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Original Research

Construction of a Prediction Model of Cancer-Specific Survival after Ovarian Clear Cell Carcinoma Surgery

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Abstract

Background: Ovarian clear cell carcinoma (OCCC) is a special pathological type of epithelial ovarian cancer (EOC). Due to its low incidence rate, there is a lack of real-world studies at present. The purpose of the study is to construct a nomogram model for predicting postoperative cancer-specific survival (CSS) of patients with OCCC and analyze in detail the risk factors associated with OCCC. To construct a nomogram model for predicting postoperative CSS of patients with OCCC and analyze in detail the risk factors associated with OCCC. **Methods**: The clinical pathological data of 596 OCCC patients were collected from the surveillance, epidemiology, and end results (SEER) database from 2010 to 2015. Of these patients, 420 were allocated to the training group and 176 patients to the validation group using bootstrap resampling. The nomogram was developed based on the Cox regression model for predicting the cancer-specific survival probability of patients at 3 and 5 years after the operation. The model was evaluated in both the training and validation groups using consistency index, receiver operating characteristic (ROC), and calibration plots. **Results**: The independent risk factors for CSS in OCCC patients included International Federation of Gynecology and Obstetrics (FIGO) stage, race, age, tumor laterality, and the log odds of positive lymph nodes (LODDS). The nomograms were established for predicting the 3-year and 5-year CSS of patients after operation. The c-index of the nomogram for CSS was 0.786 in the training group and 0.742 in the verification group. Area under the curve (AUCs) of the 3-year and 5-year ROC curves were 0.818, 0.824 in the training group; and 0.816, 0.808 in the verification group, respectively. **Conclusions**: Based on the real population data, the construction of the CSS prediction model after OCCC surgery has high prediction efficiency, can identify postoperative high-risk OCCC patients, and can be a valuable aid for the tumor staging system.

Keywords: SEER; OCCC; CSS; LODDS; nomograph; prognosis

1. Introduction

Epithelial ovarian cancer (EOC) is the second most common cancer of the female reproductive system and the leading cause of death associated with gynecologic cancers in developed countries [1]. EOC has four main histological types: serous, mucinous, endometrioid, and ovarian clear cell carcinoma (OCCC). The latter is a special tissue type characterized by a relatively young age of onset compared with other EOC subtypes. The average age of onset reported in foreign literature is 55 years old. Moreover, the incidence of OCCC has been reported to be around 11% in the majority of Asian populations, up to 10% in Caucasian women, and even as high as 29.1% in Japan. Although the clinical diagnosis is mostly established early, prognosis evaluation is still controversial [2]. There has been a study suggest that the tumor stage of the International Federation of Gynecology and Obstetrics (FIGO) is the main independent factor affecting the prognosis of OCCC [3]. The 5-year overall survival rate (OS) of FIGO stage I and II is 80%–89%, and that of FIGO stage III and IV is reduced to 52% [4]. Currently, the standard treatment for OCCC includes comprehensive staging or tumor reduction surgery, which requires total hysterectomy, bilateral appendages, and platinum-based combined chemotherapy [5].

FIGO staging system, which is widely used in clinical practice, has been established as a relatively important indicator for evaluating tumor prognosis. However, most researchers and clinicians believe that other important, relevant factors, such as demographic characteristics, residual tumor, venous thrombosis, and surgical methods, should be considered when predicting cancer survival [2]. In recent years, different prediction models after surgery, which are more advantageous than the existing FIGO staging, have emerged, helping clinicians to better predict disease recurrence and the benefit of adjuvant therapy [6]. However, nomograms are rarely used in OCCC. Most previous studies only considered the overall survival (OS) based on Kaplan Meier and COX survival analysis, rarely focusing on cancer-specific survival (CSS).

At present, initial tumor debulking surgery combined with platinum-based chemotherapy is considered the standard treatment for epithelial ovarian cancer. However, the general direction for diagnosing and treating ovarian clear cell carcinoma is still based on high-grade serous ovarian cancer. As this form of cancer is rare, the efficacy of vari-

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ous surgical modalities has not yet been prospectively evaluated [7]. In a previous study that compared the clinicopathological features and survival of OCCC patients with other EOCs, OCCC patients had worse 5-year CSS than serous carcinomas [8]. In a Japanese multicenter retrospective study, Sugiyama *et al*. [9] also reported that 48.5% of OCCCs were diagnosed as stage I, but only 16.6% of serous carcinomas were diagnosed as stage I. The recurrence rate of IC stage OCCC was as high as 37%, and the survival rate was lower than IC stage serous carcinoma [9]. After entering the advanced stage, OCCC disease progresses rapidly, the chemotherapy resistance rate is high, and the prognosis is worse [4]. Therefore, synchronizing the treatment for OCCC with other epithelial ovarian cancers has certain limitations. Hence, it is necessary to summarize the clinical characteristics of OCCC and identify more accurate solutions for diagnosis, treatment, and follow-up. Retrospective analyses through the surveillance, epidemiology, and end results (SEER) database and real-world research are effective methods for studying low-incidence diseases such as OCCC.

This study selected 11 indicators. FIGO stage is the most clearly prognostic risk factor. Studies have shown that age, race, preoperative carbohydrate antigen 125 (CA125) level, postoperative chemotherapy, and surgical method have a certain correlation with OS, while tumor laterality has rarely been studied. Log odds of positive lymph nodes (LODDS) is a new indicator that can better reflect the condition of lymph nodes. It has not been seen in OCCC prognostic studies.

2. Materials and Methods

2.1 Data Source and Inclusion Criteria

SEER database (https://seer.cancer.gov/) is a US population-based cancer registry. In the present study, SEER*Stat software version 8.4.0.1 (IMS Inc., Calverton, MD, USA) was used to extract information on patients diagnosed with OCCC between 2010 and 2015.

The inclusion criteria were the following: (1) patients diagnosed with ovarian cancer between 2010 and 2015; (2) patients whose mucinous ovarian cancer was confirmed by pathology and was identified using the site recode ICD-O-3/WHO 2008 (International Classification of Diseases for Oncology, 3rd edition); (3) with morphological codes were C56.9 (ovary); (4) with morphological codes: 8005/3, 8290/3, 8310/3, 8313/3. The exclusion criteria were the following: (1) those with unknown tumor stage, race, laterality, and marital status; (2) no surgical treatment (Rx sum surgprim site field code is 0); (3) with unknown tumor size (CS tumor size was coded as 989, 990, 991, 999); (4) the cause of death (COD) was not ovarian cancer (COD to site record non-ovarian); (5) lymph node test and positive data were unknown (regional nodes examined and positive codes are 96, 97, 98, 99); (6) with unknown CA125 and grade (Fig. 1).

2.2 Risk Factors

Risk factors for analysis included FIGO stage, race, age, tumor laterality, the log odds of positive lymph nodes (LODDS), surgery, postoperative chemotherapy, preoperative CA125 level, grade, tumor size, and marital status. The outcome variable was cancer-specific survival at the end of follow-up.

LODDS is log (number of positive lymph nodes + 0.05)/(total number of biopsy lymph nodes – number of positive lymph nodes + 0.05). The LODDS range of the modeling group in this study was –0.6~2.38, the tumor size range was 5~800 mm, and the age range was 15~85 years. The cutoff value was selected by X-tile software (version3.6.1; https://medicine.yale.edu/lab/rimm/research/software/).

LODDS was divided into three grades (–0.6~–0.02, –0.01~0.01, 0.01~2.38), tumor size was divided into two categories (5~80 mm, 82~800 mm), and age was divided into two stages (15~49 years, 50~85 years). Fertility-Sparing Surgery (FSS) included unilateral adnexectomy (preservation of the uterus and contralateral ovary) and bilateral adnexectomy (preservation of uterus). Radical surgery (RS) was defined as a complete hysterectomy and bilateral appendages. Codes of FSS in the SEER database were 17, 27, 36, 51, and 56. Meanwhile, codes of RS in SEER database were 25, 26, 28, 35, 37, 50, 52, 55, 57, 70, 71, 72, 73 and 74.

2.3 Statistical Analysis

Patients were randomly assigned to the training and validation cohorts in a 7:3 ratio. The primary endpoints were CSS. Categorical variables are expressed as frequencies and proportions. The clinicopathological characteristics of the training and validation cohorts were compared using the chi-square test. Through multivariate analysis of the COX proportional hazards model, related prognostic factors were identified, and nomograms related to CSS were constructed in combination with the final independent risk factors. The nomogram was internally validated, and the Harrell Concordance Index (C-index) of 0.5–1.0 was used to evaluate the discriminative ability of the nomogram. A calibration curve (1000 bootstrap resamples) was generated to test the agreement between predicted and actual 3-year and 5-year CSS. The receiver operating characteristic curve (ROC curve) was used to determine the correctness of the model. Decision curve analysis (DCA), as a new method, was used to evaluate the potential clinical value of nomograms. In addition, the entire cohort was risk-stratified, and Kaplan-Meier analysis was used to explore differences in survival between risk subgroups. All statistical analyses were performed using SPSS (version 25.0, SPSS, Chicago, IL, USA) and R software (version 3.6.2; http://www.r-project.org/). A p value of <0.05 was considered statistically significant.

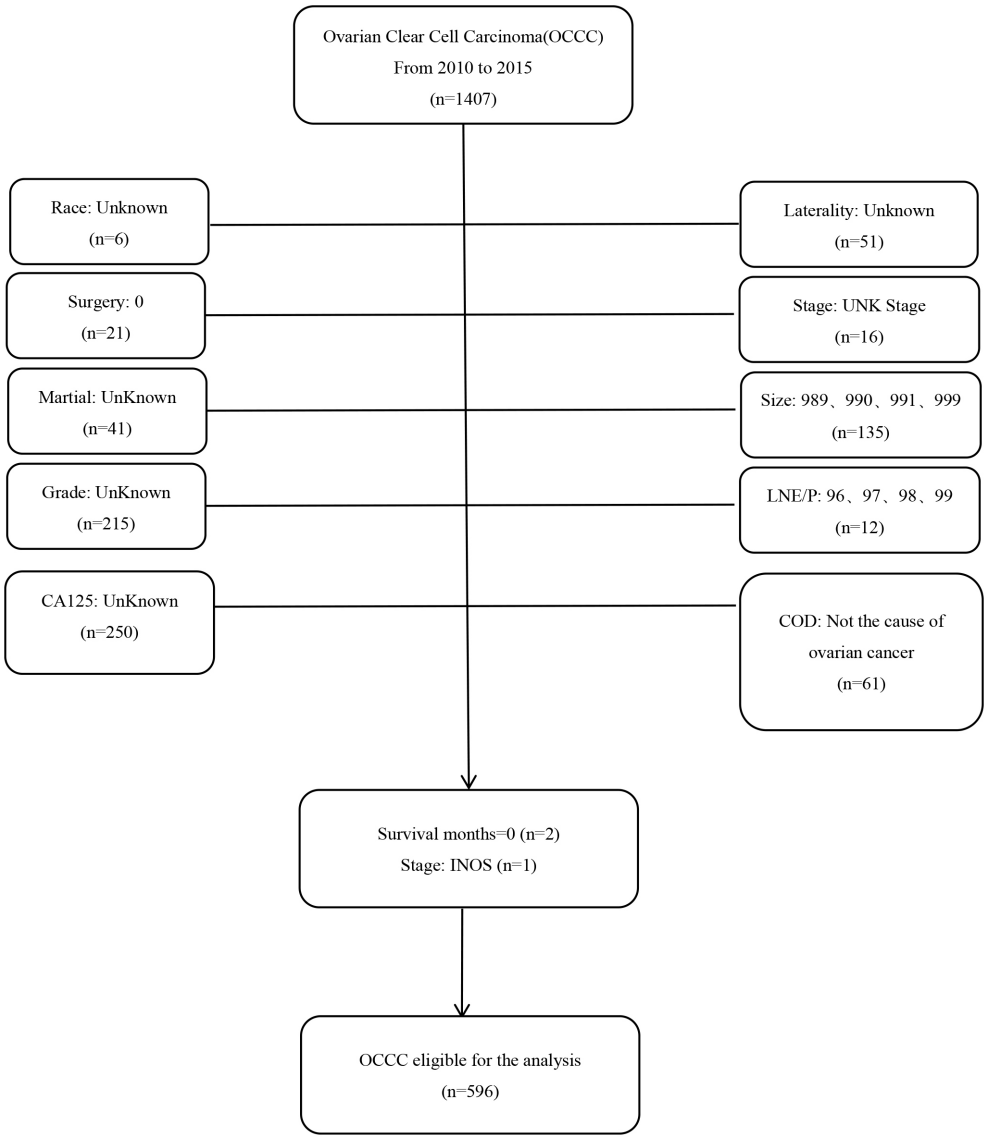

Fig. 1. Flowchart of patient selection from the surveillance, epidemiology, and end results (SEER) database ("UNK Stage" means unknown stage, "Stage: I NOS" means unknown Stage IA, IB or IC). CA125, carbohydrate antigen 125; LNE/P, lymph node test and positive data were unknown; COD, the cause of death.

3. Results

3.1 Baseline Characteristics

A total of 596 eligible patients with OCCC were included in the present study. Demographic and clinical characteristics are presented in Table 1. The majority of patients were in the early stage of the tumor (FIGO stage I; 61.07%). A great number of patients were Caucasian (71.9%), with the onset age of 55–59 years old (19.9%). Most of the tumors were unilateral, accounting for 87.58%. The data showed that married women accounted for 56.38% of patients, the tumor size ranged from 5 to 800 mm; the tumors >80 mm accounted for 70.97%; the patients with poor differentiation and undifferentiated ovarian tumors accounted for 88.59% (grade III/IV). Moreover, 27.18% of the patients were negative for CA125 before the operation, 7.2% of the patients underwent fertility-preserving surgery during the operation, 19.6% of the patients did not undergo lymph node biopsy/resection, and 14.0% of the patients did not undergo postoperative chemotherapy. All patients were divided into the training group (n = 420) and the validation group (n = 176) by resampling. There were no significant differences in the basic characteristics (FIGO stage, race, age, tumor laterality, LODDS, surgery, postoperative chemotherapy, preoperative CA125 level, grade, tumor size, and marital status) between the two groups ($p > 0.05$).

3.2 Multivariate COX Survival Analysis

The above 11 variables were included in the Cox regression model for multivariate analysis, and 5 variables, i.e., FIGO stage ($p < 0.0001$), race ($p = 0.0131$), age at di-

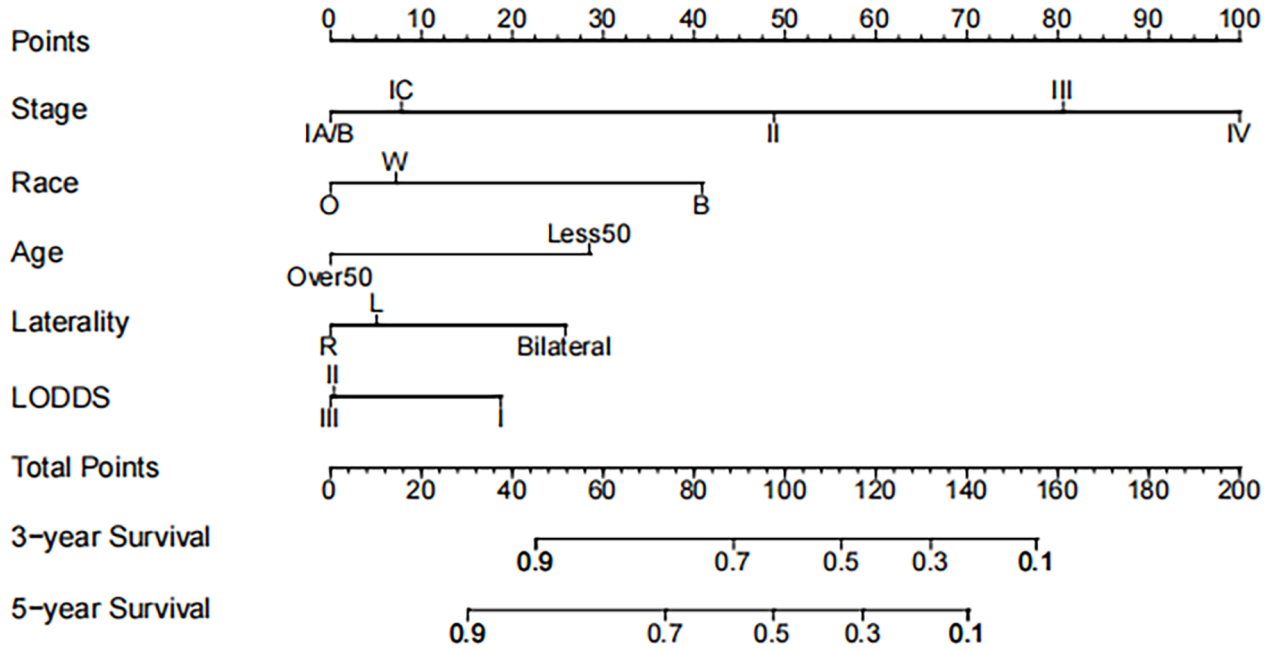

Fig. 2. Predictive model of CSS. CSS, cancer-specific survival; LODDS, the log odds of positive lymph nodes; W, white; B, black; O, other; L, left; R, right.

agnosis ($p < 0.0001$), tumor location ($p = 0.0062$), LODDS ($p = 0.0312$), were finally kept in the model, as shown in Table 2.

3.3 Construction and Application of CSS Prediction Model

According to the above variable screening results, 3-year and 5-year CSS prediction models were constructed, respectively. The proportion of each variable in the model is shown in Fig. 2. Complex Cox regression analysis was transformed into visualizations with nomograms. Each variable was plotted at a scale on the same plane using tick line segments in the nomogram to represent the contribution of each variable in the predictive model to the outcome event. At the same time, the 3-year and 5-year survival rates of OCCC patients were clearly obtained from the nomogram. The nomogram showed that scores increased with increasing tumor FIGO stage, with the highest scores among all races being achieved by African American people. OCCC patients aged <50 years had poorer survival prediction; meanwhile, the ovarian tumor prognostic model limited to unilateral was better than bilateral, and LODDS class I patients had the highest score. As shown in the nomogram, the FIGO stage was the most significant predictor of CSS in OCCC patients.

3.4 Validation of Predictive Models

The C index is in the range of 0 to 1; the closer the value is to 1, the better the differentiation of patients on the nomogram. For the CSS prediction model in this study, the C-index of CSS predicted by the model in the training set data was 0.786, and the C-index of the CSS predicted by the model in the validation set data was 0.742, which indicated that our model had high accuracy.

The area under the curve (AUC) ranged from 0.5 to 1.0; the closer the value was to 1, the greater the degree of patient differentiation on the nomogram. The AUC values of the 3-year and 5-year ROC curves of the training set were 0.818 and 0.824, respectively (as shown in Fig. 3A,B), and the AUC values of the 3-year and 5-year ROC curves of the validation set were 0.816 and 0.808, respectively (as shown in Fig. 3C,D). The predictive model accuracy was very good.

For the CSS prediction model, the calibration curves of the training set and the validation set are shown in Fig. 4A,B, respectively. The difference between the 3-year and 5-year CSS and the actual CSS was small, and the model accuracy rate was acceptable.

For the CSS prediction model, the DCA curves of the 3-year and 5-year prediction models compared with the conventional FIGO staging are shown in Fig. 5A,B, respectively. The 3-year and 5-year CSS prediction models have obvious clinical benefits compared with the FIGO staging model, where the clinical benefit of the annual CSS prediction model was particularly prominent when the predicted probability was >40%.

The Kaplan-Meier survival curves of each related factor affecting the prognosis of ovarian clear cell carcinoma are shown in Fig. 6A–E. This model could effectively identify patients with postoperative high-risk ovar-

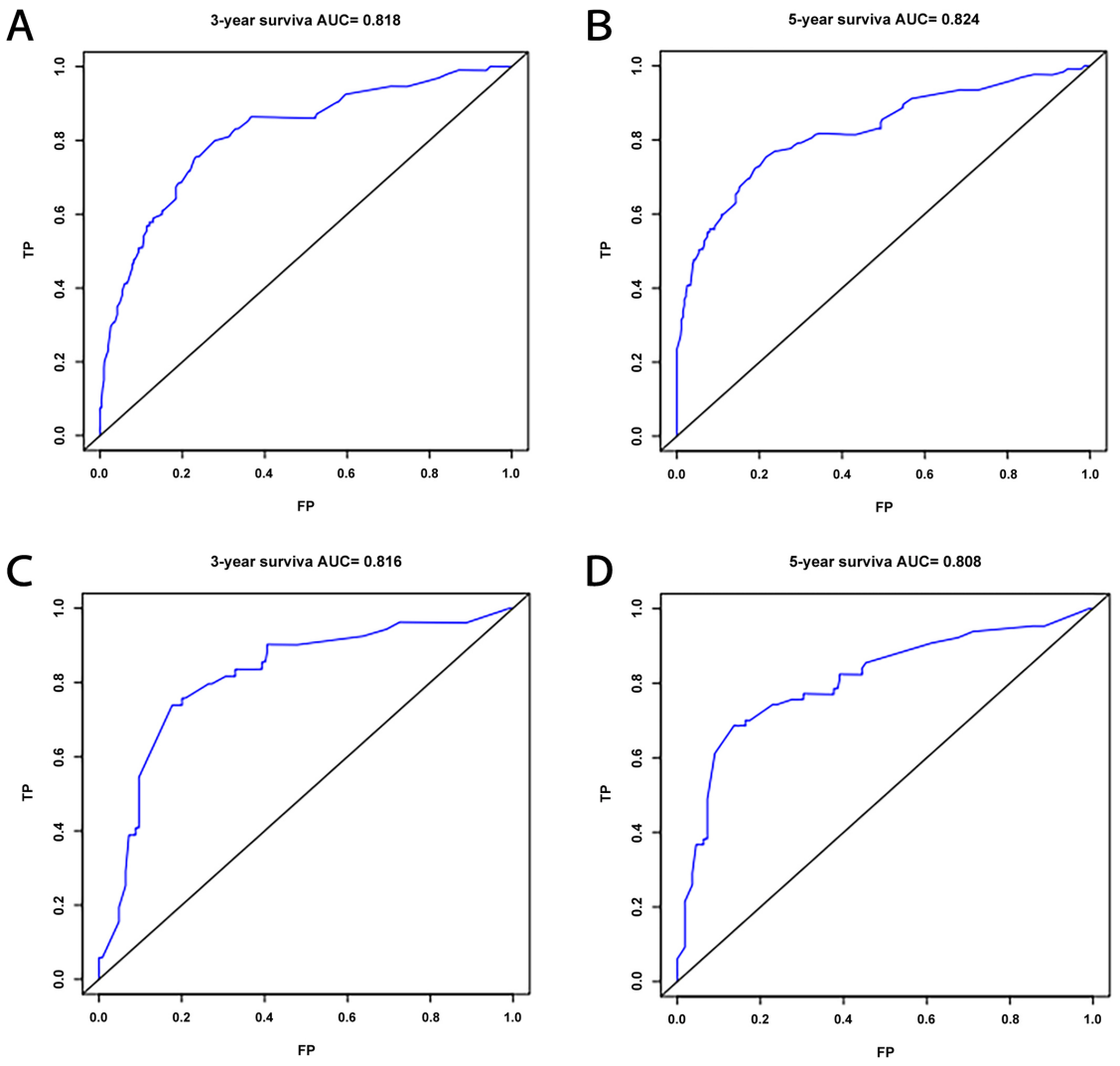

Fig. 3. 3-year and 5-year ROC curves of the training and the validation sets. (A) Three-year ROC curve of the training group. (B) Five-year ROC curve of the training group. (C) The validation set 3-year ROC curve. (D) The validation set 5-year ROC curve. ROC, receiver operating characteristic; AUC, the area under the curve; TP, ture positive; FP, false positive.

ian clear cell carcinoma. As the surgical method, postoperative chemotherapy, preoperative CA125 level, and tumor size did not result as independent risk factors in the COX survival analysis, they were not included in the prognostic model, but we could be clearly seen on the survival curve that debulking surgery other than FSS and RS, postoperative chemotherapy, preoperative CA125 positive, tumor size >80 mm indicated a lower survival probability.

4. Discussion

Among 596 OCCC patients included in the present study, the age of clinical diagnosis, which was mainly 55–59 years old, was relatively lower than in patients with other epithelial ovarian cancers. In addition, the onset was often in the early stage of the disease (namely stage I and II), and the tumor volume of >80 mm was large. These results are consistent with previous studies [10,11] and suggest the uniqueness of OCCC compared to other EOCs. In addition to the distinctive clinical features, ovarian clear cell carcinoma (OCCC) is also unique in terms of histopathological and genetic features. First, the incidence varies by ethnicity; however, the cause remains unclear. Also, Asians, especially Japanese women, have the highest incidence reaching the OCCC rate of 23% [12]. Second, tumors are often high-grade and have a relatively poor prognosis, which is in line with the fact that OCCCs in our study population was mostly differentiated tumors.

Through previous literature reading, we selected 11 relevant variables for current research. Following COX survival analysis, the final modeling variables were FIGO stage, race, tumor location, age, and LODDS. As the most definitive diagnosis and treatment basis for EOC, FIGO tumor staging is still feasible in OCCC [13] for prognosis prediction [14]. FIGO staging also has an important role in

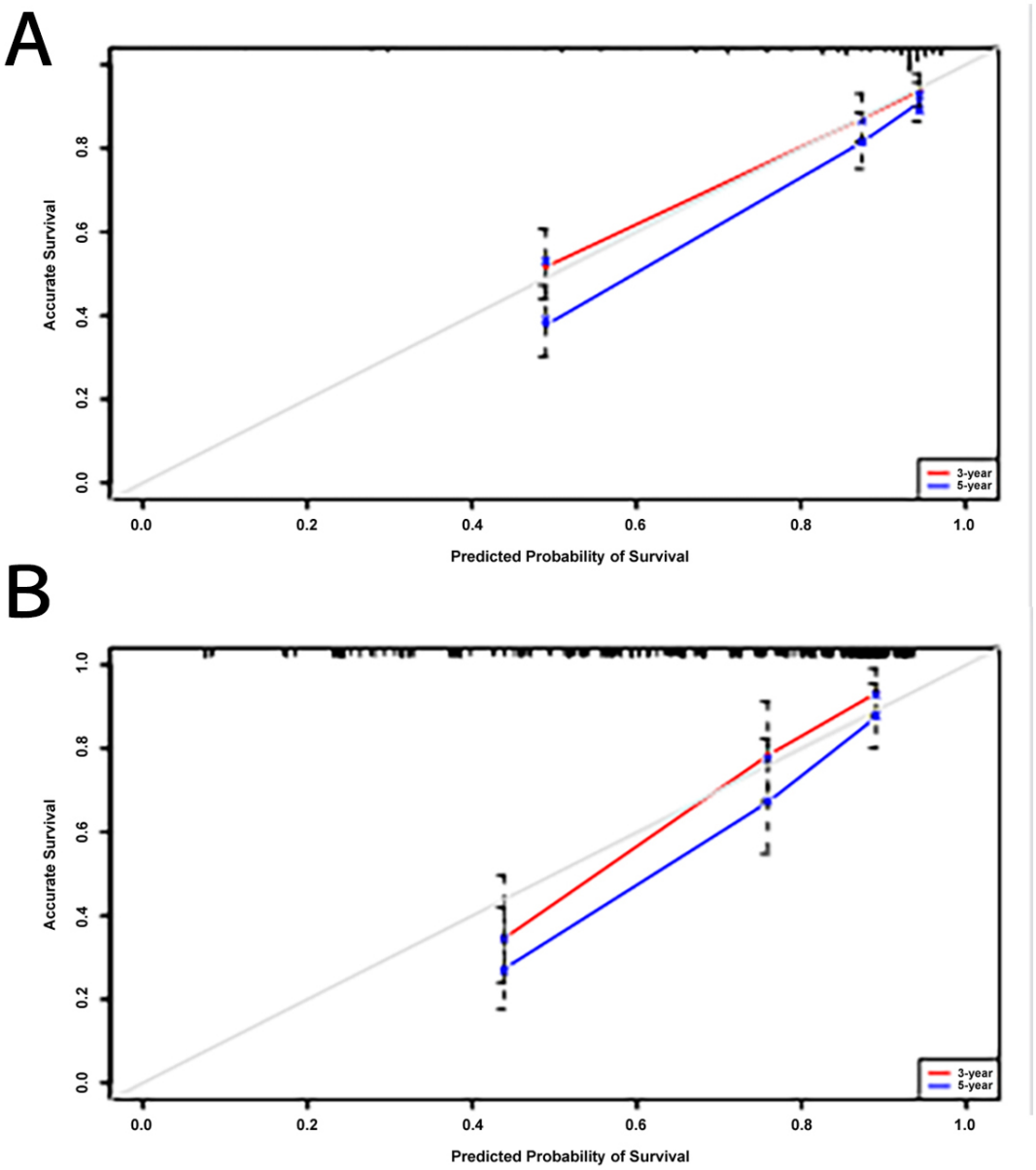

Fig. 4. Calibration curves of the training and the validation sets. (A) Training set calibration curve. (B) Validation set calibration curve.

our CSS prediction model. Because the onset of OCCC is mostly in the early stage, there are many studies on patients with stage I. Herein, we subdivided stage I into IA/B and IC stages, after which it was found that patients with IC stage had high CSS scores. FSS is feasible and whether postoperative chemotherapy is required remain research topics of interest with a certain degree of interpretation and inclination. In terms of incidence research, OCCC has a high specificity in Asian populations. In terms of mortality prediction, although some studies have reported that race is not an important indicator of progression-free survival (PFS) and OS of the disease [15], our model clearly showed that African Americans had higher 3-year and 5-year cancer-specific mortality rates, which may be related to many social, economic, and even cultural reasons, and may also be related to the population included in the SEER database. In our follow-up studies, we plan to continue to focus on the effect of race on mortality risk. Multivariate analysis showed no significant difference between the tumor located on the left and right sides; however, compared with bilateral ovarian tumors, the 3-year and 5-year survival rates of OCCC confined to one ovary were significantly improved. A larger tumor burden was associated with a greater tumor burden, which we believe is closely related to the FIGO stage of the disease; thus, future studies could subdivide stages IA and IB. Previous studies have

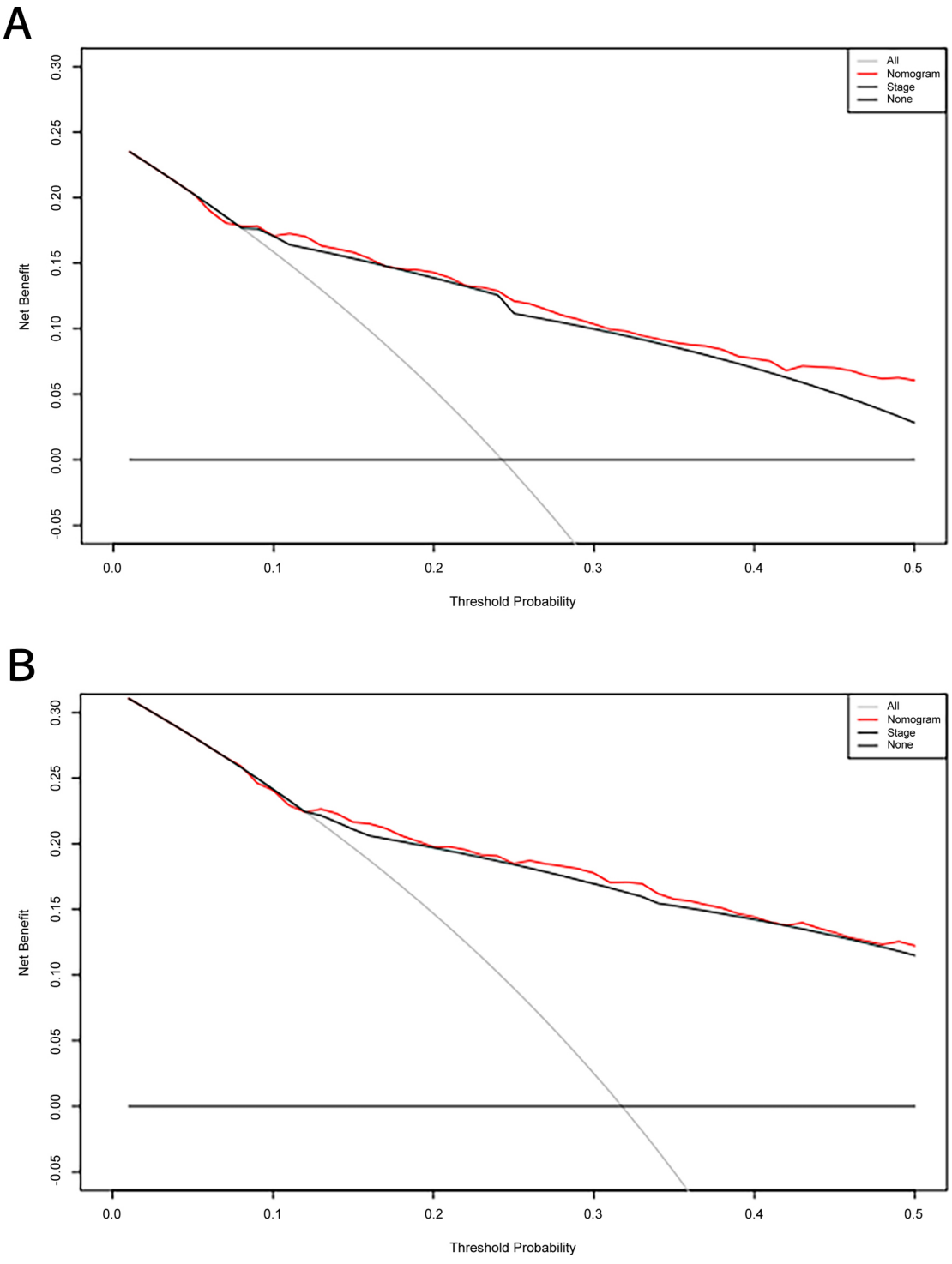

Fig. 5. 3-year and 5-year CSS DCA curves. (A) Three-year CSS DCA curve analysis. (B) Five-year CSS DCA curve analysis. CSS, cancer-specific survival; DCA, decision curve analysis.

suggested that age is a high-risk factor for a prognosis for EOC, and the study has suggested that age $\geq$70 years is associated with a 1.4-fold increased risk of CSS [16]. Our results showed that those who were $<$50 years old had a worse prognosis, which may be related to the trend of younger onset of OCCC and the faster disease progression in younger patients compared with older patients. Other studies have shown that the prognosis of OCCC has a certain correlation with the tumor size and the marital status of the patients [17], but in our study, patients with tumors $>$80 mm had a worse prognosis in the survival curve, and the marital status of the patients showed a worse prognosis. However, the ef-

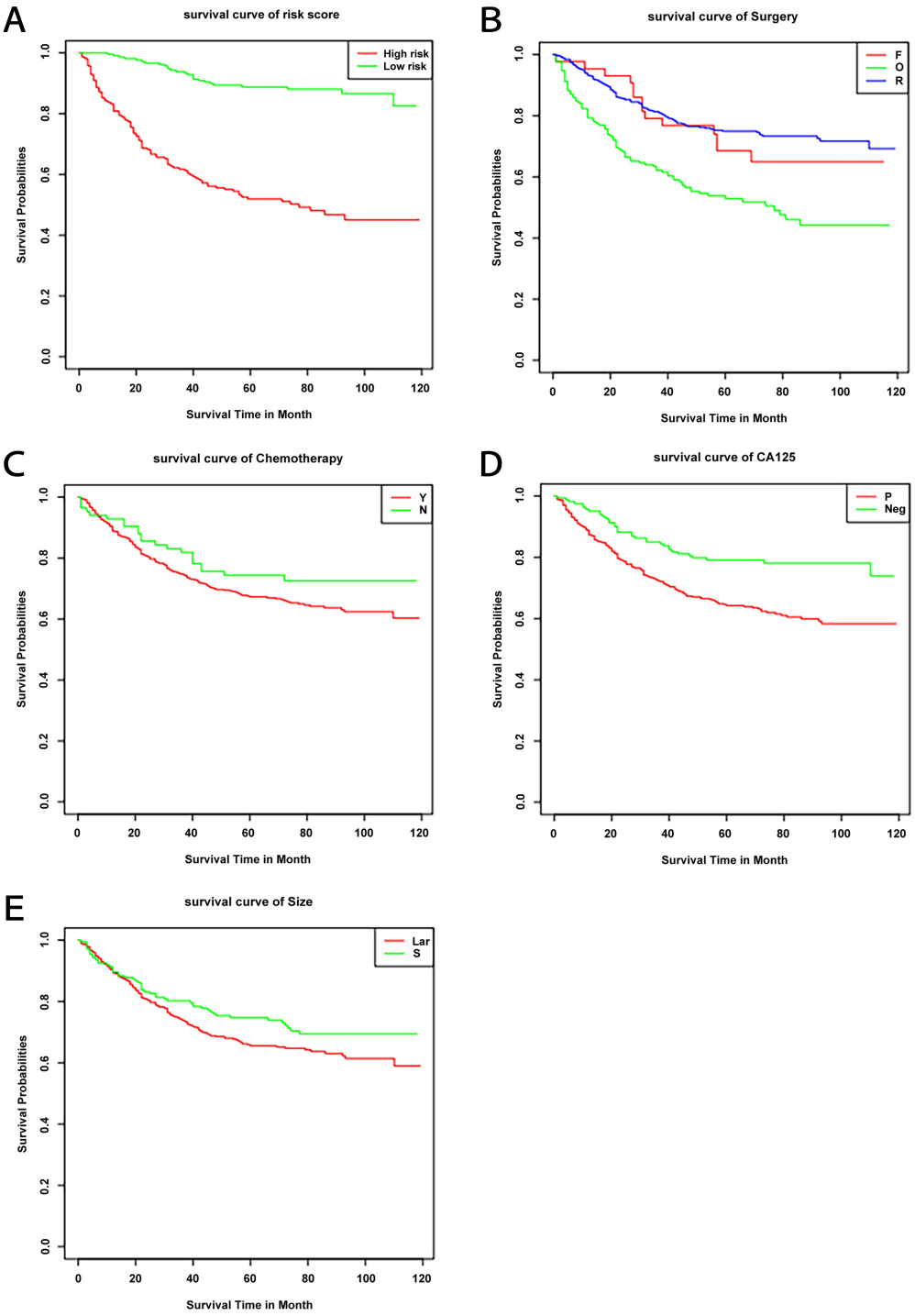

Fig. 6. Kaplan-Meier survival curves of each related factor. (A) CSS high- and low-risk associated survival curves. (B) Survival curves related to CSS surgical methods. (C) Survival curve related to chemotherapy after CSS operation. (D) Survival curve related to carbohydrate antigen 125 (CA125) level before CSS surgery. (E) Tumor size-related survival curve before CSS surgery.

fect was not obvious. It has been reported that lymph node metastasis is not common in OCCC patients with the limited disease to the ovary, but compared with node-negative patients, node-positive patients were more likely to die and more extensive. Lymphadenectomy has an important role in providing accurate staging and prognostic information [18]. Some researchers argued that for stage I OCCC, the number of resected lymph nodes $\geq$35 is an independent predictor of improving recurrence-free survival (RFS) [19]. However, a previous study showed that compared with no lymphadenectomy, systematic pelvic and para-aortic lymphadenectomy was not associated with longer OS or PFS

Table 1. Basic characteristics of the included patients (n = 596).

Variable	Total	Training group	Validation group	*p*-value
	n (%)	n (%)	n (%)	
	596	420	176	
Stage				0.106
IA/B	197 (33.05)	151 (35.95)	46 (26.14)	
IC	167 (28.02)	118 (28.09)	49 (27.84)	
II	66 (11.07)	43 (10.24)	23 (13.07)	
III	128 (21.48)	85 (20.24)	43 (24.43)	
IV	38 (6.38)	23 (5.48)	15 (8.52)	
Race				0.661
Black	22 (3.69)	15 (3.57)	7 (3.98)	
White	429 (71.98)	288 (68.57)	141 (80.11)	
Other	145 (24.33)	117 (27.86)	28 (15.91)	
Age				0.538
$<$50 years	158 (26.51)	117 (27.86)	41 (23.30)	
$\geq$50 years	438 (73.49)	303 (72.14)	135 (76.70)	
Laterality				0.445
Bilateral	74 (12.42)	48 (11.43)	26 (14.77)	
Right	235 (39.43)	199 (47.38)	88 (50.00)	
Left	287 (48.15)	173 (41.19)	62 (35.23)	
LODDS				0.288
1	399 (66.95)	285 (67.86)	114 (64.77)	
2	126 (21.14)	85 (20.24)	41 (23.30)	
3	71 (11.91)	50 (11.90)	21 (11.93)	
Surgery				0.842
Other	171 (28.69)	110 (26.19)	61 (34.66)	
RS	382 (64.09)	276 (65.71)	106 (60.23)	
FSS	43 (7.22)	34 (8.10)	9 (5.11)	
Chemotherapy				0.946
No/Unknown	84 (14.09)	64 (15.24)	20 (11.36)	
Yes	512 (85.91)	356 (84.76)	156 (88.64)	
CA125				0.092
Negative	162 (27.18)	122 (29.05)	40 (22.73)	
Positive	434 (72.82)	298 (70.95)	136 (77.27)	
Grade				0.297
1	9 (1.51)	6 (1.43)	3 (1.70)	
2	59 (9.90)	42 (10.00)	17 (9.66)	
3	320 (53.69)	226 (53.81)	94 (53.41)	
4	208 (34.90)	146 (34.76)	62 (35.23)	
Size				0.453
$\leq$80 mm	173 (29.03)	122 (29.05)	51 (28.98)	
$>$80 mm	423 (70.97)	298 (70.95)	125 (71.02)	
Martial				0.594
Single	152 (25.50)	110 (26.19)	42 (23.86)	
Married	336 (56.38)	234 (55.71)	102 (57.95)	
Other	108 (18.12)	76 (18.10)	32 (18.18)	

LODDS, log odds of positive lymph nodes; FSS, Fertility-Sparing Surgery; CA125, carbohydrate antigen 125; RS, radical surgery.

but with a higher incidence of postoperative complications [20]. In the present study, we included LODDS, which is a quantifiable indicator that can reflect the number of positive and negative lymph nodes in general. It is suitable for advanced patients who underwent systematic lymph node dissection. The cutoff value related to survival status was obtained by X-tile. It can be seen in the nomogram that the 3-year and 5-year cancer-specific survival of LODDS I grades

Table 2. Multivariate COX survival analysis of predictive model training group.

Clinical features	Total		*p*-value
Stage			
IA/B	143	Reference	
IC	120		0.5797
II	49		0.0002
III	84		<0.0001
IV	24		<0.0001
Race			
Black	15	Reference	
White	304		0.0131
Other	101		0.0058
Age			
<50 years	112	Reference	
≥50 years	308		<0.0001
Laterality			
Bilateral	51	Reference	
Right	173		0.0062
Left	196		0.0254
LODDS			
I	285	Reference	
II	85		0.0901
III	50		0.0312

were significantly reduced, suggesting that pelvic and paraaortic lymph node resection in the early stage of the disease had obvious advantages for cancer-specific survival. Although the surgical method, preoperative CA125 level, and postoperative chemotherapy did not result as independent risk factors in the multivariate regression analysis, we can see the trend of different choices in the Kaplan-Meier survival curve, which may be limited by OCCC incidence. It is also possible that due to the clear deletion of unknown data from the database, we selected the small sample size; however, it could still provide preliminary ideas for the study of predictors of OCCC. Because the age of onset of OCCC is younger than other EOCs, it is particularly important for early OCCC patients who have not completed childbirth and have a strong desire to bear children and wish to undergo FSS. Also, the research on surgical methods for stage I patients has become particularly popular in recent years. Because OCCC is mostly a tumor with poor pathological differentiation, some studies have pointed out the controversy of FSS in OCCC patients [21], while others have suggested that compared with FSS and radical surgery, there is no difference in OS between the two groups of patients, after adjusting for lymph node resection. Moreover, disease staging or FSS did not affect OS [22]. In our survival curve, we can see that the prognosis of patients who underwent intermediate and advanced tumor debulking surgery was significantly worse, while there seemed to be no significant difference between patients who underwent FSS and complete hysterectomy and bilateral adnexa, as the choice of surgical method was also closely related to disease stage. Therefore, we consider that the poor prognosis of patients undergoing debulking surgery is related to the later stage of FIGO to a certain extent. In a Japanese study on stage I-IIB OCCC patients, univariate analysis revealed that neither preoperative CA125 value nor chemotherapy regimen was a prognostic risk factor [23]. In stage I patients, adjuvant chemotherapy did not affect 5-year PFS, but in stage IC OCCC, adjuvant chemotherapy was associated with improved OS [24]. Another study showed that compared with other EOCs, OCCC preoperative CA125 levels were mostly negative [25]. In the present study, preoperative CA125 was elevated in 72.82% of patients, and 85.91% of patients chose postoperative chemotherapy, which was not completely consistent with previous studies. Existing research suggested that OCCC is associated with endometriosis [25], and patients with endometriosis are often accompanied by elevated CA125 levels, thus further adding credibility to our results. Moreover, the survival curve showed that the patients with preoperative CA125 elevation and postoperative chemotherapy were more likely to die.

OCCC accounts for 5–25% of ovarian cancers, with obvious ethnic and regional differences in incidence [26]. During the development of OCCC, *ARID1A* and *PIK3CA* genes frequently mutate, unlike the common mutations in serous carcinoma *BRCA1/2*. Therefore, standard high-grade serous ovarian cancer treatment is not fully applicable to OCCC [26]. Studying epidemiology, clinical characteristics, diagnosis, and treatment of OCCC in order to obtain a more specific diagnosis and treatment plan is of urgent importance. Also, due to the ethnic differences in its pathogenesis, we need to pay more attention to exploring disease-targeted therapy.

First of all, this study is a retrospective study, and only death and non-death outcomes were assessed, which has some inevitable bias. Tumor reduction satisfaction rates vary widely across cancer centers, and the lack of detailed information on preoperative evaluation and postoperative complications prevents more rigorous comparisons of surgical procedures and their impact. Secondly, chemotherapy data in the SEER database only recorded whether chemotherapy was performed, but there was no detailed protocol and cycle, and it was not clear whether preoperative neoadjuvant chemotherapy was performed.

5. Conclusions

The incidence of OCCC is low, and the overall prognosis is poor. The prediction model based on tumor FIGO stage, race, tumor location, age, and LODDS performed well in validation and could ideally divide postoperative patients into high-risk and low-risk groups, thus achieving certain clinical reference values.

Availability of Data and Materials

The data we used were obtained from the publicly available SEER database (https://seer.cancer.gov/).

Author Contributions

All authors contributed to the concept and design of the study. Material preparation, data collection and analysis were performed by MH, LL, YLiu and YLi. The first draft of the manuscript was written by MH and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

All procedures performed in these studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was deemed exempt by the Ethics Committee of Nanjing First Hospital, China, since the data we used were obtained from the publicly available SEER database. Written informed consents were exempt since the data we used were obtained from the publicly available SEER database.

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] McGuire V, Jesser CA, Whittemore AS. Survival among U.S. women with invasive epithelial ovarian cancer. Gynecologic Oncology. 2002; 84: 399–403.

[2] Takahashi K, Takenaka M, Kawabata A, Yanaihara N, Okamoto A. Rethinking of treatment strategies and clinical management in ovarian clear cell carcinoma. International Journal of Clinical Oncology. 2020; 25: 425–431.

[3] Liu J, Wang H, Zheng M, Deng L, Zhang X, Lin B. p53 and ANXA4/NF κB p50 complexes regulate cell proliferation, apoptosis and tumor progression in ovarian clear cell carcinoma. International Journal of Molecular Medicine. 2020; 46: 2102-2114.

[4] 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 Research and Treatment. 2020; 52: 277–283.

[5] Chan JK, Tian C, Fleming GF, Monk BJ, Herzog TJ, Kapp DS, *et al*. The potential benefit of 6 vs. 3 cycles of chemotherapy in subsets of women with early-stage high-risk epithelial ovarian cancer: an exploratory analysis of a Gynecologic Oncology Group study. Gynecologic Oncology. 2010; 116: 301–306.

[6] Zachariah R, Schmid S, Radpour R, Buerki N, Fan AXC, Hahn S, *et al*. Circulating cell-free DNA as a potential biomarker for minimal and mild endometriosis. Reproductive Biomedicine Online. 2009; 18: 407–411.

[7] Wallace S, Kumar A, Mc Gree M, Weaver A, Mariani A, Langstraat C, *et al*. Efforts at maximal cytoreduction improve survival in ovarian cancer patients, even when complete gross resection is not feasible. Gynecologic Oncology. 2017; 145: 21–26.

[8] Chan JK, Teoh D, Hu JM, Shin JY, Osann K, Kapp DS. Do clear cell ovarian carcinomas have poorer prognosis compared to other epithelial cell types? A study of 1411 clear cell ovarian cancers. Gynecologic Oncology. 2008; 109: 370–376.

[9] Sugiyama T, Kamura T, Kigawa J, Terakawa N, Kikuchi Y, Kita T, *et al*. Clinical characteristics of clear cell carcinoma of the ovary: a distinct histologic type with poor prognosis and resistance to platinum-based chemotherapy. Cancer. 2000; 88: 2584–2589.

[10] Pectasides D, Pectasides E, Psyrri A, Economopoulos T. Treatment issues in clear cell carcinoma of the ovary: a different entity? The Oncologist. 2006; 11: 1089–1094.

[11] Ye S, Yang J, You Y, Cao D, Bai H, Lang J, *et al*. Comparative study of ovarian clear cell carcinoma with and without endometriosis in People's Republic of China. Fertility and Sterility. 2014; 102: 1656–1662.

[12] Fujiwara K, Shintani D, Nishikawa T. Clear-cell carcinoma of the ovary. Annals of Oncology: Official Journal of the European Society for Medical Oncology. 2016; 27 Suppl 1: i50–i52.

[13] Ditto A, Martinelli F, Bogani G, Lorusso D, Carcangiu M, Chiappa V, *et al*. Long-term safety of fertility sparing surgery in early stage ovarian cancer: comparison to standard radical surgical procedures. Gynecologic Oncology. 2015; 138: 78–82.

[14] Mizuno M, Kikkawa F, Shibata K, Kajiyama H, Ino K, Kawai M, *et al*. Long-term follow-up and prognostic factor analysis in clear cell adenocarcinoma of the ovary. Journal of Surgical Oncology. 2006; 94: 138–143.

[15] Shu CA, Zhou Q, Jotwani AR, Iasonos A, Leitao MM Jr, Konner JA, *et al*. Ovarian clear cell carcinoma, outcomes by stage: the MSK experience. Gynecologic Oncology. 2015; 139: 236–241.

[16] Ekmann-Gade AW, Høgdall CK, Seibæk L, Noer MC, Fagö-Olsen CL, Schnack TH. Incidence, treatment, and survival trends in older versus younger women with epithelial ovarian cancer from 2005 to 2018: A nationwide Danish study. Gynecologic Oncology. 2022; 164: 120–128.

[17] Wu L, Shi S, Sun H, Zhang H. Tumor Size Is an Independent Prognostic Factor for Stage I Ovarian Clear Cell Carcinoma: A Large Retrospective Cohort Study of 1,000 Patients. Frontiers in Oncology. 2022; 12: 862944.

[18] Mahdi H, Moslemi-Kebria M, Levinson KL, Gojayev A, Lockhart D, Ali-Fehmi R, *et al*. Prevalence and prognostic impact of lymphadenectomy and lymph node metastasis in clinically early-stage ovarian clear cell carcinoma. International Journal of Gynecological Cancer: Official Journal of the International Gynecological Cancer Society. 2013; 23: 1226–1230.

[19] Takei Y, Takahashi S, Machida S, Taneichi A, Yoshiba T, Takahashi Y, *et al*. Impact of the number of removed lymph nodes on recurrence-free survival in stage I ovarian clear cell carcinoma. International Journal of Clinical Oncology. 2018; 23: 930–935.

[20] Harter P, Sehouli J, Lorusso D, Reuss A, Vergote I, Marth C, *et al*. A Randomized Trial of Lymphadenectomy in Patients with Advanced Ovarian Neoplasms. The New England Journal of Medicine. 2019; 380: 822–832.

[21] Ledermann JA, Raja FA, Fotopoulou C, Gonzalez-Martin A, Colombo N, Sessa C, *et al*. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines

for diagnosis, treatment and follow-up. Annals of Oncology: Official Journal of the European Society for Medical Oncology. 2013; 24 Suppl 6: vi24–vi32.

[22] Nasioudis D, Mulugeta-Gordon L, McMinn E, Frey MK, Chapman-Davis E, Holcomb K. Fertility sparing surgery for patients with FIGO stage I clear cell ovarian carcinoma: a database analysis and systematic review of the literature. International Journal of Gynecological Cancer: Official Journal of the International Gynecological Cancer Society. 2020; 30: 1372–1377.

[23] Sakai K, Kajiyama H, Umezu T, Shibata K, Mizuno M, Suzuki S, *et al*. Is there any association between retroperitoneal lymphadenectomy and survival benefit in advanced stage epithelial ovarian carcinoma patients? The Journal of Obstetrics and Gynaecology Research. 2012; 38: 1018–1023.

[24] Bogani G, Ditto A, Lopez S, Bertolina F, Murgia F, Pinelli C, *et al*. Adjuvant chemotherapy vs. observation in stage I clear cell ovarian carcinoma: A systematic review and meta-analysis. Gynecologic Oncology. 2020; 157: 293–298.

[25] Tay SK, Cheong MA. Evidence for ethnic and environmental contributions to frequency of ovarian clear cell carcinoma. The Australian & New Zealand Journal of Obstetrics & Gynaecology. 2014; 54: 225–230.

[26] Anglesio MS, Carey MS, Köbel M, Mackay H, Huntsman DG, Vancouver Ovarian Clear Cell Symposium Speakers. Clear cell carcinoma of the ovary: a report from the first Ovarian Clear Cell Symposium, June 24th, 2010. Gynecologic Oncology. 2011; 121: 407–415.