A Novel Clinical Nomogram for Predicting Lymph Node Metastasis in Ovarian Cancer: A SEER Analysis and External Validation in a Tertiary Center

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Research Article

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Abstract

Introduction

The aim of the study is to investigate the risk factors for developing lymph node metastases (LNM) in cases diagnosed as a presumed early-stage ovarian carcinoma (OC).

Methodology

Information of patients who had been diagnosed as OC in 2018 was obtained from the SEER database. We enrolled 104 OC patients in General Hospital of Northern Theatre Command for external validation. A logistic regression was conducted to determine the independent predictors for LNM, which were used for establishing a nomogram. In order to evaluate the reliability of nomogram, we applied a receiver operating characteristic curve (ROC) analysis, calibration curves and plotted decision curves.

Results

We found that age(≥ 70 , OR=0.544, $p=0.022$), histology type (Mucinous carcinoma, OR=0.390, $p=0.001$; Endometrioid carcinoma, OR=7.946, $p=0.053$; Others, OR=2.400, $p=0.040$), histology grade (Grade II, OR=2.423, $p=0.028$; Grade III, OR=1.982, $p=0.152$; Grade IV, OR=1.594, $p=0.063$) and preoperative serum CA125 level (positive, OR=2.236, $p=0.001$) were all significant predictors of LNM. The AUC of the model training cohort, internal validation cohort, and external validation cohort were 0.78, 0.79 and 0.76 respectively. The calibration curves showed that the predicted outcome fitted well to the observed outcome in the training cohort ($p=0.825$) internal validation cohort ($p=0.503$), and external validation cohort ($p=0.108$). The decision curves showed the nomogram had more benefits than the All or None scheme if the threshold probability is $>50\%$ and $<100\%$ in training cohort and internal validation cohort, $>30\%$ and $<90\%$ in the external validation cohort.

Conclusion

The multivariate logistic regression showed that age, histology type, histology grade and preoperative serum CA125 level were all significant predictors of LNM. The nomogram established using the above variables had great performance for clinical applying.

Introduction

Annually worldwide, there are 230 000 women diagnosing as ovarian carcinoma (OC) and 150 000 patients die. Although the incidence of OC was is the third of gynecological malignancies, its mortality rate is the highest. In recent years, the incidence of OC has gradually increased[1, 2, 3]. Because of late detection, 70% of OC patients present with advanced stages upon diagnosis[4]. OC can be transferred by

intraperitoneal route, lymphatic route, and blood-borne route. Previous studies showed that up to 15% of OC have positive lymph node metastases (LNM), which would significantly influence the lifetime of OC[5]. Whereas, there were about 80% of cases unnecessary if the lymph node dissection is routine in presumed early-stage OC[6, 7, 8]. Moreover, dissection of lymph node would increase occurrence of complications, including infection, formation of lymphocyst, which might significantly influence the quality of life[9, 10, 11]. Consequently, identifying OC cases with positive lymph node metastases (LNM) would help the oncologist institute treatment decisions which will benefit the prognosis of OC.

The aim of the study is to investigate the risk factors for developing LNM in cases diagnosed as a presumed early-stage OC. In our study, we used logical regression to construct a nomogram for predicting LNM in OC cases based on the SEER database and external validation in a Gynecological oncology Center.

Materials And Methods

Study Population and Data collection in SEER database

Information of patients who had been diagnosed as OC in 2018 was obtained from the SEER database using SEER*Stat software. In order to access the data of SEER, we obtained signed authorization. The following were the inclusion criteria: (1) Site recode ICD-O-3/WHO 2008: Ovary, (2) year of diagnosis: 2018. The exclusion criteria were as following: (1) information missing of LNM, tumor size, race, marital status, histology, or tumor grade, (2) no first tumor.

Following the processing flowchart shown in Figure 1, 921 patients with OC were enrolled in our study. At a ratio of 7:3, we randomly divided the 921 cases into a training cohort (n = 644) and validation cohort (n = 277). We collected the variables including age, race, insure, marriage, laterality, histology type and grade, tumor size, preoperative serum CA125 level and lymph nodes positive.

External Validation data

The clinical Data of 104 OC patients were extracted from electronical database of the General Hospital of Northern Theatre Command. This study was approved by the Institutional Review Board of the General Hospital of Northern Theatre Command (ID:2020016). Because the study was retrospective and observational, the board waived the patients' informed consent. Inclusion criteria: (1) The OC was primary, and diagnosed by postoperative pathology, (2) The patients did not receive preoperative biological therapy or chemoradiotherapy, (3) The clinical data were complete.

Statistical analysis

The categorical and continuous data were expressed as percentage and mean $\pm$ SD respectively. For categorical variables, we conducted t test or Mann-Whitney U test to make comparisons between the groups while for continuous variables, chi-square test or Fisher's exact tests were used. To develop a well-reliable nomogram model predicting the risk of LNM, our nomogram was built using the training cohort

with 644 patients, validated internally using the 277 patients and then validated externally using the 104 patients in the General Hospital of Northern Theatre Command. In order to check multicollinearity between clinical variables, we used the variance inflation factor (VIF) and tolerance. A logistic regression was conducted to determine the independent predictors for LNM, which were used for establishing a nomogram. In order to evaluate the reliability and the net benefit of nomogram, we applied a receiver operating characteristic curve (ROC) analysis, calibration curves and plotted decision curves. We considered statistically significant if the p value was less than 0.05. we used the statistical packages R (The R Foundation; <http://www.r-project.org>; version 3.4.3) and Empower (R) to analyze the Data (www.empowerstats.com, X&Y solutions, inc. Boston, Massachusetts).

Results

Demographic characteristics

In our study, we enrolled 644 and 277 cases into the training cohort and the validation cohort. There was no difference in various indicators between the two cohorts ($P > 0.05$, Table 1). Most of the patients were white (76.9%), the histological type was serous carcinoma (44.4%), the most histological grade was G3 (43.8%), 66.6% of the patients were with positive serum CA125 and 77.6% of the patients were with positive LNM.

Table 1
Characteristics of patients in the training and validation cohorts

Characteristics	Training cohort (N=277)	Internal Validation cohort (N=644)	P
Age (years)			0.985
<i>≤40</i>	22(7.9%)	51(7.9%)	
<i>40-70</i>	199(71.8%)	458(71.1%)	
<i>≥70</i>	56(20.2%)	135(21.0%)	
Insurance			0.317
<i>Insured</i>	193(69.7%)	427(66.3%)	
<i>Uninsured and others</i>	84(30.3%)	217(33.7%)	
Race			0.473
<i>White</i>	220(79.4%)	488(75.8%)	
<i>Black</i>	20(7.2%)	52(8.1%)	
<i>Other</i>	37(13.4%)	104(16.1%)	
Marital status			0.552
<i>Married</i>	212(76.5%)	481(74.7%)	
<i>Unmarried and others</i>	65(23.5%)	163(25.3%)	
Histology			0.751
<i>Serous adenocarcinoma</i>	123(44.4%)	286(44.4%)	
<i>Mucinous carcinoma</i>	26(9.4%)	56(8.7%)	
<i>Endometrioid carcinoma</i>	74(26.7%)	158(24.5%)	
<i>Others</i>	54(19.5%)	144(22.4%)	
Differentiation			0.358
<i>Grade I</i>	66(23.8%)	143(22.2%)	
<i>Grade II</i>	49(17.7%)	89(13.8%)	
<i>Grade III</i>	112(40.4%)	291(45.2%)	
<i>Grade IV</i>	50(18.1%)	121(18.8%)	
Laterality			0.970
<i>Left</i>	129(46.6%)	305(47.4%)	

Characteristics	Training cohort (N=277)	Internal Validation cohort (N=644)	P
<i>Right</i>	125(45.1%)	285(44.3%)	
<i>Unspecial</i>	23(8.3%)	54(8.4%)	
Tumor size (mm)	110.27±67.28	112.55±69.65	0.645
Preoperative serum CA125 level			0.175
<i>Positive</i>	195(70.4%)	418(64.9%)	
<i>Negative</i>	38(13.7%)	119(18.5%)	
<i>Not documented</i>	44(15.9%)	107(16.6%)	
lymph node metastasis			0.869
<i>Negative</i>	61(22.0%)	145(22.5%)	
<i>Positive</i>	216(78.0%)	499(77.5%)	

Nomogram Construction

We used the univariate logistic regression to analyze the association between age, insurance, race, marital status, histology type, histology grade, laterality, tumor size, preoperative serum CA125 level and LNM. We found that histology type (Mucinous carcinoma, OR=0.346, $p<0.001$; Endometrioid carcinoma, OR=11.555, $p=0.018$; Others, OR=2.807, $p=0.007$), histology grade (Grade II, OR=6.059, $p<0.001$; Grade III, OR=6.658, $p<0.001$; Grade IV, OR=1.894, $p=0.005$) and preoperative serum CA125 level (positive, OR=2.749, $p<0.001$) were all significant predictors of LNM (Table2).

Table 2

Univariate and multivariate logistic regression model for predicting lymph node metastasis in the model of training cohort

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (years)				
≤ 40	1		1	
40-70	1.344(0.566,3.190)	0.503	0.530(0.195,1.439)	0.213
≥ 70	0.791(0.493,1.269)	0.331	0.544(0.323,0.917)	0.022
Insurance				
<i>Insured</i>	1		1	
<i>Uninsured and others</i>	0.787(0.527,1.176)	0.243	0.805(0.515,1.256)	0.339
Race				
<i>White</i>	1		1	
<i>Black</i>	1.445(0.894,2.337)	0.133	1.213(0.708,2.079)	0.483
<i>Other</i>	1.160(0.542,2.481)	0.702	0.964(0.406,2.286)	0.933
Marital status				
<i>Married</i>	1		1	
<i>Unmarried and others</i>	0.922(0.600,1.418)	0.712	0.844(0.523,1.362)	0.487
Histology				
<i>Serous adenocarcinoma</i>	1		1	
<i>Mucinous carcinoma</i>	0.346(0.211,0.567)	0.000	0.390(0.227,0.669)	0.001
<i>Endometrioid carcinoma</i>	11.555(1.526,87.466)	0.018	7.946(0.977,64.622)	0.053
<i>Others</i>	2.807(1.327,5.939)	0.007	2.400(1.1041,5.534)	0.040
Differentiation				
<i>Grade I</i>	1		1	
<i>Grade II</i>	6.059(3.129,11.733)	0.000	2.423(1.098,5.345)	0.028
<i>Grade III</i>	6.658(2.954,15.004)	0.000	1.982(0.777,5.056)	0.152
<i>Grade IV</i>	1.894(1.209,2.967)	0.005	1.594(0.976,2.605)	0.063
Laterality				

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
<i>Left</i>	1		1	
<i>Right</i>	1.081(0.550,2.139)	0.815	1.067(0.498,2.284)	0.868
<i>Unspecial</i>	1.117(0.564,2.214)	0.751	1.148(0.535,2.463)	0.724
Tumor size (cm)	1.001(0.999,1.004)	0.292	0.999(0.996,1.003)	0.636
Preoperative serum CA125 level				
<i>Negative or Not documented</i>	1		1	
<i>Positive</i>	2.749(1.753,4.309)	0.000	2.236(1.373,3.641)	0.001

Using the multivariate logistic regression, we analyzed the association between age, insurance, race, marital status, histology type, histology grade, laterality, tumor size, preoperative serum CA125 level and LNM (Table 3). We found that age(≥ 70 , OR=0.544, $p=0.022$), histology type (Mucinous carcinoma, OR=0.390, $p=0.001$; Endometrioid carcinoma, OR=7.946, $p=0.053$; Others, OR=2.400, $p=0.040$), histology grade (Grade II, OR=2.423, $p=0.028$; Grade III, OR=1.982, $p=0.152$; Grade IV, OR=1.594, $p=0.063$) and preoperative serum CA125 level (positive, OR=2.236, $p=0.001$) were all significant predictors of LNM (Table2). In addition, we found the tolerance was >0.1 and VIF was <10 for the predictors, suggesting no collinearity among these independent variables (Supplement Table 1). Based on the above risk factors, we established the nomogram for predicting LNM.

Table 3
Performance of the nomogram in predicting lymph node metastasis in the training cohorts

Performance parameter	AUC	Accuracy	Specificity	Sensitivity	PLR	NLR	DOR
Nomogram	0.77	0.72	0.73	0.72	2.69	0.38	7.02
AUC: Area Under the Curve							
PLR: positive likelihood ratio							
NLR: negative likelihood ratio							
DOR: Diagnostic Odds Ratio							

Nomogram Validation

Internal Validation

The AUC of the model training cohort and validation cohort were 0.78 (figure3A) and 0.79 (figure3B) respectively, which indicated favorable discrimination. The calibration curves showed that the predicted outcome fitted well to the observed outcome in the training cohort ($p=0.825$, figure3D) and validation cohort ($p=0.503$, figure3E). The decision curves showed the nomogram had more benefits than the All or None scheme if the threshold probability is $>50\%$ and $<100\%$ in training cohort and validation cohort (figure3G, H). The AUC, accuracy, specificity, sensitivity, PLR, NLR, DOR were 0.77, 0.72, 0.73, 0.72, 2.69, 0.38, 7.02 respectively (Table3).

External Validation

A total of 104 OC patients in the Department of Gynecology, General Hospital of Northern Theatre Command were collected. In the age, the proportion of ≤ 40 , 40-70 and ≥ 70 was 11.5%, 49.0% and 39.4% respectively. Most of the patients were white (72.1%), the insured was 62.5%, the married was 70.2%, the positive serum CA125 was 58.7%, the positive LNM was 78.8%. In the differentiation, the proportion of grade I, grade II, grade III and grade IV was 33.7%, 18.3%, 37.5%, and 10.6% respectively. In the histology type, the proportion of serous adenocarcinoma, mucinous carcinoma, endometrioid carcinoma and others was 26.0%, 17.3%, 28.8%, and 27.9% respectively. The mean tumor size was 120.67 ± 74.15 mm. Characteristics of patients are shown in supplementary Table 2. The AUC of the external validation cohort were 0.76 (figure3C), which indicated favorable discrimination. The calibration curves showed that the predicted outcome fitted well to the observed outcome in the external validation cohort ($p=0.108$, figure3F). The decision curves showed the nomogram had more benefits than the All or None scheme if the threshold probability is $>30\%$ and $<90\%$ in the external validation cohort (figure3I).

Discussion

More than 70% of OC patients were diagnosed as late stage because of the insidious progress and not obvious symptoms early, which leads to the 5-year survival rate is only 30% - 40%[4]. The issue of LNM in OC has a particular interest among gynecological oncologists worldwide, because the LNM was with high occurrence and would affect the prognosis of OC[1, 12, 13, 14]. Nasioudis et al. have found that the rate of LNM was about 3.3% - 14% in early OC and as high as 40% ~ 73.7% in late OC[15, 16]. Moreover, it was observed that plenty of cases diagnosed as presumed early-stage OC already have LNM. Therefore, all these mis-staging cases are at risk for poor long-term prognosis. In consideration of the influence of LNM on prognosis, routine lymph node resection in early OC patients has been performed by most surgeons. Whereas, routine performance of lymph node resection might lead to overtreatment in a significant number of cases and give rise to more occurrence of complications, including poor wound healing, infection, formation of lymphocyst and chronic lymphedema of lower extremities, which would influence the quality of patients' daily life[5, 7, 17]. Consequently, the lymph node removal is still controversial for

OC patients. In addition, with the development of minimally invasive surgical treatment and the objective existence of complications of lymph node resection, more and more gynecological oncologists focused on appropriate, reasonable, and accurate lymphadenectomy in OC. Therefore, identifying cases which present LNM would avoid unnecessary systemic lymph node resection and enable the oncologist to provide a better selection of cases. It would not only ensure patient outcomes but also reduced the incidence of complications.

In order to assess the possibility of LNM, several researchers make efforts using different methods. Signorelli et al. used positron emission computed tomography (PECT) to detect potential positive lymph nodes. The study found that the detectable rate of positive lymph nodes was about 83.3%. Signorelli et al. concluded that PECT was safe and reliable for detecting potential positive lymph nodes and could help avoid systematic lymph node dissection[10]. The sentinel node detection was another promising method for identifying LNM in OC patients. The sentinel node detection is still under evaluation in OC patients before it was as part of the standard therapeutic protocol, despite the method using for breast cancer and cervical cancer[7, 18, 19, 20]. Bogani et al. developed a nomogram to identify LNM and found that high-grade serous histology was a strongest predictor for LNM[5, 21]. Zhou et al. found that poorly differentiation, serous histology, and higher values of CA125 may be associated LNM[22]. In our study, we found that endometrioid carcinoma, a lower degree of differentiation, and positive serum CA125 were all associated with higher occurrence of LNM, which was similar with the conclusion published by Hengeveld in 2019. Hengeveld et al. also found that higher age and the postmenopausal status were significantly associated LNM[23]. However, in our study, we found that the older age was negatively associated with LNM.

Conclusions

The multivariate logistic regression showed that age, histology type, histology grade and preoperative serum CA125 level were all significant predictors of LNM. After internal and external verification, we found the nomogram established using the above variables has great performance for clinical applying.

Abbreviations

LNM: lymph node metastases; OC: ovarian carcinoma; ROC: receiver operating characteristic; SEER: Surveillance, Epidemiology, and End Results; VIF: variance inflation factor; OR: Odds Ratio; AUC: Area Under the Curve; PLR: positive likelihood ratio; NLR: negative likelihood ratio; DOR: Diagnostic Odds Ratio; PECT: positron emission computed tomography

Declarations

Acknowledgments

None

Conflict of Interest

The authors declare that they have no conflict of interest.

Authorship statement

All authors take responsibility for the integrity and the accuracy of this manuscript. Study concept and design, Draft of the manuscript: Wei Ren; Acquisition of data, Statistical analysis, Edit: Guiping Zhang.

Conflicts of Interest and Source of Funding

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in.

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Figures

Figure 1

Flow chart for OC patients in training and validation cohorts.

Figure 2

The nomogram to predict the probability of LNM in patients with OC. Based on the risk factors selected, we developed a nomogram to predict the probability of LNM based on the logistic model.

Figure 3

Nomogram Validation The AUC of the model training cohort, internal validation cohort, and external validation cohort were 0.78 (figure3A), 0.79 (figure3B) and 0.76 (figure3C) respectively, which indicated favorable discrimination. The calibration curves showed that the predicted outcome fitted well to the observed outcome in the training cohort ($p=0.825$, figure3D) internal validation cohort ($p=0.503$, figure3E), and external validation cohort ($p=0.108$, figure3F). The decision curves showed the nomogram had more benefits than the All or None scheme if the threshold probability is $>50\%$ and $<100\%$ in training cohort and internal validation cohort (figure3G, H), $>30\%$ and $<90\%$ in the external validation cohort (figure3I).

Supplementary Files

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