Prognostic Significance of Preoperative Serum CA125, CA19-9, CA72-4, CEA, and AFP in Patients With Endometrial Cancer

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Abstract

Objective: To determine the factors related to overall survival (OS) and progression-free survival (PFS) in endometrial cancer (EC) patients.

Materials and methods: A retrospective cohort study of 906 EC patients was conducted at Shengjing Hospital, China Medical University. Baseline information about the patients, tumor characteristics, and data on five serum biomarkers (CA125, CA19-9, CA72-4, CEA, and AFP) were collected. Groups and their survival rates were compared using log-rank tests and Kaplan-Meier analysis, respectively. Hazard ratios (HRs) and 95% confidence intervals (CIs) were determined using univariate or multivariate Cox proportional hazard models. The outcome measures used were OS, defined as the time between surgery and death or last follow-up for surviving patients, and PFS, defined as the time from the completion of initial surgery to either first progression, disease recurrence, or death.

Results: Multivariate analysis showed lower PFS associated with age ≥ 66 years (P < 0.001), type II histology (P = 0.015), low degree of tumor differentiation (P = 0.004), and FIGO stage III & IV (P = 0.002). Elevated CA125 (P = 0.042) and AFP (P = 0.016) were identified as independent biomarkers for PFS. Increased CA125 (P = 0.013), age ≥ 66 years (P < 0.001), type II histology (P□0.001), and FIGO stage III & IV (P = 0.015) were independent factors associated with OS. Analysis of the CA125 sub-group showed that individuals with elevated CA125 andAFP (P = 0.049) had significantly lower PFS.

Conclusion: This study suggests that CA125 and AFP are prognostic biomarkers for EC.

Introduction

Endometrial cancer (EC) is one of the most common gynecological cancers in developed countries such as Europe and the United States [1]. With the increase in life expectancy and obesity prevalence, a corresponding rise in the incidence of EC, worldwide, is expected [2]. The American Cancer Society estimates that there will be 65,620 new cases and 12,590 deaths related to EC by 2020. The incidence of EC in women over 50 years old is 87 per 100,000 [3, 4]. In China, EC ranks second among female malignancies, and contributed to about 63,400 new cases and 21,800 deaths in 2015 [5]. An early symptom of EC is postmenopausal vaginal bleeding. While most patients can be diagnosed early, advanced stage diagnosis is seen in more than 25% of patients [6]. We, therefore, sought to find effective biomarkers to predict prognosis in EC patients and identify patients at a potentially high risk of developing EC.

A tumor marker is a substance produced and secreted by tumor cells that subsequently enters body fluids or tissues. Five serological tumor markers—carbohydrate antigen 125 (CA125), carbohydrate antigen 19 − 9 (CA19-9), carbohydrate antigen 72 − 4 (CA72-4), carcinoembryonic antigen (CEA), and alpha-fetoprotein (AFP)—are routinely used in clinical practice for the diagnosis and prediction of prognosis in different cancers. The most widely used biomarker for EC is CA125. It is used in diagnosis, detection of tumor recurrence, and prediction of survival outcomes. However, CA125 does not always specifically reflect the metastatic potential of EC and its levels do not increase during disease progression in some patients. The identification of sensitive and specific EC serum markers would provide a means of monitoring treatment responses, and facilitate the prediction of recurrence or metastasis. Numerous potential EC serological tumor markers have been studied, including Human Epididymis Protein 4 (HE4), CA19-9, CA72-4, and CEA. Serum HE4 can be an effective marker for predicting nodal metastases in women with EC [7]. HE4 appears to be more accurate in predicting disease recurrence than CA125, especially in high-risk EC patients with a large number of distant metastases [8]. Bian and colleagues showed that the use of HE4 combined with CA125, CA72-4, and CA19-9 is valuable in the early diagnosis of EC, and that these are useful immunological tissue markers for patients with EC [9]. Unfortunately, serum markers are more commonly used for the evaluation of delayed prognosis for EC patients [10, 11]. The study of EC tumor markers and their expression patterns can provide valuable additional information when making judgments about EC pathology and deciding upon a course of treatment. Tumor markers play a significant role in patient evaluation and assessing the progress of individualized treatment, and are especially important for the prediction of prognosis. We performed a retrospective study at Shengjing Hospital of China Medical University. The aims of the study were to assess the relationship between levels of pre-operative serological tumor biomarkers and clinicopathological parameters in EC patients, and to identify novel biomarkers associated with the duration of post-operative survival.

Materials And Methods

2.1 Study Population

We performed a retrospective study of EC patients attending Shengjing Hospital affiliated to China Medical University from December 2010 to March 2017. This study was approved by the Institutional Review Committee of the Shengjing Hospital of China Medical University (No. 2018PS251K). All patients included in the study met the following criteria: 1) age ≥ 18 years; 2) underwent hysterectomy at Shengjing Hospital; 3) post-operative diagnosis of EC by pathology; 4) no history of other malignant tumors; 5) no active infection; 6) no blood disease or other serious comorbidities; 7) no thromboembolic events; and 8) complete data for all of the variables included in the study. A total of 259 patients did not meet all of the inclusion criteria and were excluded (96 patients were lost to follow-up), while 906 patients were included (Fig. 1). Informed consent was acquired from all participants in the research.

2.2 Treatment details

The surgical procedures used were total hysterectomy or modified radical hysterectomy, double appendectomy, and pelvic and para-aortic lymphadenectomy for patients with type □ EC. After the operation, except for stage IA patients, cases were routinely treated with intracavitary irradiation or full pelvic irradiation radiotherapy. For patients in stage II and above, treatment was sometimes supplemented with chemotherapy, especially in cases with unusual or advanced and recurrent states of the disease. The chemotherapy regimen used at Shengjing Hospital was primarily cyclophosphamide (C) + doxorubicin (A) + cisplatin / carboplatin (P).

2.3 Data Collection

The following demographic and clinical data were collected from the electronic medical records of the Shengjing Hospital Information System: patient's age at diagnosis; pre/post-menopausal status; International Federation of Obstetrics and Gynecology Association (FIGO) stage; tumor grade; histology type; tumor myometrial invasion depth; and existing comorbidities. Pre-operative levels of serum tumor markers including CA125, CA72-4, CA19-9, AFP, and CEA in all enrolled patients were measured using a chemiluminescence immunoassay.

Data collection was conducted by professional gynecologists and pathologists. Evaluation and classification of tumors was made in accordance with the WHO classification during post-operative examinations of tumor pathology, and all tumors were clinically staged according to the FIGO guidelines (2009). Pathologists divided tumors into well (G1), moderately (G2), or poorly (G3) differentiated, and tumor histology was classified as type I (mainly endometrioid) or type II (non-endometrioid). Serum CA125 level was classified as CA125-normal (≤ 35 U/ml) or CA125-high (>35 U/ml). Serum CA72-4 level was classified as CA72-4-normal (≤ 6.9 U/ml) or CA72-4-high (>6.9 U/ml). Serum CA19-9 level was classified as CA19-9-normal (≤ 37 U/ml) or CA19-9-high (>37 U/ml). Serum AFP level was classified as AFP-normal (≤ 9 ng/ml) or AFP-high (>9 ng/ml). Serum CEA level was classified as CEA-normal (≤ 5 ng/ml) or CEA-high (>5 ng/ml).

2.4 Follow-up and Outcomes

Post-operative follow-up was conducted over the telephone. The date of the last follow-up was June 30, 2018. The primary outcomes used for assessment were OS and PFS. The date of death was obtained during follow-up or from a death certificate.

2.5 Statistical Analysis

All data were analyzed using SPSS ver. 20.0 (IBM Corp, Armonk, NY). Descriptive statistics were used to represent patients' general characteristics. To identify associations between clinicopathological features and tumor biomarkers, chi-square tests were used for qualitative variables, and t-tests were used for quantitative variables. Kaplan-Meier analysis was used to compare differences in survival, and log-rank tests were used to make comparisons between sub-groups. Univariate and multivariate analyses were used to identify factors that related to patient survival, and the Cox proportional hazards model was used to test for independence of the effect. Data were expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). Since previous studies have shown that CA125 can be used for prognosis of endometrial cancer, we performed sub-group analysis using the concentration of CA125 as a variable. The level of significance was set at a P-value of less than 0.05.

Results

3.1 Patient Baseline Characteristics

A flow chart of the patient inclusion and exclusion process is shown in Figure 1. At the end of this process, a total of 906 patients were included in the study. The median follow-up time was 44 months (IQR: 29 to 61 months). The characteristics of the eligible patients are summarized in Table 1. Of the 906 patients, 740 had tumors classified as pathological type I, and 166 had tumors classified as type II. One hundred and twenty-three patients had not experienced menopause at the time of diagnosis, and the remaining 783 cases were diagnosed with endometrial cancer after menopause. Post-operative FIGO staging by examination of EC pathology identified 652 stage I cases, 111 stage II cases, 101 stage III cases, and 42 stage IV cases. Highly differentiated tumors were present in 493 patients, 254 patients had moderately differentiated tumors, and the remaining 159 patients had poorly differentiated tumors. The seroprevalence rate of pre-operative CA125 was 27.5% (250/906), that of CA19-9 18.2% (165/906), of CA72-4 18.4% (167/906), of CEA 0.88% (8/906), and of AFP 5.07% (46/906).

3.2 Serum CA125, CA19-9, CA72-4, CEA, AFP Levels of Patients With EC

Patients were classified into two groups: event (recurrence, metastasis, or death occurred); and non-event (no recurrence, metastasis, or death). The two groups were compared for levels of pre-operatively measured CA125, CA19-9, CA72-4, CEA, and AFP. Levels of CA125 (P = 0.002), CA19-9 (P = 0.016), CEA (P = 0.021), and AFP (P = 0.008) were significantly higher in the event group than in the non-event group (Figure 2). This observation indicates that CA125, CA19-9, CEA, and AFP may be potential markers for the prognosis of EC patients.

3.3 Univariate Survival Analysis of EC Patients

The median follow-up time was 48 months. Five-year OS was 90.0%, and five-year PFS was 87.0%. Single factor survival analysis was performed to determine the effect in EC patients of the variables age, menopausal status, pathology type, degree of differentiation, FIGO stage, infiltration of myometrial location, complications, serum CA125, CA19-9, CEA, and AFP levels. According to univariate analysis (Figure 3), age (P < 0.001), menopausal status (P = 0.006), BMI (P < 0.001), pathological type (P < 0.001), degree of differentiation (P < 0.001), myometrial invasion (P < 0.001), and FIGO stage (P < 0.001) were significantly associated with poor PFS prognosis for EC patients. Serum levels of CA125 (P < 0.001), CA19-9 (P = 0.001), CEA (P < 0.001), and AFP (P = 0.003) were also associated with poor PFS prognosis for EC patients. We also identified age (P < 0.001), menopausal status (P = 0.015), BMI (P = 0.011), pathological type (P < 0.001), degree of differentiation (P < 0.001), myometrial invasion (P = 0.001), FIGO stage (P < 0.001), and serum levels of CA125 (P = 0.004), CA19-9 (P = 0.011), and CEA (P < 0.001) as factors in prognosis of OS in EC patients (Figure 4). Differences in survival according to serum CA125, CA19-9, CEA, and AFP were compared using a Kaplan-Meier analysis (Figures 5 and 6).

3.4 Multivariate Analysis of EC Patients

A multivariate analysis of factors that had been identified as being important by univariate analysis was performed. These factors included age, menopausal status, pathological type, degree of differentiation, myometrial invasion、FIGO stage, and serum CA125, CA19-9, CEA, and AFP levels. Elevated serum CA125 (P = 0.029) and AFP (P = 0.003), histological subtype (P = 0.002), obesity (P = 0.004), menopause (P = 0.024), poor degree of differentiation (P = 0.001), FIGO

stage (P < 0.001), and age ≥ 66 years (P < 0.001) were independent factors for PFS prognosis in EC patients(Figure 7). Increased serum CA125 (P = 0.042), age ≥ 66 years (P < 0.001), type Ⅱ histological classification (P Ⅱ0.001), low degree of differentiation (P =0.004), and FIGO stage (P = 0.013) were independent factors for prognosis of OS in EC patients (Figure 8).

3.5 Sub-group Analysis of Tumor Markers by CA-125 Status

CA125 is widely used for EC diagnosis and prognosis. It is primarily used for prognostic evaluation after radical surgery for endometrial cancer. It has been hypothesized that elevation of CA-125 levels might be related to recurrence and metastasis of the disease. However, in our patient cohort, CA125 was only positive in 27.5% of cases. Therefore, a sub-group analysis was performed according to CA125 status in the patients. In the high CA125 group (Table 2), serum AFP (P=0.005) remained an independent factor for PFS prognosis. Age, histological type, and FIGO staging were also identified as independent prognostic factors for PFS and OS. However, in the group with normal levels of CA125 (Table 3), age, menopause, degree of differentiation, histological type and FIGO staging were determined as the prognostic factors for PFS; only age, differentiation degree and FIGO staging were determined as the prognostic factors for OS.

Discussion

EC is one of the most common malignancies in women. The FIGO staging system provides guidance on the assessment of prognosis and treatment of EC patients. However, prognostic status can vary significantly, even for patients in the same stage of the disease. For optimally individualized patient care and management, the establishment of convenient and cost-effective methods is highly desirable. Moreover, measurement of tumor biomarkers is convenient and cost-effective. Therefore, biomarkers are promising tools for guiding treatment regimens and for the long-term monitoring of tumor recurrences and metastases. The identification and use of biomarkers for EC is an active area of research [12–15]. Serum level of CA125 has been described as an effective tumor biomarker for EC patients [17–20]. However, its use in the pre-operative assessment of EC patients remains controversial and has not been studied in depth [21]. The prognosis of EC patients can also be assessed using serum levels of HE4, CA72-4, and CA19-9. Each of these biomarkers has its own advantages and disadvantages [22–24]. Despite the availability of these options, the identification of accurate and effective EC biomarkers for identifying individuals at high risk of EC, assessing their prognosis, and deciding upon treatment remains challenging.

We performed a retrospective study of EC patients who had serum levels of CA125, CA72-4, CA19-9, AFP, and CEA measured prior to surgery. The combination of these five tumor markers was used as a preoperative routine examination for patients undergoing endometrial cancer surgery in Shengjing Hospital, to evaluate the patient's physical condition. We found that the group of patients with adverse outcomes had higher serum levels of CA125, CA19-9, AFP, and CEA compared to the group with positive outcomes. Both univariate and multivariate analyses showed that elevated serum levels of CA125 indicated a poor prognosis for OS and PFS in EC patients. Patients with serum concentration of CA125 ≥ 35.0 mM had a 1.9-fold higher risk of death due to cancer compared to patients with baseline levels of CA125 (P = 0.042, HR = 1.625, 95% CI: 1.017–2.598). This observation is consistent with those previously published [5, 10, 15]. In our study, we also identified serum concentration of AFP ≥ 9 ng/ml in EC patients to be a marker for poor prognosis for PFS (P = 0.003, HR = 4.979, 95% CI: 1.703–14.557).

AFP is a glycoprotein that is mainly synthesized by fetal liver cells and the yolk sac. It is found in high concentrations in the fetal circulatory system and declines shortly after birth to be functionally replaced by albumin. It is difficult to detect, and is present in extremely low concentrations in adult serum. AFP has many important physiological functions, including transport functions, bidirectional regulation of growth, immunosuppression, and is also involved in T cell-induced apoptosis. Although AFP is a well-characterized tumor marker for hepatocellular carcinoma and yolk sac tumors [25]. but is also elevated in a variety of extrahepatic tumors including gastrointestinal tumors and pancreatic, gallbladder, lung, and bladder cancers [26]. AFP is therefore a non-specific biomarker, which can indicate the presence of a variety of tumors. However, so far, there are no published studies to prove that AFP can be used as a prognostic indicator of endometrial cancer. Our study is the first to describe the use of serum AFP as a potential diagnostic and prognostic tool in EC. Patients with elevated serum AFP are likely to have worse outcomes than patients with normal concentrations of serum AFP. AFP measurements may provide further information after stratification of surgical risk, aiding clinicians in the prediction of prognosis, and providing a basis for clinical treatment.

Tumor-related markers cannot be systematically screened and comprehensively detected in all individuals, because of financial and technical limitations [27]. Concurrent detection of specific tumor biomarkers could therefore have a large impact on clinical practice [28]. Our study suggested that serum levels of CA125 and AFP might be used together for effective monitoring of cancer recurrence and for predicting patient prognosis.

The study has some limitations. Some detailed patient information could not be obtained due to a lack of follow-up. However, as a large EC patient sample population was enrolled, and the data from the electronic medical records system of Shengjing Hospital of China Medical University were verified, the sample size was large enough to provide a statistically significant basis for the conclusions drawn. In conclusion, the levels of serum CA125, CA19-9, AFP, and CEA prior to surgery appear to be related to the clinicopathological characteristics of EC patients. AFP concentration is a promising biomarker for EC, and could be a valuable independent factor for the prediction of patient prognosis and survival.

Conclusions

Our study identifies elevated CA125 in combination with AFP as being independent biomarkers for OS and PFS of patients with EC, with a higher serum levels indicating poorer prognosis. Serum levels of CA125 and AFP might be used together for effective monitoring of cancer recurrence and for predicting patient prognosis, These findings provide insight into the prognostic significance of serum tumor markers and identification of patients with poor prognosis in EC..

Abbreviations

EC endometrial cancer

OS overall survival

PFS progression-free survival

FIGO International Federation of Gynecology and Obstetrics

CA125 carbohydrate antigen 125

CA19-9 carbohydrate antigen 19 – 9

CA72-4 carbohydrate antigen 72 – 4

AFP alpha-fetoprotein

CEA carcinoembryonic antigen

HE4 human epididymal protein 4

Declarations

Author contributions

Zi-hao Wang participated in the design of the work, methodology, data interpretation, and analysis for the work; and drafted the manuscript. Yun-zheng Zhang and Yu-shan Wang carried out the statistical analyses and drafted the manuscript. Kun Yang and Lu-he Shan participated in the methodology, data interpretation, and analysis for the work. Qi-jun Wu and Xiao-xin Ma designed the study; participated in data interpretation, analysis for the work, and methodology. All authors read and approved the final manuscript.

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Availability of data and materials

There are no linked research data sets for this paper. Data are available from the corresponding author on reasonable request.

Consent for publication

All listed authors have actively participated in the study and have read and approved the submitted manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Shengjing Hospital of China Medical University.

Competing interests

The authors declare no conflict of interest.

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Tables

Table 1. Patient characteristics and relationships between the clinicopathological characteristics and serum tumor markers.

	cases	CA125			CA199			CA724			AFP	
	No.(%)	<=35	>35	P	<=37	>37	P	<=6.9	>6.9	P	<=9	>9
Age				0.387			0.821			0.699		
<66	811(89.5)	589(90.1)	222(88.1)		665(89.6)	146(89.0)		662(89.7)	149(88.7)		804(89.5)	7(8
≥66	95(10.5)	65(9.9)	30(11.9)		77(10.4)	18(11.0)		76(10.3)	19(11.3)		94(10.5)	1(1
BMI				0.146			0.389			0.410		
Non-obesity	729(80.5)	534(82.7)	195(77.4)		601(81.0)	128(78.0)		590(79.9)	139(82.7)		723(80.5)	6(7
Obesity	177(19.5)	120(18.3)	57(22.6)		141(19.0)	36(22.0)		148(20.1)	29(17.3)		175(17.5)	2(2
Menopause				0.210			0.115			0.766		
No	123(13.6)	83(12.7)	40(15.9)		107(14.4)	16(9.8)		99(13.4)	24(14.3)		123(13.7)	0(0
Yes	783(86.4)	571(87.3)	212(84.1)		635(85.6)	148(90.2)		639(86.6)	144(85.7)		775(86.3)	8(1
Histological type				0.463			0.014			0.031		
I	740(81.7)	538(82.3)	202(80.2)		595(80.2)	145(88.4)		593(80.4)	147(87.5)		734(81.7)	6(7
II	166(18.3)	116(17.7)	50(19.8)		147(19.8)	19(11.6)		145(19.6)	21(12.5)		164(18.3)	2(2
Differentiation degree				0.929			0.729			0.618		
G1	493(54.4)	358(54.7)	135(53.6)		406(54.7)	87(53.0)		404(54.7)	89(53.0)		489(54.5)	4(5
G2	254(28.0)	183(28.0)	71(28.2)		204(54.5)	50(30.5)		202(27.4)	52(31.0)		250(27.8)	4(5
G3	159(17.5)	113(17.3)	46(18.3)		132(17.8)	27(16.6)		132(17.9)	27(16.1)		159(17.7)	0(0
Myometrial invasion				<0.001			<0.001			0.004		
Mucosa	110(12.1)	85(13.0)	25(9.9)		100(13.5)	10(6.1)		91(12.3)	19(11.3)		108(12.0)	2(2
Myometrial <1/2	489(54.0)	403(61.6)	86(34.1)		421(56.7)	68(41.5)		415(56.2)	74(44.0)		486(54.1)	3(3
Myometrial ≥1/2	307(33.9)	166(25.4)	141(56.0)		221(29.8)	86(52.4)		232(31.4)	75(44.6)		304(33.9)	3(3
FIGO stage				<0.001			<0.001			0.001		
I	652(72.0)	526(80.4)	126(50.0)		560(75.5.)	92(56.1)		551(74.7)	101(60.1)		648(73.3)	4(5
II	111(12.3)	79(12.1)	32(12.7)		93(12.5)	18(11.0)		85(11.5)	26(15.5)		110(12.2)	1(1
III	101(11.1)	38(5.8)	63(25.0)		62(8.4)	39(23.8)		73(9.9)	28(16.7)		100(11.1)	1(1
IV	42(4.6)	11(1.7)	31(12.3)		27(3.6)	15(9.1)		29(3.9)	13(7.7)		40(4.5)	2(3
Complication				0.260			0.600			0.386		
No	854(94.3	620(94.8)	234(92.9)		698(94.1)	156(95.1)		698(94.6)	156(92.9)		847(94.3)	7(8
Yes	52(5.7)	34(5.2)	18(7.1)		44(5.9)	8(4.9)		40(5.4)	12(7.1)		51 (5.7)	1(1

Table 2. Subgroup analyses of tumor antigens on OS and PFS in CA125–high EC patients.

	PFS				OS			
	Univariate analysis HR (95%CI)	P	Multivariate analysis HR (95%CI)	P	Univariate analysis HR (95%CI)	P	Multivariate analysis HR (95%CI)	P
Age (years)		<0.001		<0.001		<0.001		<0.001
<66	1.000		1.000		1.000		1.000	
≥66	4.373 (2.323-8.232)		3.437 (1.718-6.873)		6.345 (3.056-13.175)		4.144 (1.890-9.088)	
BMI		0.015		0.030		0.201		
Non-obesity	1.000		1.000		1.000			
obesity	2.031 (1.149-3.591)		1.928 (1.066-3.488)		1.577 (0.784-3.174)			
Menopause		0.052				0.122		
no	1.000				1.000			
yes	3.177 (0.988-10.213)				3.096 (0.740-12.948)			
Histological type		<0.001		0.005		<0.001		<0.001
□	1.000		1.000		1.000		1.000	
□	3.495 (2.012-6.071)		2.528 (1.328-4.815)		4.552 (2.364-8.765)		4.018 (1.907-8.465)	
Differentiation degree		<0.001		0.294		<0.001		0.141
G1	1.000		1.000		1.000		1.000	
G2	2.448 (1.199-4.997)		1.505 (0.683-3.315)		5.320 (1.938-14.604)		2.603 (0.899-7.533)	
G3	4.559 (2.255-9.215)		1.954 (0.845-4.520)		8.391 (3.013-23.368)		3.005 (0.978-9.233)	
Myometrial invasion		0.020		0.902		0.115		
Mucosa	1.000		1.000		1.000			
Myometrial <1/2	0.711 (0.218-2.317)		0.880 (0.250-3.095)		1.594 (0.333-7.634)			
Myometrial ≥1/2	1.904 (0.677-5.353)		1.078 (0.303-3.830)		3.054 (0.719-12.970)			
FIGO		<0.001		0.027		0.012		0.038
I	1.000		1.000		1.000		1.000	
II	0.788 (0.259-2.398)		0.910 (0.279-2.964)		0.562 (0.124-2.554)		0.623 (0.132-2.873)	
III	2.240 (1.116-4.496)		2.420 (0.959-6.103)		2.412 (1.090-5.338)		2.732 (1.131-6.601)	
IV	4.615 (2.265-9.403)		3.347 (1.360-8.238)		3.290 (1.369-7.907)		2.593 (1.041-6.459)	
Complication		0.283				0.165		
no	1.000				1.000			
yes	0.521 (0.158-1.713)				0.239 (0.032-1.804)			
CA199		0.169				0.144		
≤37	1.000				1.000			
□37	1.476 (0.847-2.572)				1.663 (0.841-3.288)			
CA724		0.306				0.876		

≤6.9	1.000				1.000			
6.9	1.351 (0.759-2.404)				1.058 (0.519-2.156)			
AFP		0.021		0.005		0.673		
≤9	1.000		1.000		1.000			
9	3.998 (1.236-12.936)		6.436 (1.758-23.562)		1.536 (0.209-11.279)			
CEA		0.002		0.069		0.001		0.063
≤5	1.000		1.000		1.000		1.000	
5	3.046 (1.509-6.149)		2.022 (0.947-4.317)		3.724 (1.664-8.331)		2.223 (0.958-5.157)	

Table 3. Subgroup analyses of tumor antigens on OS and PFS in CA125-normal EC patients.

	PFS				OS			
	Univariate analysis HR (95%CI)	P	Multivariate analysis HR (95%CI)	P	Univariate analysis HR (95%CI)	P	Multivariate analysis HR (95%CI)	P
Age (years)		<0.001		<0.001		<0.001		<0.001
<66	1.000		1.000		1.000		1.000	
≥66	6.840 (3.938-11.879)		4.472 (2.438-8.205)		11.050 (5.929-20.594)		9.352 (4.760-18.375)	
BMI		0.025		0.068		0.032		0.085
Non-obesity	1.000		1.000		1.000		1.000	
obesity	1.949 (1.087-3.496)		1.799 (0.958-3.376)		2.053 (1.063-3.966)		1.839 (0.919-3.678)	
Menopause		0.047		0.036		0.062		
no	1.000		1.000		1.000			
yes	4.173 (1.016-17.142)		4.861 (1.104-21.395)		6.632 (0.911-48.283)			
Histological type		0.008		0.034		0.002		0.057
□	1.000		1.000		1.000		1.000	
□	2.168 (1.219-3.854)		1.995 (1.053-3.783)		2.741 (1450-5.184)		1.920 (0.980-3.761)	
Differentiation degree		<0.001		0.003		0.002		0.014
G1	1.000		1.000		1.000		1.000	
G2	2.746 (1.355-5.565)		2.829 (1. 377-5.815)		2.625 (1.217-5.663)		3.001 (1.372-6.567)	
G3	5.618 (2.827-11.165)		3.182 (1.539-6.580)		4.014 (1.819-8.857)		2.650 (1.146-6.128)	
Myometrial invasion		<0.001		0.019		0.075		
Mucosa	1.000		1.000		1.000			
Myometrial <1/2	0.531 (0.230-1.224)		0.575 (0.241-1.374)		0.612 (0.253-1.483)			
Myometrial ≥1/2	1.992 (0.906-4.376)		1.561 (0.591-4.128)		1,336 (0.553-3.229)			
FIGO		<0.001		<0.001		<0.001		0.019
I	1.000		1.000		1.000		1.000	
II	1.206 (0.502-2.897)		1.059 (0.407-2.756)		0.637 (0.193-2.108)		0.817 (0.240-2.775)	
III	3.800 (1.803-8.009)		1.780 (0.720-4.396)		2.434 (0.997-5.945)		2.010 (0.756-5.343)	
IV	16.520 (7.433-36.716)		7.610 (2.925-19.796)		9.426 (3.515-25.278)		5.798 (1.805-18.619)	
Complication		0.017		0.673		0.017		0.752
no	1.000		1.000		1.000		1.000	
yes	2.632 (1.188-5.833)		1.218 (0.488-3.039)		2.897 (1.214-6.914)		1.181 (0.421-3.310)	
CA199		0.329				0.570		

≤37	1.000		1.000	
37	1.487 (0.671-3.293)		1.312 (0.514-3.352)	
CA724		0.108		0.295
≤6.9	1.000		1.000	
6.9	0.433 (0.156-1.202)		0.575 (0.204-1.618)	
AFP		0.294		0.249
≤9	1.000		1.000	
9	3.136 (0.371-26.514)		3.591 (0.409-31.539)	
CEA		0.061		0.105
≤5	1.000		1.000	
5	2.648 (0.955-7.341)		2.651 (0.817-8.608)	

Figures

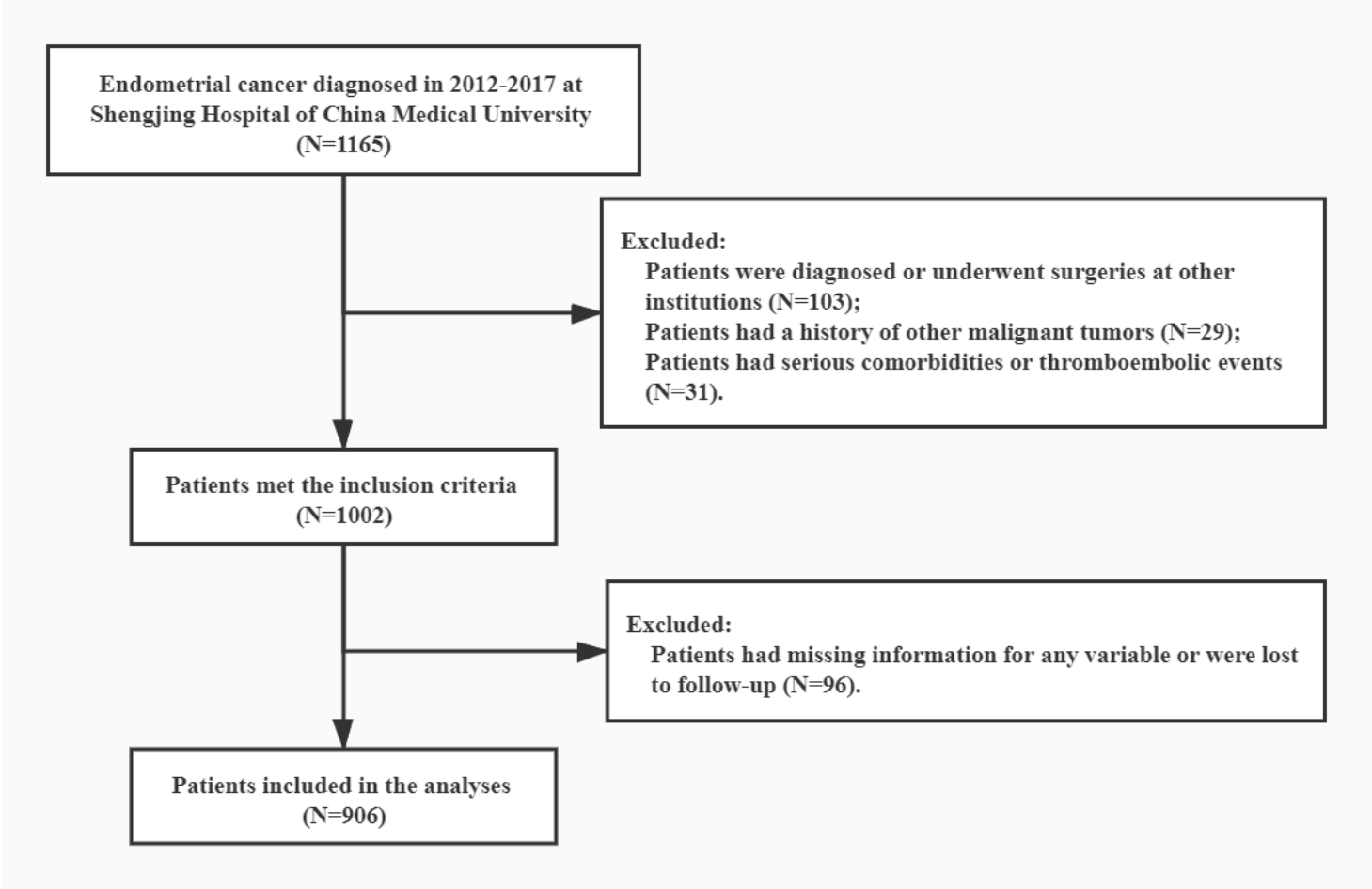

Figure 1

complete data for all of the variables included in the study. A total of 259 patients did not meet all of the inclusion criteria and were excluded (96 patients were lost to follow-up, while 906 patients were included (Figure 1).

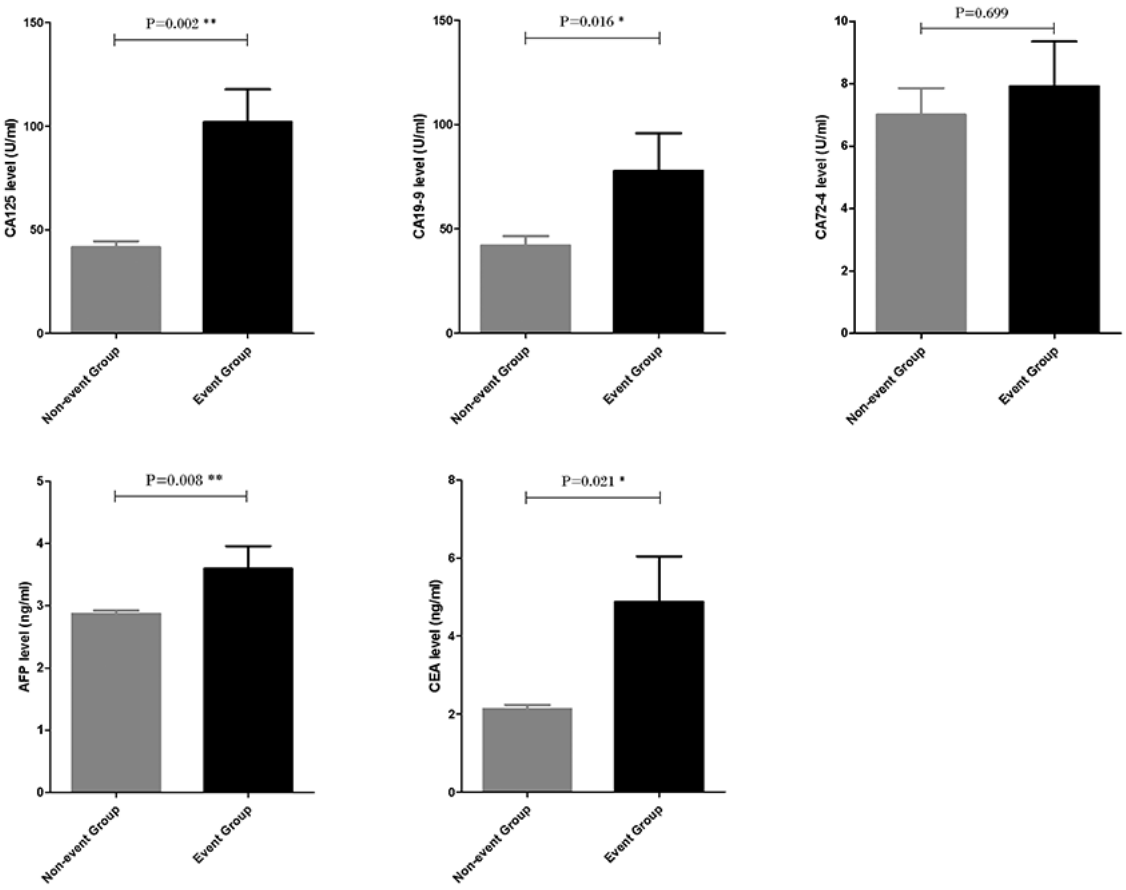

Figure 2

Levels of CA125 (P = 0.002), CA19-9 (P = 0.016), CEA (P = 0.021), and AFP (P = 0.008) were significantly higher in the event group than in the non-event group (Figure 2).

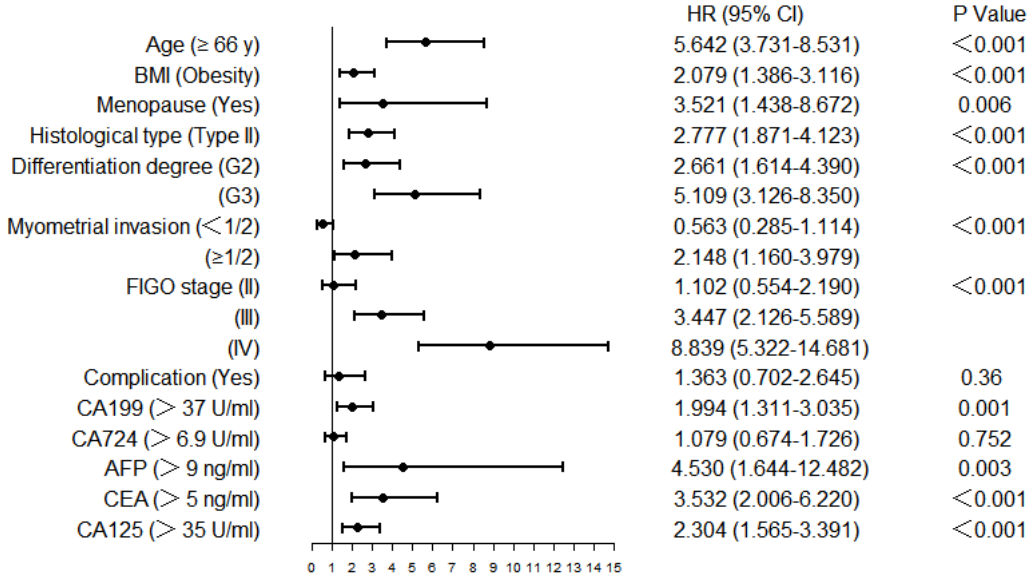

Figure 3

The median follow-up time was 48 months. Five-year OS was 90.0%, and five-year PFS was 87.0%. Single factor survival analysis was performed to determine the effect in EC patients of the variables age, menopausal status, pathology type, degree of differentiation, FIGO stage, infiltration of myometrial location, complications, serum CA125, CA19-9, CEA, and AFP levels. According to univariate analysis (Figure 3)

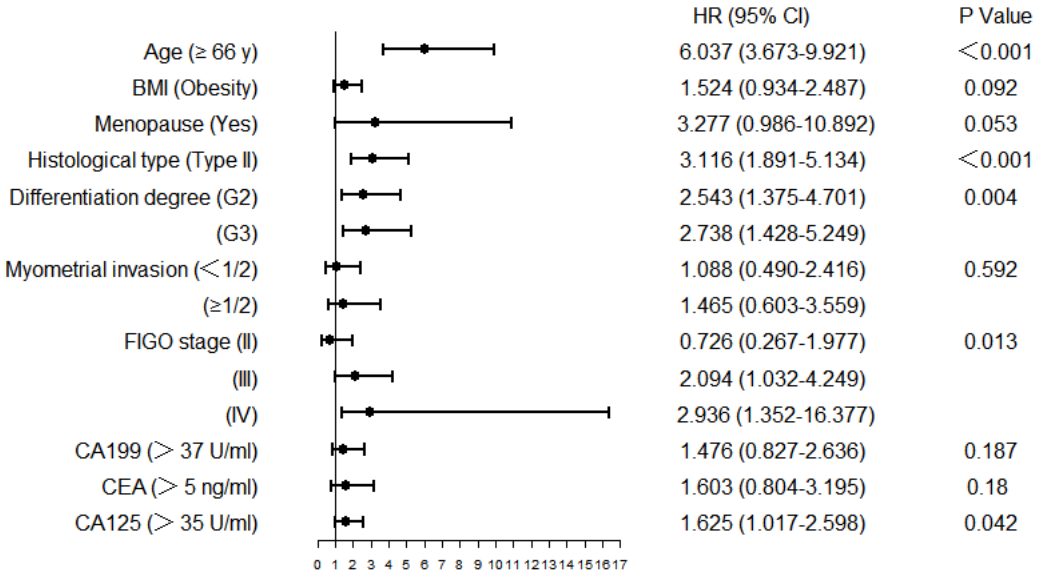

Figure 4

We also identified age (P < 0.001), menopausal status (P = 0.015), BMI (P = 0.011), pathological type (P < 0.001), degree of differentiation (P < 0.001), myometrial invasion (P = 0.001), FIGO stage (P < 0.001), and serum levels of CA125 (P = 0.004), CA19-9 (P = 0.011), and CEA (P < 0.001) as factors in prognosis of OS in EC patients (Figure 4).

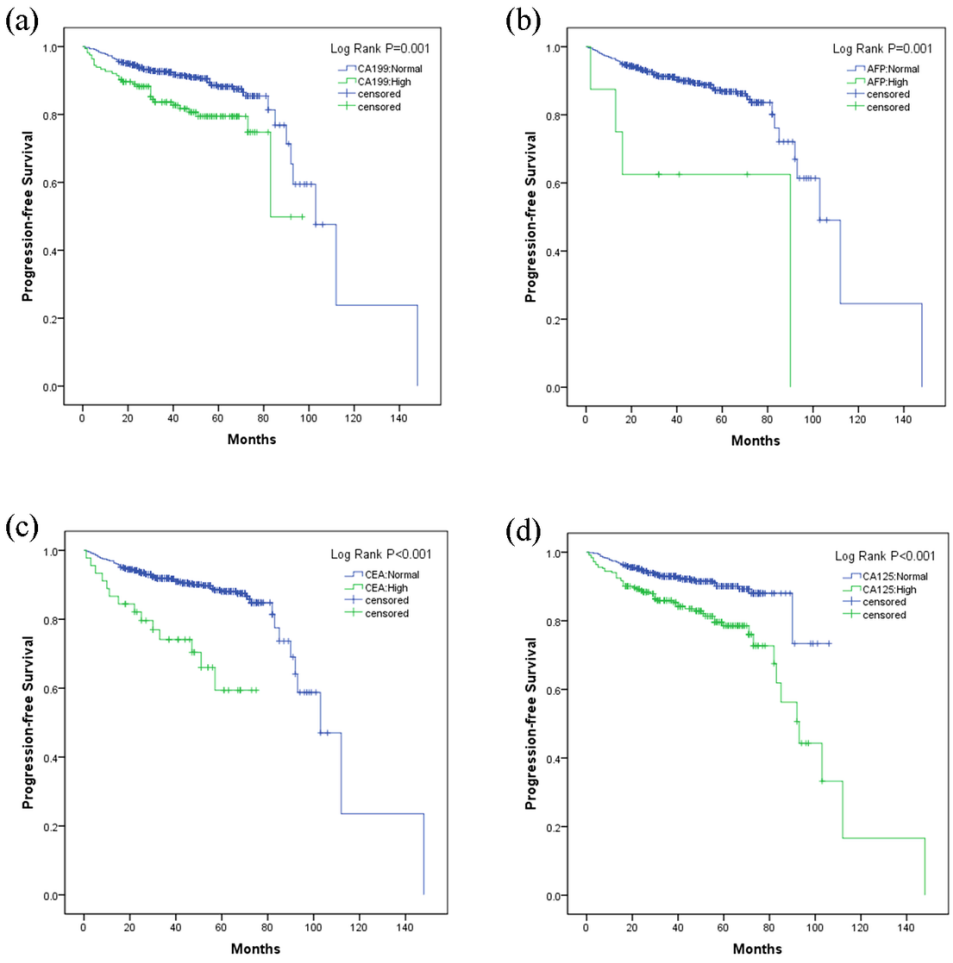

Figure 5

Differences in survival according to serum CA125, CA19-9, CEA, and AFP were compared using a Kaplan-Meier analysis (Figures 5 and 6).

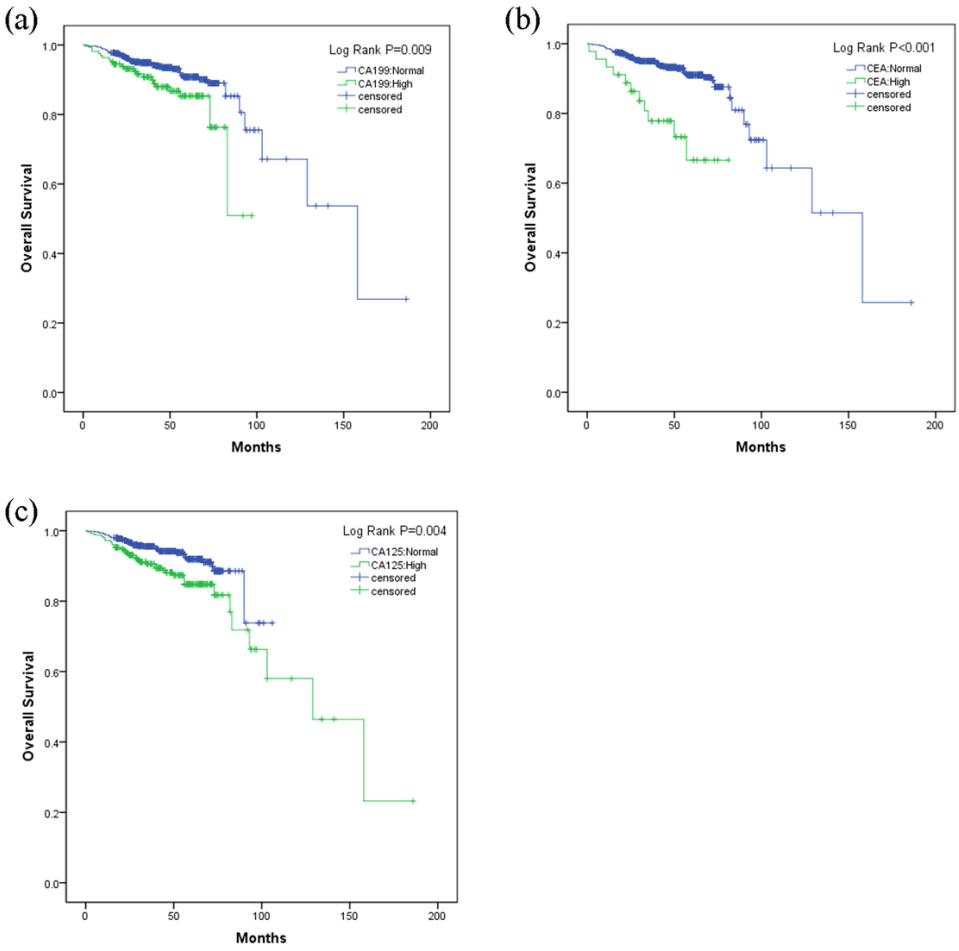

Figure 6

Differences in survival according to serum CA125, CA19-9, CEA, and AFP were compared using a Kaplan-Meier analysis (Figures 5 and 6).

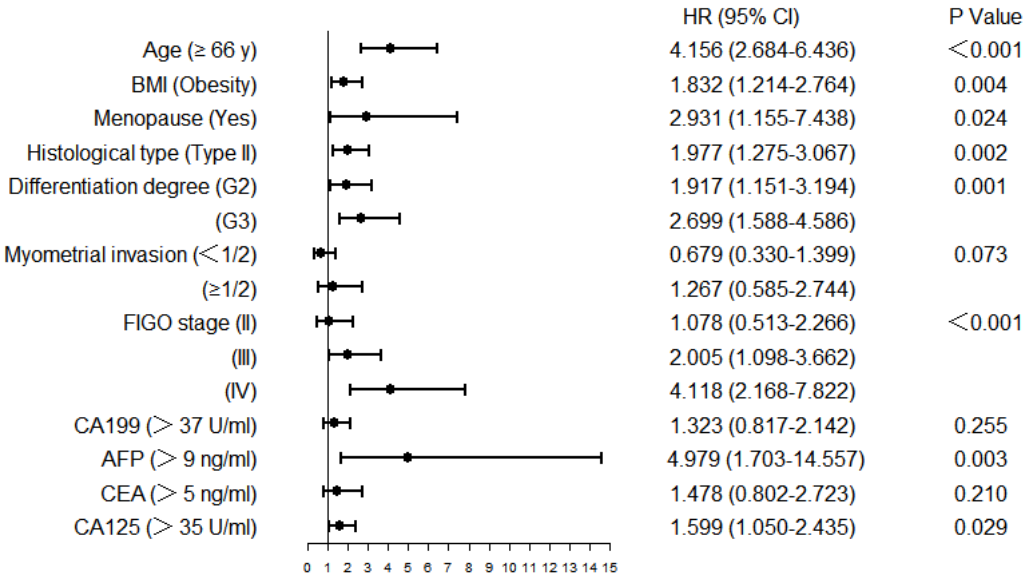

Figure 7

Elevated serum CA125 (P = 0.029) and AFP (P = 0.003), histological subtype (P = 0.002), obesity (P = 0.004), menopause (P = 0.024), poor degree of differentiation (P = 0.001), FIGO stage (P < 0.001), and age ≥ 66 years (P < 0.001) were independent factors for PFS prognosis in EC patients(Figure 7).

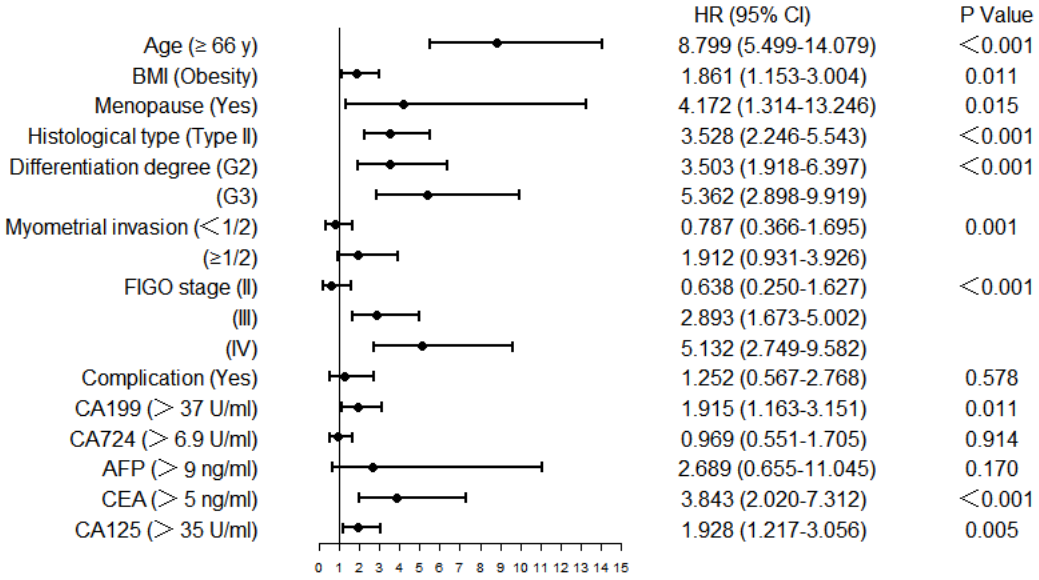

Figure 8

Increased serum CA125 (P = 0.042), age ≥ 66 years (P < 0.001), type Ⅱ histological classification (P 0.001), low degree of differentiation (P =0.004), and FIGO stage (P = 0.013) were independent factors for prognosis of OS in EC patients (Figure 8).