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Original Research

Characteristics and Prognosis of Ovarian Pure Clear Cell Carcinoma: A Retrospective Experience of 136 Patients

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Abstract

Background: Ovarian clear cell carcinoma (OCCC) is the most common pathological type of ovarian cancer associated with endometriosis. The effect of endometriosis on the prognosis of ovarian clear cell carcinoma remains controversial. This study aimed to investigate the clinical features and prognostic factors of pure OCCC. **Methods**: This single-center retrospective study analyzed 136 cases of pure OCCC after surgical treatment between 2010 and 2019. Patients were divided into two groups according to whether the pathologically relevant background lesion was ovarian endometriosis. Clinical data were compared between the groups. The Kaplan–Meier test and Cox regression analysis determined prognostic factors for survival. The primary outcome measure of the study was the duration of survival. **Results**: 83 (61%) participants had ovarian endometriosis of pure OCCC. Patients with ovarian endometriosis were significantly younger (50.55 ± 8.25 *vs*. 54.57 ± 6.71 years, $p = 0.004$), with lower deep venous thrombosis incidence and lower mortality and recurrence rates. Univariate analysis showed preoperative serum cancer antigen 125 (CA-125) level, endometriosis, tumor size, ascites, International Federation of Gynecology and Obstetrics (FIGO) stage, and chemotherapy resistance were significant prognostic factors. In particular, patients with endometriosis have an improved prognosis ($p < 0.05$). Multivariate analysis showed that chemotherapy resistance and FIGO stage were significantly associated with progression-free survival (PFS) and overall survival (OS) ($p < 0.001$). **Conclusions**: Pure OCCC with endometriosis has unique clinical features. However, endometriosis has no independent prognostic significance. Our findings indicate that FIGO stage and chemotherapy resistance affect prognosis.

Keywords: clear cell carcinoma of the ovary; chemotherapy resistance; endometriosis; FIGO stage; prognostic factors

1. Introduction

Ovarian clear cell carcinoma (OCCC) is a rare ovarian malignancy, accounting for <10% of epithelial ovarian carcinoma cases in North America and Europe but as high as 25% in Japan [1]. The main characteristics of OCCC are as follows: it is related to region and race; the early prognosis is good, while the late prognosis is worse than high-grade serous ovarian cancer; the tumors frequently present as large adnexal masses, primarily unilateral, and often accompanied by endometriosis; and there is no effective therapy owing to chemotherapy resistance [2–5].

Endometriosis is a prevalent benign gynecopathy that affects approximately 11% of reproductive-aged patients [6]. Two meta-analyses of studies have shown an increased risk of ovarian cancer in patients with endometriosis (risk ratio [RR], 1.964; 95% confidence interval [CI], 1.685–2.29 and summary relative risks [SRR], 1.93; 95% CI, 1.28–2.22, respectively) that was strongest for clear cell subtype (SRR 3.44; 95% CI, 2.82–4.42) [7,8]. Subsequently, researchers have identified ovarian clear cell carcinoma as the most common pathological type of endometriosis-associated ovarian cancer [9]. Early menarche, infertility, low parity, and late menopause affect endometriosis malignancy. Genetic factors such as *PTEN, p53, PI3KCA* and *ARID1A* mutations may promote the malignant transformation of endometriosis to ovarian cancer [10].

It is widely acknowledged that endometriosis plays a crucial role in the occurrence of OCCC, but opinions differ on whether endometriosis affects the prognosis. Orezzoli *et al*. [11] concluded that the median overall survival of patients with OCCC with endometriosis was 196 months versus 34 months in patients with OCCC without endometriosis ($p = 0.001$). It has also been suggested that ovarian cancer patients with endometriosis have progression-free survival (PFS) and overall survival (OS). Nevertheless, endometriosis was not an independent prognostic factor for OCCC [12]. A meta-analysis reported that the presence of endometriosis did not affect the prognosis of ovarian cancer [13]. However, the sample sizes in the previous studies were small and mainly included mixed ovarian clear cell carcinoma. This study included a relatively large number of patients, excluded mixed tumors, and aimed to investigate whether endometriosis was a prognostic factor for pure OCCC.

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2. Materials and Methods

2.1 Data Collection

We retrospectively reviewed the data of 136 consecutive patients with OCCC treated at the Department of Gynecology, Tianjin Central Hospital of Gynecology and Obstetrics, China, between January 1, 2010, and December 1, 2019. Approval for this retrospective study was obtained from the Ethics Committee of the Tianjin Central Obstetrics and Gynecology Hospital, and all procedures were performed by the ethical standards of the institutional and national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

The inclusion criteria were as follows: patients diagnosed with OCCC and those who received treatment by initial staging or debulking surgery and underwent follow-up. Pure OCCC was histologic considered relative to mixed OCCC. The mixed component was less than 10% from the pathological point of view. The exclusion criteria were as follows: patients with mixed OCCC or metastatic ovarian carcinoma and those who received preoperative chemotherapy. Pathologic tissue sections were reviewed by two pathologists at our institution.

Clinicopathological and follow-up data were collected from medical records, including age at diagnosis, menopausal status, gravidity, parity, dysmenorrhea, family history of cancer, initial symptom, preoperative serum cancer antigen 125 (CA-125) level, tumor size, ovarian involvement, ascites, lymphatic metastasis, International Federation of Gynecology and Obstetrics (FIGO) stage, phlebothrombosis, chemotherapy and chemotherapy periods, chemoresistance and survival state. Patients were divided into OCCC with endometriosis group and OCCC without endometriosis group according to whether the pathologically associated background lesion was ovarian endometriosis. The median follow-up was 61 months (12–119 months). OS refers to the time from treatment to death, and PFS refers to the time from diagnosis/treatment to disease progression or death. The interval between the recurrence and the last chemotherapy was less than six months and was defined as chemotherapeutic resistance.

2.2 Statistical Analysis

Descriptive statistics were used to describe the outcomes. Continuous variables that followed a normal distribution pattern and had homogenous variance were expressed as means $\pm$ standard deviations and were compared using Student's *t*-test. Nonnormally distributed data were expressed as medians and analyzed using the MannWhitney *U* test. The χ^2 test (more than 20% of the lattices have an expected value less than 5) or Fisher's exact test (the total number of samples is less than 40 or the expected value of a lattice is less than 1) was used to compare the categorical variables between the two groups. The *t*-test was used for continuous variables. The Kaplan–Meier model and log-rank test compared the survival rates. A Cox regression model was used for multivariate survival analysis to obtain the hazard ratio (HR) and 95% confidence interval (CI). Statistical significance was set at $p < 0.05$ based on a two-tailed hypothesis. All statistical analyses were performed using SPSS version 26.0 (IBM, Armonk, NY, USA).

3. Results

Among the 136 patients diagnosed with pure OCCC between 2010 and 2019, 83 (61%) were rendered as OCCC with endometriosis (Fig. 1), and 53 (39%) were assigned to OCCC without endometriosis (Fig. 2).

The patients' clinical and pathological characteristics are summarized in Table 1. Patients in the OCCC with endometriosis group were younger than those in the OCCC without endometriosis group (50.55 $\pm$ 8.25 *vs.* 54.57 $\pm$ 6.71 years; $p = 0.004$). Adnexal masses were the most common initial clinical manifestation in the OCCC with endometriosis group. Lower extremity venous thrombosis was found in 6.0% and 20.8% of the OCCC with endometriosis group and OCCC without endometriosis group, respectively ($p = 0.009$). The other variables, menopausal status, gravidity, parity, dysmenorrhea, family history of cancer, CA-125, tumor size, ovarian involvement, ascites, lymphatic metastasis, FIGO stage, phlebothrombosis, chemotherapy periods, and chemoresistance, were no statistical significance.

The survival information for patients with and without endometriosis is summarized in Table 2. The death and recurrence rates in OCCC with endometriosis and OCCC without endometriosis groups were 8.4% *vs.* 24.5% and 12.1% *vs.* 28.9%, respectively. The 5-year and 3-year OS rates between the two groups were 89.8% *vs.* 57.9% and 95.4% *vs.* 68.8%, respectively. The 5-year and 3-year PFS rates between the two groups were 87.8% *vs.* 52.6% and 93.85% *vs.* 62.5%, respectively.

Kaplan–Meier univariate analysis using survival time as the dependent variable was performed for various factors that might affect patient prognosis (Fig. 3). The results showed that CA-125 level, endometriosis, tumor size, ascites, FIGO stage, and chemotherapy resistance were significant prognostic factors for OS ($p < 0.05$). In contrast, age at onset, menopausal status, and phlebothrombosis were not associated with the prognosis ($p > 0.05$).

Kaplan–Meier univariate analysis using survival time as the dependent variable was performed for various factors that might affect patient prognosis (Fig. 4). The results showed that CA-125 level, endometriosis, ascites, FIGO stage, and chemotherapy resistance were significant prognostic factors for PFS ($p < 0.05$). In contrast, age at onset, menopausal status, tumor size, and phlebothrombosis were not associated with PFS ($p > 0.05$).

The Cox proportional hazards model of pure OCCC survival is shown in Table 3. Multivariate analysis demon-

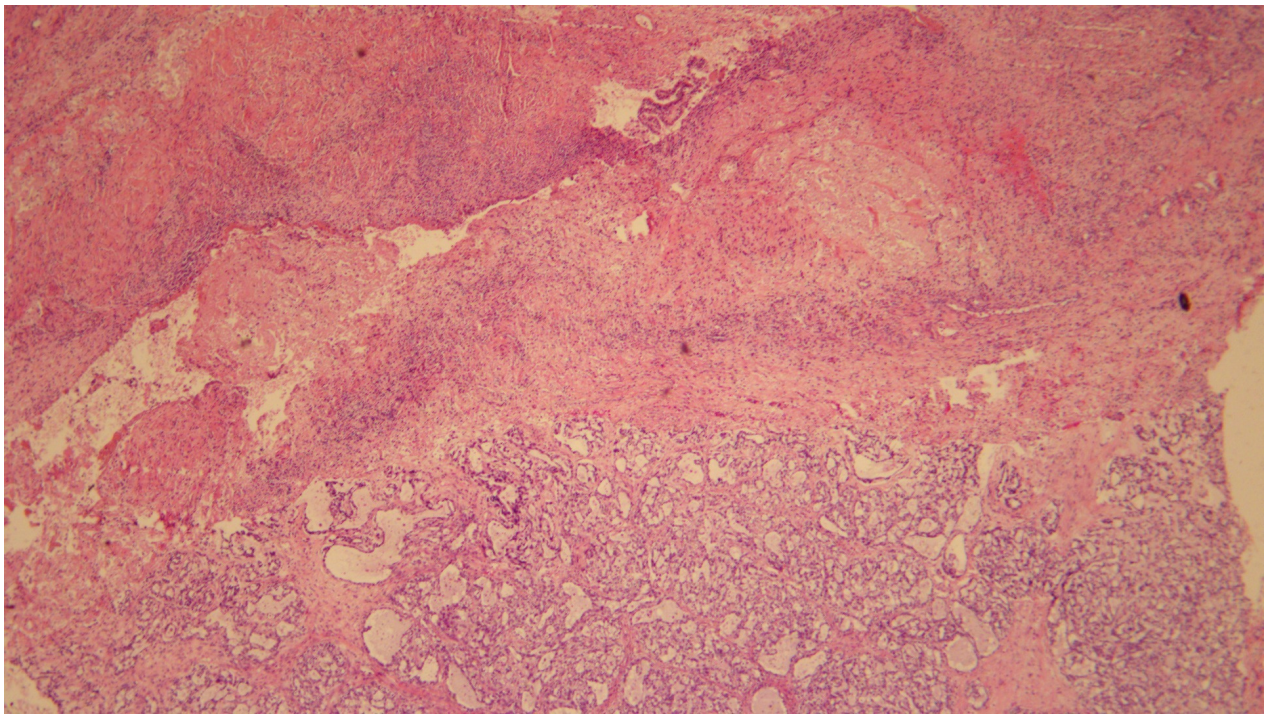

Fig. 1. Pure OCCC with endometriosis A typical OCCC arising from the wall of an endometriotic cyst. Endometrial stroma and hemosiderin cells were found in the ovarian sac wall (Hematoxylin and eosin stain; original magnification, ×200).

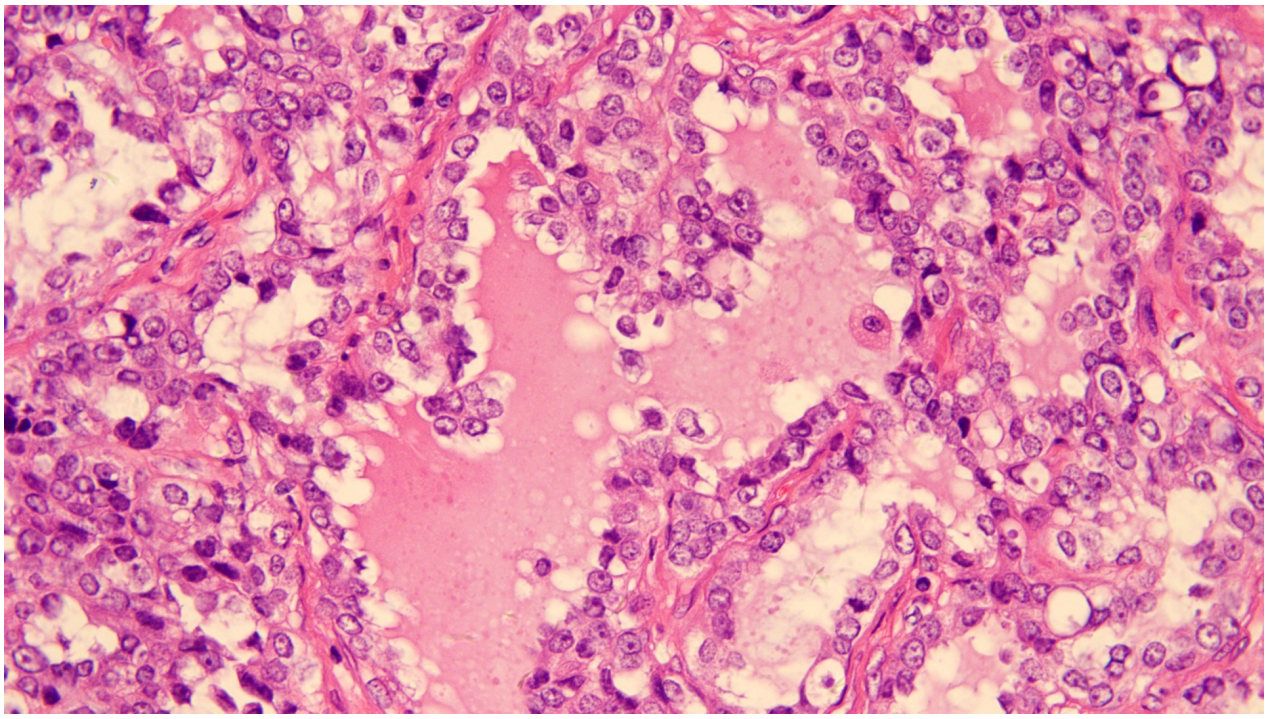

Fig. 2. Pure OCCC without endometriosis. A carcinoma composed of clear cells, eosinophils, and shoenail-like cells, without an endometriotic background (Hematoxylin and eosin stain; original magnification, ×400).

strated that chemotherapy resistance and FIGO stage were independent prognostic factors, whereas endometriosis was not an independent predictor of survival.

4. Discussion

In this study, OCCC with endometriosis occurred more frequently in younger women and had lower deep venous thrombosis incidence. In univariate analysis, the pres-

Table 1. Clinicopathologic features of pure OCCC with or without endometriosis.

	OCCC with endometriosis (n = 83)	OCCC without endometriosis (n = 53)	*p*-value
Age, years (mean ± standard deviation)	50.55 ± 8.25	54.57 ± 6.71	0.004
Menopausal status			0.186
Premenopausal	31 (37.3%)	14 (26.4%)	
Postmenopausal	52 (62.7%)	39 (73.6%)	
Gravidity			0.420
<2	29 (34.9%)	15 (28.3%)	
≥2	54 (65.1%)	38 (71.7%)	
Parity			0.296
0	13 (15.7%)	5 (9.4%)	
≥1	70 (84.3%)	48 (90.6%)	
Dysmenorrhea	28 (33.7%)	17 (32.1%)	0.841
Family history of cancer	12 (14.5%)	11 (20.8%)	0.339
Initial symptom			
Adnexal mass	59 (71.1%)	32 (60.4%)	0.196
Pelvic pain	18 (21.7%)	17 (32.1%)	0.177
Postmenopausal bleeding	2 (2.4%)	3 (5.7%)	0.326
Abnormal uterine bleeding	4 (4.8%)	2 (3.8%)	0.772
Serum CA-125 (U/mL)			0.063
≤35 U/mL	40 (48.2%)	17 (32.1%)	
>35 U/mL	43 (51.8%)	36 (67.9%)	
Tumor size (Max diameter)			0.166
<10 cm	28 (33.7%)	12 (22.6%)	
≥10 cm	55 (66.3%)	41 (77.4%)	
Ovarian involvement			0.561
Unilateral	80 (96.4%)	52 (98.1%)	
Bilateral	3 (3.6%)	1 (1.9%)	
Ascites	16 (19.3%)	16 (30.2%)	0.143
Lymphatic metastasis	6 (7.2%)	5 (9.4%)	0.646
FIGO stage			0.089
I	67 (80.7%)	34 (64.2%)	
II	7 (8.4%)	7 (13.2%)	
III	9 (10.8%)	12 (22.6%)	
IV	0	0	
Phlebothrombosis	5 (6.0%)	11 (20.8%)	0.009
Chemotherapy	78 (94.0%)	51 (96.2%)	0.562
Chemotherapy periods			0.526
≤4	18 (21.7%)	14 (26.4%)	
>4	65 (78.3%)	39 (73.6%)	
Chemoresistance	3 (3.6%)	6 (11.3%)	0.078

OCCC, ovarian clear cell carcinoma; CA-125,cancer antigen 125; FIGO, International Federation of Gynecology and Obstetrics.

ence of endometriosis was related to improved PFS and OS rates in OCCC patients ($p < 0.05$). Endometriosis tended to be associated with better PFS and OS outcomes in multivariate analysis ($p = 0.073$ and $p = 0.068$), although the independent prognostic factor could not be defined.

Endometriosis-associated ovarian cancer has distinctive clinical features. Most patients are 7–10 years younger than those without endometriosis and are diagnosed at an earlier stage [11,14]. Our study showed that the OCCC with endometriosis group was four years younger than the OCCC without endometriosis group. Our data on the stage at diagnosis agree with the data that 80.7% of patients with endometriosis were in FIGO stage I versus 64.2% in patients without endometriosis, suggesting that the younger age is due to a higher number of stage I patients and early detection. Furthermore, early diagnosis is credited to the unique symptoms of endometriosis and the standardized long-term management of the disease [15].

It is well known that endometriosis is closely related to the occurrence and development of OCCC. Ogawa *et al.* [16] reported that the incidences of ovarian serous adenocarcinoma, mucinous adenocarcinoma, OCCC, and

Table 2. Survival information for patients with and without endometriosis.

	OCCC with endometriosis (n = 83)	OCCC without endometriosis (n = 53)	*p*-value
Living condition			
Death	7 (8.4%)	13 (24.5%)	0.014
Recurrence	10 (12.1%)	15 (28.9%)	0.021
OS analysis			
Median survival time (months)	56	26	
Range	6–119	4–114	
5-year OS rate	89.9%	57.9%	0.003
3-year OS rate	95.4%	68.8%	<0.001
PFS analysis			
Median survival time (months)	54	23	
Range	3–119	4–114	
5-year PFS rate	87.7%	52.6%	<0.001
3-year PFS rate	93.85%	62.5%	<0.001

OS, overall survival; PFS, progression-free survival; OCCC, ovarian clear cell carcinoma.

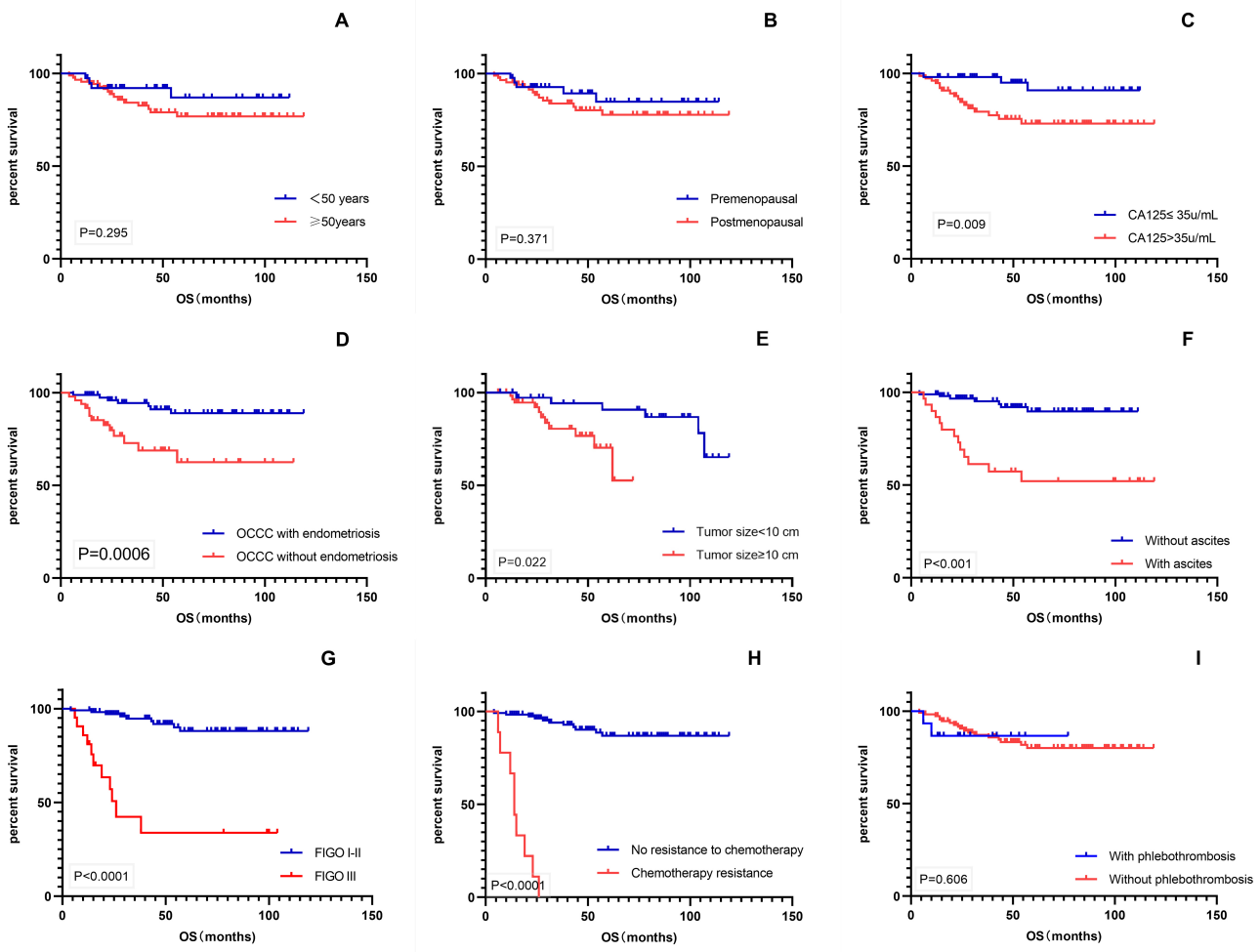

Fig. 3. Kaplan–Meier survival curves. (A–I) OS of patients with age, menopausal status, CA-125 level, endometriosis, tumor size, ascites, FIGO stage, chemotherapy resistance, and phlebothrombosis. OS, overall survival; CA-125, cancer antigen 125; FIGO, International Federation of Gynecology and Obstetrics.

endometrioid carcinoma complicated with endometriosis were 6.7%, 0%, 69.7%, and 42.9%, respectively. In our study, 61% of OCCC cases were associated with endometriosis, consistent with the published reports. Furthermore, studies have shown that endometriosis increases the risk of developing OCCC three-fold [17]. Although

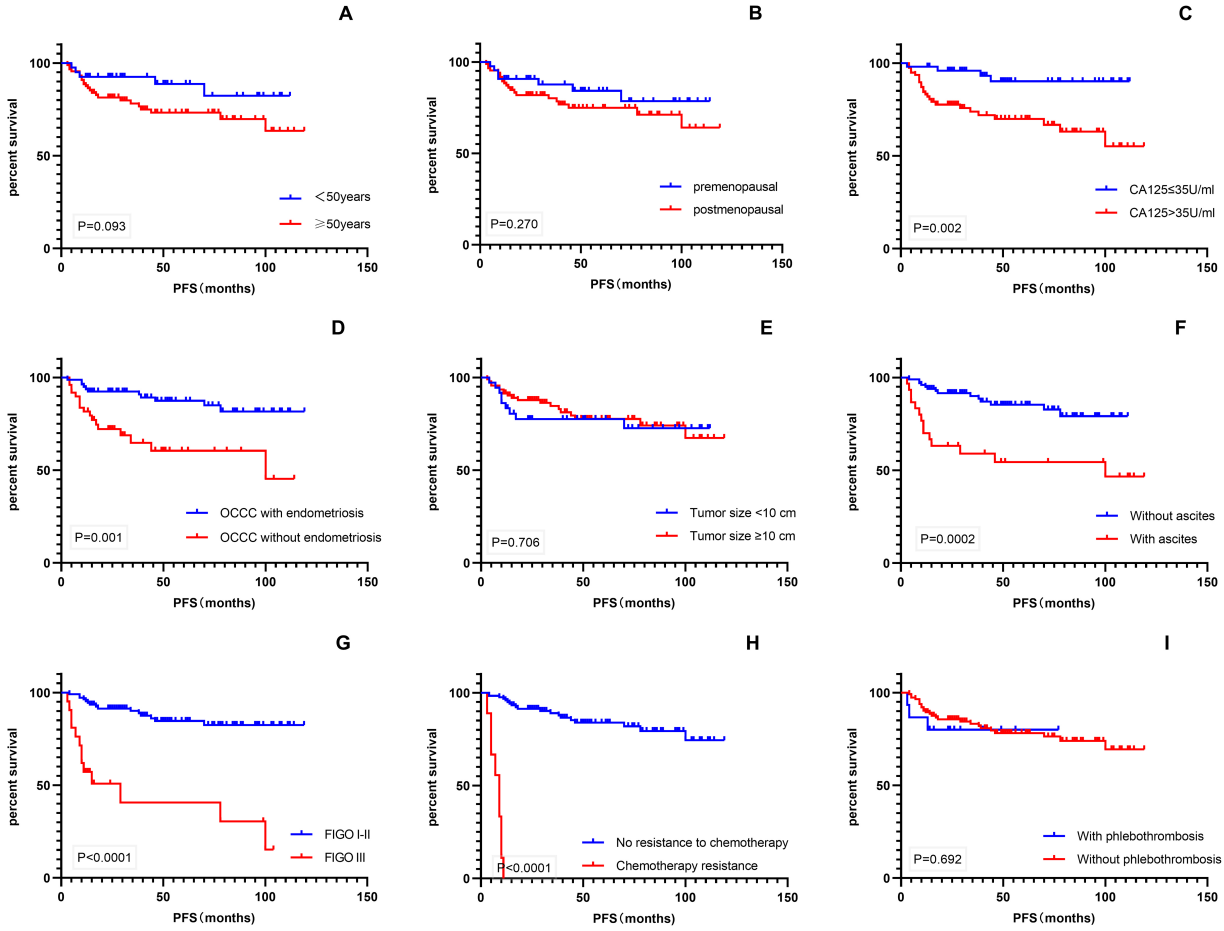

Fig. 4. Kaplan–Meier survival curves. (A–I) PFS of patients with age, menopausal status, CA-125 level, endometriosis, tumor size, ascites, FIGO stage, chemotherapy resistance, and phlebothrombosis. PFS, progression-free survival; CA-125, cancer antigen 125; FIGO, International Federation of Gynecology and Obstetrics.

Table 3. Prognostic factors for OS and PFS of pure OCCC patients.

	OS		PFS	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Endometriosis (yes *vs.* no)	0.36 (0.12–0.18)	0.068	1.1 (0.93–5.15)	0.073
Serum CA-125 (>35 *vs.* ≤35 U/mL)	0.61 (0.15–2.43)	0.610	1.13 (0.77–4.40)	0.131
Tumor size (≥10 cm *vs.* <10 cm)	1.63 (0.55–4.82)	0.377		
Ascites (yes *vs.* no)	0.43 (0.13–1.44)	0.172	1.31 (0.52–3.34)	0.568
FIGO stage (III *vs.* I–II)	2.79 (1.37–10.60)	<0.001	2.28 (1.78–6.66)	<0.001
Chemoresistance (yes *vs.* no)	3.25 (1.81–14.25)	<0.001	10.58 (4.39–27.58)	<0.001

OS, overall survival; PFS, progression-free survival; CA-125, cancer antigen 125; FIGO, International Federation of Gynecology and Obstetrics.

OCCC and ovarian endometrioid carcinoma are widely recognized as associated with endometriosis, the differentiation mechanism of these two morphologically distinct tumors remains unclear. Studies investigating the potential origins of OCCC concluded that it might arise from the endometrium, endometriotic cyst epithelium, fallopian tube epithelial cells, or ovarian surface epithelium [18–20]. Recent opinions favor an extra ovarian origin, suggesting that the ovary provides fuel for the growing cancer cells [21]. Tsuchiya *et al.* [22] demonstrated for the first time that hepatocyte nuclear factor 1β was positively detected in the cells of 95% of patients with OCCC. Interestingly, hepatocyte nuclear factor 1β was positively expressed in the normal endometrial epithelium, especially in the middle-late secretory and gestational endometrium, but not in the ovarian tissue [23]. These findings further suggest that OCCC might originate from the ectopic endometrial epithelium.

It has been reported that approximately 20% of patients with OCCC have venous thrombosis [17]. The possible mechanism might be *FVII* gene activation via the sterol regulatory element-binding protein-1 and glucocorticoid-induced leucine zipper pathway in OCCC cells. This pathway is activated by cholesterol starvation and hypoxia, producing procoagulant microvesicles and resulting in thrombosis [24]. In our study, 6.0% and 20.8% of the OCCC with endometriosis group and OCCC without endometriosis group were associated with lower extremity venous thrombosis. Given these results, it is tempting to speculate the existence of two OCCC subtypes. This question will be the focus of future research efforts.

To the best of our knowledge, endometriosis is closely related to OCCC. The loss of expression following mutations in the *ARID1A* and *PI3KCA* genes plays an essential role in the early transition from endometriosis to ovarian cancer [25,26]. *PIK3CA* mutation increases cell invasion and metastasis by stimulating downstream *AKT*. In addition, activation of this pathway is related to cell cycle regulation and chemotherapy resistance in ovarian cancer. Therefore, it plays a vital role in the development and prognosis of ovarian cancer [27]. It has been suggested that patients with OCCC with endometriosis have a good prognosis [28]. However, other researchers found no difference in stage, grade, survival, and cancer incidence between patients with or without endometriosis [12,14]. From the survival information of this study, patients with endometriosis appeared to have a good prognosis, such as lower mortality and recurrence rates. However, multivariate analysis showed that endometriosis was not an independent prognostic factor for pure OCCC. Larger prospective studies are required to validate the prognostic role of endometriosis.

Several studies have reported that FIGO staging was the main factor affecting the OCCC prognosis. Kajiyama *et al*. [29] found the 5-year OS rates with ovarian clear cell carcinoma were as follows: stage I (90.2%), stage II (57.9%), and stage III/IV (39.3%), respectively ($p < 0.0001$). Bennett *et al*. [30] analyzed 100 patients and proposed that the 5-year survival rate was 92% for stage I patients and 31% for the other stages. Lee *et al*. [28] reported the median relapse-free survival of stages I, II, III, and IV were 138.5, 33.4, 19.3, and 9.7 months, respectively. We found a significant difference in overall survival between stage I, II, and III patients. The univariate and multivariate analyses supported FIGO stage as a valuable independent prognostic predictor in pure OCCC. Therefore, regular physical examinations, including vaginal ultrasonography, should be promoted to achieve early diagnosis and treatment. This is especially important for perimenopausal women.

The consensus is that the current first-line chemotherapy regimens, namely platinum-based chemotherapy, have little effect on OCCC, with sensitivity rates of 11–27%. When combined with paclitaxel, platinum-based chemotherapy regimen sensitivity rates were 22–56% [31]. Goff *et al*. [32] assessed 24 patients with stage III OCCC who received conventional platinum-based chemotherapy and found that 70% of the patients had progressed. Cox regression analysis in our study indicated that chemotherapy resistance was an independent prognostic predictor. Consequently, new chemotherapeutic agents and protocols are needed to improve the efficacy of OCCC treatment.

OCCC differs from other ovarian epithelial carcinomas because of its distinctive characteristics. Presently, no effective treatment is available. Therefore, it is worth investigating the difference in prognosis between the two pure ovarian clear cell carcinoma subtypes. Further studies are needed to elucidate its molecular mechanism, discover new tumor markers and develop targeted drug therapy to improve the early diagnosis rate, overcome chemotherapy resistance, and improve the prognosis.

The strengths of this study include its relatively large cohort and relatively complete data. We rule out the mixed histology to avoid possible bias. Compared to the previous studies, our cohort seems more homogenous with all pure clear cell histology. The limitation of this work lies in the single-institutional retrospective design. The high proportion of stage I patients and the limited number of advanced patients may be one of the reasons why endometriosis did not affect the prognosis. Therefore, multicenter studies are needed for further confirmation.

5. Conclusions

In conclusion, patients of pure OCCC with endometriosis showed better prognosis. However, "endometriosis" could not be identified as an independent prognostic factor in pure OCCC. The prognostic trend shown in the study is clinically meaningful. Further large-scale, long-term studies focusing on OCCC are required.

Abbreviations

OCCC, ovarian clear cell carcinoma; CA-125, cancer antigen 125; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; SIR, standardized incidence ratio.

Availability of Data and Materials

All data generated or analyzed in the course of this study are included in this paper. Further enquiries can be directed to the corresponding author.

Author Contributions

PQ and YG contributed to designing the study. YG collected the data and wrote the manuscript. WD contributed to data collection and data analysis. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Approval for this retrospective study was obtained from the Ethics Committee of the Tianjin Central Obstetrics and Gynecology Hospital (2019KY198). Informed consent was obtained from all individual participants included in the study.

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Conflict of Interest

The authors declare no conflict of interest.

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