Cancer in Females

ORIGINAL ARTICLE

Study on prognostic factors of low-grade serous ovarian cancer and establishment of nomogram prognostic model

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ABSTRACT

Background: Low-grade serous ovarian cancer is a low incidence type of ovarian cancer, and this study aimed to investigate the clinical features and effective treatment strategies that may influence its prognosis. **Methods:** We retrospectively examined the clinical characteristics of patients with a diagnosis of low-grade plasma ovarian cancer recorded in the Surveillance, Epidemiology, and End Results (SEER) database between 1988-2017. The Kaplan-Meier method and Cox regression proportional risk method were used to assess overall survival (OS). A column-wise model that could predict OS was constructed based on Cox proportional risk. **Results:** The study found that age, marital status, side, International Federation of Gynecology and Obstetrics (FIGO) stage, serum cancer antigen 125 (*CA125*), surgery, postoperative residual disease diameter and chemotherapy all significantly affected the prognosis of the disease. Among them, serum CA125, FIGO stage, surgery, postoperative residual disease diameter and chemotherapy were independent factors affecting prognosis. According to the nomogram, FIGO staging and prognosis of low-grade serous ovarian cancer (LGSOC) patients were the most significant, followed by surgery and chemotherapy, while age at presentation and chemotherapy had little effect on OS. **Conclusion:** The better prognosis of LGSOC is associated with surgery, surgical outcomes, chemotherapy, and early-stage patients. However, large sample studies are needed to further clarify whether patients with early serous ovarian cancer are suitable for fertility-sparing surgery, and whether chemotherapy and radiotherapy should be added in patients with advanced ovarian cancer.

Key words: low-grade serous ovarian cancer, Surveillance, Epidemiology, and End Results database, overall survival

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INTRODUCTION

Ovarian cancer is a common gynecological tumor, low-grade serous ovarian cancer (LGSOC) is a rare subtype of ovarian cancer, accounting for about 6%-10% of serous ovarian cancer, its clinical characteristics are different from high-grade serous ovarian cancer, compared with high-grade serous ovarian cancer, it has the characteristics of younger age of onset, less invasiveness and better prognosis, but it is not sensitive to radiotherapy. This article aims to further analyze the clinical features affecting the prognosis of LGSOC and the treatment options for better prognosis through a retrospective case study.

METHODS

Patients and data collection

This is a retrospective pooled analysis of data from patients with pathologically diagnosed LGSOC from 1988 to 2017 in the Surveillance, Epidemiology, and End Results (SEER) database. Pathological diagnosis was based on the primary site using the *International Classification of Neoplastic Diseases* (3rd edition). Inclusion criteria for cases were: (1) Diagnosis is based on cases completed by postoperative pathological diagnosis. (2) The primary site of the cancer is in the ovary, the pathological type is serous adenocarcinoma, and the degree of differentiation is grade I (well differentiated). Exclusion criteria were: (1) Cases with missing follow-up information, survival status, and other information were excluded. (2) Cases with unclear information, such as treatment plans, were excluded (Figure 1). A total of 857 cases were included in this study according to the above criteria, and the following baseline variables were statistically analyzed for these cases: age, marital status, and clinicopathological variables such as International Federation of Gynecology and Obstetrics (FIGO) stage, preoperative cancer antigen 125 (*CA125*) level, and treatment regimens for these cases. The clinical staging of all cases was determined according to the 2015 FIGO staging criteria.

Data analysis

Qualitative data were analyzed using the chi-squared test. Univariate and multivariate Cox regression analyses were used to identify independent prognostic factors for overall survival (OS). Based on the results of Cox regression analysis, nomograms were constructed using the R package "rms" to integrate survival time, survival status, and 4 characteristics to predict OS at 3 and 5 years. Internal validation of the model was performed using 1000 bootstrap resamplings. The C-index, which expresses pairwise proportions measured on a scale from 0.5 (no greater than chance) to 1 (perfect discrimination), was calculated to verify the predictive accuracy of the nomogram, with responders having a higher C-index than non-responders. The higher the C-index value, the more accurate the prediction. Simply put, it is used to quantify the degree of agreement between the predicted probability and the actual chance of an event occurring. Calibration plots were made to compare the predicted and observed 3-5-year prognosis of the nomogram. A P value < 0.05 was considered statistically significant.

RESULTS

Clinicopathological characteristics and treatment plan of the case

The characteristics and treatments of the 857 confirmed patients finally extracted from the SEER database are shown in Table 1. Among all patients, 308 (35.9%) were younger than 50 years, 549 (64.1%) were 50 years or older, and among 855 patients with known race categories, white, black, and other, there were 743 cases (86.9%), 70 cases (8.2%), and 42 cases (4.9%), respectively. The marital status of 834 of the included cases was known, of which 485 (58.2%) and 349 (41.8%) were married and unmarried, respectively. We also included the preoperative serum *CA125* index in the study. In the 194 cases with this information, CA125 was related to the clinicopathological characteristics of the tumor. Of the 751 patients with FIGO staging information, 246 (32.8%) had early stage disease (FIGO I stage), while 505 patients (67.2%) had advanced stage disease (FIGO II-IV stage). Of the 836 patients with tumor side effects, 382 (45.7%) had bilateral tumors. Regarding the initial treatment, the treatment modalities were very different: 342 cases (40%), 480 cases (56.0%), 4 cases (0.5%), 13 cases (1.5%), 1 case (0.1%), 12 cases (1.4%) and 5 patients (0.5%) received cytoreductive surgery (CRS) alone, surgery combined with chemotherapy, surgery combined with radiotherapy, surgery combined with radiochemotherapy, radiochemotherapy, chemotherapy alone and other or no treatment (P < 0.01, Table 1).

Regression analysis of prognostic factors and treatment options

Survival analysis was performed on all patients included in the study, and the overall 1-, 3-, and 5-year survival rates were 94.3%, 80.6% and 70.6%, respectively. The 1-, 3-, and 5-year survival rates for early stage patients were 97.2%, 90.5%, and 89.2%, respectively, while the 1-, 3-, and 5-year survival rates for advanced stage patients were 92.0%, 72.1%, and 59.3%, respectively.

Univariate regression analysis showed that age, marital status, *CA125* index, side (referring to unilateral or bilateral), FIGO stage, tumor debulking surgery and chemotherapy were associated with OS (P < 0.05). Race

Table 1: Demographic and clinicopathological characteristics and treatment of patients

	Variables	*n* (%)
Age at diagnosis	< 50	308 (35.9%)
	⩾ 50	549 (64.1%)
	Unknown	0
Race	White	743 (86.9%)
	Black	70 (8.2%)
	Other	42 (4.9%)
	Unknown	2
Laterality	Bilateral	382 (45.7%)
	Unilateral	454 (54.3%)
	Unknown	21
Marital status at diagnosis	Married	485 (58.2%)
	Single	349 (41.8%)
	Unknown	23
FIGO stage	I	246 (32.8%)
	II	62 (8.3%)
	III	324 (43.1%)
	IV	119 (15.8%)
	Unknown	106
CA125 level (*n* = 194)	Positive	151 (77.8%)
	Negative	43 (22.2%)
	Unknown	663
CRS	Yes	839 (97.9%)
	No	18 (2.1%)
Residual tumor size after CRS (*n* = 76)	No residual tumor	68 (89.5%)
	⩽ 1 cm	8 (10.5%)
	⩾ 1 cm	0
FSS (*n* = 132)	Yes	13 (18.6%)
	No	57 (81.4%)
	Unknown	62
Radiotherapy	Yes	18 (2.1%)
	No	839 (97.9%)
Chemotherapy	Yes	506 (59.0%)
	No	351 (41.0%)
Radiation recode (*n* = 18)	Beam radiation	14 (77.8%)
	Radioactive implants (includes brachytherapy)	1 (5.5%)
	Radioisotopes	3 (16.7%)
Treatment method	CRS	342 (40.0%)
	Chemotherapy	12 (1.4%)
	Surgery + Chemotherapy	480 (56.0%)
	Surgery + Radiotherapy	4 (0.5%)
	Surgery + Chemoradiation	13 (1.5%)
	Chemoradiation	1 (0.1%)
	No treatment	5 (0.5%)

CA125, cancer antigen 125; FIGO, International Federation of Gynecology and Obstetrics; CRS, cytoreductive surgery; FSS, fertility-sparing surgery.

and whether or not to receive radiotherapy were not associated with OS ($P > 0.05$, Figure 2).

Currently, fertility-sparing surgery (FSS) is feasible for patients with early LGSOC if they still need fertility. Therefore, we also performed a univariate regression analysis on the effect of FSS on the prognosis of early LGSOC. There was no significant association with OS ($P = 0.785$).

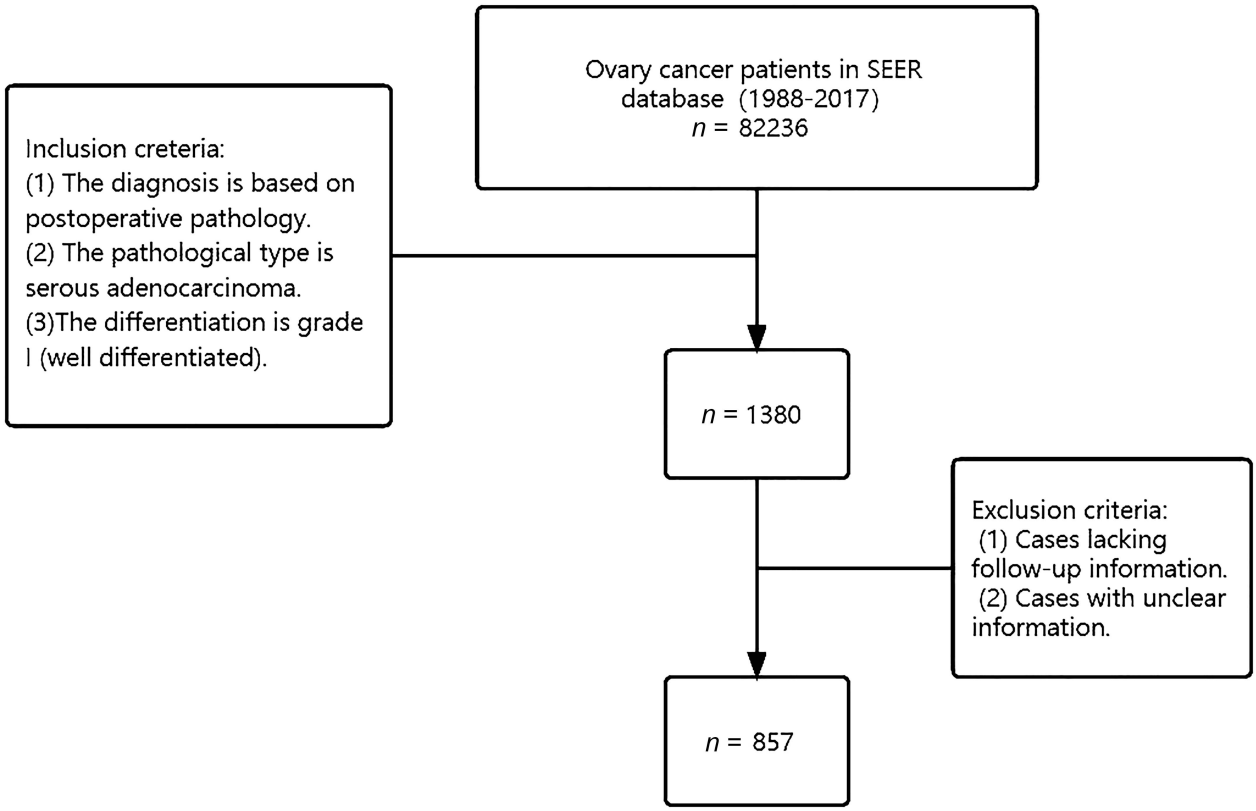

Figure 1. Inclusion and exclusion criteria of the study population. SEER, Surveillance, Epidemiology, and End Results.

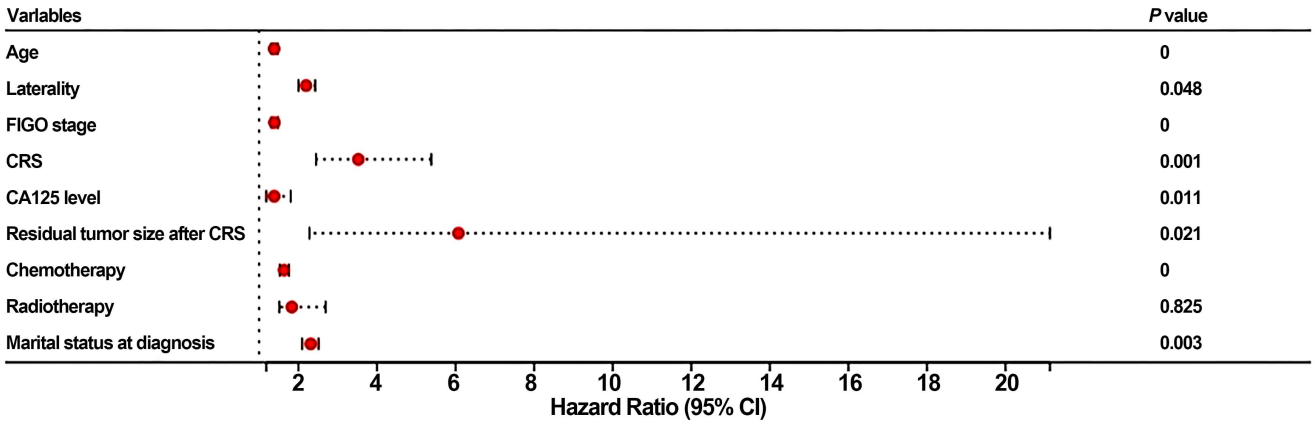

Figure 2. Univariate analysis of the OS in the overall cohort. OS, overall survival; FIGO, International Federation of Gynecology and Obstetrics; CRS, cytoreductive surgery; *CA125*, cancer antigen 125; CI, confidence intervals.

Multivariate regression analysis excluding potential confounders showed that FIGO stage, *CA125* index, surgery, whether chemotherapy, and the size of residual disease after tumor debulking were independent prognostic factors for OS ($P < 0.05$, Figure 3).

Construct a nomogram for predicting OS based on Cox regression analysis of hazard ratios

After stepwise positive selection in the Cox regression analysis, prognostic factors were included in the construction of a nomogram. A nomogram is used by plotting a single patient variable value on each variable axis and drawing a line up from each variable axis to determine the score to which each variable value

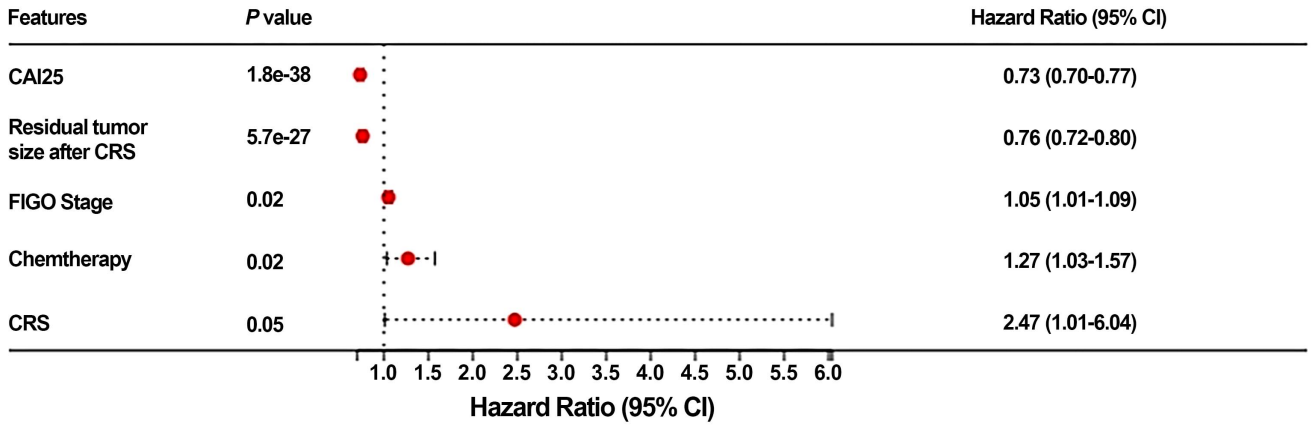

Figure 3. Multivariate analysis of the OS in the overall cohort. OS, overall survival; *CA125*, cancer antigen 125; CRS, cytoreductive surgery; FIGO, International Federation of Gynecology and Obstetrics; CI, confidence intervals.

corresponds. The total score represents the sum of the scores for each variable, and a line is drawn from the total score axis to the survival axis, and the 3-, 5- and 10-year OS rates are predicted from the total score obtained. According to the results of the nomogram, it can be seen that the FIGO stage has the greatest impact on OS, followed by surgery and chemotherapy, and age has the least impact on OS (Figure 4).

The obtained model was validated by Kaplan-Meier survival analysis (Figure 5). The overall C-index of the model is 0.86, the 95% confidence interval (CI) is 0.84-0.88, $P = 0.023$. We performed receiver operating characteristic (ROC) curve analysis using the R software package pROC (version 1.17.0.1) to obtain the area under the curve (AUC). Specifically, we obtained the patient's follow-up time and FIGO stage, whether surgery, whether chemotherapy, and the patient's age. ROC analysis was performed, and the AUC and confidence intervals were evaluated using the CI function of pROC to obtain the final AUC results (Figure 6).

DISCUSSION

Main findings

This study confirmed that age, marital status, profile, FIGO stage and *CA125* level all influence the OS of LGSOC patients. It can be concluded that patients with earlier staging who receive surgery and chemotherapy have a better prognosis according to the established programs.

Strengths and limitations

Due to the low incidence of LGSOC, research on prognostic factors and treatment strategies for LGSOC is not very mature. Most of the previous LGSOC-related studies included less than 100 cases. In this paper, we extracted and analyzed the relevant data information of patients diagnosed with LGSOC from 1988 to 2017 in the SEER database. Our study has several limitations. First, due to the lack of data on recurrence status, detailed chemotherapy regimens and doses in the SEER database, our assessment of the patient's condition is inevitably biased, and it will also affect the evaluation of the effects of treatment regimens including radiotherapy and chemotherapy. Second, most patients are identified from a small number of cases, making it difficult to verify the quality of the information, and there is potential heterogeneity within the patient population of these small cases that cannot be excluded from the data analysis. confounding factors, a limitation inherent in retrospective studies. The main strength of this study is that a large population-based study can be used to characterize the epidemiological and clinicopathological features, treatment trends and survival outcomes of this low incidence disease. In addition, our nomogram based on multivariate analysis was able to effectively assess the individual prognosis of patients.

Results in the published literature

LGSOC and high-grade serous ovarian cancer (HGSOC), which are more common, are very different in clinical characteristics, pathological features, prognosis and treatment options, making it difficult to draw lessons from the experience of prognosticating high-grade serous ovarian cancer or clinical treatment strategies. LGSOC is characterized by a younger age of presentation and a better survival prognosis.[1–3] The 5-year survival rate of LGSOC can reach 70.6%, while the 5-year survival rate of high-grade serous ovarian cancer is only about 30%,[4] and the average 5-year survival rate of ovarian cancer is only 47.4%.[5]

Implications for practice and future research

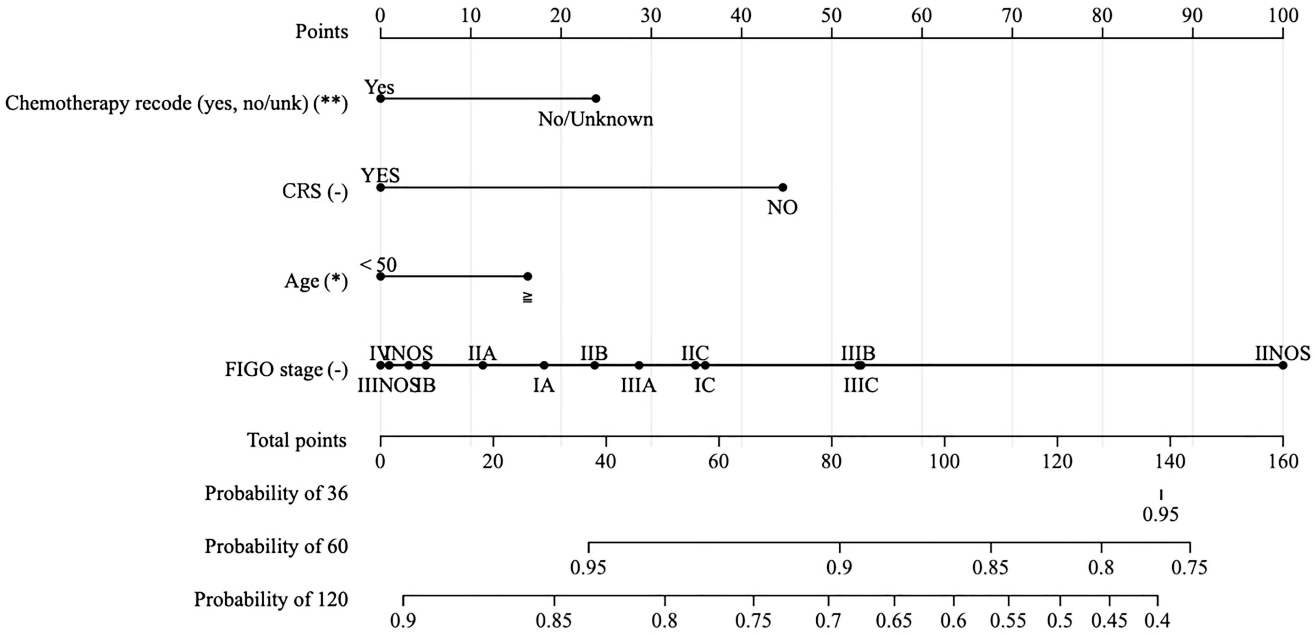

Figure 4. Nomogram evaluation of patients with LGSOC. LGSOC, low-grade serous ovarian cancer; CRS, cytoreductive surgery; FIGO, International Federation of Gynecology and Obstetrics.

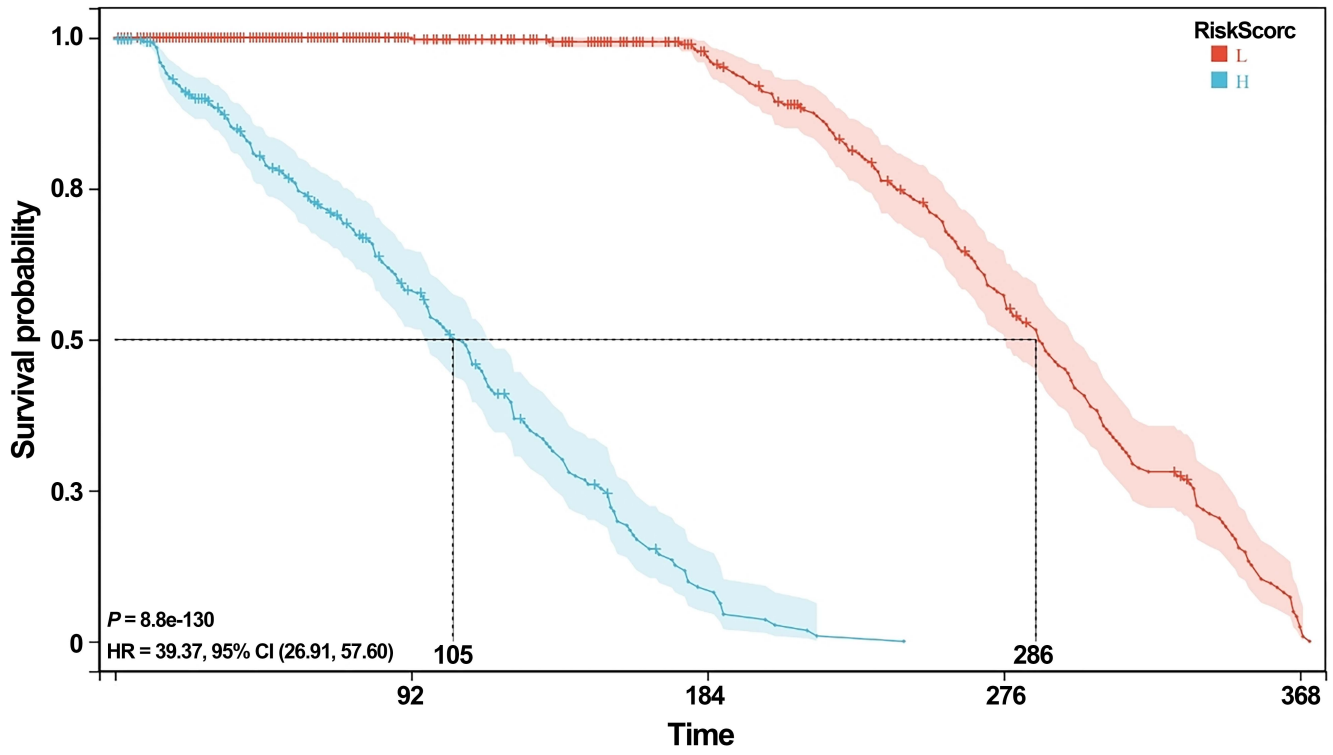

Figure 5. Kaplan-Meier curve based on the nomogram evaluation. HR, hazard ratio; CI, confidence intervals.

This study confirms that age is one of the factors affecting the OS of LGSOC patients. This study suggests that LGSOC patients tend to have a younger age at presentation, and an older age at presentation predicts a worse prognosis. However, a study by Gershenson *et al.* in 2015 suggested that patients aged 35 years or older at onset A had longer OS than patients aged less than 35 years at onset.[6] However, after

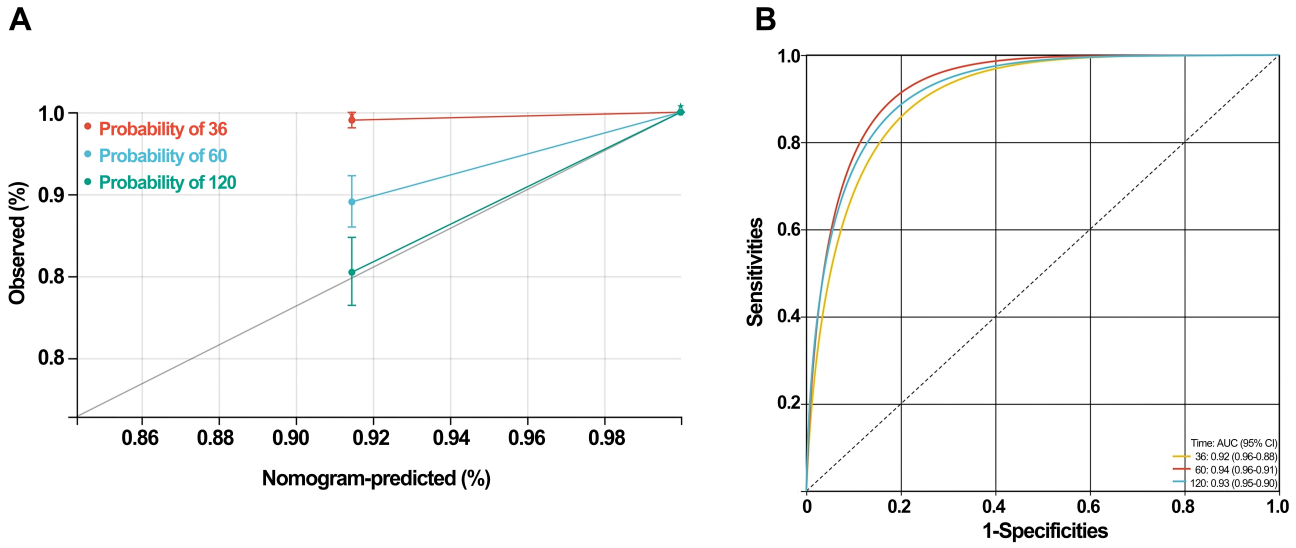

Figure 6. (A) ROC curve used to evaluate the nomogram. (B) AUC used to evaluate the nomogram. ROC, receiver operating characteristic; AUC, area under the curve.

including more research samples in this study, it was found that the median age of onset of LGSOC patients was 50-59 years, so 50 years was used as the cut-off for the study, and it was confirmed that patients with onset after the age of 50 years had a worse survival prognosis.

Previous large sample studies have investigated the effect of marital status on the prognosis of malignant tumors,[7–11] and Gardenr *et al.*[12] suggested that uncertain marital status (single, divorced and widowed) leads to worse outcomes in LGSOC patients. Survival prognosis, and the analysis results of this study also confirm this view. The analysis in this paper shows that the serum *CA125* index of most LGSOC patients is higher than normal, but the abnormality of the *CA125* index does not affect the prognosis of the disease, but the *CA125* value can still be used as one of the indicators for the initial diagnosis of LGSOC and the evaluation of possible recurrence. The study by Durmus *et al.*[13] suggested that the abnormal increase in the *CA125* index may be related to lymphovascular invasion. For patients with limited early lesions and no lymph node dissection, preoperative serum *CA125* $\geqslant$ 180 U/mL and/or the presence of lymph-vascular space invasion (LVSI) in the pathological evaluation report. Repeat lymph node dissection may be considered in these patients.

This study re-emphasizes the importance of surgery in improving the prognosis of LGSOC. For patients with early LGSOC, if the patient still needs fertility and the disease is unilateral, FSS can be performed to preserve the uterus and contralateral ovary. Their OS has a significant impact. However, the selection of patients for FSS surgery in LGSOC patients is crucial. Patients undergoing FSS surgery should be women of childbearing age less than or equal to 40 years. Patients with stage IC or grade I differentiation and surgery under the premise of ensuring patient compliance,[14,15] and any suspected peritoneal lesions should be removed during surgery, although the effect of lymph node dissection on survival and prognosis in patients with early LGSOC remains unclear. However, in patients requiring FSS, multiple intraoperative peritoneal biopsies, omentectomy, and traditional pelvic and para-aortic lymphadenectomy should be performed and sent for pathological examination. When tumor debulking surgery is performed in LGSOC patients, the tumor lesions should be removed as completely as possible. If the diameter of the residual lesions is less than or equal to 1 cm, it will also lead to a worse survival prognosis. However, in this study, there were no cases of postoperative residual lesions larger than 1 cm, so the effect of larger residual disease on OS is unknown. However, according to the results of Grabowski *et al.*,[16] the prognosis is better when postoperative residual lesions are 1-10 mm compared with no surgery or when the residual lesions are larger in diameter. Some studies have also shown that the intraoperative complete resection rate of LGSOC patients is lower than that of HGSOC, which may be related to the pathological characteristics of LGSOC itself, such as connective tissue hyperplasia and calcification.[17] Given the important influence of residual disease diameter on prognosis, secondary tumor debulking should be performed in patients who are suitable for surgery, especially those who can complete satisfactory tumor debulking.[18–20]

In this study, radiotherapy did not have a significant effect on the prognosis of LGSOC, but only a small proportion of LGSOC patients included in this study received radiotherapy in their treatment regimen, so it is difficult to draw any firm conclusions about the relationship between radiotherapy and the prognosis of LGSOC patients. In contrast to HGSOC patients, for whom adjuvant chemotherapy is recommended after successful CRS in almost all patients,[21] LGSOC is relatively chemoresistant, with response rates ranging from 4% to 25% in retrospective studies.[22] Due to the toxicity and low response rate of chemotherapy in patients with LGSOC, chemotherapy is still not used as a first-line treatment option.[22–24] Therefore, the role of intraperitoneal chemotherapy, including hyperthermic intraperitoneal chemotherapy (HIPEC), in the treatment of LGSOC still requires further evidence-based medical evidence. Given the relative chemoresistance of LGSOC, some clinicians have abandoned adjuvant chemotherapy and switched to hormone therapy. Some studies have confirmed the clinical efficacy of MEKi, BRAF inhibitors and bevacizumab, but there is no specific targeted drug for LGSOC, and the therapeutic efficacy of experimental drugs still needs further verification.[25–27]

We developed a nomogram to assess individual prognosis. According to the nomogram calculation, patients with higher FIGO stages had the highest scores, followed by patients without surgical treatment and patients without adjuvant chemotherapy, and the lowest age-related scores indicated that they had less influence on the patient's prognosis. Two independent prognostic factors, serum *CA125* and postoperative residual disease diameter, were not included in the nomogram because too many cases in the database lacked data on these two characteristics. The consistency of the nomogram's predicted OS with the actual OS was verified by C-index calculation and calibration. From this model, we can derive a simple algorithm to individually assess patient outcomes. However, to improve the accuracy and generality of this model, it needs to be applied to large prospective case studies.

CONCLUSION

LGSOC is a type of ovarian cancer with a good prognosis. With early detection, aggressive surgical treatment and chemotherapy tailored to the patient's situation, a very good survival prognosis can be achieved.

DECLARATION

Author contributions

Bao MY, Jia QC, Tang HM: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing—Original draft. Dong ZY, Shan WL, Chen Y, Zhang SF, Wei WW, Qin ZY, Wang HH: Data curation, Methodology, Software, Validation, Formal analysis, Investigation. Xia BR, Chen JM: Writing—Review and Editing, Visualization, Supervision, Project administration. All authors have read and approved the final version.

Ethics approval

Not applicable.

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Conflict of interest

The author has no conflicts of interest to declare.

Data availability statement

Data used to support the findings of this study are available from the corresponding author upon request.

REFERENCES

1. Plaxe SC. Epidemiology of low-grade serous ovarian cancer. *Am J Obstet Gynecol.* 2008;198(4):459.e1-e9.
2. Chang LC, Huang CF, Lai MS, Shen LJ, Wu FL, Cheng WF. Prognostic factors in epithelial ovarian cancer: a population-based study. *PLoS One.* 2018;13(3):e0194993.
3. Gershenson DM, Sun CC, Wong KK. Impact of mutational status on survival in low-grade serous carcinoma of the ovary or peritoneum. *Br J Cancer.* 2015;113(9):1254-1258.
4. Gockley A, Melamed A, Bregar AJ, *et al.* Outcomes of women with high-grade and low-grade advanced-stage serous epithelial ovarian cancer. *Obstet Gynecol.* 2017;129(3):439-447.
5. Lisio MA, Fu L, Goyeneche A, Gao ZH, Telleria C. High-grade serous ovarian cancer: basic sciences, clinical and therapeutic standpoints. *Int J Mol Sci.* 2019;20(4):952.
6. Gershenson DM, Bodurka DC, Lu KH, *et al.* Impact of age and primary disease site on outcome in women with low-grade serous carcinoma of the ovary or peritoneum: results of a large single-institution registry of a rare tumor. *J Clin Oncol.* 2015;33(24):2675-2682.
7. Cai W, Fan J, Shen T, Yu J. The influence of marital status on the survival of patients with uveal melanoma. *J Ophthalmol.* 2020;2020:7012940.
8. Jin JJ, Wang W, Dai FX, *et al.* Marital status and survival in patients with gastric cancer. *Cancer Med.* 2016;5(8):1821-1829.
9. El Ibrahimi S, Pinheiro PS. The effect of marriage on stage at diagnosis and survival in women with cervical cancer. *Psycho-oncology.* 2017;26(5):704-710.
10. Osazuwa-Peters N, Christopher KM, Cass LM, *et al.* What's Love Got

to do with it? Marital status and survival of head and neck cancer. *Eur J Cancer Care*. 2019;28(4):e13022.

11. Chen Z, Pu L, Gao W, *et al*. Influence of marital status on the survival of adults with extrahepatic/intrahepatic cholangiocarcinoma. *Oncotarget*. 2017;8(17):28959-28970.
12. Gardner AB, Sanders BE, Mann AK, *et al*. Relationship status and other demographic influences on survival in patients with ovarian cancer. *Int J Gynecol Cancer*. 2020;30(12):1922-1927.
13. Durmuş Y, Meydanlı MM, Akıllı H, *et al*. Factors associated with the involvement of lymph nodes in low-grade serous ovarian cancer. *J Surg Oncol*. 2022;125(2):264-272.
14. Bentivegna E, Gouy S, Maulard A, *et al*. Fertility-sparing surgery in epithelial ovarian cancer: a systematic review of oncological issues. *Ann Oncol*. 2016;27(11):1994-2004.
15. Gershenson DM. Treatment of ovarian cancer in young women. *Clin Obstet Gynecol*. 2012;55(1):65-74.
16. Grabowski JP, Harter P, Heitz F, *et al*. Operability and chemotherapy responsiveness in advanced low-grade serous ovarian cancer. An analysis of the AGO Study Group metadatabase. *Gynecol Oncol*. 2016;140(3):457-462.
17. Bogani G, Leone Roberti Maggiore U, Paolini B, *et al*. The detrimental effect of adopting interval debulking surgery in advanced stage low-grade serous ovarian cancer. *J Gynecol Oncol*. 2019;30(1):e4.
18. Amante S, Santos F, Cunha TM. Low-grade serous epithelial ovarian cancer: a comprehensive review and update for radiologists. *Insights Imaging*. 2021;12(1):60.
19. Gadducci A, Cosio S. Therapeutic approach to low-grade serous ovarian carcinoma: state of art and perspectives of clinical research. *Cancers*. 2020;12(5):1336.
20. Slomovitz B, Gourley C, Carey MS, *et al*. Low-grade serous ovarian cancer: state of the science. *Gynecol Oncol*. 2020;156(3):715-725.
21. Pauly N, Ehmann S, Ricciardi E, *et al*. Low-grade serous tumors: are we making progress? *Curr Oncol Rep*. 2020;22(1):8.
22. Gershenson DM, Bodurka DC, Coleman RL, Lu KH, Malpica A, Sun CC. Hormonal maintenance therapy for women with low-grade serous cancer of the ovary or peritoneum. *J Clin Oncol*. 2017;35(10):1103-1111.
23. Buttarelli M, Mascilini F, Zannoni GF, *et al*. Hormone receptor expression profile of low-grade serous ovarian cancers. *Gynecol Oncol*. 2017;145(2):352-360.
24. Oswald AJ, Gourley C. Low-grade epithelial ovarian cancer: a number of distinct clinical entities? *Curr Opin Oncol*. 2015;27(5):412-419.
25. Monk BJ, Grisham RN, Banerjee S, *et al*. MILO/ENGOT-ov11: binimetinib versus physician's choice chemotherapy in recurrent or persistent low-grade serous carcinomas of the ovary, fallopian tube, or primary peritoneum. *J Clin Oncol*. 2020;38(32):3753-3762.
26. Fernandez ML, Dawson A, Hoenisch J, *et al*. Markers of MEK inhibitor resistance in low-grade serous ovarian cancer: EGFR is a potential therapeutic target. *Cancer Cell Int*. 2019;19:10.
27. Hyman DM, Puzanov I, Subbiah V, *et al*. Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. *N Engl J Med*. 2015;373(8):726-736.