic vascular space invasion; MI, myometrial invasion; R, radiotherapy; S, surgery; VBT, vaginal brachytherapy.

<sup>a</sup>Endometrioid cancers were designated as grade 1, 2, or 3. All poorly differentiated cancers, uterine papillary serous cancers, and clear cell cancers were designated as grade 3.

sites of metastasis included the peritoneum, lung, liver, bone, brain, adrenal gland, and lymph node.

### 3.4 Analysis of prognostic factors

In the univariate analysis, age, preoperative serum CA125, surgical type and time interval between surgery and radiotherapy were significant for 5-year OS. Age, surgical type, LVSI and time interval between surgery and radiotherapy were significant for 5-year DFS, as shown in Table 1.

The results of the multivariate analysis of all 447 patients for OS showed that older age (HR 4.33, p = .0007) and CA125 positivity (HR 2.86, p = .0162) were independent prognostic factors for OS. In the multivariate analysis for DFS, age, complete surgical stage, LVSI and time interval between surgery and radiotherapy were independent
FIGURE 2  Survival function of CA125 and age alone (A and B) and in combination (C) to predict 5-year overall survival (OS) after adjusting surgical type, time interval between surgery and radiotherapy, grade, lymphatic vascular space invasion (LVSI), ESMO-ESGO-ESTRO risk classification, external beam radiotherapy (EBRT), and chemotherapy covariates [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2  Value of CA125 and age alone or in combination in predicting overall survival (OS) in early-stage endometrial cancer (EC)

|                  | AUC  | Sensitivity (%) | Specificity (%) | p-Value |
|------------------|------|----------------|-----------------|---------|
| CA125 combined with age | .692 | .682           | .682            | .002    |
| CA125 alone      | .590 | .409           | .772            | .152    |
| Age alone        | .654 | .545           | .765            | .015    |

Abbreviation: AUC, area under the curve.

prognostic factors, while CA125 was not statistically significant in the multivariate analyses.

We further analyzed the relationship between CA125 and clinical parameters. The clinical characteristics of each group are shown in Table 3. We found that there were more patients with deep MIs, with LUSI(+), with FIGO 2009 stage Ib and II, and receiving EBRT and chemotherapy (p < .05) in the CA125-positive group. The survival function is shown in Figure 2. There was a significant difference between the two groups. After adjusting the clinicopathological covariates, such as Surgical type, time interval between S and R, grade, LVSI, ESMO-ESGO-ESTRO risk classification, EBRT, and chemotherapy, the 5-year OS of the patients in the CA125-positive group and CA125-negative group were 91.3% and 96.0% (p = .033).

After adjusting the above clinicopathological covariates, the 5-year OS among patients aged ≤61 years and those aged >61 years were 96.9% and 88.8%, respectively (p = .001). The survival function is shown in Figure 2.

Finally, the relationship between CA125 combined with age and other clinical features was analyzed. The AUC of CA125 combined with age at diagnosis was .692 (sensitivity = 68.2%, specificity = 68.2%, p < .002), which was significantly better than the predictive value of CA125 or age alone, as shown in Table 2.

Therefore, patients were divided into four groups according to age and CA125: age ≤61 years and CA125 < 37.7 U/ml, age ≤61 years and CA125 > 37.7 U/ml, age >61 years and CA125 < 39.35 U/ml, and
TABLE 3  The baseline characteristics of the 447 patients with endometrial cancer (EC) stratified by CA125 and age

| Characteristic                       | CA125 groups |  | Page and CA125 combined groups |  |
|--------------------------------------|--------------|---|-------------------------------|---|
|                                      | Negative     | Positive | 250 (%) | 85 (%) | 91 (%) | 21 (%) |  |
| Age                                  |              |          |          |        |        |        |  |
| ≤61 years                            | 341 (73.5%)  | 106 (%)  | /        | /      | /      | /      |  |
| >61 years                            | 91 (26.7%)   | 21 (19.8%) | /       | /      | /      | /      |  |
| Endometrioid carcinoma               | 318 (93.3%)  | .827     | 234 (93.6%) | 79 (92.9%) | 84 (92.3%) | 19 (90.5) | .938 |
| Surgical type                        |              |          |          |        |        |        |  |
| Completely surgically staged         | 242 (71.0%)  | 71 (67.0%) | .467    | 186 (74.4%) | 61 (71.8%) | 56 (61.5%) | 10 (47.6%) | .014 |
| Grade                                |              |          |          |        |        |        |  |
| G1                                   | 124 (36.4%)  | 37 (34.9%) | .963    | 93 (37.2%) | 30 (35.3%) | 31 (34.1%) | 7 (33.3%) | .997 |
| G2                                   | 142 (41.6%)  | 45 (42.5%) |        | 104 (41.6%) | 36 (42.4%) | 38 (41.8%) | 9 (42.9%) |          |
| G3                                   | 75 (22.0%)   | 24 (22.6%) |        | 53 (21.2%) | 19 (22.4%) | 22 (24.2%) | 5 (23.8%) |          |
| MI                                   |              |          |          |        |        |        |  |
| ≥1/2                                 | 156 (45.7%)  | 60 (56.6%) | .049    | 100 (40.0%) | 45 (52.9%) | 56 (61.5%) | 15 (71.4%) | .000 |
| <1/2                                 | 185 (54.3%)  | 46 (43.4%) |        | 150 (60.0%) | 40 (47.1%) | 35 (38.5%) | 6 (28.6%) |          |
| LVSI                                 |              |          |          |        |        |        |  |
| Positive                             | 47 (13.8%)   | 21 (19.8%) | .163    | 34 (13.6%) | 16 (18.8%) | 13 (14.3%) | 5 (23.8%) | .453 |
| Negative                             | 294 (86.2%)  | 85 (80.2%) |        | 216 (86.4%) | 69 (81.2%) | 78 (85.7%) | 16 (76.2%) |          |
| LUSI                                 |              |          |          |        |        |        |  |
| Yes                                  | 121 (35.5%)  | 50 (47.2%) | .039    | 94 (37.6%) | 45 (52.9%) | 27 (29.7%) | 5 (23.8%) | .006 |
| No                                   | 220 (64.5%)  | 56 (52.8%) |        | 156 (62.4%) | 40 (47.1%) | 64 (70.3%) | 16 (76.2%) |          |
| CSI                                 |              |          |          |        |        |        |  |
| Yes                                  | 26 (7.6%)    | 13 (12.3%) | .167    | 20 (8%)   | 13 (15.3%) | 6 (6.6%)   | 0 (0%)   | .063 |
| No                                   | 315 (92.4%)  | 93 (87.7%) |        | 230 (92.0%) | 72 (84.7%) | 85 (93.4%) | 21 (100%) |          |
| FIGO 2009 stage                      |              |          |          |        |        |        |  |
| Ia                                   | 172 (50.4%)  | 41 (38.7%) | .048    | 139 (55.6%) | 36 (42.4%) | 33 (36.3%) | 5 (23.8%) | .000 |
| Ib                                   | 143 (41.9%)  | 51 (48.1%) |        | 91 (36.4%) | 36 (42.4%) | 52 (57.1%) | 15 (71.4%) |          |
| II                                   | 26 (7.6%)    | 14 (13.2%) |        | 20 (8.0%)   | 13 (15.3%) | 6 (6.6%)   | 1 (4.8%)  |          |
| ESMO-ESGO-ESTRO risk classification  |              |          |          |        |        |        |  |
| Low risk                             | 108 (31.7%)  | 28 (26.4%) | .367    | 88 (35.2%) | 24 (28.2%) | 20 (22.0%) | 4 (19.0%) | .088 |
| Intermediate risk                    | 109 (32.0%)  | 31 (29.2%) |        | 71 (28.4%) | 21 (24.7%) | 38 (41.8%) | 10 (47.6%) |          |
| High-intermediate risk               | 57 (16.7%)   | 18 (17.0%) |        | 42 (16.8%) | 16 (18.8%) | 15 (16.5%) | 2 (9.5%)  |          |
| High risk                            | 67 (19.6%)   | 29 (27.4%) |        | 49 (19.6%) | 24 (28.2%) | 18 (19.8%) | 5 (23.8%) |          |
| Radiotherapy mode                    |              |          |          |        |        |        |  |
| VRT alone                            | 238 (69.8%)  | 57 (53.8%) | .003    | 178 (71.2%) | 43 (50.6%) | 60 (65.9%) | 14 (66.7%) | .007 |
| EBRT ± VBT                           | 103 (30.2%)  | 49 (46.2%) |        | 72 (28.8%) | 42 (49.4%) | 31 (34.1%) | 7 (33.3%) |          |
| Chemotherapy                         |              |          |          |        |        |        |  |
| Yes                                  | 65 (19.1%)   | 30 (28.3%) | .049    | 48 (19.2%) | 25 (29.4%) | 17 (18.7%) | 5 (23.8%) | .217 |
| No                                   | 276 (80.9%)  | 76 (71.7%) |        | 202 (80.8%) | 60 (70.6%) | 74 (81.3%) | 16 (76.2%) |          |
| Time interval between S and R        |              |          |          |        |        |        |  |
| ≤49 days                             | 244 (71.6%)  | 70 (66.0%) | .277    | 180 (72%)  | 56 (65.9%) | 64 (70.3%) | 14 (66.7%) | .736 |
| >49 days                             | 97 (28.4%)   | 36 (34%)  |        | 70 (28%)   | 29 (34.1%) | 27 (29.7%) | 7 (33.3%) |          |
| Overall mortality                    |              |          |          |        |        |        |  |
| Yes                                  | 13 (3.8%)    | 9 (8.5%)  | .069    | 6 (2.4%)   | 4 (4.7%)   | 7 (7.7%)   | 5 (23.8%) | .000 |
| No                                   | 328 (96.2%)  | 97 (91.5%) |        | 244 (97.6%) | 81 (95.3%) | 84 (92.3%) | 16 (76.2%) |          |

Note: 1 = age ≤ 61 years and CA125 < 37.7, 2 = age ≤ 61 years and CA125 > 37.7, 3 = age > 61 years and CA125 < 39.35, and 4 = age > 61 years and CA125 > 39.35.

Abbreviations: CSI, cervical stromal invasion; EBRT, external beam radiotherapy; LUSI, lower uterine segment invasion; LVSI, lymphatic vascular space invasion; MI, myometrial invasion; R, radiotherapy; S, surgery; VBT, vaginal brachytherapy.

DISCUSSION

The purpose of this study was to evaluate the predictive value of CA125 and age for the prognosis of early-stage EC after postoperative adjuvant therapy. The results of survival analysis show that only preoperative serum CA125 and age at diagnosis were independent...
prognostic factors for 5-year OS with early-stage EC. The results of previous literatures also proved that preoperative tumor markers such as CA125 and age are prognostic factors for EC.6,7

CA125 is a glycoprotein expressed in mesenchymal cells of the adult pleura, pericardium, and peritoneum, as well as cells derived from embryonic Mullerian tubes, namely, the oviduct, endometrium, and endometrial cells of the cervix. In premenopausal women, its level can be elevated due to a variety of physiological states and benign diseases, including inflammation, endometriosis, and menstruation, among others.8 In EC, CA-125 levels have been shown to be associated with several clinicopathological factors (2–4, 6, 9–17) to predict LVSI, MI, lymph node metastasis, adnexal involvement, distant metastasis, OS, and DFS. There are different cut-off values for different age groups and for predicting different endpoints.2,11,13,16

Most of the current studies on CA125 in EC are focused on finding ways to predict of advanced EC, such as distinguishing cases of extraterine spread of EC from those with localized disease or monitoring advanced and recurrent cases.2–5,9,10,13,15,16 Only two studies have reported the independent predictive value of CA125 for OS, LRFS and DFS after adjuvant therapy for early-stage EC.17,18 However, they were single-center retrospective studies with a small number of cases.

Age is another important clinical factor for EC. Our previous results showed that age was an important independent prognostic factor for early-stage EC and that the disease-related mortality of patients increased gradually with increasing age.7

Due to the influence of age on CA125, there are different cut-off values of CA125 for different age groups. In this study, the CA125-positive group had worse clinicopathological features and OS. But its AUC and sensitivity were not high. In addition, the elderly group also showed worse survival. However, its AUC, sensitivity, and specificity were still unsatisfactory. Combined with CA125 and age after adjusting other clinicopathological factors showed better AUC, sensitivity, and specificity and predicted a group with poor survival in the final results. Therefore for patients with early-stage EC, CA125 and age also had their own predictive value, but the predictive abilities alone were limited. CA125 combined with age showed better AUC, sensitivity, and specificity that can make it easier and faster to distinguish high-risk patient groups, which is very helpful to the decision-making of clinical treatment plan.

In the previous literature, CA125 combined with a variety of clinicopathological factors was also suggested to increase the accuracy of clinical diagnosis, such as MRI.11 Mesothelin20 and HE4. At present, HE4 and CA125 are clinically approved tumor markers for the diagnosis and prognosis of EC. Among them, HE4 is considered to be more correlated with the prognostic factors of EC. The sensitivity of HE4 to predict the survival of EC patients was better than that of CA125 (.71 vs .35), but there was no significant difference in the specificity between the two markers. However, in the subgroup analysis, the sensitivity of HE4 in Asian patients (.53) was significantly lower than that in Caucasian patients (.86).5,11,12,14 Therefore, the role of HE4 needs further clinical investigation in Asian populations. In addition, Njoku et al. pointed out that urine CA125 exhibited good discriminatory potential for Type I and early-stage tumors (AUC .93 and .90, respectively).26

In addition, it was worth mentioning that CA125 did not show statistical significance for DFS in this study. Why did CA125 not show any statistical significance for DFS? In most previous studies, CA125 elevation was associated with extraterine invasion. However, in stage I–II EC, there is no extraterine spread, such as lymph node metastasis or adnexal involvement. Therefore, CA125 did not show significance for DFS in these patients with early-stage EC in this study. However, the increase in CA125 indicates that there is a potential risk of tumor progression, such as MI and LUSI. Age plus CA125 as an overall indicator showed greater significance for OS. Therefore, for older patients with CA125 positivity, a more active treatment approach should be considered as the clinical treatment strategy, if possible.

This study is the only multicenter study to evaluate the prognostic value of preoperative serum CA125 for early-stage EC after initial treatment thus far. This study provides new and valuable evidence for the application of CA125 in early-stage EC. However, its limitation is that it is a retrospective study, which leads to the lack of some clinical information. In addition, due to the limitation of enrollment time, there is no molecular typing in the current data. Only patients with data on CA125 were included, which may result in selection bias.

The combination of CA125 and age can better evaluate the prognosis of patients with early-staged EC before operation and clarify the risk classification of patients earlier in a simpler way, so as to make a more suitable clinical scheme for patients with early-staged EC. In future research, we hope to combine imaging and gene detection to enhance the accuracy of prediction.

5 | CONCLUSION

Although preoperative CA125 has limited sensitivity in predicting the prognosis of early-stage EC after initial treatment, it remains a useful serum marker for the risk assessment of early-stage EC. Combining CA125 with age increases its predictive sensitivity. Thus, this study provides new and valuable evidence for the application of CA125 in early-stage EC.

AUTHOR CONTRIBUTIONS

Conceptualization, data curation, formal analysis, investigation, methodology, resources, software, supervision, validation, visualization, roles/writing - original draft, writing - review and editing: Shuai Sun. Data curation and validation: Lijuan Zou. Data curation and validation: Tiejun Wang. Data curation and validation: Zi Liu. Data curation and validation: Jianli He. Data curation and validation: Xiaoge Sun. Data curation and validation: Wei Zhong. Data curation and validation: Fengju Zhao. Data curation and validation: Xiaomei Li. Data curation and validation: Sha Li. Data curation and validation: Hong Zhu. Data curation and validation: Zhanshu Ma. Data curation, investigation, and resources: Wenhui Wang. Data curation, investigation, and resources: Meng Jin. Conceptualization, data curation, funding acquisition, project administration, resources, validation, writing - review and editing: Fuquan Zhang. Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology,
project administration, resources, software, supervision, validation, visualization, writing - review and editing: Xiaorong Hou. Conceptualization, data curation, funding acquisition, project administration, resources, validation, writing - review and editing: Lichun Wei. Conceptualization, data curation, funding acquisition, project administration, resources, validation, writing - review and editing: Ke Hu. Read and approved the final manuscript: Shuai Sun, Lijuan Zou, Tiejun Wang, Zi Liu, Jianli He, Xiaoge Sun, Wei Zhong, Fengjui Zhao, Xiaomei Li, Sha Li, Hong Zhu, Zhanhua Ma, Wenhui Wang, Fuquan Zhang, Xiaorong Hou, Lichun Wei, and Ke Hu.

ACKNOWLEDGMENTS
The study is supported by the Nonprofit Central Research Institute Fund of Chinese Academy of Medical Sciences (grant number: 2019XK320046), Peking Union Medical College Postgraduate Education Reform Program (grant number: 10023201900104), and the Ministry of Science and Technology of China (grant number: 2016YFC0105207).

CONFLICT OF INTEREST
The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT
This retrospective study was approved by the Ethics Review Committee of Peking Union Medical College Hospital, Chinese Academy of Medical Sciences (protocol number: S-K139). The clinical trial ID of the study is ChiCTR-PRC-17010712. Evaluation of all data met the requirements of the Helsinki Declaration. The authors declare that the paper is being submitted for consideration for publication in Radiation Oncology and the content has not been published or submitted for publication elsewhere.

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How to cite this article: Sun S, Wei L, Zou L, et al. Preoperative serum CA125 level and age at diagnosis: An effective prognosis prediction tool for patients with early-stage endometrial cancer. Asia-Pac J Clin Oncol. 2023;19:e258-e266. https://doi.org/10.1111/ajco.13895