Original Article

A clinical model to predict the risk of liver metastases in newly diagnosed ovarian cancer: a population-based study

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Background: Liver metastases are important in determining the prognosis of ovarian cancer. We aimed to develop and validate nomograms to predict the risk of liver metastases in patients with early-stage ovarian cancer.

Methods: A total of 13,487 patients were enrolled in the study based on their records in the Surveillance, Epidemiology, and End Results (SEER) database. Risk factors of liver metastases were assessed based on univariable and multivariable logistic regression. A nomogram was also formulated based on the results of multivariable logistic analysis. The area under the receiver-operating characteristic curve was calculated to evaluate the discrimination abilities of the metastasis-related factors and liver metastases nomogram. A calibration plot was generated to analyze the consistency between the observed probability and predicted probability of liver metastases in patients with ovarian cancer.

Results: Four related factors were determined based on univariable and multivariable logistic regression, including the T1 stage, N1 stage, and presence of lung and bone metastases. The liver metastases nomogram composed of four features could be used to determine the prediction effect. The calibration plot showed good consistency between the nomogram prediction and actual observation. The receiver-operating characteristic curve showed that the forecast nomogram exhibited a good forecast value.

Conclusions: This clinical prediction model has high accuracy to identify patients with newly diagnosed ovarian cancer who carry a high risk of liver metastases and provide a personalized treatment plan for these patients.

Keywords: Ovarian cancer; liver metastases; nomogram; receiver-operating characteristic curve; Surveillance, Epidemiology, End Results (SEER) database

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Introduction

Ovarian cancer is one of the most common malignant tumors that affects the female reproductive system. It is estimated that 21,750 women in the US will be diagnosed with ovarian cancer. Ovarian cancer is the fifth most common cause of cancer-related deaths among American women. It is estimated that 13,940 individuals will die from this disease this year (1). Because the symptoms are unclear and there is currently no effective screening method, most

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patients are already harboring the advanced stage (III and IV) when they are diagnosed (2).

Ovarian cancer is called the "silent killer". It is estimated that only 15% of ovarian cancers are restricted to the ovaries, whereas 17% are localized metastases, and 62% are associated with distant metastases. Ovarian cancer can spread through the intraperitoneal, lymphatic, and blood-borne pathways (3). The most common distant metastatic site is the liver, followed by the distant lymph nodes, lungs, bones, and brain (4). Distant metastases to the liver, lungs, brain, and bones are associated with poor overall survival (5,6). The median survival time from the diagnosis of distant metastases is only 4 months (7,8). Therefore, early detection of liver metastases from ovarian cancer is important for modifying treatment strategies and improving patient prognosis.

Most studies of ovarian cancer metastases use liver metastases to predict the prognosis and recurrence of ovarian cancer (9-11). Little is known about the clinical and pathological risk factors of liver metastases in patients with early-stage ovarian cancer. Therefore, we aimed to predict the risk factors based on statistical prediction models.

The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database is the largest publicly available cancer dataset, covering approximately 30% of the US population. It regularly records data on patient demographic information, tumor characteristics, general treatment, and survival time, and important information status updates are provided every year. We aimed to use nomograms to evaluate patients with early-stage ovarian cancer, identify patients with high risk scores, and help modify treatment strategies in clinical applications.

We present the following article in accordance with the TRIPOD reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-2321).

Methods

Data source

The SEER database includes information on demographics, cancer incidence, and survival outcomes from population-based registries for approximately 30% of the US population. Data of this study were obtained from the SEER program of the National Cancer Institute using the Surveillance, Epidemiology, and End Results *Stat software (version 8.3.5). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The research was exempt from ethics statement as the SEER is a publicly available database, and data extracted from SEER were identified as an exempted study. Since the data collected from the SEER database were anonymized and de-identified prior to release, informed patient consent was not required in our study.

Study population

Data were obtained from the National Cancer Institute's SEER program between 2010 and 2014, as the statuses of liver metastases and other sites of distant metastases were collected in the SEER database from 2010, and the data were last updated on December 31, 2014. Initially, 29,313 patients diagnosed with ovarian cancer were identified in the database. After excluding 15,826 unqualified cases, we finally collected 13,487 patients with ovarian cancer. The flowchart of the subjects' selection is illustrated in *Figure 1*. We collected patient demographics and tumor variables. The demographic variables included age, race, marital status, insurance status, and household income at the time of diagnosis. The tumor variables included laterality; tumor grade; tumor size; histological type; whether the disease was stage T or N; and whether bone, brain, liver, and lung distant metastases occurred at the time of initial diagnosis.

Statistical analysis

Statistical analysis was performed using SPSS 21 software. Categorical data were presented as frequencies (%) and analyzed using the chi-squared test. The Kolmogorov–Smirnov test was used to verify the normality of the variables. Normally distributed variables were expressed as means ± standard deviations, while non-normally distributed variables were expressed as medians (interquartile ranges). Univariable and multivariable logistic regression analyses were used to determine the risk factors of liver metastases in patients with ovarian cancer. Factors with a P value less than 0.05 were incorporated into the multivariable regression model.

A nomogram was also formulated based on the results of multivariable logistic analysis using the rms package in R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org). The receiver-operating characteristic (ROC) curve was generated, and the area under the ROC curve (AUC) was calculated to evaluate the discrimination abilities of the metastasis-related factors and liver metastases nomogram. Finally, we evaluated the

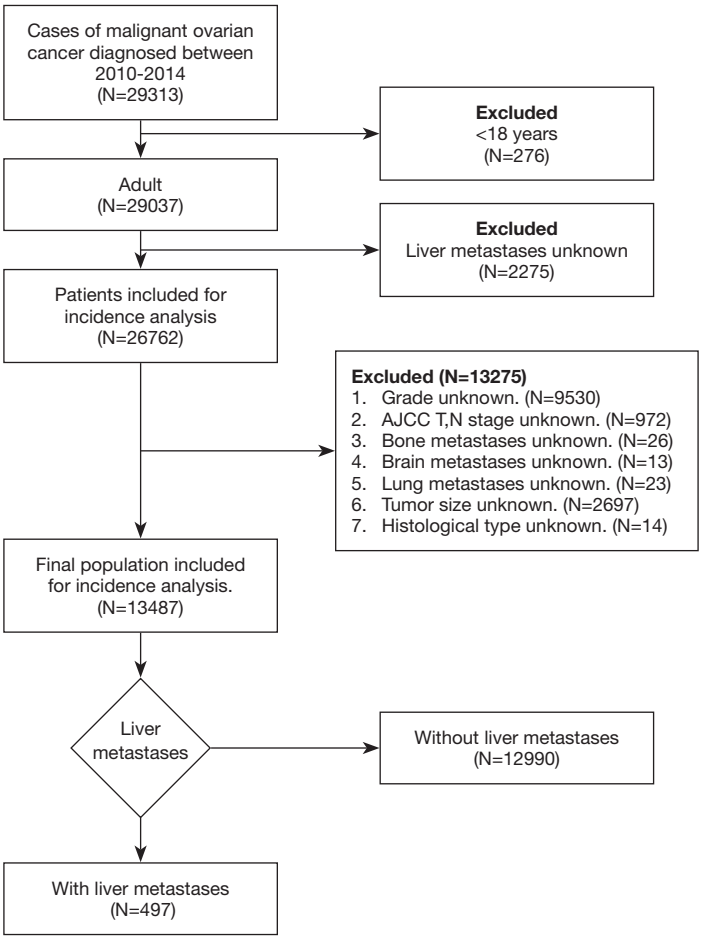

Figure 1 Study flowchart.

stability of the prognostic nomogram by internal validation using 1,000 bootstrap samples. A calibration plot was generated to analyze the consistency between the observed probability and predicted probability of liver metastases in patients with ovarian cancer.

Results

Demographic and clinical characteristics

A total of 13,487 patients with ovarian cancer met the inclusion criteria. The median age of the patients was 59 years (51–68 years). Among these patients, 487 (3.61%) patients with liver metastases had a median age of 63 years (54–71 years). The demographic and clinical characteristics of the included patients are shown in *Table 1*. Age (P<0.001), tumor grade (P<0.001), laterality (P<0.001), American Joint Committee on Cancer T stage (P<0.001) and N stage (P<0.001), histological type (P<0.001), bone metastases (P<0.001), brain metastases (P=0.017), and lung metastases (P<0.001) exhibited significant differences. There were no statistically significant differences in race (P=0.232), year of diagnosis (P=0.462), household income (P=0.103), marital status (P=0.274), insurance status (P=0.308), and tumor size (P=0.463).

Risk factors of developing liver metastases

Univariable logistic analysis showed that advanced age, bilateral tumors, N1 stage, poorly differentiated and undifferentiated grade, lung metastases, bone metastases, and brain metastases were all positively associated with a risk of developing liver metastases. Non-serous histology and T1 stage were negatively related to liver metastases (*Table 2*).

Multivariable logistic regression indicated that the T1

Table 1 Demographical and clinical characteristics between patient with liver metastases and patients without liver metastases

Variables	All patients (N=13,487)	Patients with liver metastases (N=487)	Patients without liver metastases (N=12,990)	P value
Age	59 (51–68)	63 (54–71)	59 (50–68)	<0.001
Race				0.232
White	11,142 (82.6%)	416 (83.7%)	10,726 (82.6%)	
Black	883 (6.5%)	39 (7.8%)	844 (6.5%)	
Other (American Indian/ AK Native, Asian/Pacific Islander)	1,408 (10.4%)	41 (8.2%)	1,367 (10.5%)	
Unknown	54 (0.4%)	1 (0.2%)	53 (0.4%)	
Marital status				0.274
Unmarried	2,795 (20.7%)	104 (20.9%)	2,691 (20.7%)	
Married	7,180 (53.2%)	249 (50.1%)	6,931 (53.4%)	
Separated	2,964 (22.0%)	126 (25.4%)	2,838 (21.8%)	
Unknown	548 (4.1%)	18 (3.6%)	530 (4.1%)	
Insurance status				0.308
Uninsured	501 (3.7%)	13 (2.6%)	488 (3.8%)	
Insured	12,845 (95.2%)	477 (96.0%)	12,368 (95.2%)	
Unknown	141 (1.0%)	7 (1.4%)	134 (1.0%)	
Household income	70,296 (63,636–87,648)	67968 (60,816–82,848)	70,296 (63,900–87,648)	0.103
Year of diagnosis				0.462
2010	2,571 (19.1%)	83 (16.7%)	2,488 (19.2%)	
2011	2,771 (20.1%)	114 (22.9%)	2,597 (20.0%)	
2012	2,686 (19,9%)	99 (19.9%)	2,587 (19.9%)	
2013	2,755 (20.4%)	100 (20.1%)	2,655 (20.4%)	
2014	2,764 (20.5%)	101 (20.3%)	2,663 (20.5%)	
Tumor size				0.463
<2 cm	1,116 (8.3%)	36 (7.2%)	1,080 (8.3%)	
2–5 cm	2,246 (16.7%)	91 (18.3%)	2,155 (16.6%)	
>5 cm	10,125 (75.1%)	370 (74.4%)	9,755 (75.1%)	
Laterality				<0.001
Left	4,086 (30.3%)	105 (21.1%)	3,981 (30.6%)	
Right	4,132 (30.6%)	97 (19.5%)	4,035 (31.1%)	
Bilateral	5,044 (37.4%)	268 (53.9%)	4,776 (36.8%)	
Others/unknown	225 (1.7%)	27 (5.4%)	198 (1.5%)	
Grade				<0.001
Well differentiated	1,662 (12.3%)	13 (2.6%)	1,649 (12.7%)	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	All patients (N=13,487)	Patients with liver metastases (N=487)	Patients without liver metastases (N=12,990)	P value
Moderate differentiated	2,337 (17.3%)	45 (9.1%)	2,292 (17.6%)	
Poor differentiated	5,549 (41.1%)	265 (53.3%)	5,284 (40.7%)	
Undifferentiated	3,939 (29.2%)	174 (35.0%)	3,765 (29.0%)	
AJCC T stage				<0.001
T0	22 (0.2%)	3 (0.6%)	19 (0.1%)	
T1	4,579 (34.0%)	22 (4.4%)	4,557 (35.1%)	
T2	2,085 (15.5%)	39 (7.8%)	2,046 (15.8%)	
T3	6,801 (50.4%)	433 (87.1%)	6,368 (49.0%)	
AJCC N stage				<0.001
N0	10,518 (78.0%)	288 (57.9%)	10,230 (78.8%)	
N1	2,969 (22.0%))	209 (42.1%)	2,760 (21.2%)	
Bone metastasis				<0.001
Yes	41 (0.3%)	10 (2.0%)	31 (0.2%)	
No	13,446 (99.7%)	487 (98.0%)	12,959 (99.8%)	
Brain metastasis				0.017
Yes	12 (0.1%)	2 (0.4%)	10 (0.1%)	
No	13,475 (99.9%)	495 (99.6%)	12,980 (99.9%)	
Lung metastasis				<0.001
Yes	355 (2.6%)	84 (16.9%)	271 (2.1%)	
No	13,132 (97.4%)	413 (83.1%)	12,719 (97.9%)	
Histological type				<0.001
Serous	7,120 (52.8%)	339 (68.2%)	6,781 (52.2%)	
Non-serous	6,367 (47.2%)	158 (31.8%)	6,290 (47.8%)	

stage was negatively associated with liver metastases, while the N1 stage and presence of lung and bone metastases were positively associated with liver metastases development. Statistically significant factors in multivariable logistic regression were used to develop risk models for predicting liver metastases (*Table 2*).

Liver metastases nomogram for ovarian cancer

Through the logistic regression model, we built a liver metastasis nomogram incorporating the aforementioned independent metastases factors for visualization and facilitating clinical practice, as shown in *Figure 2A*. We used bootstrapping to internally validate the model. Stability and internal validation were studied using 1,000 bootstrap samples. The calibration plot, displayed in *Figure 2B*, for the probability of liver metastases after diagnosis, showed good consistency between the nomogram predictions and actual observations.

ROC curve analysis and predictive value assessment

The ROC curve was plotted to determine the predictive value of the nomogram for the presence of liver metastases in patients with ovarian cancer. As shown in *Figure 3*, the AUCs of the presence of lung and bone metastases, T1 stage, and N1 stage were 0.765, respectively, indicating their good predictive value.

Table 2 Univariable and Multivariable Logistic Regression for analyzing the associated factors for developing liver metastases in ovarian cancer patients

Variables	Univariable			Multivariable		
	OR	95% CI	P value	OR	95% CI	P value
Age	1.016	1.009–1.023	<0.001	1.004	0.996–1.012	0.319
Race			0.236			0.913
White	References			References		
Black	1.191	0.852–1.667	0.306	1.039	0.727–1.485	0.832
Other	0.773	0.558–1.071	0.122	0.889	0.631–1.252	0.5
Unknown	0.486	0.067–3.526	0.476	0.923	0.123–6.906	0.938
Marital status			0.275			0.207
Unmarried	References			References		
Married	0.930	0.736–1.174	0.539	0.776	0.605–0.995	0.046
Separated	1.149	0.881–1.497	0.305	0.897	0.671–1.199	0.461
Unknown	0.879	0.528–1.462	0.619	0.798	0.468–1.361	0.407
Insurance status			0.312			0.457
Uninsured	References			References		
Insured	1.448	0.828–2.530	0.194	1.368	0.762–2.455	0.294
Others/unknown	1.961	0.767–5.013	0.160	1.734	0.633–4.752	0.284
Household income	1.000	1.000–1.000	0.133	1.000	1.000–1.000	0.065
Year of diagnosis			0.463			0.474
2010	References			References		
2011	0.880	0.655–1.182	0.395	1.325	0.984–1.785	0.064
2012	1.157	0.881–1.521	0.294	1.166	0.858–1.584	0.327
2013	1.009	0.761–1.338	0.950	1.149	0.847–1.56	0.372
2014	0.993	0.749–1.316	0.961	1.13	0.831–1.536	0.435
Tumor size			0.464			0.686
<2 cm	References			References		
2–5 cm	1.267	0.855–1.876	0.238	1.099	0.723–1.67	0.660
>5 cm	1.138	0.804–1.611	0.467	1.164	0.799–1.696	0.429
Laterality			<0.001			<0.001
Left	References			References		
Right	0.911	0.689–1.205	0.516	0.882	0.66–1.178	0.396
Bilateral	2.128	1.691–2.676	<0.001	1.113	0.868–1.425	0.399
Others/unknown	5.170	3.309–8.079	<0.001	2.733	1.689–4.421	<0.001
Grade			<0.001			0.050
Well differentiated	References			References		

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Univariable			Multivariable		
	OR	95% CI	P value	OR	95% CI	P value
Moderate differentiated	2.490	1.339–4.631	0.004	1.432	0.758–2.702	0.268
Poor differentiated	6.362	3.636–11.131	<0.001	1.931	1.077–3.463	0.027
Undifferentiated	5.862	3.327–10.330	<0.001	1.661	0.918–3.006	0.094
AJCC T stage			<0.001			<0.001
T0	References			References		
T1	0.031	0.008–0.111	<0.001	0.152	0.036–0.639	0.01
T2	0.121	0.034–0.425	0.001	0.447	0.111–1.81	0.259
T3	0.431	0.127–1.461	0.176	1.4	0.358–5.48	0.629
AJCC N stage			<0.001			<0.001
N0	References			References		
N1	2.690	2.240–3.230	<0.001	1.490	1.228–1.808	<0.001
Bone metastasis			<0.001			0.001
No	References			References		
Yes	8.584	4.184–17.609	<0.001	4.287	1.878–9.787	0.001
Brain metastasis			0.33			0.306
No	References			References		
Yes	5.244	1.146–23.999	0.33	2.51	0.463–13.597	0.286
Lung metastasis			<0.001	<0.001		<0.001
No	References			References		
Yes	9.546	7.334–12.425	<0.001	5.902	4.474–7.788	<0.001
Histological type			<0.001			0.116
Serous	References			References		
Non-serous	0.509	0.420–0.617	<0.001	1.189	0.958–1.477	0.116

Discussion

Liver metastases are common in patients with ovarian cancer. Previous studies have shown that liver metastases are found in up to 50% of patients who die from ovarian cancer (12). Liver metastases are the main cause of death from ovarian cancer. Chemotherapy is currently the main treatment for ovarian cancer with metastases. However, studies have shown that performing cytoreductive surgery, including hysterectomy, bilateral salpingo-oophorectomy, omentum resection, and resection of all metastatic lesions, is beneficial to the survival of patients (13). Performing complete resection of liver metastases can confer benefits to survival (14). A patient's disease-free survival and overall survival improve (15). Valerio Gallotta's study found that hepatic resection during the second cytoreductive surgery was beneficial for patients with recurrent ovarian cancer, and BRCA gene mutations were associated with better progression-free survival after hepatic resection (16). It was feasible and safe to apply laparoscopy to remove the lesions in the abdominal cavity including the liver, allowing patients to benefit (17). Therefore, early detection of liver metastasis, clarification of the molecular characteristics of tumors, and selection of appropriate multi-channel treatment are of great significance to improve the prognosis of patients with ovarian cancer.

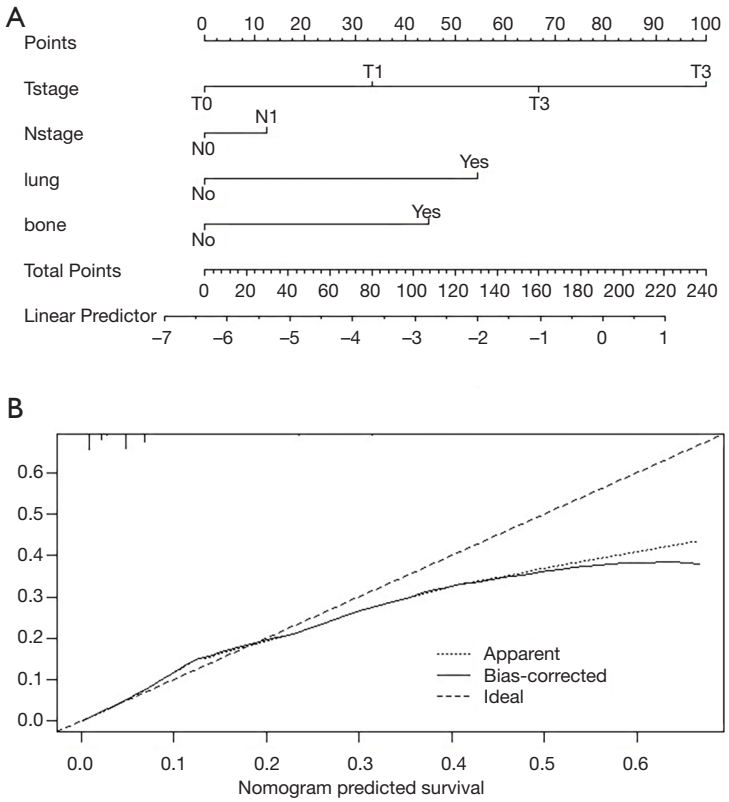

Figure 2 The nomogram and the calibration curve for liver metastasis in patients with ovarian cancer. (A) The nomogram for liver metastasis in patients with ovarian cancer. The total point score is projected on the bottom scales to determine the probability of cancer metastasis in an individual; (B) the calibration curves for predicting liver metastases.

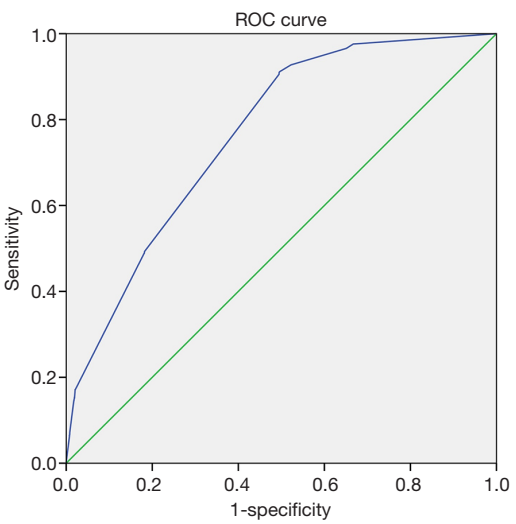

Figure 3 The ROC curve. The sensitivity of the ROC curve is 0.911 and the specificity is 0.504.

In order to better solve this problem, this study is the first to generate a risk model based on clinical and tumor characteristics through the population-based SEER database to predict the risk of liver metastases in newly diagnosed patients with ovarian cancer. We found a series of risk factors associated with the development of liver metastases in patients with ovarian cancer, including a high T stage (T1) and N stage (N1) and the presence of lung and bone metastases. Deng *et al.*'s study showed that poor differentiation and lymph node involvement are positively correlated with the occurrence of distant metastases (5). Our study findings were in line with these findings. In the univariable logistic regression, we found that the degree of differentiation and N1 stage were positively correlated with liver metastases. In the multivariable logistic regression, the correlation between differentiation and liver metastases was not statistically significant. Previous studies have shown

that the histological type of ovarian cancer is related to the occurrence of bone metastases in patients with ovarian cancer and their prognosis (9,18). In the univariable logistic regression, we found that serous ovarian cancer was more prone to liver metastases than non-serous ovarian cancer. Bone metastases and brain metastases are independent risk factors affecting the prognosis of patients with ovarian cancer (6). Our study found that bone metastases and lung metastases were risk factors of liver metastases. If a patient with ovarian cancer harbors bone metastases and lung metastases, the cancer cells are more prone to spread. Multivariable logistic regression has shown that the T1 stage is negatively correlated with liver metastases. The T1 stage is associated with the tumor being limited to the ovaries, with no ovarian surface, pelvic, extraperitoneal, or peritoneal metastasis. Therefore, the risk of liver metastasis is low (19). Zecchin *et al*. found that tumor size affects the prognosis of patients with ovarian cancer (20). Our study did not reveal a relationship between tumor size and liver metastases.

We constructed a nomogram for ovarian cancer liver metastases and verified the results. It can be used to predict the risk of liver metastases in patients with ovarian cancer. The nomogram of liver metastases included 4 factors: T stage, N stage, whether bone metastases occur, and whether lung metastases occur. The nomogram showed good consistency between the predicted and observed results in the verification. In addition, the area under the ROC curve was 0.765, which also showed good diagnostic efficiency. For patients whose risk of metastases is predicted to be higher by this model, periodic computed tomography scans can be considered for prevention and care, so as to better guide clinical procedures.

This study has several limitations. First, in this study, the existence or absence of liver metastases was analyzed based only on preliminary diagnosis. Because the liver metastases that appear later in the disease course may not be recorded in the SEER database, patients with late-stage liver metastases cannot be analyzed. Second, this model does not include some clinical indicators and genetic markers, and biomarkers can be included to improve the accuracy of the model. Third, because the patients in this study were from the American population, further verification is needed in populations of other countries to apply the risk prediction model more accurately.

Liver metastases are the most common distant metastatic site of ovarian cancer. Early detection of liver metastases through routine screening at the initial diagnosis of ovarian cancer will be beneficial for patients carrying a high risk. Here, this clinical prediction model has high accuracy to identify patients with newly diagnosed ovarian cancer who carry a high risk of liver metastases and provide a personalized treatment plan for these patients.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at http://dx.doi.org/10.21037/tcr-20-2321

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr-20-2321). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The research was exempt from ethics statement as the SEER is a publicly available database, and data extracted from SEER were identified as an exempted study. Since the data collected from the Surveillance, Epidemiology, and End Results database were anonymized and de-identified prior to release, informed patient consent was not required in our study.

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