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Prognostic Nomograms for Predicting Survival of Liver-only Ovarian Cancer Metastasis: A Population - Based Study

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Abstract

Objective: The present study was aim to construct and validate related nomograms to help individual survival prediction in patients with ovarian cancer liver-only metastasis (OCLM).

Methods: OCLM diagnosed between 2010 and 2015 were selected in the study from the Surveillance, Epidemiology, and End Results (SEER) database. Univariate and multivariate Cox proportional hazard models were performed to screen independent prognostic variables to establish nomograms for predicting overall survival (OS) and cancer-specific survival (CSS). The performance of the established models was evaluated by the calibration curve, Harrell's concordance (C-index), and decision curve analysis (DCA).

Results: A total of 1335 patients with OCLM were final identified. Those individuals were randomly classified into development (n=668) and validation (n=667) cohorts. Nomograms predicting OS and CSS were built based on 4 independent variables. In the development cohort, the C-index for the constructed nomogram to predict OS and CSS was 0.725 and 0.724, respectively. The nomogram achieved perfect discriminative power in the validation cohort to predict OS and CSS, with C-indexes of 0.735 and 0.738, respectively. The calibration plots displayed an acceptable agreement between nomogram-predicted survival probability and the actual observed outcomes. The DCA revealed that the nomogram was clinically useful.

Conclusions: The novel proposed nomograms for patients with OCLM can effectively predict the individualized probability of OS and CSS, and this predictive power can help clinicians formulate suitable individual treatments and conduct personalized prognostic evaluation.

Keywords: nomogram; ovarian cancer; liver metastasis; survival

1. Introduction

Ovarian cancer (OC), a malignant aggressive gynecologic disease, is the sixth most common tumor in women, with the highest mortality rate among gynecology malignancies[1]. It was reported that up to 13,850 women died from OC yearly in the United States, and the 5-year survival probability of all types of OC was about 47%[2, 3]. The incidence of OC is also steadily growing in China[4]. Despite advancements in diagnosis and treatments of OC, most patients still suffer death owing to the fact that more than 60% women are diagnosed in advanced stage of the disease (stage III-IV) when distant metastases are already present, which can partly account for the serious mortality rate[5, 6]. It has been proved that OC has a high propensity to metastasize to distant organs through hematogenous, peritoneal, and lymphatic route at the time of diagnosis[7]. A study found that liver is the most frequent site of distant metastases for OC[8]. Liver metastases usually present at the time of diagnosis or during the evolution of OC, which commonly related to widespread dissemination and adverse performance status[4]. Although the incidence of such metastasis is rare, increasing evidence has indicated that the prevalence of liver metastases may be underestimated, and nearly 50% of the patients had liver metastasis at the time of death[9]. However, OC with liver metastases has a very disappointing outcome, with a median untreated survival time of 3 to 4 months[10, 11].

Early assessment of the survival for metastatic OC can facilitate the doctors to plan individual treatment programs. Nevertheless, a reliable

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prognostic model on the survival probability of liver-only metastatic in OC patients in a large population is lacking. Nomogram, a statistical prediction tool incorporated important prognostic factors, has been commonly utilized in clinical help to predict outcome[12-14]. However, the application of nomogram in OC patients with liver metastases is still missing at present. Therefore, we aimed to construct and validate nomograms involving a large population to visually predict the OS and CSS of OCLM.

2. Methods

Study population and inclusion criteria

Data for this study were collected from the SEER database, which comprises 18 population-based cancer registries and represents nearly 30% of US population[15]. Primary ovarian cancer patients initially diagnosed between 2010 and 2015 were included (since the information of liver metastases was unavailable until 2010). National Cancer Institute SEER*Stat software (version 8.3.5) was used to filter and collect the information of the eligible patients. The site recodes ICD-O-3/WHO 2008 was limited to "Ovarian". The SEER database was publicly available, so no institutional review board approval was needed for this work. Finally, 35328 patients were initially included. The inclusion criteria were (1) diagnosed with OC as primary malignancy; (2) age at diagnosis≥18 and female patients; (3) metastases site limited to a liver only; (4) detailed information on survival time and cause of death; (5) known surgery status. Finally, the whole cohort consisted of 1335 patients. The detailed patient selection process is shown in **Figure 1**. To construct and validate the models, individuals were randomly divided in a 1-to-1 ratio, forming a development cohort (n = 668) and a validation cohort (n =667).

Prognostic factors

Demographic and clinicopathological factors were collected to predict the prognosis of OCLM in the development cohort, including age, tumor size, race, insurance status, marital status, surgery records, histological grade, laterality (left, right, bilateral, and other), primary T category, primary N category, follow-up duration and reason of death. Continuous variables including age and tumor size were stratified into three groups (**Figure 2**), using the X-tile software to explore the optimal cutoff values[16]. The tumor size was stratified into four groups, namely, ≤8 mm, 8–129 mm, ≥130 and other. The age was stratified into three groups, namely, ≤70, 71 to 79, and ≥80 years. The OS referred to the time duration from initial diagnosis to death or last follow-up, without limitation the reason of death. CSS was defined as the time duration from the initially diagnosis to death attributed to OCLM in the absence of other causes. Censored events indicated that patients who were still alive at the time point of last follow-up.

Statistical analyses

The differences between categorical factors were compared with Chi-square test. Kaplan-Meier method and log-rank test were applied to perform univariate prognostic analysis. The candidate factors with $P < 0.05$ in the univariate analysis were fitted into multivariate analysis. The identified prognostic variables for OCLM were used to establish nomogram for predicting 1-, 3- and 5-year OS and CSS. We validated the performance of nomograms in two cohorts using concordance index (C-index)[17]. The calibration curves were constructed to show consistency between predicted and observed outcome using 1000 bootstrap resamples. In addition, the rcorrp.cens package in Hmisc in R was used to compare the novel model and the AJCC^{7th} TNM staging system. All statistical analyses were performed using R software version 3.6.3. A two-tailed $P < 0.05$ was considered as statistically significant during all analyses process.

3.Results

Patient characteristics

Through rigorous screening, a total of 1,335 patients diagnosed with OCLM that met our criteria were included from the SEER database. Those individuals were randomly allocated to two groups, therefore obtaining two groups with 668 patients in the training group and 667 in the validation group. A total of 433 patients died from OCLM, and 38 patients died from other reasons in the development group. In the validation group, 464 patients died from OCLM, while 26 died from other reasons. When compared among two subgroups, it was found that there were no obvious differences between the development and validation groups in all included clinicopathological characteristics. The demographic and clinicopathological features of the patients in the two groups are illustrated in **Table 1.**

Prognostic variables associated with OS and CSS and Nomogram construction

As is shown in **Table 2** and **Table 3**, age at diagnosis, race, marital status, surgery status, tumor size, laterality, primary T category, and

primary N category were found initially related to OS and CSS in the univariate analysis in the training group. These factors were further selected to perform the multivariate Cox analysis in order to control for confounding variables. After adjusting for the above potential variables, the multivariate Cox analysis revealed that four factors including age at diagnosis, race, marital status as well as surgery status were remained independent prognostic predictors for OS and CSS. Nomograms for predicting 1-, 3- and 5-year OS and CSS were constructed with the four identified variables in the development group (**Figure 3**). Accordingly, every factor yielded a corresponding score in the two models (**Table 4**). An individual subject's score was placed on each variable axis, and a vertical line is drawn upward to locate the number of points received for each variable value. After repeating the process for each variable, a line is drawn downward to the survival axes to identify the risk of 1-, 3- and 5-year survival.

Calibration and Validation of the Nomograms

We performed both internal and external validation of the nomograms. Internal validation demonstrated the Concordance-index of the nomograms for OS and CSS was 0.725 (95% confidence interval [CI]: 0.701–0.750) and 0.724 (95%CI: 0.700-0.750), respectively. Moreover, the Concordance-index for the nomograms predicting OS and CSS were 0.735 (95%CI: 0.712–0.758) and 0.738 (95%CI: 0.715–0.761) in the validation group, respectively. The nomogram showed perfect accuracy for OS and CSS prediction. A calibration plot along the 45-degree line in two groups would illustrate an ideal calibration model between the bootstrap-predicted probabilities and the actual survival. The calibration plots of the models for the OS and CSS in the development group (**Figure 4A, C**) and validation group (**Figure 4B, D**) displayed a good consistency between the model prediction and observed survival for 1-, 3- and 5-year OS and CSS. Furthermore, we compared the OCLM nomograms for OS and CSS with the conventional AJCC^{7th} TNM staging system in term of C-index. As expected, the C-index of the AJCC staging system for predicting OS and CSS was 0.528 (95%CI: 0.497–0.557) and 0.550 (95% CI: 0.521–0.579) in the development group, which obviously did not fare as well as the present models. Moreover, these results were also confirmed in the validation group. These evidences revealed that the models of discrimination yielded superiority than the AJCC staging system.

Decision curve analysis

The clinical usability of between the nomograms and AJCC^{7th} TNM staging system as well as grade was carried out using decision curve analysis (DCA) plot in the combined evaluation and validation cohorts[18]. It was revealed that if the threshold probability ranged from 0.33–0.96 in the entire cohorts, using the nomogram to predict OS yields more net benefit than the treat-all or treat-none strategies. Furthermore, the nomogram showed a higher net benefit than the AJCC staging system and grade (**Figure 5A**). Moreover, the nomogram also had excellent clinical usability in predicting CSS with threshold probabilities from 0.32 to 0.94, which was excellent than the AJCC staging system and grade (**Figure 5B)**. These results indicate that the nomograms presented powerful predictive ability for survival.

4. Discussion

OC has historically been termed the "silent killer" since up to 62% of the disease occurs as distant disease, which influencing the survival of patients seriously[6]. It has been widely accepted that metastasize via intraperitoneal route of dissemination is the common typical form of extraovarian tumor spread. OCLM was reported in approximately half of patients at autopsy[9]. However, the overall and cancer-specific survival probability of liver-only metastatic in OC patients has not been well studied. In the present study, we screened lots of records from the SEER database. We identified potential independent prognostic variables and constructed a nomogram to accurate predict OS and CSS probability in patients with OCLM. The findings revealed that the two constructed nomograms predicting 1-, 3- and 5-year OS and CSS of OCLM effectively. In addition, the nomograms presented good discrimination and calibration as shown by calibration plots. Furthermore, our nomograms demonstrated more powerful predictive effect than the AJCC^{7th} TNM staging system and grade. Therefore, we deemed that the novel models trustworthy and its predicting power strong.

According to the multivariate Cox proportional hazards model, four clinicopathological factors, patient age, race, surgery, and marital status, were found to be independently related to OS and CSS in patients with OCLM. In our study, an increasing age (≥80 years) was revealed to be associated with a poor survival outcome. Previous studies have been reported similar results[19]. Increasing age was associated with hematogenous metastases to liver in serous ovarian cancer[19-21]. A recently nomogram

based on SIRT3 to predict survival of serous ovarian cancer illustrated age as an independent factor sharing the largest contribution to OS[20]. It was also revealed that age and distant metastasis were independent prognostic factors in malignant Brenner tumors, and younger age and negative distant metastasis were related to favorable prognosis[21]. Besides, patient marital status as well as race was also found to be independent prognostic factors for OC[22-24]. It was found that widowed epithelial ovarian cancer patients had worse outcome than other conditions, while the never married patients presented similar risk of mortality as the married ones revealed by a SEER-based study[23]. It was confirmed that patients with only one tumor suffer more distress, depression, and anxiety than married ones[25]. Racial and ethnic differences in survival have been previously reported for several gynecologic malignancies, including ovary cancers[26]. A population-based study also revealed that Black populations were positive associated with survival of epithelial ovarian cancer, while married ones were negatively associated with prognosis of epithelial ovarian cancer[24]. It was known that surgery is currently the best available potentially curative treatment in patients with OC who present with early stage disease. Surgical operation was associated with decreased all-cause and cancer-specific mortality in patients with ovarian carcinosarcoma[22]. We found that age older than 80 years of age, black, unmarried, and surgery not performed were the main factors that increased the mortality rate of patients. All of these important variables were incorporated into precise nomogram models for predicting OS and CSS, respectively, which provided an effective tool for estimating prognosis.

The C-indexes of internal validation regarding OS and CSS were 0.725 and 0.724, respectively. Moreover, the C-index in the external validation group was 0.735 and 0.738, respectively. Several studies have demonstrated that nomogram presents better predictive power than the AJCC staging system in a few cancers, and therefore its usability has been validated as an alternative or even a new promising standard[27-29]. Notably, the discrimination of our nomograms was superior to that of the AJCC TNM classification (0.72 vs 0.58 for development cohort and 0.55 vs 0.73 for validation cohort with respect to OS). Furthermore, these results were also confirmed in the validation group. Moreover, according to the findings of the DCA, the nomograms also presented perfect clinical usability in predicting OS and CSS with a wide range of threshold probabilities.

Although these nomograms have good accuracy, certain limitations also deserved mention. First, they were established using retrospective data derived from a public database, which may not completely avoid inherent bias. Second, some information regarding chemotherapy, serum tumor markers, and vascular infiltration, are not available in the present SEER database. Therefore, more well-designed studies could improve our nomograms by incorporating these factors based on their predictive power. Finally, as a simple-to-use clinical nomogram for clinicians to make decisions, the nomogram failed to include all potential prognostic variables and therefore may not constantly present absolutely accurate prognoses in clinical practice.

In conclusion, we established two nomograms that estimated 1-, 3- and 5-year OS and CSS for patients with OCLM. These nomograms revealed an accurate and effective predictive power as suggested by internal and external validation. These easy-to-use nomograms can help clinicians formulate suitable individual treatments and conduct personalized prognostic evaluation. However, further external validation in different populations is still needed.

Data statement

The raw data of this study are derived from the SEER database, which is a publicly available database. All detailed data included in the study are available to all at https://seer.cancer.gov/

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Ethics statement:
Not necessary

Conflict of interest:
None

Author contributions:
Liu Jin and Zhongwen Chen conceived and designed the study; Liu Jin MD and Weiling Gu collected the data. Liu Jin, Weiling Gu, Liang Xie, Xueqin Li, and Linhong Wang analyzed the data. Liu Jin MD, Weiling Gu, Liang Xie, Xueqin Li and Linhong Wang contributed to the writing of the manuscript and Zhongwen Chen edited the manuscript.

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References

[1] Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA: a cancer journal for clinicians 2015; 65: 87-108. 2015/02/06. DOI: 10.3322/caac.21262.

[2] Yeung TL, Leung CS, Yip KP, et al. Cellular and molecular processes in ovarian cancer metastasis. A Review in the Theme: Cell and Molecular Processes in Cancer Metastasis. American journal of physiology Cell physiology 2015; 309: C444-456. 2015/08/01. DOI: 10.1152/ajpcell.00188.2015.

[3] Nasioudis D, Ko EM, Haggerty AF, et al. Isolated distant lymph node metastases in ovarian cancer. Should a new substage be created? Gynecologic oncology reports 2019; 28: 86-90. 2019/04/13. DOI: 10.1016/j.gore.2019.03.008.

[4] Niu GC, Shen CM, Cui W, et al. Hepatic Resection is Safe for Metachronous Hepatic Metastases from Ovarian Cancer. Cancer biology & medicine 2012; 9: 182-187. 2013/05/22. DOI: 10.7497/j.issn.2095-3941.2012.03.005.

[5] Bacalbasa N, Balescu I, Dima S, et al. Long-term Survivors After Liver Resection for Ovarian Cancer Liver Metastases. Anticancer research 2015; 35: 6919-6923. 2015/12/08.

[6] Jelovac D and Armstrong DK. Recent progress in the diagnosis and treatment of ovarian cancer. CA: a cancer journal for clinicians 2011; 61: 183-203. 2011/04/28. DOI: 10.3322/caac.20113.

[7] Nakayama K, Nakayama N, Katagiri H, et al. Mechanisms of ovarian cancer metastasis: biochemical pathways. International journal of molecular sciences 2012; 13: 11705-11717. 2012/10/31. DOI: 10.3390/ijms130911705.

[8] Cormio G, Rossi C, Cazzolla A, et al. Distant metastases in ovarian carcinoma. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society 2003; 13: 125-129. 2003/03/27.

[9] Rose PG, Piver MS, Tsukada Y, et al. Metastatic patterns in histologic variants of ovarian cancer. An autopsy study. Cancer 1989; 64: 1508-1513. 1989/10/01. DOI: 10.1002/1097-0142(19891001)64:7<1508::aid-cncr2820640725>3.0.co;2-v.

[10] Harries M and Gore M. Part II: chemotherapy for epithelial ovarian cancer-treatment of recurrent disease. The Lancet Oncology 2002; 3: 537-545. 2002/09/10.

[11] Janicke F, Holscher M, Kuhn W, et al. Radical surgical procedure improves survival time in patients with recurrent ovarian cancer. Cancer 1992; 70: 2129-2136. 1992/10/15. DOI: 10.1002/1097-0142(19921015)70:8<2129::aid-cncr2820700820>3.0.co;2-u.

[12] Balachandran VP, Gonen M, Smith JJ, et al. Nomograms in oncology: more than meets the eye. The Lancet Oncology 2015; 16: e173-180. 2015/04/08. DOI: 10.1016/s1470-2045(14)71116-7.

[13] Valentini V, van Stiphout RG, Lammering G, et al. Nomograms for predicting local recurrence, distant metastases, and overall survival for patients with locally advanced rectal cancer on the basis of European randomized clinical trials. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2011; 29: 3163-3172. 2011/07/13. DOI: 10.1200/jco.2010.33.1595.

[14] Callegaro D, Miceli R, Bonvalot S, et al. Development and external validation of two nomograms to predict overall survival and occurrence of distant metastases in adults after surgical resection of localised soft-tissue sarcomas of the extremities: a retrospective analysis. The Lancet Oncology 2016; 17: 671-680. 2016/04/14. DOI: 10.1016/s1470-2045(16)00010-3.

[15] Cronin KA, Ries LA and Edwards BK. The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute. Cancer 2014; 120 Suppl 23: 3755-3757. 2014/11/21. DOI: 10.1002/cncr.29049.

[16] Camp RL, Dolled-Filhart M and Rimm DL. X-tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. Clinical cancer research : an official journal of the American Association for Cancer Research 2004; 10: 7252-7259. 2004/11/10. DOI: 10.1158/1078-0432.ccr-04-0713.

[17] Wolbers M, Koller MT, Witteman JC, et al. Prognostic models with competing risks: methods and application to coronary risk prediction. Epidemiology (Cambridge, Mass) 2009; 20: 555-561. 2009/04/16. DOI: 10.1097/EDE.0b013e3181a39056.

[18] Vickers AJ and Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. Medical decision making : an international journal of the Society for Medical Decision Making 2006; 26: 565-574. 2006/11/14. DOI: 10.1177/0272989x06295361.

[19] O'Neill AC, Somarouthu B, Tirumani SH, et al. Patterns and Prognostic Importance of Hepatic Involvement in Patients with Serous Ovarian Cancer: A Single-Institution Experience with 244 Patients. Radiology 2017; 282: 160-170.

2016/08/02. DOI: 10.1148/radiol.2016152595.
[20] Li J, Yue H, Yu H, et al. Development and validation of SIRT3-related nomogram predictive of overall survival in patients with serous ovarian cancer. Journal of ovarian research 2019; 12: 47. 2019/05/23. DOI: 10.1186/s13048-019-0524-2.
[21] Lan A and Yang G. Clinicopathological parameters and survival of invasive epithelial ovarian cancer by histotype and disease stage. Future oncology (London, England) 2019; 15: 2029-2039. 2019/05/30. DOI: 10.2217/fon-2018-0886.
[22] Rauh-Hain JA, Diver EJ, Clemmer JT, et al. Carcinosarcoma of the ovary compared to papillary serous ovarian carcinoma: a SEER analysis. Gynecologic oncology 2013; 131: 46-51. 2013/08/03. DOI: 10.1016/j.ygyno.2013.07.097.
[23] Wang X, Li X, Su S, et al. Marital status and survival in epithelial ovarian cancer patients: a SEER-based study. Oncotarget 2017; 8: 89040-89054. 2017/11/29. DOI: 10.18632/oncotarget.21648.
[24] Xu XL, Cheng H, Tang MS, et al. A novel nomogram based on LODDS to predict the prognosis of epithelial ovarian cancer. Oncotarget 2017; 8: 8120-8130. 2017/01/04. DOI: 10.18632/oncotarget.14100.
[25] Goldzweig G, Andritsch E, Hubert A, et al. Psychological distress among male patients and male spouses: what do oncologists need to know? Annals of oncology : official journal of the European Society for Medical Oncology 2010; 21: 877-883. 2009/10/14. DOI: 10.1093/annonc/mdp398.
[26] Chan JK, Zhang M, Hu JM, et al. Racial disparities in surgical treatment and survival of epithelial ovarian cancer in United States. Journal of surgical oncology 2008; 97: 103-107. 2007/11/06. DOI: 10.1002/jso.20932.
[27] Fang C, Wang W, Feng X, et al. Nomogram individually predicts the overall survival of patients with gastroenteropancreatic neuroendocrine neoplasms. British journal of cancer 2017; 117: 1544-1550. 2017/09/28. DOI: 10.1038/bjc.2017.315.
[28] Cao J, Yuan P, Wang L, et al. Clinical Nomogram for Predicting Survival of Esophageal Cancer Patients after Esophagectomy. Scientific reports 2016; 6: 26684. 2016/05/25. DOI: 10.1038/srep26684.
[29] Guo M, Li B, Yu Y, et al. Delineating the pattern of treatment for elderly locally advanced NSCLC and predicting outcomes by a validated model: A SEER based analysis. Cancer medicine 2019; 8: 2587-2598. 2019/04/05. DOI: 10.1002/cam4.2127.

Figures and Tables

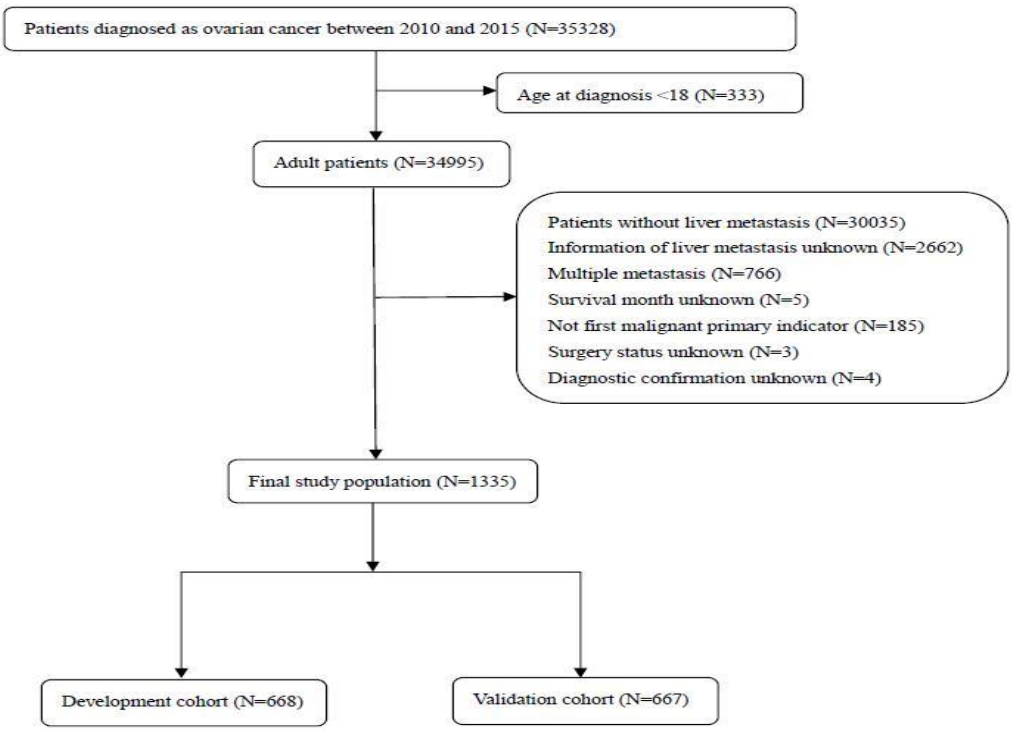

Figure 1**. The flow diagram of the detailed process of patients screen**

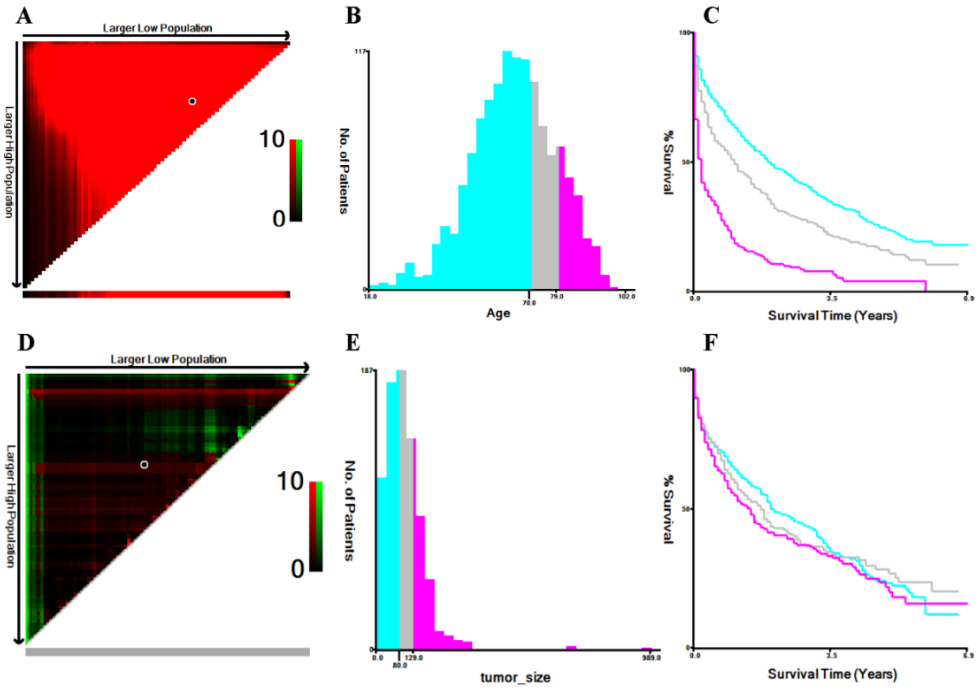

Figure 2**. The graphs illustrate defining the optimal cutoff points of age and tumor size using X-tile software. The black dot demonstrates the ideal cutoff points of age and tumor size that had been determined (A, D). The histogram (B, E) and Kaplan–Meier (C, F) were established according to the**

determined cutoff points. Ideal cutoff points of age and tumor size were determined as 70 and 79 years, 8 and 130 mm based on survival, respectively.

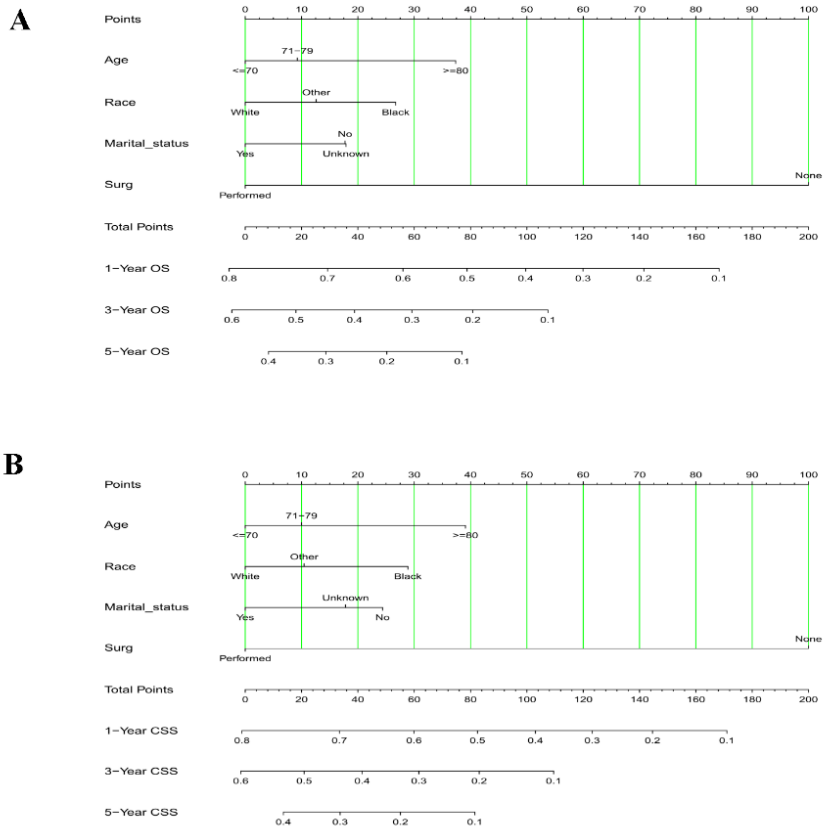

Figure 3. **(A) Nomograms for predicting 1-, 3- and 5-year overall survival (OS) and (B) cancer-specific survival (CSS) of patients with OCLM.**

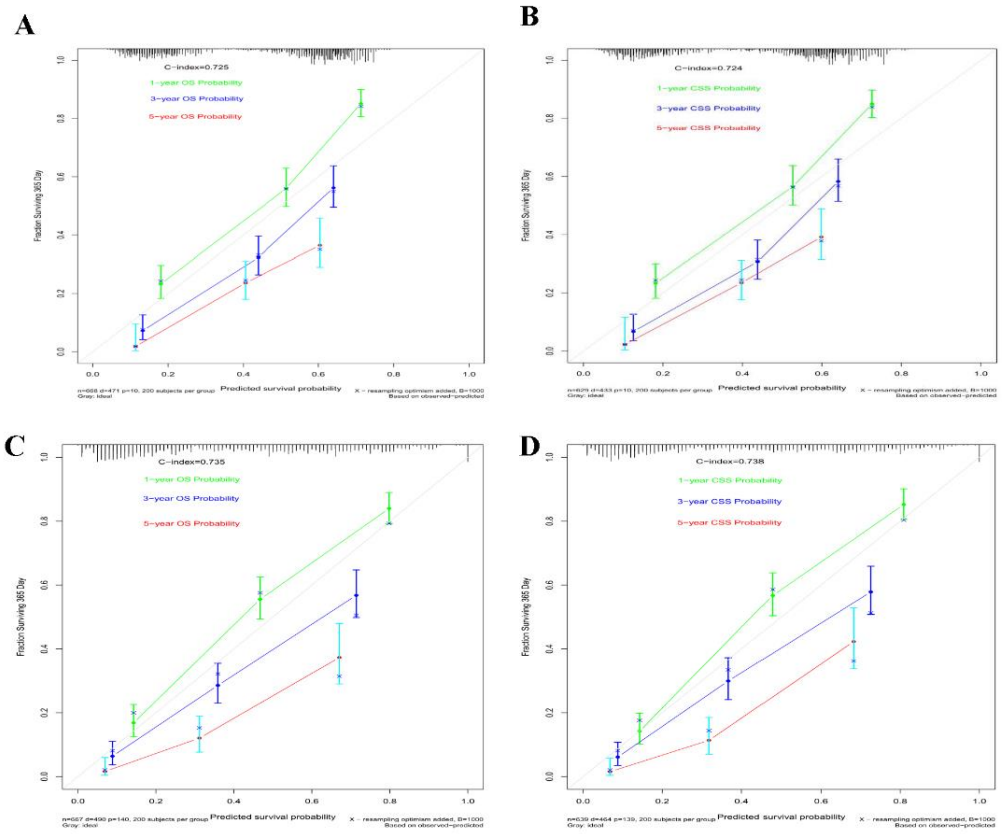

Figure 4**. Calibration plot curves for predicting 1-, 3- and 5-year OS and CSS in the development (A, C) and validation sets (B, D). Bootstrap-predicted outcome is placed on the x-axis, and actual probabilities were plotted on the y-axis. Vertical bars illustrate 95% CIs measured by Kaplan-Meier analysis. Gray lines along the 45° line passing the origin point indicate a perfect calibration nomogram.**

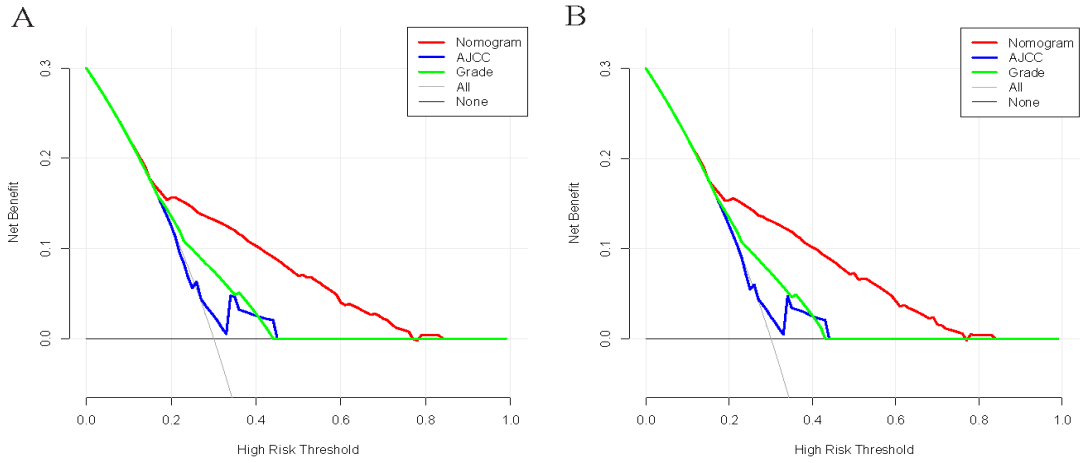

Figure 5. **Decision curve analysis for the ovarian cancer liver metastasis risk nomogram in terms of overall survival (A) and cancer-specific survival (B). The x-axis demonstrates the threshold probability. The y-axis suggests the net benefit.**

Table 1. **Clinicopathological characteristics of patients in the development cohort and validation cohort**

Characteristics	Development cohort (N=668)	Validation cohort (N=667)	P value
Age			0.701
18-70 years	438	423	
71-79 years	129	139	
≥80 years	101	105	
Race			0.084
Black	76	94	
White	536	534	
Other	56	39	
Marital status			0.573
Married	312	294	
Unmarried	324	336	
Unknown	32	37	
Insurance status			
Yes	631	622	0.331
No	29	30	
Unknown	8	15	
Laterality			0.754
Left	108	101	
Right	112	125	
Bilateral	436	427	
Other	12	14	
Histological grade			0.655
I	4	8	
II	24	24	
III	189	172	
IV	109	117	
Unknown	342	346	
T stage			0.211
T0	6	13	
T1	30	24	
T2	54	46	
T3	474	460	
TX	104	124	
N stage			0.407
N0	342	317	
N1	208	223	
NX	118	127	
Tumor size			0.449
≤8mm	10	18	
8.1-129mm	277	282	
≥130mm	104	103	
Unknown	277	264	
Surgery			0.379
Performed	377	360	
None	291	307	

Table 2. **Univariate and multivariate analyses of prognostic factors associated with overall survival of patients with liver metastasis in ovarian cancer in the development cohort**

	Univariate analysis		Multivariate analysis	
Variables	**HR(95%CI)**	**P value**	**HR(95%CI)**	**P value**
Age				
18-70 years	1 (Reference)		1 (Reference)	
71-79 years	1.3790(1.095-1.736)	0.00625	1.1340(0.8935-1.4393)	0.300989
≥80 years	3.2043(2.522-4.071)	<2E-16	1.6276(1.2392-2.1379)	0.000463
Race				
Black	1 (Reference)		1 (Reference)	
White	0.6413(0.4915-0.8367)	0.00106	0.7206(0.5455-0.952)	0.021081
Other	0.5725(0.3788-0.8651)	0.0081	0.8282(0.5418-1.2659)	0.383872
Marital status				
Unmarried	1 (Reference)		1 (Reference)	
Married	0.6132(0.5083-0.7397)	3.22E-07	0.7973(0.6522-0.9748)	0.027152
Unknown	0.9822(0.6459-1.4938)	0.933	0.9488(0.6109-1.4734)	0.814877
Insurance status				
No	1 (Reference)			
Yes	0.9510(0.6135-1.474)	0.822		
Unknown	0.8515(0.2920-2.483)	0.768		
Laterality				
Left	1 (Reference)		1 (Reference)	
Right	0.808(0.5927-1.1015)	0.1774	1.0793(0.7825-1.4886)	0.642006
Bilateral	0.7715(0.6068-0.9808)	0.0342	0.855(0.6588-1.1097)	0.239055
Other	1.9231(1.0495-3.5240)	0.0343	0.857(0.4552-1.6136)	0.632692
Histological grade				
I	1 (Reference)			
II	1.7817(0.2352-13.50)	0.576		
III	2.2131(0.3092-15.84)	0.429		
IV	1.6334(0.2261-11.80)	0.627		
Unknown	4.2476(0.5959-30.28)	0.149		
T stage				
T0	1 (Reference)		1 (Reference)	
T1	0.6113(0.2328-1.6052)	0.3177	2.1961(0.4728-10.1998)	0.315381
T2	0.3933(0.1546-1.005)	0.0501	1.2016(0.2697-5.3545)	0.809604
T3	0.2767(0.1140-0.6713)	0.0045	1.3088(0.3002-5.7069)	0.720213
TX	0.7758(0.3154-1.9083)	0.5804	1.7597(0.3998-7.7454)	0.454803
N stage				
N0	1 (Reference)		1 (Reference)	
N1	0.8708(0.7052-1.075)	0.199	0.9478(0.7632-1.1771)	0.627733
NX	1.7762(1.4041-2.247)	1.67E-06	1.1598(0.8993-1.4958)	0.253305
Tumor size				
≤8mm	1 (Reference)		1 (Reference)	
8.1-129mm	0.3492(0.1716-0.7108)	0.00371	0.4662(0.1453-1.4956)	0.199418
≥130mm	0.3921(0.1884-0.8163)	0.01233	0.5237(0.1612-1.7012)	0.281894
Unknown	0.5874(0.2898-1.1905)	0.13987	0.5046(0.1567-1.6252)	0.251732
Surgery				
None	1 (Reference)		1 (Reference)	
Performed	0.2264(0.1869-0.2742)	<2.00E-16	0.2861(0.2268-0.3608)	<2.00E-16

Table 3. **Univariate and multivariate analyses of prognostic factors associated with cancer-specific survival of patients with liver metastasis in ovarian cancer in the development cohort**

	Univariate analysis		Multivariate analysis	
Variables	HR(95%CI)	P value	HR(95%CI)	P value
Age				
18-70 years	1 (Reference)		1 (Reference)	
71-79 years	1.39(1.098-1.759)	0.00613	1.1403(0.8927-1.4564)	0.293192
≥80 years	3.363(2.597-4.355)	2.00E-16	1.6782(1.2516-2.2504)	0.000542
Race				
Black	1 (Reference)		1 (Reference)	
White	0.6198(0.4725-0.8130)	0.00055	0.707(0.5313-0.9408)	0.017365
Other	0.5496(0.3569-0.8464)	0.00658	0.7791(0.4996-1.2149)	0.270766
Marital status				
Unmarried	1 (Reference)		1 (Reference)	
Married	0.5841(0.4801-0.7106)	7.66E-08	0.7334(0.5947-0.9043)	0.003719
Unknown	0.9387(0.6113-1.4414)	0.772	0.9057(0.5772-1.4212)	0.666527
Insurance status				
No	1 (Reference)			
Yes	0.9562(0.5958-1.534)	0.853		
Unknown	0.8708(0.2944-2.756)	0.803		
Laterality				
Left	1 (Reference)		1 (Reference)	
Right	0.7923(0.5735-1.095)	0.1581	1.1264(0.8027-1.5807)	0.490967
Bilateral	0.7481(0.5823-0.961)	0.02314	0.8814(0.6709-1.1579)	0.364358
Other	2.4117(1.2775-4.553)	0.00662	1.3371(0.6914-2.5858)	0.387947
Histological grade				
I	1 (Reference)			
II	1.812(0.2391-13.73)	0.565		
III	2.208(0.3083-15.82)	0.43		
IV	1.679(0.2323-12.13)	0.608		
Unknown	4.165(0.584-29.7)	0.155		
T stage				
T0	1 (Reference)		1 (Reference)	
T1	0.6163(0.2347-1.6183)	0.32574	2.1563(0.462-10.0641)	0.328305
T2	0.3846(0.1505-0.9831)	0.04599	1.1826(0.2638-5.3011)	0.826534
T3	0.2733(0.1126-0.6636)	0.00416	1.3082(0.2988-5.7279)	0.721438
TX	0.7355(0.2980-1.8154)	0.50518	1.5655(0.3531-6.9417)	0.555282
N stage				
N0	1 (Reference)		1 (Reference)	
N1	0.8734(0.7005-1.089)	0.229	0.9594(0.7646-1.20339)	0.720641
NX	1.8661(1.4627-2.381)	5.17E-07	1.2462(0.9579-1.6214)	0.101147
Tumor size				
≤8mm	1 (Reference)		1 (Reference)	
8.1-129mm	0.3357(0.1647-0.6844)	0.00267	0.4659(0.1447-1.5006)	0.20059
≥130mm	0.394(0.1889-0.8215)	0.01298	0.5295(0.1623-1.7277)	0.291995
Unknown	0.5814(0.2685-1.1798)	0.13308	0.5382(0.1665-1.7398)	0.300714
Surgery				
None	1 (Reference)		1 (Reference)	
Performed	0.2248(0.1841-0.2745)	2.00E-16	0.2841(0.2239-0.3605)	2.00E-16

Table 4. **Detailed points of each predictor in the nomograms**

Characteristic	overall survival nomogram	cancer-specific survival nomogram
Age		
18-70 years	0	0
71-79 years	9	10
≥80 years	37	39
Race		
Black	27	29
White	0	0
Other	13	10
Marital status		
Married	0	0
Unmarried	18	24
Unknown	18	18
Surgery		
Performed	0	0
None	100	100