

# Clinical Characteristics and Prognosis of Ovarian Clear Cell Carcinoma: A 10-Year Retrospective Study

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## Research article

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## Abstract

# Background

Ovarian clear cell carcinoma (OCCC) is a special pathological type of epithelial ovarian carcinoma (EOC), we conducted this research in order to investigate the clinical characteristics and outcomes of OCCC and to provide additional supporting evidence to aid in the clinical diagnosis and management.

## Methods

This was a retrospective study investigating the clinical characteristics and survival outcomes of 87 patients with OCCC treated at our center between January 2010 and March 2020. Survival analysis was also performed on 179 patients with OCCC obtained from the Surveillance, Epidemiology and End Results (SEER) cancer registry database.

## Results

The median age of participants was  $49.28 \pm 9.8$  years old, with 74.71% diagnosed at early stage. Median CA125 level was 607.26 IU/mL, with 23.94% having normal CA125 levels. 16 patients (18.39%) had co-existing endometriosis and 8 patients (9.2%) developed venous thromboembolism (VTE). There were 5 patients received suboptimal cytoreduction. 67 patients (77.01%) underwent lymphadenectomy, and only 3 (4.48%) were found to have positive lymph nodes. Patients diagnosed at an early stage had higher 3-year overall survival (OS) and progression-free survival (PFS) rates than those with advanced stage OCCC. CA199 ( $P = 0.025$ ) and ascites ( $P = 0.001$ ) were significantly associated with OS, while HE4 ( $P = 0.027$ ) and ascites ( $P = 0.001$ ) were significantly associated with PFS. Analysis of data from the SEER database showed that positive lymph nodes is also an independent prognostic factor for OS ( $P = 0.001$ ).

## Conclusions

OCCC often presents at an early stage and young age with a mildly elevated CA125. CA199, HE4, massive ascites and positive lymph node are independent prognostic factors.

## 1. Background

Epithelial ovarian carcinoma (EOC) is the seventh most commonly diagnosed cancer among women worldwide, and carries the highest mortality rate of all gynecological cancers(1, 2). Ovarian clear cell carcinoma (OCCC) is a subtype of EOC with differing prevalence depending on geographical location. OCCC accounts for 5–10% of all EOC in North America and 12% in western countries, but appears to have a higher prevalence in East Asia, accounting for 25–30% and 10.3–11.6% of all EOC in Japan and Korea, respectively(3–5).

There are several reproductive and hormonal risk factors linked to an increased risk of developing OCCC, such as early menarche, late menopause, low use of oral contraceptives and low pregnancy rate(6). In addition, endometriosis is recognized as precancerous lesion of OCCC, as women with endometriosis have a 3-fold increased risk of developing OCCC compared with women without endometriosis(7). Patients with OCCC tend to be diagnosed at younger age and earlier stage, and occasionally are found to have thromboembolic complications(8), usually with a mild-to-moderate elevation of serum CA125. The conventional tumor marker CA125 used for detection of high-grade serous carcinoma (HGSC) is a poor marker for OCCC, elevated in only 57.6% of OCCC cases with a high false-negative rate(9). Therefore, there is a need for specific serological biomarkers for OCCC. Immunohistochemically, OCCC are usually positive for hepatocyte nuclear factor 1 $\beta$  (HNF1 $\beta$ ), and negative for in estrogen receptor (ER), progesterone receptor (PR) and Wilms Tumor 1 (WT-1) in more than 95% of the cases(10). OCCC shows little association with family history, with BRCA1 and BRCA2 germline mutations being rare in OCCC, however, somatic mutations of Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) and AT-rich interactive domain-containing protein 1A (ARID1A) are present in 20–51% and 40–57% respectively(11, 12).

Standard surgical staging procedure or optimal cytoreduction, followed by systemic chemotherapy, is recommended as the primary treatment for patients with OCCC. However, the response rate of platinum-based chemotherapy is only 20–50% for OCCC, therefore there is a need for further research into more effective therapies(13). Due to this inherent chemoresistance, the prognosis of patients with OCCC is extremely poor, especially at advanced stage. Suboptimal cytoreduction, lymph node (LN) metastasis and occurrence of VTE are also prognostic predictors of poor outcome(13, 14).

Therefore, the purpose of our research is to assess the clinical characteristics and outcomes of patients with OCCC, and to provide additional supporting evidence to aid in the clinical diagnosis and management of OCCC.

## 2. Materials And Methods

### 2.1 Patients

This is a retrospective study of 87 patients diagnosed with primary ovarian clear cell carcinoma between January 2010 and March 2020 at The First Affiliated Hospital of University of Science and Technology of China (USTC). Patients with histologically confirmed OCCC who had undergone complete surgical staging or cytoreductive surgery with adjuvant chemotherapy as the primary treatment were included. Patients were excluded from this study if they received neoadjuvant chemotherapy, had insufficient data or were lost to follow-up within one month of surgery. Patient information, including demographic and pathological characteristics, pre-operative biomarkers, surgical procedure, chemotherapy, and disease status at last contact, was collected from medical records and evaluated. Patient records and information were anonymized prior to analysis; thus, consent was not required. This study was approved by the ethics committees of The First Affiliated Hospital of USTC and was conducted in accordance with the Helsinki Declaration.

## 2.2 Treatment and follow-up

The predominant primary surgical procedure was total hysterectomy, bilateral salpingo-oophorectomy, lymphadenectomy, and omentectomy, with peritoneal biopsies from multiple random sites. 25 patients with a pelvic mass had previously undergone surgical procedures including oophorectomy, unilateral/bilateral ovariectomy  $\pm$  total hysterectomy, and were diagnosed with OCCC according to the pathological results from our or other hospitals and subsequently received additional staging or cytoreductive surgery in our hospital. The other 62 patients were diagnosed and treated within our hospital. First line adjuvant chemotherapy was combined platinum and taxane of 3–6 cycles.

After the initial treatment, all patients were closely followed up with clinical examination, including pelvic examination and evaluation of tumor markers at each visit. In addition, ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and/or positron emission tomography-CT (PET-CT) scans were performed when necessary. Where follow up information was not available from patient records, patients were contacted directly by telephone to obtain the relevant information. Recurrence was defined as histologic evidence of disease in tumor biopsy or fine-needle biopsy and/or the appearance of new lesions on imaging. Survival data were last collected on 31 April 2020.

## 2.3 Clinical data collection

The following information was collected from the medical records of eligible patients: age, body mass index (BMI), results of genetic tests, presence of endometriosis, history of thromboembolism, stage, comorbidities, American Society of Anesthesiologists class (ASA), stage, preoperative serum laboratory test values, surgical procedures performed, presence of ascites, size of residual tumor, number of LN removed, presence of LN metastasis, pathologic results, length of hospital stay, chemotherapy regimen, length of follow-up, recurrence and survival status.

Fasting venous blood samples were collected from all patients on the morning prior to their planned surgery. Electrochemiluminescence immunoassay (ELICA) was performed on all samples using the Cobas E601 analyzer (Roche Diagnostics) to measure the levels of CA125, HE4 and CA199. For patients who had undergone primary surgery at other institutes, the results of serum analysis were collected from their medical notes. All tumors were staged according to the 2014 International Federation of Gynecology and Obstetrics (FIGO) staging system. In patients treated prior to 2014, the stage of disease was classified retrospectively on the basis of surgical and pathological assessment. Optimal cytoreduction was defined as maximal diameter of the residual tumor  $\leq$  1 cm following surgery. Progression-free survival (PFS) was defined as the time from initial surgical staging or cytoreductive surgery to the date of disease progression or recurrence, and overall survival (OS) was defined as the time from surgical staging or cytoreductive surgery to the date of death, or to the last follow-up date, if still alive.

The histological cell types were determined according to the World Health Organization (WHO) criteria, and the diagnosis was conducted by at least two pathologists. Pathological slides of patients who underwent primary surgery at other institutes were obtained for histological reconfirmation. Presence of endometriosis was obtained from pathological reports from surgical procedures.

## 2.4 Data collection from the Surveillance, Epidemiology and End Results (SEER) database

Patient data was collected from the latest version of the SEER cancer registry database. There were 849 cases initially identified with diagnosis of OCCC obtained between 1975 and 2017 and with at least 3 years of follow-up available. Exclusion criteria were as follows: incomplete clinical information (621 cases), no surgical procedure performed (8 cases) and the presence of primary malignancy elsewhere (41 cases). Following the selection process, a total of 179 eligible patients were enrolled in the study. Survival analysis was performed using the following demographic and clinicopathological parameters: age, race (white, black, or 'other'), SEER summary stage (localized, regional, or distant), American Joint Committee on Cancer (AJCC) stage (I, II, III, or IV), number of LN resected (1, 2, 3, or  $\geq$  4), number of positive LN (1, 2, 3, or  $\geq$  4), and the presence of distant metastasis.

## 2.5 Statistic analysis

Statistical analysis was performed using SPSS v.20.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean, standard deviation and range, and categorical variables were expressed as counts and percentages. Comparisons between groups were analyzed using Student's t-test or Wilcoxon-Mann-Whitney test according to the data distribution for continuous variables or the  $\chi^2$  or Fisher's exact test for categorical variables. Youden's index and the receiver operating characteristic (ROC) curve were used to find the optimal cut-off value of age, CA125, HE4, and CA199, based on sensitivity and specificity of each point, generated by a computerized program. Univariate and multivariable Cox regression analyses were performed to identify predictors of RFS and OS. Multivariate analysis was performed with all variables with a p-value of  $<$  0.1 at univariate analysis. Multivariate logistic regression analysis was also performed with bootstrap in SPSS. A p-value of  $<$  0.05 was considered statistically significant, and all p-values reported were two-sided.

## 3. Results

### 3.1 The characteristics of the patients with OCCC

Overall, 87 patients were included in this study who were diagnosed with OCCC between January 2010 and March 2020. The demographic and clinical characteristics of these patients are summarized in Table 1. 25 patients with a pelvic mass had previously undergone surgical procedures including oophorectomy, unilateral/bilateral ovariectomy  $\pm$  total hysterectomy and were diagnosed with OCCC in our or other hospitals according to pathological results. Of these patients, 24 of them received additional staging surgery and were diagnosed as early stage, and one patient received cytoreductive surgery and was diagnosed as FIGO  $\geq$ C in our hospital. The other 62 patients received primary cytoreductive or staging surgery within our hospital, and detailed information is presented in Fig. 1.

Table 1  
Baseline clinical characteristics of patients (n = 87).

	No	%
Age (years) <sup>a</sup>	49.28 ± 9.87(25 ~ 70)	
< 40	15	17.24
40 ~ 49	27	31.03
50 ~ 59	34	39.08
≥ 60	11	12.64
Body mass index (kg/m <sup>2</sup> )	22.98 ± 3.00(16.94 ~ 33.71)	
< 18	2	2.30
18 ~ 23.9	52	59.77
24 ~ 27.9	27	31.03
≥ 28	3	3.45
NA	3	3.45
FIGO stage		
Ⅰ	57	65.52
ⅡA	25	28.74
ⅡB	2	2.30
ⅢC	30	34.48
ⅢC1	13	14.94
ⅢC2	9	10.34
ⅢC3	3	3.45
ⅢC NA	5	5.75
Ⅳ	3	3.45
ⅣA	0	0
ⅣB	3	3.45
Ⅴ	24	27.59
ⅤA	4	4.60
ⅤB	1	1.15
ⅤC	19	21.84
Ⅵ	3	3.45
BRAC mutation (n = 15)		
+	1	6.67
-	13	86.67
Unknown significance mutation	1	6.67
Endometriosis	16	18.39
Thrombosis	8	9.20
Preoperative	4	4.60
postoperative	4	4.60
CDC <sup>b</sup>	31	35.63
a. Mean ± standard deviation, range		
b. CDC, Chronic disease comorbidities		
NA. Not available		

	No	%
Hypertension	16	18.39
Diabetes	4	4.60
Heart disease	3	3.45
Cerebral infarction	6	6.90
Other cancer history	4	4.60
Hepatic cancer	1	1.15
Breast cancer	1	1.15
Cervical cancer	1	1.15
Endometrial cancer	1	1.15
Hepatitis	2	2.30
Systemic lupus erythematosus	1	1.15
Rheumatoid arthritis	1	1.15
Bronchial asthma	1	1.15
Hypothyroidism	1	1.15
Moyamoya disease	1	1.15
Tuberculosis	1	1.15
American Society of Anesthesiologists class (ASA)		
I	7	8.05
II	40	45.98
III	31	35.63
IV	3	3.45
NA	6	6.90
Preoperative laboratory test		
CA125(U/ml) <sup>a</sup>	607.26 ± 1545.55(9.16 ~ 9035.00)	
Normal (< 35)	17	19.54
35 ~ 99	16	18.39
100 ~ 499	23	26.44
500 ~ 999	5	5.75
≥ 1000	10	11.49
NA	16	18.39
CA199(U/ml) <sup>a</sup>	1555.99 ± 11796.47(0.60 ~ 96649.00)	
Normal (< 37)	36	41.38
37 ~ 99	13	14.94
100 ~ 499	15	17.24
≥ 500	2	2.30
NA	21	24.14
HE4 (pM) <sup>a</sup>	111.09 ± 110.96(14.00 ~ 669.00)	
Normal (< 140)	45	51.72
a. Mean ± standard deviation, range		
b. CDC, Chronic disease comorbidities		
NA. Not available		

	No	%
140 ~ 499	13	14.94
≥ 500	1	1.15
NA	28	32.18
Serum albumin (g/l) <sup>a</sup>	40.75 ± 4.43(31.10 ~ 51.60)	
< 40	31	35.63
≥ 40	39	44.83
NA	17	19.54
Prealbumin(mg/l) <sup>a</sup>	194.65 ± 56.29(58.00 ~ 332.00)	
< 170	20	22.99
≥ 170	43	49.43
NA	24	27.59
D-Dimer(ug/ml) <sup>a</sup>	2.24 ± 3.17(0.03 ~ 12.86)	
< 3.5	47	54.02
≥ 3.5	10	11.49
NA	30	34.48
Ca <sup>2+</sup> (mmol/l) <sup>a</sup>	2.32 ± 0.25(1.90 ~ 3.50)	
< 2.11	7	8.05
2.11 ~ 2.52	54	62.07
> 2.52	7	8.05
NA	19	21.84
a. Mean ± standard deviation, range		
b. CDC, Chronic disease comorbidities		
NA. Not available		

The median age at diagnosis was 49.28 ± 9.8 years (range 25–70 years). The majority of patients (65/87, 74.71%) were diagnosed as early stage (FIGO I–II). In terms of gene analysis, only 6.67% (1/15) displayed a positive BRCA mutation. CA125 assay was performed in 71 patients, with a median CA125 level of 607.26 IU/mL (range 9.16–9035 IU/mL). Of these 71 patients, 17 (23.94%) had a normal CA125 level (mean = 20.21 ± 7.72 IU/mL). More than half of patients assayed had a normal CA199 (mean = 12.96 ± 9.01 IU/mL) and/or HE4 value (mean = 65.86 ± 35.70 pM) (36/66, 54.55%; 45/59, 76.27%) respectively. Co-existing endometriosis was found in 16 patients (18.39%) and 8 patients (9.2%) had a preoperative history or postoperative complications of VTE (Table 2).

Table 2  
Characteristic of patients with developed venous thromboembolism (VTE)

Case	Age	FIGO stage	Ascites	SCS	R0/R1/RX	D-D <sup>a</sup>	D-D <sup>b</sup>	CA125	CA199	Time	DVT	PE	Survival	OS
1	55.00	ⅢC	3000	2	R0	1.36	15.32	1664	96649	Pre-operation	Left lower extremity		Alive	9
2	42.00	ⅢC	2000	4	R0	12.86	17.42	446.2	35.78	Pre-operation	-	Yes	Alive	24
3	45.00	ⅢC	200	4	R0	/	13.68	2612	10.72	Pre-operation	Right lower extremity		Alive	75
4	40.00	ⅢC	200	2	R1	8.77	40	239.3	251.7	Pre-operation	Both lower extremity	Yes	Alive	24
5	70.00	Ⅰ	0	1	RX	2.43	5.25	911.5	1469	Post-operation	-	Yes	Alive	10
6	25.00	Ⅰ	2000	1	R0	12.48	5.69	9035	2.96	Post-operation	Both lower extremity		NA	-
7	66.00	ⅣA	0	5	R0	0.78	6.15	9.5	10.54	Post-operation	Both lower extremity	Yes	Alive	9
8	56.00	ⅣA	0	3	R0	/	/	103.1	8.42	Post-operation	Both lower extremity		Alive	13
a. Preoperative d-dimer value														
b. Postoperative d-dimer value														
SCS: Surgical complexity score														
DVT: Deep venous thrombosis														
PE: Pulmonary embolism														
OS: Overall survival														

### 3.2 Treatments of the patients with OCCC

Complete staging surgery was performed in 65 (74.71%) patients and cytoreductive surgery was performed in 22 (25.29%) patients. Data related to the surgical procedures are summarized in Table 3. Lymphadenectomy was performed in 67 women (77.01%), of which 3 (4.48%) were found to have positive LN. Of the 2261 LN resected, 2.03% (46/2261) were found to have metastatic lesions. Most patients at an early stage had over 20 lymph nodes removed (86.15%, 56/65), whereas most patients at advanced stage had less than 20 lymph nodes removed (17/22, 77.27%). Among patients with advanced OCCC, optimal cytoreduction was achieved in 77.27% (17/22) patients. Of the 5 patients that underwent suboptimal cytoreductive surgery, 1 patient's family refused to remove the involved bowel, and 4 patients had multiple metastatic lesions. The mean length of hospital stays for patients undergoing staging surgery was  $10.96 \pm 5.69$  days following completion of initial postoperative chemotherapy; and the mean length of hospital stays for those undergoing cytoreductive surgery was  $15.00 \pm 6.50$  days following completion of initial postoperative chemotherapy.

Table 3  
Surgical procedures and clinical outcomes.

	Total	%	FIGO stage			
			⅀~⅀b(n = 65)	%	⅀c~⅀(n = 22)	%
Residual disease						
No gross residual	78	89.66	65	100	13	59.09
0.1 ~ 1.0 cm	4	4.60	0	0	4	18.18
> 1 cm	5	5.75	0	0	5	22.73
Ascites (ml)						
< 500	69	79.31	59	90.77	10	45.45
500 ~ 1999	7	8.05	3	4.62	4	18.18
2000 ~ 4999	6	6.90	1	1.54	5	22.73
≥ 5000	3	3.45	0	0	3	13.64
NA	2	2.30	2	3.08	0	
Number of lymph node resected						
0	20	22.99	5	7.69	15	68.18
1 ~ 20	6	6.9	4	6.15	2	9.09
21 ~ 40	46	52.87	42	64.62	4	18.18
≥ 40	15	17.24	14	21.54	1	4.55
Lymph node positive ratio	46/2261	2.03	45/2070	2.17	1/191	0.52
Estimated blood loss (ml)						
< 100	4	4.60	3	4.62	1	4.55
100 ~ 499	46	52.87	38	58.46	8	36.36
500 ~ 999	27	31.03	20	30.77	7	31.82
≥ 1000	9	10.34	3	4.62	6	27.27
NA	1	1.15	1	1.54	0	0
Operation type						
Staging surgery	65	74.71	65	100	0	0
Standard cytoreduction	13	14.94	0	0	13	59.09
Radical cytoreduction	1	1.15	0	0	1	4.55
Extral-radical cytoreduction	3	3.45	0	0	3	13.64
Palliative surgery	5	5.75	0	0	5	22.73
Surgical complexity score (SCS)						
1 ~ 3	26	29.89	14	21.54	12	54.55
4 ~ 7	60	68.97	51	78.46	9	40.91
≥ 8	1	1.15	0	0	1	4.55
Interval of initial postoperative chemotherapy(days) <sup>a</sup>	16.76 ± 8.01(6 ~ 39)		17.86 ± 7.94(6 ~ 39)		13.47 ± 7.28(6 ~ 32)	
Length of hospital stays (days) <sup>a</sup>	11.87 ± 6.07(5 ~ 37)		10.96 ± 5.69(5 ~ 37)		15.00 ± 6.50(8 ~ 35)	
Recurrence	13		6	9.23	7	31.82
Endpoint status						
Alive	62		52	80.00	10	45.45
Cancer specific deaths	10		2	3.08	8	36.36

a. Lymph node ratio (LNR), defined as the ratio of the number of metastatic lymph nodes (MLNs) to the number of resected lymph nodes (RLNs)

	Total	%	FIGO stage			
			IIb (n = 65)	%	IIc (n = 22)	%
Loss to follow-up	15		11	16.92	4	18.18

a. Lymph node ratio (LNR), defined as the ratio of the number of metastatic lymph nodes (MLNs) to the number of resected lymph nodes (RLNs)

Adjuvant chemotherapy was administered in our hospital in 76 patients (87.36%), with a combination of paclitaxel and platinum following surgery. The other 11 patients were discharged and attended a local hospital for their adjuvant chemotherapy. Among the 76 patients who received chemotherapy in our hospital, 36 (47.37%) completed the initial chemotherapy within 2 weeks of surgery and 68 (89.47%) within 4 weeks of surgery. The remaining 8 patients did not complete chemotherapy within 4 weeks due to anemia, infection, or personal reasons. The mean interval between surgery and initial postoperative chemotherapy was  $16.76 \pm 8.01$  days (range 6–39 days).

### 3.3 Clinical characteristics of OCCC patients with co-existing endometriosis

There were 16 patients found to have co-existing endometriosis. A comparison of the clinical characteristics of patients with and without co-existing endometriosis is presented in Table 4. Patients with co-existing endometriosis had a mean age of  $45.50 \pm 6.19$  years old, and majority of them (68.75%) were under 50 years old. Patients with endometriosis tended to be younger than those without endometriosis but without statistical significance ( $P = 0.078$ ). Most patients (87.5%) with co-existing endometriosis were diagnosed as early stage, more than those without endometriosis, and had lower levels of biomarkers, such as CA125, CA199 and HE4, however, these differences were not statistically significant.

Table 4  
Clinical characteristics of patients with/without endometriosis.

	With (n = 16)		Without (n = 71)		P value
	No.	%	No.	%	
Age (years) <sup>a</sup>	45.50 ± 6.19(35 ~ 54)		50.16 ± 10.34(25 ~ 70)		0.078
< 40	3	18.75	12	16.90	
40 ~ 49	8	50.00	19	26.76	
50 ~ 59	5	31.25	29	40.85	
≥ 60	0	0	11	15.49	
FIGO stage					0.325
ⅠA~ⅠB	14	87.50	51	71.83	
ⅠC~Ⅱ	2	12.50	20	28.17	
Synchronous endometrial cancer	0	0	3	4.23	1.000
Preoperative laboratory test					
CA125(U/ml) <sup>a</sup>	117.17 ± 126.84(9.81 ~ 446.20)		668.94 ± 1654.52(9.16 ~ 9035.00)		0.290
Normal (< 35)	3	18.75	14	19.72	
35 ~ 99	3	18.75	13	18.31	
100 ~ 499	4	25.00	19	26.76	
500 ~ 999	0	0	5	7.04	
≥ 1000	0	0	10	14.08	
NA	6	37.50	10	14.08	
CA199(U/ml) <sup>a</sup>	67.31 ± 70.10(15.14 ~ 251.70)		1791.04 ± 12677.65(0.60 ~ 96649.00)		0.692
Normal (< 37)	4	25.00	32	45.07	
37 ~ 99	4	25.00	9	12.68	
100 ~ 499	1	6.25	14	19.72	
≥ 500	0	0	2	2.82	
NA	7	43.75	14	19.72	
HE4 (pM) <sup>a</sup>	73.01 ± 63.86(21.00 ~ 228.00)		117.94 ± 116.13(14.00 ~ 669.00)		0.271
Normal (< 140)	8	50.00	37	52.11	
140 ~ 499	1	6.25	12	16.90	
≥ 500	0	0	1	1.41	
NA	7	43.75	21	29.58	

a. Mean ± standard deviation, range; NA. Not available

### 3.4 Pathological characteristics

The immunohistochemical results are presented in Table 5. Most (26/31, 83.87%) patients tested positive for HNF1β and 91.80% (56/61), 72.41% (42/58) and 82.35% (42/51) of patients tested negative for WT-1, ER and PR respectively. Of the 20 patients who were tested containing HNF1β, WT-1, ER and PR, 11 (55%) had the combination of positive HNF1β, and negative WT-1, ER and PR characteristics for the diagnosis of clear cell carcinoma. Of these 20 patients, 19 were alive and one was lost to follow-up. In addition, Ki-67 was positive in 1–20% of cells in 18/70 (25.71%) cases; 21–40% of cells in 26/70 (37.14%) cases; 41–60% of cells in 18/70 (25.71%) cases; 61–80% of cells in 7/70 (10.00%) cases; and > 80% of cells in 1/70 (1.43%) cases.

Table 5  
Immunohistochemical characteristics of patients

	Total number <sup>a</sup>	Positive (%)	Negative (%)	Weak/partial positive (%)
HNF1β	31	26/31(83.87%)	1/31(3.23%)	4/31(12.90%)
WT-1	61	2/61(3.28%)	56/61(91.80%)	3/61(4.92%)
ER	58	3/58(5.17%)	42/58(72.41%)	13/58(22.41%)
PR	51	1/51(1.96%)	42/51(82.35%)	8/51(15.69%)
NapsinA	61	29/61(47.54%)	22/61(36.07%)	10/61(16.39%)
CK7	67	62/67(92.54%)	3/67(4.48%)	2/67(2.99%)
P53	55	16/55(29.09%)	16/55(29.09%)	23/55(41.82%)
P16	26	14/26(53.85%)	4/26(15.38%)	8/26(30.77%)
PAX8	42	41/42(97.62%)	1/42(2.38%)	0
CK20	34	0	32/34(94.12%)	2/34(5.88%)
CD10	18	1/18(5.56%)	14/18(77.78%)	3/18(16.67%)
CD15	47	24/47(51.06%)	11/47(23.40%)	12/47(25.53%)
Vim	38	7/38(18.42%)	28/38(73.68%)	3/38(7.89%)
CA125	37	26/37(70.27%)	4/37(10.81%)	7/37(18.92%)
a. Number of patients who had this test.				

### 3.5 Survival analysis of the clinical data

There were 71(81.61%) patients follow-up continuously. Among the 71 patients followed up, 49 were followed up for more than one year, 28 for more than three years, and only 7 for more than five years. Survival analysis was conducted among the 49 patients followed up for more than one year. Recurrence occurred in 13 patients (26.53%), including 7 cases at an advanced stage and 6 cases at an early stage. For patients with early and advanced stage OCCC, 1-year PFS rates were 94.59% and 33.33% respectively and 3-year PFS rates were 78.95% and 22.22% respectively; OS rates at 1-year were 97.30% and 66.67% respectively and at 3-years were 89.47% and 44.44% respectively.

Analysis of demographic and clinicopathological parameters associated with OS and PFS is presented in Table 6. Univariate analysis demonstrated that CA199  $\geq$  70.3U/mL (P = 0.038), advanced stage (P = 0.001) and ascites  $\geq$  2000 mL (P = 0.015) were significantly associated with reduced OS. Besides those factors, suboptimal cytoreduction(P = 0.085) was also included in multivariate analysis. Multivariate analysis revealed that CA199  $\geq$  70.3U/mL (P = 0.025) was an independent prognostic indicator of OS. Bootstrap analysis found ascites  $\geq$  2000 mL (P = 0.001) also had statistical significance. In univariate analyses of PFS, age  $\geq$  58 years (P = 0.038) and advanced stage (P = 0.002) were significantly associated with reduced PFS. Age  $\geq$  58 years and advanced stage, along with CA199  $\geq$  70.3U/mL, HE4  $\geq$  94.5pM, and ascites  $\geq$  2000 mL were included in multivariate analysis. None of these factors had statistical significance, however, additional bootstrap analysis found that HE4  $\geq$  94.5pM (P = 0.027) and ascites  $\geq$  2000 mL (P = 0.001) were associated with a decreased PFS.

Table 6  
Univariate and multivariate analysis of factors associated with overall survival(n = 49)

	Overall survival					Progression free survival				
	Univariate analysis		Multivariate analysis			Univariate analysis		Multivariate analysis		
	OR (95% CI)	P value	OR (95% CI)	P value	Bootstrap P value <sup>a</sup>	OR (95% CI)	P value	OR (95% CI)	P value	Bootstrap P value <sup>a</sup>
Age	2.615(0.693 ~ 9.865)	0.156				3.274(1.069 ~ 10.030)	<b>0.038</b>	1.149(0.111 ~ 11.872)	0.907	0.736
ASA (Ⅱ+Ⅲ vs. Ⅳ)	0.204(0.025 ~ 1.668)	0.138				0.411(0.113 ~ 1.504)	0.179			
CA125	33.280(0.040 ~ 27705.853)	0.307				25.129(0.008 ~ 79761.009)	0.433			
CA199	9.707(1.134 ~ 83.096)	<b>0.038</b>	19.599(1.441 ~ 266.656)	<b>0.025</b>	0.104	3.930(0.933 ~ 16.554)	0.062	6.122(0.737 ~ 50.873)	0.094	0.052
HE4	64.472(0.089 ~ 46669.453)	0.215				5.014(0.959 ~ 26.217)	0.056	9.898(0.962 ~ 101.809)	0.054	<b>0.027</b>
FIGO stage (ⅠA~ⅠB vs. ⅡC~Ⅲ)	12.800(2.654 ~ 61.724)	<b>0.001</b>	1.637(0.145 ~ 18.447)	0.690	0.338	5.835(1.909 ~ 17.838)	<b>0.002</b>	1.369(0.130 ~ 14.396)	0.794	0.331
Ascites (≥ 2000 ml)	8.150(1.508 ~ 44.054)	<b>0.015</b>	20.924(0.940 ~ 465.542)	0.055	<b>0.001</b>	3.746(0.787 ~ 17.841)	0.097	18.498(0.964 ~ 354.767)	0.053	<b>0.001</b>
Lymphadenectomy	0.459(0.115 ~ 1.837)	0.271				0.448(0.137 ~ 1.466)	0.184			
Comorbid illnesses	0.755(0.188 ~ 3.026)	0.691				0.893(0.292 ~ 2.730)	0.842			
Multiple comorbid illnesses	1.263(0.155 ~ 10.301)	0.827				0.679(0.088 ~ 5.228)	0.710			
Thrombosis	0.042(0.000 ~ 911.409)	0.533				0.044(0.000 ~ 329.984)	0.492			
Endometriosis	0.549(0.069 ~ 4.402)	0.573				0.340(0.044 ~ 2.619)	0.300			
Interval <sup>b</sup> (> 14days)	0.419(0.104 ~ 1.686)	0.221				0.440(0.143 ~ 1.349)	0.151			
Suboptimal cytoreduction	4.112(0.821 ~ 20.583)	0.085	1.026(0.064 ~ 16.408)	0.986	0.715	3.116(0.687 ~ 14.130)	0.141			
SCS (< 4 vs. ≥4)	0.523(0.140 ~ 1.959)	0.336				0.725(0.237 ~ 2.218)	0.573			
a. Based on 5000 bootstrap samples.										
b. Interval. The interval of initial postoperative chemotherapy(days)										
ASA: American Society of Anesthesiologists class; SCS: Surgical complexity score										

### 3.6 Analysis of data from the SEER database

We analyzed data from 179 patients enrolled from the SEER database, with an average age of 55.22 ± 10.47 (range 18–85) years. In terms of SEER summary stage, there were 55 cases of localized, 77 cases of regional and 47 cases of distant, while 40 patients were diagnosed as advanced stage (AJCC ⅢC and Ⅳ). Lymphadenectomy was performed in 134 patients, of which 19 (14.18%) had positive LN. We also found that 6 patients had distant metastasis in bone (1 case), lung (1 case) and liver (4 cases).

Survival analysis was performed on these 179 cases of OCCC which resulted in a 3-year OS rate of 56.98%. Kaplan-Meier survival curves (Fig. 2) were generated which showed that AJCC stage (P < 0.001), SEER summary stage (P < 0.001), ≥ 4 LN removed (P = 0.003), and positive LN (P < 0.001) were significantly associated OS in patients with OCCC. Multivariate analysis was performed with variables including AJCC stage, SEER summary stage, number of LN removed, and positive LN (Table 7). Patients with summary stage of distant had poorer survival (P = 0.011). Positive LN was also an independent prognostic factor on survival of OCCC (P = 0.001). AJCC stage and number of LN removed had no significant impact on OS.

Table 7  
Multivariate analysis of factors associated with overall survival of the data from SEER database(n = 178)

Multivariate analysis			
	OR (95% CI)	P value	P value <sup>a</sup>
AJCC stage group			
0	1		
1	1.880(0.186 ~ 18.983)	0.593	0.354
2	3.043(0.255 ~ 36.253)	0.378	0.214
3	0.526(0.236 ~ 1.171)	0.116	0.119
Summary stage			
Localized	1		
Regional	1.361(0.489 ~ 3.787)	0.555	0.556
Distant	21.152(2.019 ~ 221.646)	<b>0.011</b>	<b>0.009</b>
Regional lymph nodes removed			
None	1		
1 to 3 regions	1.847(0.929 ~ 3.672)	0.080	0.103
4 or more regions	0.621(0.243 ~ 1.587)	0.319	0.370
Positive lymph nodes	5.531(2.102 ~ 14.553)	<b>0.001</b>	<b>0.002</b>
a. Based on 5000 bootstrap samples.			

## 4. Discussion

OCCC is a rare pathological type of EOC, and there is geographic variance in the prevalence of OCCC, being more common in Asia(3–5). Prevalence also differs by race, being higher in Asians (11.1%) and lower in black, white, and other populations (3.1%, 4.8%, and 5.5%, respectively) (15). However, among patients analyzed from the SEER database in our research, only 15.08% of the 179 cases were Asians, with 78.21% of cases being white; this is likely related to the racial differences in the USA population. In the present study of 87 cases of OCCC in our hospital, most patients were diagnosed at an early stage (74.71%) and a younger age ( $49.28 \pm 9.87$ ), consistent to previous studies, showing the distinct epidemiology of OCCC from HGSC, which is more frequently diagnosed at an advanced stage and carries a poor prognosis(8).

Endometriosis is a common disease in women of reproductive age, which is recognized as a precancerous lesion of OCCC and is associated with triple the risk of OCCC(7, 16), approximately 18–43% of women with OCCC have a history of endometriosis(17, 18). Endometriotic lesions often carry multiple somatic mutations, such as high expression of HNF1 $\beta$  and mutations in ARID1A and PIK3CA, which are thought to occur early in the malignant transformation of OCCC(16). The risk of tumorigenesis in endometriosis is about 1% among premenopausal women and 1–2.5% among postmenopausal women(17, 19). A study by Ye et al. demonstrated that patients with OCCC and concurrent endometriosis were on average 8 years younger than those without, and were more likely to present at early stage (78.5%)(20). However, although patients with co-existing endometriosis tend to have better survival outcomes, endometriosis was not an independent predictor of survival(21). In the present study, OCCC patients with endometriosis also tended to be diagnosed at an early stage (87.50%) and were younger (average age of  $45.50 \pm 6.19$ ) compared to patients without endometriosis, however this difference was not significant ( $P = 0.325$  and  $P = 0.078$ , respectively). Unfortunately, due to the small sample of our research, survival analysis of OCCC patients with and without endometriosis could not be constructed.

Currently, there is no specific biomarker for OCCC, patients with OCCC usually present with a mild elevation of serum CA125(9). In the present study, 19.54% of the patients had a normal level of CA125, and 37.93% of the patients had a CA125 level of  $< 100\text{U/mL}$ . Thus, there is a need for novel diagnostic markers to improve early diagnosis of OCCC. Chronic inflammation appears to have an effect on tumorigenesis and response to therapy, as well as affecting prognosis(22). Several systemic inflammatory response (SIR) biomarkers have been investigated as potential biomarkers of OCCC, such as the neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-monocyte ratio (LMR). Most OCCC patients diagnosed at an early stage showed complete response to initial treatment with decreased NLR levels, and NLR was found to return to preoperative high levels with recurrence, reflecting inflammation caused by the tumor(23). Low LMR has been shown to be associated with advanced stage disease, LN metastases, platinum-resistance, and poor prognosis, suggesting a decreased level of peripheral lymphocytes results in weakened immune surveillance and poor response to chemotherapy(22). In addition, genetic testing offers some potential diagnostic biomarkers for OCCC, such as HNF1 $\beta$ , which is expressed in almost all cases of OCCC and now used to distinguish histological subtypes by immunohistochemistry (IHC)(24). OCCC lesions tend to be positive for CK7 and negative for CK20, ER, PR, WT-1, and p53(10, 25). Testing negative for  $\alpha$ -fetoprotein and CD10 can be used to exclude yolk cell tumors and renal cell carcinoma(26). We analyzed

immunohistochemical results of our patients, and 55%(11/20) of them had positive HNF1 $\beta$  and negative WT-1, ER and PR. However, there remains an urgent need to discover novel biomarkers in peripheral blood or body fluids and validate their efficacy in the diagnosis of OCCC.

VTE, i.e. deep vein thrombosis (DVT) and pulmonary embolism (PE), are common in patients with OCCC, with a 2.5–4 times higher risk than in other subtypes of EOC(20, 27). VTE is more commonly seen in advanced stage OCCC (21.9%) compared with early stage (8.2%) disease, and occurred most commonly prior to primary surgery (36.4%), or with recurrence or progression (33.3%)(20). There are some measurable biomarkers of increased risk of VTE in ovarian cancer, such as elevated platelet count, white blood cell counts, d-dimer and CA125 level, decreased hemoglobin and albumin levels preoperatively, and elevated d-dimer and decreased albumin postoperatively(28). In our study, 8 patients developed VTE (Table 2), 4 preoperatively and 4 postoperatively. The low occurrence of VTE in our research might be associated with the use of appropriate prophylaxis. In spite of prophylaxis, patients with OCCC can still develop VTE, suggesting that an aggressive postoperative anticoagulation regimen and prolonged post-discharge VTE prophylaxis should be considered for patients with OCCC.

Staging surgery or optimal cytoreduction combined with chemotherapy is a common therapeutic strategy recommended for OCCC, however, only 11–27% of patients with OCCC respond to conventional platinum-based chemotherapy, resulting in a poor prognosis(29, 30). Disorder of the cell's detoxification effects of the glutathione system, low proliferation activity of OCCC and overexpression of EGFR, HNF1 $\beta$ , and HER2 may be involved in chemoresistance(31). In our clinical practice, OCCC patients often developed resistance characterized by a slow decline or elevation of tumor markers during postoperative chemotherapy. However, in the absence of more effective treatments, platinum-based chemotherapy remains the first line adjuvant therapy for OCCC patients, and more effective therapies are urgently needed. Recently, several targeted therapies and immunotherapies have been investigated for use in OCCC, such as PARP, EZH2, and ATR inhibitors combined with synthetic lethality of ARID1A-deficiency, and MAPK/PI3K/HER2, VEGF/bFGF/PDGF, HNF1 $\beta$ , and PD-1/PD-L1 inhibitors. Some regimens have demonstrated efficacy and revealed a potential therapeutic benefit for OCCC patients, but further research is required(32–35).

Survival analysis of our clinical data identified CA199 level and massive ascites as independent prognostic factors of OS, as well as HE4 level and massive ascites as independent prognostic factors of PFS in OCCC. Elevated postoperative CA199 has been reported as an independent risk factor for reduced survival outcomes in OCCC patients with normal postoperative CA125 levels(36). HE4 is not commonly used in OCCC prediction, however, Mckinnon found that since HE4 is sensitive to hormonal treatment and menstrual cycle variation, it may be potentially superior to CA125 as an endometriosis marker and therefore has potential as a marker for the risk of developing ovarian cancer(37). Suboptimal cytoreduction and advanced stage have been found to be associated with less favorable survival outcomes in univariate analysis, however, neither is an independent prognostic factor in the present study, which may be related to the small sample size. In our survival analysis of 179 cases of OCCC from the SEER, we found that positive LN is an independent prognostic factor. OCCC tends to metastasize most frequently via the lymphatic system(38). However, among patients in our hospital, only 4.48% of patients had metastatic LNs, which may be due to the fact that most (89.55%) of the 67 patients who received lymphadenectomy were at an early stage. Mueller found that 4.4–20% of clinically stage I OCCC had lymph node involvement, and this rate will be higher with positive cytology or ovarian surface involvement, accounting for 37.5% of metastases(39). Therefore, systematic pelvic and para-aortic lymphadenectomy is vital to accurately determine disease stage, provide prognostic information, and guide adjuvant therapy, especially for patients at early stage.

In conclusion, our study presents the clinicopathological features, treatment regimens and prognosis of OCCC in China, and confirms that OCCC typically presents at an early stage and at a younger age, with a mild elevation in CA125 level. Positive HNF1 $\beta$ , and negative WT-1, ER, and PR are reliable immunohistochemical indicators of OCCC. Patients with early stage OCCC tend to have a better OS and PFS, with CA199, HE4, massive ascites and positive lymph nodes being independent prognostic indicators. The present study confirms the unique features of OCCC, and further research is required to illustrate the molecular mechanisms and discover novel diagnostic biomarkers and targeted therapies, in order to benefit early diagnosis and therefore prognosis of OCCC.

## Abbreviations

EOC  
Epithelial ovarian carcinoma  
OCCC  
Ovarian clear cell carcinoma  
SEER  
Surveillance, Epidemiology and End Results  
VTE  
Venous thromboembolism  
OS  
Overall survival  
PFS  
Progression-free survival  
HGSC  
High-grade serous carcinoma  
HNF1 $\beta$   
hepatocyte nuclear factor 1 $\beta$

ER  
estrogen receptor  
PR  
progesterone receptor  
WT-1  
Wilms Tumor 1  
PIK3CA  
Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha  
ARID1A  
AT-rich interactive domain-containing protein 1A  
LN  
Lymph node  
USTC  
The First Affiliated Hospital of University of Science and Technology of China  
CT  
Computed tomography  
MRI  
Magnetic resonance imaging  
PET-CT  
Positron emission tomography-CT  
BMI  
Body mass index  
ASA  
American Society of Anesthesiologists class  
SCS  
Surgical complexity score  
ELICA  
Electrochemiluminescence immunoassay  
FIGO  
International Federation of Gynecology and Obstetrics  
WHO  
World Health Organization  
AJCC  
American Joint Committee on Cancer  
ROC  
Receiver operating characteristic  
SIR  
Systemic inflammatory response  
NLR  
Neutrophil-to-lymphocyte ratio  
LMR  
Lymphocyte-to-monocyte ratio  
IHC  
Immunohistochemistry  
DVT  
Deep vein thrombosis  
PE  
Pulmonary embolism

## **Declarations**

### **Ethics approval and consent to participate**

This study was approved by the ethics committees of The First Affiliated Hospital of USTC and was conducted in accordance with the Helsinki Declaration.

### **Consent for publication**

Patient records and information were anonymized prior to analysis; thus, consent was not required.

## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Competing interests

No conflicts of interest to disclose.

## Funding

No funding had a role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

## Authors' contributions

CZ was a major contributor in designing study and writing the manuscript; JZ analyzed and interpreted the patient data; SC and QZ collected the patient data; HL, SD, and LL completed the patient's follow-up together; YZ play an important role in critical revision of the manuscript.

All authors read and approved the final manuscript.

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## References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin.* 2020;70(1):7–30.
2. Reid BM, Permuth JB, Sellers TA. Epidemiology of ovarian cancer: a review. *Cancer Biol Med.* 2017;14(1):9–32.
3. Oliver KE, Brady WE, Birrer M, Gershenson DM, Fleming G, Copeland LJ, et al. An evaluation of progression free survival and overall survival of ovarian cancer patients with clear cell carcinoma versus serous carcinoma treated with platinum therapy: An NRG Oncology/Gynecologic Oncology Group experience. *Gynecol Oncol.* 2017;147(2):243–9.
4. Kim SI, Lim MC, Lim J, Won YJ, Seo SS, Kang S, et al. Incidence of epithelial ovarian cancer according to histologic subtypes in Korea, 1999 to 2012. *J Gynecol Oncol.* 2016;27(1):e5.
5. Okamoto A, Glasspool RM, Mabuchi S, Matsumura N, Nomura H, Itamochi H, et al. Gynecologic Cancer InterGroup (GCIG) consensus review for clear cell carcinoma of the ovary. *Int J Gynecol Cancer.* 2014;24(9 Suppl 3):20-5.
6. Yamamoto A, Johnstone EB, Bloom MS, Huddleston HG, Fujimoto VY. A higher prevalence of endometriosis among Asian women does not contribute to poorer IVF outcomes. *J Assist Reprod Genet.* 2017;34(6):765–74.
7. Pearce CL, Templeman C, Rossing MA, Lee A, Near AM, Webb PM, et al. Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies. *Lancet Oncol.* 2012;13(4):385–94.
8. Machida H, Matsuo K, Yamagami W, Ebina Y, Kobayashi Y, Tabata T, et al. Trends and characteristics of epithelial ovarian cancer in Japan between 2002 and 2015: A JSGO-JSOG joint study. *Gynecol Oncol.* 2019;153(3):589–96.
9. Liu H, Xu Y, Ji J, Dong R, Qiu H, Dai X. Prognosis of ovarian clear cell cancer compared with other epithelial cancer types: A population-based analysis. *Oncol Lett.* 2020;19(3):1947–57.
10. Prat J. Ovarian carcinomas: five distinct diseases with different origins, genetic alterations, and clinicopathological features. *Virchows Arch.* 2012;460(3):237–49.
11. Rice MS, Hankinson SE, Tworoger SS. Tubal ligation, hysterectomy, unilateral oophorectomy, and risk of ovarian cancer in the Nurses' Health Studies. *Fertil Steril.* 2014;102(1):192–8 e3.
12. Enomoto T, Aoki D, Hattori K, Jinushi M, Sugiyama T. The first Japanese nationwide multicenter study of BRCA mutation testing in ovarian cancer: CHARACTERizing the cross-sectional approach to Ovarian cancer geneTic TESting of BRCA (CHARLOTTE). *Int J Gynecol Cancer.* 2019;29(6):1043–9.
13. Tang H, Liu Y, Wang X, Guan L, Chen W, Jiang H, et al. Clear cell carcinoma of the ovary: Clinicopathologic features and outcomes in a Chinese cohort. *Med (Baltim).* 2018;97(21):e10881.
14. Lee HY, Hong JH, Byun JH, Kim HJ, Baek SK, Kim JY, et al. Clinical Characteristics of Clear Cell Ovarian Cancer: A Retrospective Multicenter Experience of 308 Patients in South Korea. *Cancer Res Treat.* 2020;52(1):277–83.
15. Takahashi K, Takenaka M, Kawabata A, Yanaihara N, Okamoto A. Rethinking of treatment strategies and clinical management in ovarian clear cell carcinoma. *Int J Clin Oncol.* 2020;25(3):425–31.
16. King CM, Barbara C, Prentice A, Brenton JD, Charnock-Jones DS. Models of endometriosis and their utility in studying progression to ovarian clear cell carcinoma. *J Pathol.* 2016;238(2):185–96.

17. Ishibashi H, Takano M, Miyamoto M, Soyama H, Matsuura H, Aoyama T, et al. Role of endometriosis as a prognostic factor for post-progression survival in ovarian clear cell carcinoma. *Mol Clin Oncol*. 2017;7(6):1027–31.
18. Paik ES, Kim T-J, Choi CH, Kim B-G, Bae D-S, Lee J-W. Clinical outcomes of patients with clear cell and endometrioid ovarian cancer arising from endometriosis. *Journal of Gynecologic Oncology*. 2018;29(2):e18-.
19. Son JH, Yoon S, Kim S, Kong TW, Paek J, Chang SJ, et al. Clinicopathologic characteristics of ovarian clear cell carcinoma in the background of endometrioma: a surveillance strategy for an early detection of malignant transformation in patients with asymptomatic endometrioma. *Obstet Gynecol Sci*. 2019;62(1):27–34.
20. Ye S, Yang J, Cao D, Bai H, Huang H, Wu M, et al. Characteristic and prognostic implication of venous thromboembolism in ovarian clear cell carcinoma: a 12-year retrospective study. *PLoS One*. 2015;10(3):e0121818.
21. Shuang Y, Jiabin, Yang Y. You, et al. Comparative study of ovarian clear cell carcinoma with and without endometriosis in People's Republic of China. *Fertility Sterility*. 2014;102(6):1656–62.
22. Kwon BS, Jeong DH, Byun JM, Lee TH, Choi KU, Song YJ, et al. Prognostic value of preoperative lymphocyte-monocyte ratio in patients with ovarian clear cell carcinoma. *J Cancer*. 2018;9(7):1127–34.
23. Yoshida K, Yoshikawa N, Shirakawa A, Niimi K, Suzuki S, Kajiyama H, et al. Prognostic value of neutrophil-to-lymphocyte ratio in early-stage ovarian clear-cell carcinoma. *J Gynecol Oncol*. 2019;30(6):e85.
24. Mabuchi S, Sugiyama T, Kimura T. Clear cell carcinoma of the ovary: molecular insights and future therapeutic perspectives. *J Gynecol Oncol*. 2016;27(3):e31.
25. Köbel M, Piskorz AM, Lee S, Lui S, Brenton JD. Optimized p53 immunohistochemistry is an accurate predictor of TP53 mutation in ovarian carcinoma. *Journal of Pathology Clinical Research*. 2016;2(4):247–58.
26. Marks EI, Brown VS, Dizon DS. Genomic and Molecular Abnormalities in Gynecologic Clear Cell Carcinoma. *Am J Clin Oncol*. 2020;43(2):139–45.
27. Swier N, Versteeg HH. Reciprocal links between venous thromboembolism, coagulation factors and ovarian cancer progression. *Thromb Res*. 2017;150:8–18.
28. Zhou Q, Zhu C, Shen Z, Zhang T, Li M, Zhu J, et al. Incidence and potential predictors of thromboembolic events in epithelial ovarian carcinoma patients during perioperative period. *Eur J Surg Oncol*. 2020;46(5):855–61.
29. Takano M, Tsuda H, Sugiyama T. Clear cell carcinoma of the ovary: is there a role of histology-specific treatment? *J Exp Clin Cancer Res*. 2012;31:53.
30. Kobayashi H, Sugimoto H, Onishi S, Nakano K. Novel biomarker candidates for the diagnosis of ovarian clear cell carcinoma. *Oncol Lett*. 2015;10(2):612–8.
31. Itamochi H, Kigawa J, Terakawa N. Mechanisms of chemoresistance and poor prognosis in ovarian clear cell carcinoma. *Cancer Sci*. 2008;99(4):653–8.
32. Caumanns JJ, Wisman GBA, Berns K, van der Zee AGJ, de Jong S. ARID1A mutant ovarian clear cell carcinoma: A clear target for synthetic lethal strategies. *Biochim Biophys Acta Rev Cancer*. 2018;1870(2):176–84.
33. Konstantinopoulos PA, Brady WE, Farley J, Armstrong A, Uyar DS, Gershenson DM. Phase II study of single-agent cabozantinib in patients with recurrent clear cell ovarian, primary peritoneal or fallopian tube cancer (NRG-GY001). *Gynecol Oncol*. 2018;150(1):9–13.
34. Komiya S, Kato K, Inokuchi Y, Takano H, Matsumoto T, Hongo A, et al. Bevacizumab combined with platinum-taxane chemotherapy as first-line treatment for advanced ovarian cancer: a prospective observational study of safety and efficacy in Japanese patients (JGOG3022 trial). *Int J Clin Oncol*. 2019;24(1):103–14.
35. Matulonis UA, Shapira-Frommer R, Santin AD, Lisyanskaya AS, Pignata S, Vergote I, et al. Antitumor activity and safety of pembrolizumab in patients with advanced recurrent ovarian cancer: results from the phase II KEYNOTE-100 study. *Ann Oncol*. 2019;30(7):1080–7.
36. Zhu J, Jiang L, Wen H, Bi R, Wu X, Ju X. Prognostic Value of Serum CA19-9 and Perioperative CA-125 Levels in Ovarian Clear Cell Carcinoma. *Int J Gynecol Cancer*. 2018;28(6):1108–16.
37. McKinnon B, Mueller MD, Nirgianakis K, Bersinger NA. Comparison of ovarian cancer markers in endometriosis favours HE4 over CA125. *Mol Med Rep*. 2015;12(4):5179–84.
38. Szubert M, Suzin J, Obirek K, Sochacka A, Loszakiewicz M. Clear cell ovarian cancer and endometriosis: is there a relationship? *Prz Menopauzalny*. 2016;15(2):85–9.
39. Mueller JJ, Holzapfel M, Han CH, Santos K, Gunderson C, Moore K, et al. Staging Lymphadenectomy in Patients With Clear Cell Carcinoma of the Ovary. *Int J Gynecol Cancer*. 2016;26(1):120–4.

## Figures

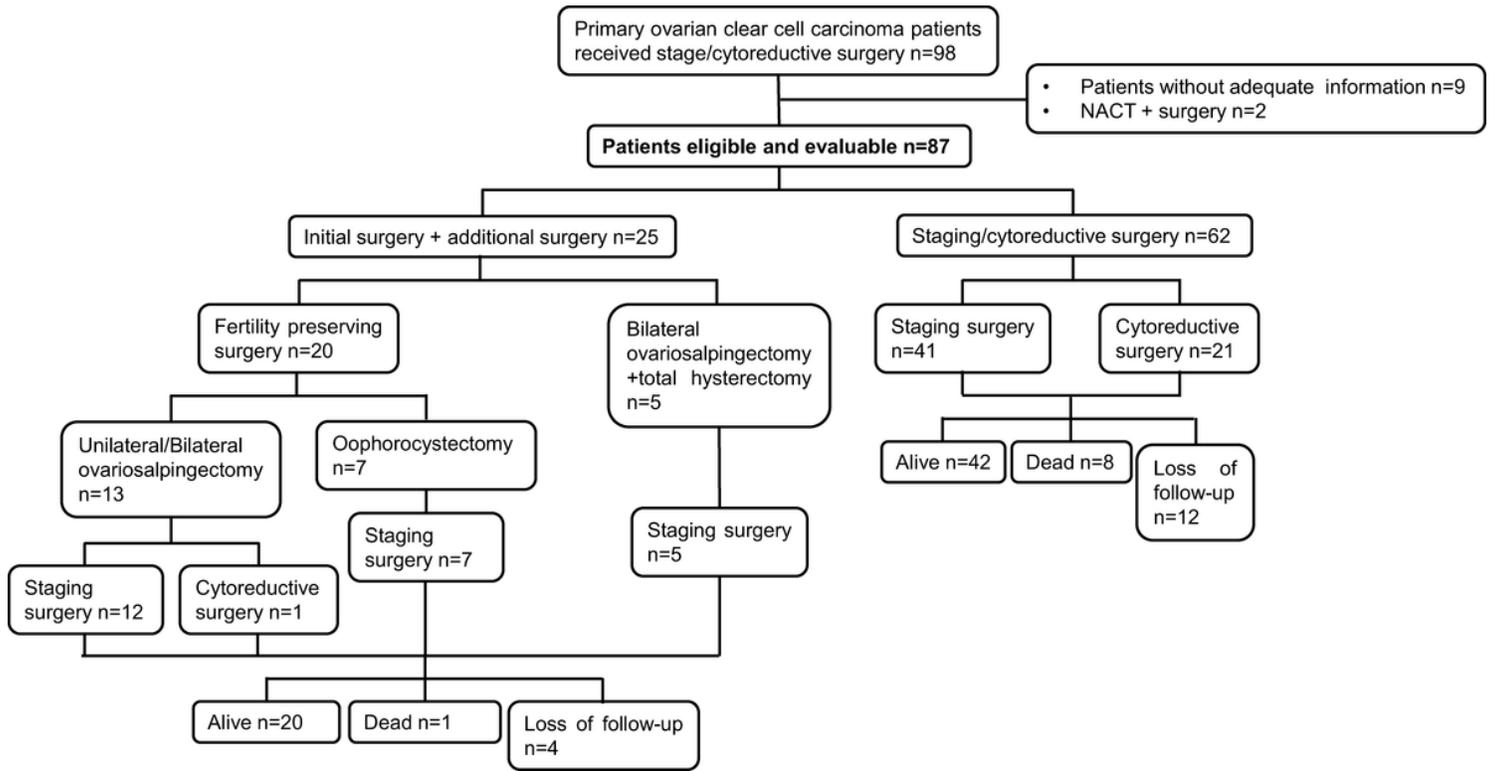


Figure 1

The inclusion process and treatment process of the 87 patients recruited in this study. a. NACT, neoadjuvant chemotherapy + interval cytoreduction; b. Including 1 case with OCCC at stage III received left ovariectomy and primary cytoreduction.

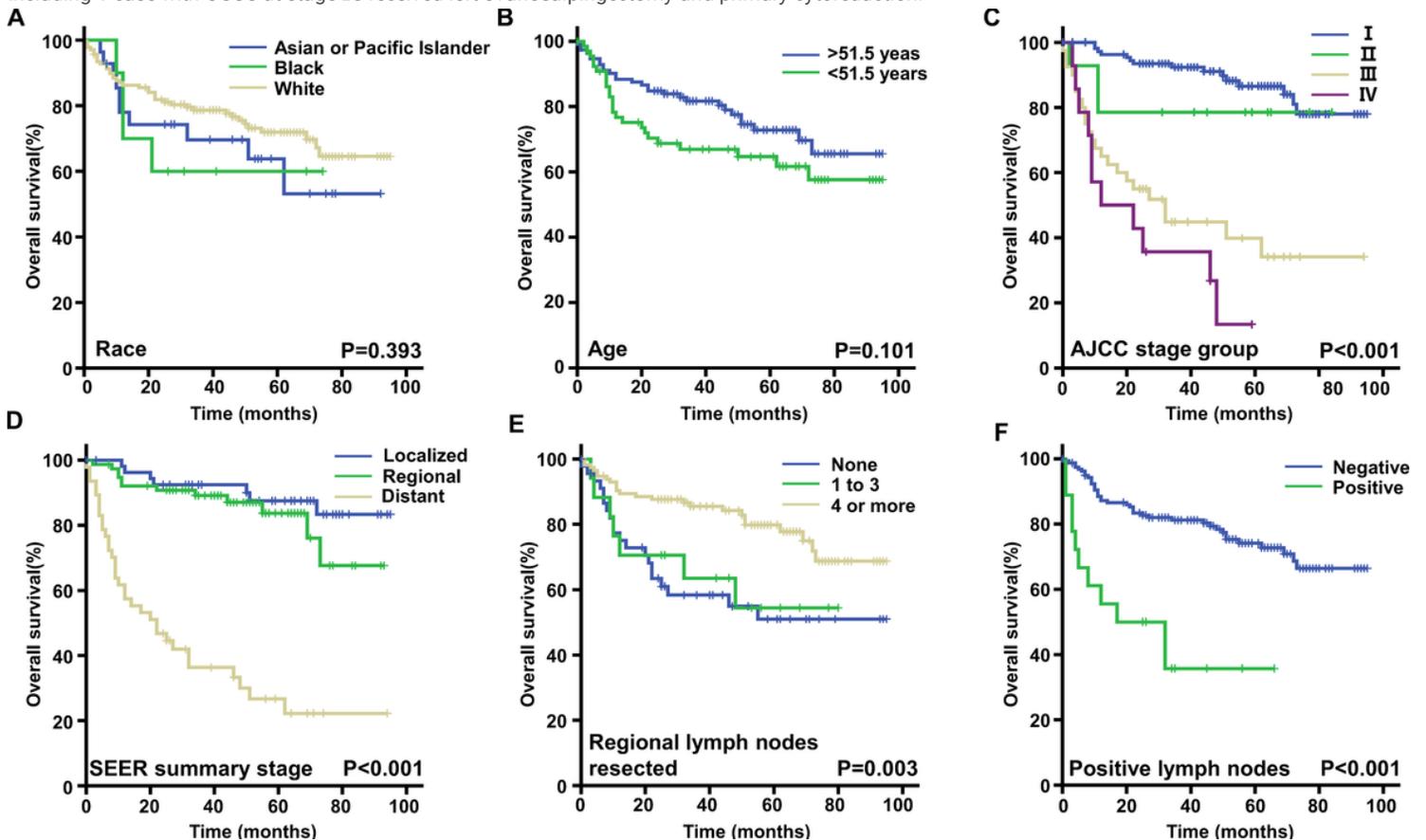


Figure 2

Kaplan-Meier curves for overall survival of OCCC patients obtained from SEER database. Grouped by race(A), age(B), AJCC stage group(C), SEER Summary stage(D), number of regional lymph nodes resected(E), positive lymph nodes (F) for all the 179 patients obtained from SEER database.